1,011,112

PATENT SPECIFICATION

NO DRAWINGS

1,011,112

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Int. Cl.:—C 07 c, d

The inventors of this invention in the sense of being the actual devisers thereof within the meaning of Section 16 of the Patents Act, 1949 are ALBERT HOFMANN, Oberwilerstrasse 11, Bottmingen/BL, Switzerland; ALBERT FREY, Rudolf Wackernagelstrasse 45, Riehen, Switzerland and HANS OTT, Florastrasse 8, Reinach/BL, Switzerland, all Swiss citizens.

COMPLETE SPECIFICATION

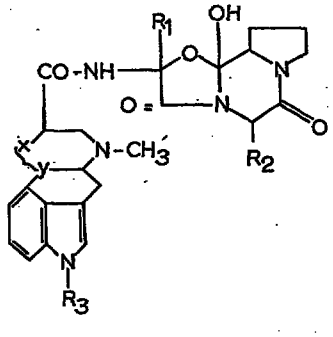
Improvements in or relating to Ergot Alkaloids

We, SANDOZ PATENTS LIMITED, of 590 Jarvis Street, Toronto 5, Ontario, Canada, a Canadian Body Corporate, 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 relates to a process for the production of ergot alkaloids and to certain novel ergot alkaloids.

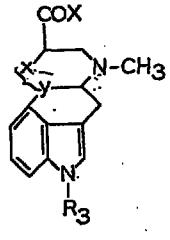
The present invention provides ergovaline, ergovalinine, and 9,10 - dihydro-ergovaline; these three compounds have hitherto not been found in nature.

The present invention also provides a process for the production of compounds of general formula I,



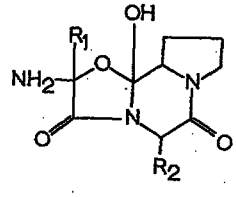
I

in which each of R_1 and R_3 signifies a hydrogen atom or an alkyl radical containing from 1 to 3 carbon atoms inclusive
and R_2 signifies a hydrogen atom, an alkyl radical containing from 1 to 5 carbon atom inclusive or the benzyl radical
and $\overset{\frown}{x\ y}$ signifies the radical $-CH=C\diagup\diagdown$ or $-CH_2-CH\diagup\diagdown$,
and their acid addition salts, characterized in that a compound of general formula II,



II

in which R_3 and $\overset{\frown}{x\ y}$ have the above significance and X signifies a chlorine or bromine atom or the radical $-OSO_3H$,
is reacted with a salt of a compound of general formula III,



III

in which R_1 and R_2 have the above significance,
in the presence of a tertiary base and, when an acid addition salt is required, salification is effected with an organic or inorganic acid.

[*Price 4s. 6d.*]

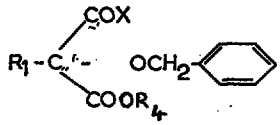
Salification of the compounds of formula I may be effected by reaction of the base with an organic or inorganic acid, e.g. hydrochloric, hydrobromic, sulphuric, citric, tartaric, succinic, maleic, malic, acetic, benzoic, hexahydrobenzoic, methanesulphonic, fumaric, gallic and hydriodic acid.

When a compound II, in which X signifies a chlorine or bromine atom, e.g. (+)-lysergic acid chloride hydrochloride, is used for the reaction, it may be suspended together with a salt of a compound III in an inert solvent, e.g. chloroform, and a tertiary amine solution, e.g. tributyl amine, added. The reaction mixture may be concentrated, diluted with a water immiscible solvent, e.g. methylene chloride, chloroform or ethyl acetate, and the basic constituents removed by shaking with a dilute aqueous solution of an organic acid, e.g. acetic acid or tartaric acid. Subsequently the aqueous solution may be made alkaline and extracted with an organic solvent (e.g. ethyl acetate or ether), the extract dried and the solvent evaporated. The resulting crude product may subsequently be purified by chromatography on aluminium oxide and subsequent crystallization.

When a compound II, in which X signifies the $-OSO_3H$ radical, is used for the reaction, it is produced *in situ* by reacting lysergic acid or dihydrolysergic acid with sulphuric acid. The resulting anhydride is then reacted with a salt of a compound III. In this particular process a suspension of a salt of the compound III and the calculated quantity of a tertiary base in dimethyl formamide may be added to a freshly prepared solution of the anhydride in dimethyl formamide at 0° and the reaction mixture may be further worked up as described above.

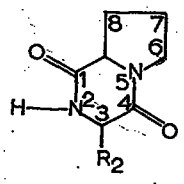
Compounds II, in which X signifies a chlorine or a bromine atom (described and claimed in patent specification No. 31189/61) (991,115) may, for example, be produced as follows:— Finely divided (+)-lysergic acid is suspended in freshly distilled phosphorus oxyhalide and freshly sublimated, finely pulverized phosphorus pentahalide is added while stirring. The reaction mixture is shaken at room temperature and then heated to 90°. The phosphorus oxyhalide is then evaporated off in a water jet vacuum and the remaining grey powder washed twice with hexane.

The compounds III, (described and claimed in patent specification No. 17400/62) (1,011,113) may be produced as follows: A 2 - bromo - 2 - alkyl(C_1—C_3) or 2 - bromomalonic acid dialkyl (alkyl C_1—C_4) ester is converted with sodium benzylate and the resulting 2-benzyloxy malonic acid dialkyl ester saponified with the calculated quantity of an alcoholic potassium hydroxide solution to form the 2-benzyloxy malonic acid semi-ester. This is reacted with thionyl halide to produce a 2-benzyloxy-malonic acid halide monoalkyl ester of general formula IV,



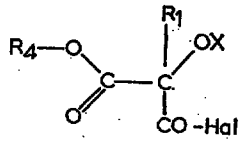
IV

in which R_1 and X have the above significance and
R_4 signifies an alkyl radical containing from 1 to 4 carbon atoms inclusive,
(described and claimed in patent specification No. 17401/62), which is converted with a diketopiperazine of general formula V,



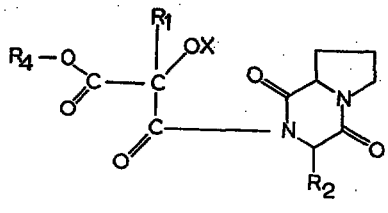
V

in which R_2 has the above significance,
with a compound of general formula VIII,



VIII

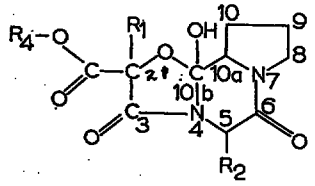
in which R_1, X and R_4 have the above meaning,
and Hal signifies a chlorine, bromine or iodine atom,
to form a compound of general formula VI,



VI

in which R_1, R_2, R_4 and X have the above significance,
(described and claimed in patent specification No. 17400/62) (1,011,113). The benzyloxy radical of this compound is then converted to the free hydroxyl radical by hydrogenating the compound VI in glacial acetic acid or alcohol or a mixture of these solvents at a pressure of 2—80 atmospheres in the presence

of a palladium catalyst. Spontaneous cyclization occurs to form a compound of general formula VII,



VII

in which R_1, R_2 and R_4 have the above significance,
(described and claimed in patent specification No. 17400/62) (1,011,113).

The compound VII is converted to the corresponding amino compound in manner known *per se*.

Two diastereoisomers are formed if a racemic compound IV is used as starting material whilst the optically pure product is obtained by using an optically active compound IV which may be produced in manner known *per se*.

To produce the natural ergot alkaloids, e.g. (+)-ergotamine, in accordance with the above process, it is necessary to use a cyclol the configuration of which corresponds to the peptide portion of the natural ergot alkaloids to be produced. Should other cyclols be used, compounds having a similar structure but differing in the configuration at one or more of the asymmetric centers, result.

It is known that ergot alkaloids and their derivatives have pharmaceutical properties; especially ergotamine is widely known as a pharmaceutical.

The compounds of the invention may be employed as pharmaceuticals as such, or in the form of appropriate medicinal preparations for administration, e.g. enterally, parenterally or intranasally. In order to produce such medicinal preparations, the compounds of the invention are worked up with inorganic or organic adjuvants which are physiologically inert. Examples of such adjuvants or carriers for various medicinal preparations are as follows:—

(1) Tablets and dragees	:	lactose, starch, talc and stearic acid.
(2) Syrups	:	solutions of cane sugar, invert sugar and glucose.
(3) Injectable solutions	:	water, physiologically acceptable alcohols, glycerine and physiologically acceptable vegetable fats.
(4) Suppositories	:	physiologically acceptable natural or hardened oils and waxes.
(5) Ointments, suspensions and emulsions	:	inorganic and organic lipophilic or hydrophilic compounds, paraffin, alginates, cellulose derivatives, polyoxyethylene derivatives, bentonite and petroleum jelly.

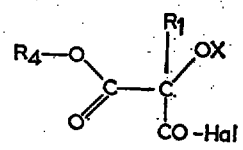
The preparations may contain suitable preserving, stabilizing or wetting agents, solubilizers, sweetening and colouring substances or flavourings, with the proviso that they must be physiologically acceptable in so far as they are for internal use.

The invention therefore includes pharmaceutical compositions containing, in addition to a physiologically acceptable carrier, a compound I and/or an acid addition salt thereof whenever produced by the process of the present invention.

Whilst that constituent of ergot which has a utero-tonic activity, i.e. ergobasine (also known as ergometrine or orgonovine), has been prepared synthetically for some time, the ergot alkaloids of the peptide type, ergotamine and the alkaloids of the ergotoxine group, which have a wide spectrum of activity in medicine and neurology, as have their dihydro-derivatives, have only been obtainable from the naturally occurring material. The peptide portion of these alkaloids is extremely complex and thus has hitherto hindered their synthetic production.

It is also within the scope of the present invention to produce the compound III, used in the process of the invention, in such a way that the ester radical of the compound of general formula VII is saponified to form the corresponding free acid which is converted to the corresponding acid chloride and subsequently to the corresponding azide in manner known *per se*, the azide is heated in a non-polar solvent to produce the isocyanate which is reacted with benzyl alcohol to give the corresponding benzyl urethane which is then hydrogenated in solution in the presence of a mineral acid to produce the desired amine salt III. The compound VII may be produced by hydrogenating a compound of general formula VI so as to split off the protective radical whereupon spontaneous cyclization occurs to form the desired compound VII. The

compound VI may be produced by acylating a compound V with a compound of general formula VIII,



VIII

in which R_1, R_4 and X have the above significance
and Hal signifies a chlorine, bromine or iodine atom.

The term "known" as used herein designates a method described in the literature on the subject or in actual use.

In the following non-limitative examples all temperatures are stated in degrees Centigrade and the melting points are corrected.

EXAMPLE 1.

(+)-ERGOTAMINE.

a) 2 - benzyloxy - 2 - methyl - malonic acid diethylester.

44.3 g of a sodium hydride suspension (50%) in oil are suspended in 1.25 litres of toluene and 91.3 g of benzyl alcohol are added dropwise at room temperature whilst stirring and the mixture then boiled at reflux for 1 hour. 214.8 g of 2 - bromo - 2 - methyl-malonic acid diethylester are then added dropwise to the cooled solution and the reaction mixture is boiled at reflux for a further 2 hours, then poured onto ice, the mixture made acidic with dilute hydrochloric acid and extracted with ether. The ethereal solution is washed consecutively with water, a sodium bicarbonate solution and a saturated solution of sodium chloride. After evaporation in a vacuum the 2 - benzyloxy - 2 - methyl-malonic acid diethylester results as a yellowish oil having a boiling point of 120—125° at 0.01 mm of Hg.

b) 2 - benzyloxy - 2 - methyl - malonic acid chloride monoethyl - ester.

181.3 g of crude 2 - benzyloxy - 2 - methyl-malonic acid diethylester are dissolved in 693 cc of absolute alcohol at room temperature and a solution of 36.4 g of potassium hydroxide in 450 cc of absolute alcohol is added whilst cooling with ice. The reaction solution is left to stand for 15 hours at room temperature and then evaporated in a vacuum at a bath temperature of 40°, the residue taken up in a mixture of 500 cc of a concentrated $NaHCO_3$ solution and 500 g of ice, extracted with ether and made acid with an ice cold 10% phosphoric acid and the separated oil taken up in methylene chloride. After evaporation of the solvent in a vacuum the crude 2-benzyloxy-2-methyl-malonic acid monoethyl ester remains as a yellow oil. 320 cc of thionyl chloride are added to 265.6 g of 2 - benzyloxy - 2 - methyl - malonic acid monoethyl ester and the mixture is boiled at reflux for 2 hours. The excess thionyl chloride is then distilled off in a vacuum and the residue distilled in a high vacuum. The resulting 2-benzyloxy - 2 - methyl - malonic acid chloride monoethyl ester has a boiling point of 138—141° at 0.03 mm of Hg. $n_D^{20}=1.5150$.

c) 2 - (2 - benzyloxy - 2 - methyl - O - ethyl-malonyl - 3 - benzyl - 1,4 - diketo - octahydro - pyrrolo[1,2 - a] - pyrazine.

A solution of 92.5 g of 3 - benzyl - 1,4-diketo - octahydro - pyrrolo[1,2 - a] - pyrazine (produced from L-phenylalanine and L-proline) in 580 cc of absolute pyridine is cooled to −30° and 95.5 g. of 2 - benzyloxy-2 - methyl - malonic acid chloride monoethyl ester are added dropwise whilst stirring. The reaction is left to stand for 15 hours at 0° and 100 cc of water are added, the mixture is stirred for a further half hour at 0° and then poured onto ice, made acid to Congo red indicator with an 18% hydrochloric acid and extracted a number of times with methylene chloride. The organic extracts are washed consecutively with a 2 N hydrochloric acid, water and a concentrated sodium bicarbonate solution dried with sodium sulphate and the solvent removed in a vacuum. The residue is taken up in ether, the ethereal solution washed well a number of times with water, dried again and evaporated in a vacuum, the 2 - (2 - benzyloxy - 2 - methyl-O - ethyl - malonyl) - 3 - benzyl - 1,4-diketo - octahydro - pyrrolo[1,2 - a] - pyrazine resulting as a light yellow oil. This is a diastereoisomer mixture of the D,L,L- and L,L,L-compound as the optically active 3-benzyl - 1,4 - diketo - octahydro - pyrrolo-[1,2 - a] - pyrazine was converted with D,L-2 - benzyloxy - 2 - methyl - malonic acid chloride monoethyl ester. The two isomers may be separated by chromatography on silica gel with a mixture of chloroform containing 0.5% of methanol. However, it is advantageous to convert the mixture further as the two isomer cycloesters of the following stage may be separated by crystallization.

d) 2 - carbethoxy - 2 - methyl - 5 - benzyl-10b - hydroxy - 3,6 - dioxo - octahydro-oxazolo[3,2 - a]pyrrolo[2,1 - c]pyrazine.

A solution of 146 g of 2 - (2 - benzyloxy-2 - methyl - O - ethyl - malonyl) - 3 - benzyl-1,4 - diketo - octahydro - pyrrolo[1,2 - a]-pyrazine in 500 cc of glacial acetic acid is added to a suspension of 145 g of pre-hydrogenated palladium (5%) on aluminium oxide in 500 cc of glacial acetic acid. By shaking over night in an atmosphere of hydrogen approximately 10 litres of hydrogen are taken up. The catalyst is then filtered off and the

solution evaporated in a vacuum. The oily residue is taken up in methylene chloride, the solution washed a number of times with water and dried over sodium sulphate. After evaporation of the solvent a colourless oil results from which the 2 - carbethoxy - 2-methyl - 5 - benzyl - 10b - hydroxy - 3,6-dioxo - octahydro - oxazolo[3,2 - a]pyrrolo-[2,1 - c]pyrazine, isomer B, crystallizes upon the addition of a little ethyl acetate. Melting point 202—204°, $[\alpha]_D^{20}=-35°$ (c=1 in pyridine). The mother liquor is again evaporated so that an oil forms and recrystallized from a little ethyl acetate. Isomer A, melting point 135—136°, $[\alpha]_D^{20}=-34°$ (c=0.2 in pyridine).

e) 2 - carboxy - 2 - methyl - 5 - benzyl-10b - hydroxy - 3,6 - dioxo - octahydro-oxazolo[3,2 - a]pyrrolo[2,1 - c]pyrazine.

65 cc of a 1 N sodium hydroxide solution are added to 10 g of 2 - carbethoxy - 2-methyl - 5 - benzyl - 10b - hydroxy - 3,6-dioxo - octahydro - oxazolo[3,2 - a]pyrrolo-[2,1 - c]pyrazine. The clear solution is left to stand at room temperature for two hours and 65 cc of a 1 N hydrochloric acid are added whilst cooling with ice and the mixture left to crystallize at 0°. 2 - carboxy - 2 - methyl-5 - benzyl - 10b - hydroxy - 3,6 - dioxo-octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]-pyrazine results. Isomer A: melting point 120—122°, $[\alpha]_D^{20}=-10°$ (c=0.2 in pyridine). Isomer B: melting point 201—202° (decomposition), $[\alpha]_D^{20}=-42°$ (c=1 in pyridine).

f) 2 - chloroformyl - 2 - methyl - 5 - benzyl-10b - hydroxy - 3,6 - dioxo - octahydro-oxazolo[3,2 - a]pyrrolo[2,1 - c]pyrazine.

1.115 g of sodium and then 17.4 g of 2-carboxy - 2 - methyl - 5 - benzyl - 10b-hydroxy - 3,6 - dioxo - octahydro - oxazolo-[3,2 - a]pyrrolo[2,1 - c]pyrazine are dissolved in 224 cc of absolute methanol whilst cooling with ice until the solution is clear and the solution is then evaporated to dryness in a vacuum. The residue is dried in a high vacuum for 1 hour at 100° and suspended in 150 cc of oxalyl chloride whilst cooling with ice and the dispersion then stirred well at 0° for half an hour and at room temperature for 1 hour. The excess oxalyl chloride is then distilled off in a vacuum, the residue taken up in absolute methylene chloride, the solution filtered, again evaporated to dryness and the resulting 2-chloroformyl - 2 - methyl - 5 - benzyl - 10b-hydroxy - 3,6 - dioxo - octahydro - oxazolo-[3,2 - a]pyrrolo[2,1 - c]pyrazine recrystallized from ether. Isomer A: melting point 125—126°. Isomer B: melting point 173—174°, $[\alpha]_D^{20}=+14°$ (c=0.5 in $CHCl_3$).

g) 2 - azidocarbonyl - 2 - methyl - 5 - benzyl-10b - hydroxy - 3,6 - dioxo - octahydro-oxazolo[3,2 - a]pyrrolo[2,1 - c]pyrazine.

12 g of 2 - chloroformyl - 2 - methyl - 5-benzyl - 10b - hydroxy - 3,6 - dioxo - octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]-pyrazine are dissolved in 500 cc of acetone and a solution of 2.58 g of sodium azide in 8 cc of water is added dropwise whilst stirring. The reaction mixture is then stirred vigorously for 1 hour, the solution evaporated in a vacuum, the residue stirred into 100 cc of water and the aqueous solution extracted with methylene chloride. After evaporation of the solvent the 2 - azidocarbonyl - 2 - methyl-5 - benzyl - 10b - hydroxy - 3,6 - dioxo-octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]-pyrazine results. Isomer A: melting point approximately 100° (decomposition), $[\alpha]_D^{20}=-42°$ (c=0.3 in pyridine). Isomer B: melting point approximately 130° (decomposition), $[\alpha]_D^{20}=+24°$ (c=1 in $CHCl_3$).

h) 2 - isocyano - 2 - methyl - 5 - benzyl - 10b-hydroxy - 3,6 - dioxo - octahydro - oxazolo-[3,2 - a]pyrrolo[2,1 - c]pyrazine (isomer B).

193 mg of 2 - azidocarbonyl - 2 - methyl-5 - benzyl - 10b - hydroxy - 3,6 - dioxo-octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]-pyrazine are heated in 2 cc of toluene for 4 minutes to 130° with the formation of nitrogen. Upon cooling the 2 - isocyano - 2-methyl - 5 - benzyl - 10b - hydroxy - 3,6-dioxo - octahydro oxazolo[3,2 - a]pyrrolo-[2,1 - c]pyrazine crystallizes from the solution in an almost quantitative yield. Melting point 153—154° in an evacuated tube. $[\alpha]_D^{20}=+45°$ (c=1 in $CHCl_3$).

i) 2 - benzylcarbamoyl - 2 - methyl - 5-benzyl - 10b - hydroxy - 3,6 - dioxo-octahydro - oxazolo[3,2 - a]pyrrolo-[2,1 - c]pyrazine.

872 mg of 2 - isocyano - 2 - methyl - 5 benzyl - 10b - hydroxy - 3,6 - dioxo - octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]-pyrazine in 5 cc of absolute benzyl alcohol are heated for 5 minutes to 130° accompanied by a strong evolution of nitrogen. The excess benzyl alcohol is subsequently evaporated in a high vacuum and the residue recrystallized from ether. Isomer A: melting point 172—174°, $[\alpha]_D^{20}=-4°$ (c=0.3 in pyridine). Isomer B: melting point 224—225°, $[\alpha]_D^{20}=-45°$ (c=1 in pyridine).

j) 2 - amino - 2 - methyl - 5 - benzyl - 10b-hydroxy - 3,6 - dioxo - octahydro - oxazolo-[3,2 - a]pyrrolo[2,1 - c]pyrazine chlorohydrate.

A solution of 11 g of 2 - benzyl - carbamoyl - 2 - methyl - 5 - benzyl - 10b-hydroxy - 3,6 - dioxo - octahydro - oxazolo-

[3,2 - a]pyrrolo[2,1 - c]pyrazine in 200 cc of a mixture of equal parts of methanol and methylene chloride containing 8 cc of a methanolic hydrochloric acid (360 mg HCl per cc) is added to a suspension of 24 g of 5% pre-hydrogenated palladium on aluminium oxide in 96 cc of absolute methanol containing 40 cc of methylene chloride. The reaction mixture is shaken for 45 minutes at room temperature in an atmosphere of hydrogen, 540 cc of hydrogen being used. The catalyst is filtered off from the resulting colourless solution, the mixture evaporated in a vacuum and the residue taken up in ether, the chlorohydrate of the amine precipitating as an amorphous powder. The latter is washed three times with absolute ether and then dried over phosphorus pentoxide. The hydrochloride of the 2 - amino - 2 - methyl - 5 - benzyl-10b - hydroxy - 3,6 - dioxo - octahydro-oxazolo[3,2 - a]pyrrolo[2,1 - c]pyrazine chlorohydrate results. Isomer A: melting point range 170—183°. Isomer B: melting point 131—133° (decomposition) (amorphous, light yellow, hygroscopic powder).

k) (+)-lysergic acid chloride hydrochloride.

536 mg of (+)-lysergic acid are finely suspended in 10 cc of freshly distilled phosphorus oxychloride and 416 mg of finely pulverized, freshly sublimated phosphorus pentachloride are added thereto whilst stirring. The reaction mixture is shaken for 2 minutes at room temperature, then heated to 90° and left at this temperature for 2 minutes. The phosphorus oxychloride is then evaporated off in a water jet vacuum and the remaining powder dissolved twice in n-hexane and the solvent again evaporated in a vacuum, so as to remove the volatile impurities azeotropically. The (+)-lysergic acid chloride hydrochloride resulting as a light grey crystalline powder has a melting point of 310—315° in an evacuated tube.

l) 9,10-dihydro-(+)-lysergic acid chloride.

The hydrochloride of 9,10 - dihydro - (+)-lysergic acid chloride having a melting point of 325—330° (decomposition) is produced from 9,10 - dihydro - (+) - lysergic acid in a manner analogous to that described in sub-section k).

m) (+) - lysergic acid sulphuric acid anhydride.

212 mg of lithium hydroxide are added to a solution of 1.43 g of (+)-lysergic acid monohydrate in 50 ml of methanol and the solvent is evaporated in a vacuum. The residue is dissolved in 100 ml of anhydrous dimethyl formamide, half the solvent is distilled off for the purpose of the azeotropic removal of the remaining water, the resulting anhydrous solution is cooled to 0° and 10 ml of a 1 molar solution of SO_3 in dimethyl formamide quickly added whilst stirring. The resulting solution of the anhydride is immediately used for further reaction.

n) 9,10-dihydro-(+)-ergotamine.

1 g of 2 - amino - 2 - methyl - 5 - benzyl-10b - hydroxy - 3,6 - dioxo - octahydro-oxazolo[3,2 - a]pyrrolo[2,1 - c]pyrazine chlorohydrate (isomer A) and 1 g of 9,10-dihydro - (+) - lysergic acid chloride hydrochloride are suspended in 50 cc of a mixture of chloroform and tertiary butanol (3:1) and a solution of 1.6 g of tributyl amine in 50 cc of the same solvent mixture is added dropwise, the mixture is stirred at room temperature for 15 minutes, the solvent evaporated in a vacuum, the residue diluted with ethyl acetate and the organic phase shaken with a 5% acetic acid. The acid, aqueous solution is made alkaline with $NaHCO_3$ and extracted with ethyl acetate, the solution dried over sodium sulphate and evaporated. By chromatographing the evaporation residue on aluminium oxide and crystallization from aqueous acetone 9,10 - dihydro - (+) - ergotamine results in the form of prisms having a melting point of 239—240°, $[\alpha]_D^{20} = -63°$ (c=0.2 in pyridine).

o) (+)-ergotamine.

The (+)-ergotamine is obtained in the shape of prisms from 570 mg of 2-amino-2-methyl - 5 - benzyl - 10b - hydroxy - 3,6-dioxo - octahydro - oxazolo[3,2 - a]pyrrolo-[2,1 - c]pyrazine chlorohydrate (isomer A) and 570 mg of (+)-lysergic acid chloride hydrochloride in a manner analogous to that described in sub-section n). Melting point approximately 180°, $[\alpha]_D^{20} = -158°$ (c=0.5 in chloroform).

p) A stereoisomer alkaloid of dihydro-(+)-ergotamine.

10 g of 9,10 - dihydro - (+) - lysergic acid chloride hydrochloride are dissolved in 150 cc of pyridine at −30° and 8 g of 2-amino - 2 - methyl - 5 - benzyl - 10b-hydroxy - 3,6 - octahydro - oxazolo[3,2 - a]-pyrrolo[2,1 - c]pyrazine hydrochloride (isomer B) are added. The mixture is slowly heated to room temperature and then stirred for a further hour. The solvent is evaporated in a vacuum and the residue divided between methyl chloride and a sodium bicarbonate solution. The evaporation residue of the organic phase is purified by chromatography on aluminium oxide using chloroform containing increasing quantities of alcohol. A fraction which crystallizes from acetone in the shape of colourless needles having a melting point of 190—198° is eluted with $CHCl_3$ containing 1% of alcohol. $[\alpha]_D^{20} = -51°$ (c=1 in pyridine). This base having an empirical formula of $C_{35}H_{37}O_5N_5$ is a stereoisomer of dihydro - (+) - ergotamine.

q) (+)-ergotamine.

The solution of the (+)-lysergic acid sulphuric acid anhydride in dimethyl formamide obtained according to sub-section m) is cooled to 0° and a suspension of 7 g of 2-amino-2-methyl - 5 - benzyl - 10b - hydroxy - 3,6-dioxo - octahydro - oxazolo[3,2 - a]pyrrolo-[2,1 - c]pyrazine chlorohydrate (isomer A) in 30 cc of dimethyl formamide is added. 5 ml of tributyl amine are added dropwise at 0°, the mixture is stirred for a further 10 minutes at 0°, 100 ml of water and 50 ml of a saturated aqueous sodium chloride solution are subsequently added and the ergotamine extracted by shaking 10 times, each time with 50 ml of ethyl acetate. The combined ethyl acetate extracts are shaken 5 times, each time with 50 ml of a 50% aqueous acetic acid solution, the combined aqueous extracts made alkaline with $NaHCO_3$ and again extracted with ethyl acetate. The organic phase is dried over sodium sulphate and evaporated. By chromatographing the evaporation residue on aluminium oxide and crystallization from aqueous acetone, pure ergotamine results in the shape of prisms having a melting point of 180°.

Example 2.

ergosine and ergosinine.

a) N - carbobenzoxy - L - prolyl - L - leucine methylester.

A solution of 45 g (0.22 mol) of dicyclohexyl-carbodiimide in 50 ml of absolute ether is added dropwise to a solution of 29 g (0.2 mol) of L-leucine methylester and 50 g (0.2 mol) of N-carbobenzoxy - L - proline in 50 ml of methylene chloride and 100 ml of absolute ether whilst stirring at 20°. Subsequently the reaction mixture is heated to the boil at reflux for one hour. The excess dicyclohexyl - carbodiimide is decomposed with 2 ml of glacial acetic acid and the separated dicyclohexyl urea filtered off. The filtrate is first washed with a $NaHCO_3$ solution and then with water, dried with Na_2SO_4 and the solvent removed. The crude product which results is crystallized from benzene/heptane and yields N - carbobenzoxy - L - prolyl - L-leucine methyl ester in the form of colourless pointed rodlets having a melting point of 76—77°.

b) 3 - isobutyl - 1,4 - dioxo - octahydro-pyrrolo[1,2 - a]pyrazine.

69 g (0.183 mol) of N - carbobenzoxy - L-prolyl - L - leucine methyl ester are hydrogenated in 750 ml of absolute methanol with 25 g of prehydrogenated palladium catalyst on aluminium oxide (5% by weight Pd) at room temperature and normal pressure. After three hours the taking up of hydrogen is completed, the catalyst filtered off and the solvent removed in a vacuum. 41.8 g of oily L-prolyl-L - leucine - methyl ester result and this is cyclized in a vacuum at 120° during the course of 2½ hours to yield L - leucyl - L-proline-lactam. The crude product is crystallized by heating and then purified by recrystallization from ethyl acetate to yield L-leucyl-L-proline-lactam having a melting point of 144—146°. $[\alpha]_D^{20} = +91.4°$ (c=1 in water).

c) 2 - (2 - benzyloxy - 2 - methyl - O - ethyl-malonyl) - 1,4 - diketo - 3 - isobutyl-octahydro - pyrrolo[1,2 - a]pyrazine.

10,5 g (50 millimol) of L - leucyl - L-proline-lactam are suspended in 6 ml of absolute dioxane, 3.95 g (50 millimol) of absolute pyridine are first added and then 13.5 g (50 millimol) of 2 - methyl - 2 - benzyloxy-malonic acid ethyl ester chloride. The mixture is then heated to 70° for 1½ hours whilst stirring. After cooling, the reaction mixture is diluted with ether and ice cold 2 N HCl, is then extracted with ice water in a $NaHCO_3$ solution and again with ice water. The ethereal solutions are dried thoroughly with Na_2SO_4 and the solvent carefully removed. 20.5 g of a honey-like, unstable crude product, which eventually crystallizes, results as a residue. Melting point undefined at approximately 80°.

d) 2 - ethoxycarbonyl - 2 - methyl - 10b-hydroxy - 5 - isobutyl - 3,6 - dioxo-octahydro - oxazolo[3,2 - a]pyrrolo-[2,1 - c]pyrazine.

20.5 g of crude 2 - (2 - benzyloxy - 2-methyl - O - ethyl - malonyl) - 1,4 - diketo-3 - isobutyl - octahydro - pyrrolo - [1,2 - a]-pyrazine are hydrogenated in 250 ml of fine spirit with 10 g of a palladium on activated charcoal (5% by weight Pd) as catalyst at 20° and at normal pressure. After 20 hours the theoretical quantity of hydrogen is taken up whereupon the hydrogenation ceases. The catalyst is filtered off and the solvent removed in a vacuum. The 15.5 g of oily residue crystallizes upon standing. 2 - ethoxycarbonyl-2 - methyl - 10b - hydroxy - 5 - isobutyl-3,6 - dioxo - octahydro - oxazolo[3,2 - a]-pyrrolo[2,1 - c]pyrazine is recrystallized from isopropyl ether/heptane in the form of rod-like crystals having a melting point of 100—101°. $[\alpha]_D^{20} = -21°$ (c=1 in ethanol).

e) 2 - carboxy - 2 - methyl - 10b - hydroxy-5 - isobutyl - 3,6 - dioxo - octahydro-oxazolo[3,2 - a]pyrrolo[2,1 - c]pyrazine.

15.3 g of crude 2 - ethoxycarbonyl - 2-methyl - 10b - hydroxy - 5 - isobutyl - 3,6-dioxo - octahydro - oxazolo[3,2 - a]pyrrolo-[2,1 - c]pyrazine are dissolved in 10 ml of methyl alcohol and 100 ml of 1 N NaOH solution added whilst cooling. The mixture is left to stand for 2½ hours at 20° and is then extracted twice with ether so as to remove the non-saponified components, the aqueous methanolic solution is then filtered through

active charcoal and the filtrate acidified with 60 ml of 2 N HCl. The resulting crystalline 2 - carboxy - 2 - methyl - 10b - hydroxy-5 - isobutyl - 3,6 - dioxo - octahydro-oxazolo[3,2 - a]pyrrolo[2,1 - c]pyrazine is recrystallized a number of times from methanol, yielding colourless needles having a melting point of 192—193°. $[\alpha]_D^{20} = -25.5°$ (c=1 in pyridine).

f) 2 - chlorocarbonyl - 2 - methyl - 10b-hydroxy - 5 - isobutyl - 3,6 - dioxo-octahydro - oxazolo[3,2 - a]pyrrolo-[2,1 - c]pyrazine.

9.8 g (30 millimol) of finely pulverized 2 - carboxy - 2 - methyl - 10b - hydroxy - 5-isobutyl - 3,6 - dioxo - octahydro - oxazolo-[3,2 - a]pyrrolo[2,1 - c]pyrazine dried in a high vacuum and 18.7 g of freshly sublimed finely pulverized phosphorus pentachloride are suspended in 200 ml of absolute ether and stirred well for 2 hours. The precipitate is filtered off with suction, the filter residue washed well with absolute ether and dried in a high vacuum. 2 - chlorocarbonyl - 2 - methyl - 10b-hydroxy - 5 - isobutyl - 3,6 - dioxo - octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]-pyrazine having a melting point of 146—147° results.

g) 2 - azidocarbonyl - 2 - methyl - 10b-hydroxy - 5 - isobutyl - 3,6 - dioxo - octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]-pyrazine.

A concentrated aqueous solution of 2.65 g of sodium azide is added dropwise to a solution of 9.3 g of crude 2 - chlorocarbonyl - 2-methyl - 10b - hydroxy - 5 - isobutyl - 3,6-dioxo - octahydro - oxazolo[3,2 - a]pyrrolo-[2,1 - c]pyrazine in 150 ml of acetone at room temperature. The mixture is then stirred for 2 hours at 20° and the major portion of the acetone removed in a vacuum without heating. The residue is shaken between methylene chloride and sodium bicarbonate solution. The methylene chloride is removed in a vacuum at 20° and the crude azide suspended in ether, the ether filtered off and the residue, the crude 2 - azidocarbonyl - 2 - methyl - 10b-hydroxy - 5 - isobutyl - 3,6 - dioxo - octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]pyrazine is immediately processed further after carefully drying in a high vacuum at 20°, without further purification.

h) 2 - benzyloxycarbonyl - amino - 2 - methyl-10b - hydroxy - 5 - isobutyl - 3,6 - dioxo-octahydro - oxazolo[3,2 - a]pyrrolo-[2,1 - c]pyrazine.

4.5 g of crude 2 - azidocarbonyl - 2-methyl - 10b - hydroxy - 5 - isobutyl - 3,6-dioxo - octahydro - oxazolo[3,2 - a]pyrrolo-[2,1 - c]pyrazine and 2.76 g of absolute benzyl alcohol are heated to boil at reflux in 30 ml of absolute chloroform for 1½ hours, the volatile components of the reaction mixture removed in a vacuum and the residue recrystallized from methylene chloride/ethyl acetate, yielding crystalline 2-benzyloxycarbonyl - amino - 2 - methyl - 10b - hydroxy-5 - isobutyl - 3,6 - dioxo - octahydro-oxazolo[3,2 - a]pyrrolo[2,1 - c]pyrazine in the form of rodlets having a melting point of 212—213° (decomposition). $[\alpha]_D^{20} = +19.1°$ (c=2 in ethanol).

i) 2 - amino - 2 - methyl - 10b - hydroxy-5 - isobutyl - 3,6 - dioxo - octahydro-oxazolo[3,2 - a]pyrrolo[2,1 - c]pyrazine hydrochloride.

1.0 g (2.3 millimol) of 2 - benzyloxycarbonyl - amino - 2 - methyl - 10b - hydroxy-5 - isobutyl - 3,6 - dioxo - octahydro-oxazolo[3,2 - a]pyrrolo[2,1 - c]pyrazine in 75 ml of methanol containing 7.4 millimol of gaseous HCl, is hydrogenated with 2 g of pre-hydrogenated palladium catalyst on activated charcoal (5% by weight Pd) 22 ml of hydrogen are taken up within 2 minutes whereupon the hydrogenation ceases. The mixture is stirred for a further 15 minutes to make sure that no further hydrogen is taken up. The catalyst is then filtered off and the filtrate concentrated to approx. 30 ml at 20°, whereupon scratching with a glass rod causes crystallization to commence. So as to obtain the maximum yield of hydrochloride the mixture is diluted with absolute ether to a volume of approx. 200 ml. After filtering off the crystals and drying in a high vacuum the 2-amino - 2 - methyl - 10b - hydroxy - 5-isobutyl - 3,6 - dioxo - octahydro - oxazolo-[3,2 - a]pyrrolo[2,1 - c]pyrazine hydrochloride results in the form of microscopically small rodlets pointed at both ends and having a melting point of 192—193° (decomposition).

j) Ergosine and ergosinine.

0.5 g (1.5 millimol) of 2 amino-2-methyl-10b - hydroxy - 5 - isobutyl - 3,6 - dioxo-octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]-pyrazine chlorohydrate and 1.0 g of lysergic acid chloride hydrochloride (3.1 millimol) are suspended in 10 ml of absolute methylene chloride and cooled to 0°. 5.5 ml of absolute pyridine are added at once to this suspension and the reaction mixture stirred for a further ½ hour at 0°. The ice bath is then removed and the mixture heated to room temperature and stirred for a further 1½ hours at 20°. 20 ml of a saturated soda solution and 20 ml of chloroform are added to the dark brown solution and the mixture is stirred for a further 15 minutes. The mixture is then diluted with 30 ml of chloroform and 20 ml of water and the two phases separated from each other by means of a separating funnel. The aqueous solution is subsequently extracted a further three times with chloroform, the

chloroform solutions boiled once with water, dried well and the solvent removed. After removal of the pyridine in a high vacuum 1.0 g of a dark resin result, this is dissolved in methanol, filtered through active charcoal and evaporated once more. The remaining residue is chromatographed on 30 g of dry silica gel Merck. A solution of methylene chloride containing 0.7 to 1% of methanol is used for the elution. After crystallizing the eluate twice from methanol, pure ergosinine results in the form of colourless needles having a melting point of 190—191° (decomposition). Upon admixture with natural ergosinine no depression of melting point was observed. $[\alpha]_D^{20} = +390°$ (c=0.5 in chloroform). The synthetic product and the natural ergosinine behaved identically when tested with thin layer chromatography both on aluminium oxide and silica gel plates in various solvent systems. The IR spectra, taken in Nujol suspension and in a methylene chloride solution, again showed the two compounds to be identical. UV spectra: λ_{max} 242 mμ (log ε 4.23) and 309 mμ (log ε 3.93). Minimum at 269.5 mμ.

After eluting some mixed fractions of ergosinine and ergosine with methylene chloride containing 1.5% of methanol, practically pure ergosine is eluted with methylene chloride containing 2% of methanol. By recrystallizing twice from methyl acetate, colourless rectangular plates having a melting point of 224—225° (decomposition) result. The crystals have the same shape as natural ergosine and admixture with autentic ergosine caused no depression of the melting point—$[\alpha]_D^{20} = -150°$ (c=0.45 in chloroform). The synthetic product and the natural ergosine behaved identically in thin layer chromatography both on silica gel and aluminium oxide plates. UV spectra: λ_{max} 239.5 mμ (log ε 4.33) and 312 mμ (log ε 3.97). Minimum at 234 and 269.5 mμ. The IR spectra, which were taken in methylene chloride and in Nujol and the NMR spectra, taken in $CHCl_3$ were also identical for the two compounds. *L - di - para - tolyl-tartrate of synthetic ergosine*: microscopically small, rectangular crystals having a melting point of 199—200°; A mixture of the synthetic and the authentic compound has a melting point of 199—200°, $[\alpha]_D^{20} = -62°$ (c=0.5 in ethanol).

Example 3.

Ergovaline, ergovalinine and 9,10-dihydro-ergovaline.

a) N - benzyloxycarbonyl - L - prolyl - L-valine methyl ester.

98.4 g (0.75 mols) of L-valine methyl ester (boiling point 60°/11 mm of Hg) and 187.5 g (0.75 mols) of N-benzyloxycarbonyl-L-proline are dissolved in 750 ml of absolute ether and 171.0 g (0.83 mols) of N,N¹-dicyclohexyl-carbodiimide in 250 ml of absolute ether are added dropwise whilst stirring well during the course of half an hour, whereby the temperature slowly rises to 35° and a precipitate of N,N¹ - dicyclohexylurea results. Heating to the boil is subsequently effected for one hour, the reaction mixture is then cooled and percipitated N,N¹ - dicyclohexylurea is filtered off. In order to remove unreacted starting materials the filtrate which has been diluted with ether is first washed twice with a N sodium bicarbonate solution each time with 500 ml, then twice with the same amount of N hydrochloric acid and finally with water until neutral. After subsequently extracting the aqueous phases twice, each time with 1 litre of ether, the ethereal solutions are dried and the solvent is evaporated, whereby a colourless, viscous oil, $n_D^{20} = 1.5115$, results, which is further worked up without additional purification, as the N-benzyloxycarbonyl - L - prolyl - L - valine methyl ester cannot be crystallized.

b) 1,4 - dioxo - 3 - isopropyl - octahydro-pyrrolo[1,2-a]pyrazine.

25.5 g (0.070 mols) of crude N-benzyloxycarbonyl - L - prolyl - L - valine methyl ester are hydrogenated with 10 g of a palladium/charcoal catalyst (5% by weight of palladium) in 150 ml of ethyl acetate and 100 ml of glacial acetic acid. After the taking up of hydrogen diminishes the hydrogenating flask is evacuated and hydrogenation is continued, whereby hydrogen is again taken up. A total of 1360 ml of hydrogen is taken up. When hydrogen is no longer taken up, the catalyst is filtered off, the solvent is removed and the oily residue is heated in a high vacuum for 4 hours to 120—130°, whereby crystallization occurs after approximately one hour. After recrystallization from ethyl acetate pure 1,4 - dioxo - 3 - isopropyl-octahydro - pyrrolo[1,2 - a]pyrazine, having a melting point of 190—192°, is obtained in the form of colourless needles, $[\alpha]_D^{20} = -159°$ (c=0.7 in ethanol).

c) 2 - (2 - benzyloxy - 2 - methyl - O - ethyl-malonyl) - 1,4 - dioxo - 3 - isopropyl-octahydro - pyrrolo[1,2 - a]pyrazine.

58.8 g (0.3 mols) of 1,4 - dioxo - 3 - isopropyl - octahydro - pyrrolo[1,2 - a]pyrazine are suspended in 40 ml of absolute dioxane and 23.7 g (0.3 mols) of absolute pyridine are added thereto. 81 g (0.3 mols) of methyl-benzyloxy - malonic acid ethyl ester chloride are added dropwise to the mixture at +10° during the course of 10 minutes and heating is subsequently effected to 70° for 1½ hours whilst stirring. After cooling the reaction mixture is poured on ice, an excess of 2N hydrochloric acid is added and extraction is effected three times with ether. The ethereal solutions are first washed with a sodium bicarbonate solution and then with water. After drying the ether solution with sodium sulphate and remov-

ing the solvent a crystalline crude product is obtained which is recrystallized from ether and yields 2 - (2 - benzyloxy - 2 - methyl-O - ethyl - malonyl) - 1,4 - dioxo - 3 - isopropyl - octahydro - pyrrolo[1,2 - a]pyrazine having a melting point of 110—111°. Further portions of acylation product, having a melting point of 104—105°, may be obtained from the mother liquors by repeated crystallization. $[\alpha]_D^{20}=+138°$ (in ethanol).

d) 2 - ethoxycarbonyl - 2 - methyl - 5 - isopropyl - 10b - hydroxy - 3,6 - dioxo - octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]-pyrazine.

20 g (46.5 millimols) of 2 - (2 - benzyloxy-2 - methyl - O - ethyl - malonyl) - 1,4-dioxo - 3 - isopropyl - octahydro - pyrrolo-[1,2 - a]pyrazine are hydrogenated at 20° and normal pressure in 200 ml of absolute ethyl acetate and 20 g of prehydrogenated palladium on active charcoal (5% of palladium) as catalyst. After the theoretical amount of hydrogen has been taken up (approximately 15 hours) hydrogenation stops. The catalyst is then filtered off, the residue is washed well with ethyl acetate and the solvent is removed in a vacuum. After repeated recrystallization from isopropyl ether pure 2 - ethoxycarbonyl-2 - methyl - 5 - isopropyl - 10b - hydroxy-3,6 - dioxo - octahydro - oxazolo[3,2 - a]-pyrrolo[2,1 - c]pyrazine, having a melting point of 104—105°, is obtained. $[\alpha]_D^{20}=-7°$ (c=2 in ethanol). Ultraviolet spectrum $\lambda_{max}=200.5$ mμ (log ε=4.17 in ethanol).

e) 2 - carboxy - 2 - methyl - 5 - isopropyl-10b - hydroxy - 10b - hydroxy - 3,6-dioxo - octahydro - oxazolo[3,2 - a]-pyrrolo[2,1 - c]pyrazine.

52.5 g (0.154 mols) of finely pulverized 2 - ethoxycarbonyl - 2 - methyl - 5 - isopropyl - 10b - hydroxy - 3,6 - dioxo - octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]-pyrazine are dissolved at room temperature in 230 ml of N sodium hydroxide and left to stand for 2 hours. In order to liberate the 2 - carboxy - 2 - methyl - 5 - isopropyl-10b - hydroxy - 3,6 - dioxo - octahydro-oxazolo[3,2 - a]pyrrolo[2,1 - c]pyrazine which results, acidification is effected with 60 ml of 4N hydrochloric acid, whereby the acid crystallizes out. After filtration the residue is recrystallized from methanol/water: colourless needles having a melting point of 187—188°, $[\alpha]_D^{20}=-16.5°$ (c=2.2 in pyridine). Ultraviolet spectrum: $\lambda_{max}=201$ mμ (log ε=4.16 in ethanol).

f) 2 - chlorocarbonyl - 2 - methyl - 5 - isopropyl - 10b - hydroxy - 3,6 - dioxo - octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]-pyrazine.

15.6 g (50 millimols) of finely pulverized 2 - carboxy - 2 - methyl - 5 - isopropyl-10b hydroxy - 3,6 - dioxo - octahydro-oxazolo[3,2 - a]pyrrolo[2,1 - c]pyrazine are suspended in 250 ml of absolute ether and a total of 20.8 g of freshly sublimed phosphorus pentachloride is added portionwise to the suspension. The reaction mixture is subsequently stirred at room temperature for 1½ hours and the precipitated residue of the acid chloride is filtered off from the ether solution, is washed well with absolute ether and dried at 20° in a high vacuum: 2 - chlorocarbonyl-2 - methyl - 5 - isopropyl - 10b - hydroxy-3,6 - dioxo - octahydro - oxazolo[3,2 - a]-pyrrolo[2,1 - c]pyrazine, melting point 133—134° (decomposition), $[\alpha]_D^{20}=+18°$ (c=1 in $CHCl_3$).

g) 2 - azidocarbonyl - 2 - methyl - 5 - isopropyl - 10b - hydroxy - 3,6 - dioxo - octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]-pyrazine.

18.7 g (56.5 millimols) of 2-chlorocarbonyl-2 - methyl - 5 - isopropyl - 10b - hydroxy-3,6 - dioxo - octahydro - oxazolo[3,2 - a]-pyrrolo[2,1 - c]pyrazine are dissolved at room temperature in absolute acetone which is free of methanol and 7.3 g of sodium azide in 18 ml of water are added to the solution, whereby a portion of the sodium azide crystallizes out again on combining the two solutions. The suspension is stirred at 20° for half an hour and is subsequently concentrated almost to dryness at 20° in a rotatory evaporator. The residue is shaken out between an ice cold sodium bicarbonate solution and methylene chloride and the bicarbonate solution is extracted a further twice with methylene chloride. The methylene chloride solution of 2 - azido - carbonyl - 2 - methyl - 5 - isopropyl - 10b - hydroxy - 3,6 - dioxo - octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]-pyrazine is washed once with ice water, dried well and the solvent is removed in a vacuum at 20° as the azide is liable to compose. Crystalline 2 - azidocarbonyl - 2 - methyl-5 - isopropyl - 10b - hydroxy - 3,6 - dioxo-octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]-pyrazine is obtained by recrystallization from methylene chloride/petroleum ether. Fine, cotton wool like needles having a melting point of 98° (decomposition), $[\alpha]_D^{20}=-22°$ (c=1 in $CHCl_3$). Infrared spectrum: most important bands at 3480—3400 (broad) 2250, 2190, 2145, 1721, 1686 and 1650 cm^{-1} (in methylene chloride).

h) 2 -N - benzyloxycarbonyl - amino - 2-methyl - 5 - isopropyl - 10b - hydroxy-3,6 - dioxo - octahydro - oxazolo[3,2 - a]-pyrrolo[2,1 - c]pyrazine.

6.5 g (19.2 millimols) of 2 - azidocarbonyl-2 - methyl - 5 - isopropyl - 10b - hydroxy-3,6 - dioxo - octahydro - oxazolo[3,2 - a]-pyrrolo[2,1 - c]pyrazine and 6.5 ml of absolute benzyl alcohol are heated to the boil at

reflux in 40 ml of absolute chloroform for one hour. The reaction mixture is then freed from the readily volatile components and subsequently the major portion of the excess benzyl alcohol is removed in a high vacuum. After recrystallization from ethyl acetate the residue yields 2 - N - benzyloxycarbonyl - amino - 2-methyl - 5 - isopropyl - 10b - hydroxy - 3,6-dioxo - octahydro - oxazolo[3,2 - a]pyrrolo-[2,1 - c]pyrazine having a melting point of 187—188°. For purposes of analysis a sample of the compound is repeatedly recrystallized from ethyl acetate, whereby the melting point reaches 190—191°. Colourless prisms $[\alpha]_D^{20}=+13°$ (c=2 in ethanol).

i) 2 - amino - 2 - methyl - 5 - isopropyl-10b - hydroxy - 3,6 - dioxo - octahydro-oxazolo[3,2 - a]pyrrolo[2,1 - c]pyrazine hydrochloride.

3.7 g (8.86 millimols) of 2 - N - benzyloxycarbonyl - amino - 2 - methyl - 5 - isopropyl-10b - hydroxy - 3,6 - dioxo - octahydro-oxazolo[3,2 - a]pyrrolo[2,1 - c]pyrazine are dissolved in 50 ml of absolute methanol and the solution is added to a suspension of 5 g of prehydrogenated palladium/active charcoal catalyst (5% of palladium) in 50 ml of absolute methanol. Directly before hydrogenation 11 ml of an 11% solution of hydrochloric acid in absolute methanol are added to the mixture and hydrogenation is effected as rapidly as possible. After hydrogenation has been completed, the catalyst is filtered off, the filtrate is concentrated to approximately 20 ml at approximately 20° and diluted with absolute ether, whereupon 2 - amino - 2-methyl - 5 - isopropyl - 10b - hydroxy - 3,6-dioxo - octahydro - oxazolo[3,2 - a]pyrrolo-[2,1 - c]pyrazine hydrochloride crystallizes rapidly. Filtration is effected, the precipitate is washed well with absolute ether and dried at 20° in a high vacuum: colourless or slightly green coloured microcrystalline powder having a melting point of 163° (decomposition).

j) Ergovaline and ergovalinine.

2.0 g (6.25 millimols) of 2-amino-2-methyl-5 - isopropyl - 10b - hydroxy - 3,6 - dioxo-octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]-pyrazine hydrochloride and 5 g (12.4 millimols) of d-lysergic acid chloride hydrochloride are suspended in 40 cc of absolute methylene chloride, the mixture is cooled to 0° and 22 cc of absolute pyridine are added in one batch at this temperature. The mixture is stirred for a further half hour at 0°, warmed to 20° and the reaction allowed to go to completion at this temperature while stirring for one hour. For the purposes of working up, the reaction mixture is diluted with methylene chloride and the methylene chloride solution is first extracted with a saturated sodium carbonate solution and then twice with water. The aqueous phases are shaken out a further twice with methylene chloride, the methylene chloride solutions which have been washed until neutral are combined, dried with Na_2SO_4 and the solvent is removed in a vacuum: the crude product results as a brown resin from which ergovalinine may be separated directly by recrystallization from methanol. After further recrystallization from methanol the ergovalinine is pure in the thin layer chromatogram. Colourless rectangular plates, melting point 221—222°, $[\alpha]_D^{20}=+419°$ (c=0.3 in chloroform), $[\alpha]_D^{20}=+438°$ (c=0.5 in pyridine), Keller's colour reaction blue, UV spectrum: $\lambda_{max}=239$ mμ (log ε=4.32) and 311 mμ (log ε=3.93). Minima at 230 and 268.5 mμ.

The mother liquor remaining after crystallization is chromatographed on 95 g of aluminium oxide (Merck). A further quantity of ergovalinine is eluted from the column with methylene chloride and 0.1% of methanol, followed by fractions which are a mixture of ergovaline and ergovalinine. Practically pure ergovaline can be eluted from the column with methylene chloride and 0.2 to 0.5% of methanol. After crystallization from ethyl acetate this compound is pure in the thin layer chromatogramm: practically colourless fine needles, melting point 177—178° (decomp.), $[\alpha]_D^{20}=-143°$ (c=0.6 in chloroform), $[\alpha]_D^{20}=-15°$ (c=0.6 in pyridine), UV spectrum: $\lambda_{max}=241$ mμ (log ε=4.32) and 311.5 mμ (log ε=3.97). Minima at 232 and 269.5 mμ.

Ergovaline sulphate: fine cottonwool-like needles from methanol, melting point 205—206° (decomp.), $[\alpha]_D^{20}=+100.5°$ (c=0.5 in water).

k) 9,10-dihydro-ergovaline.

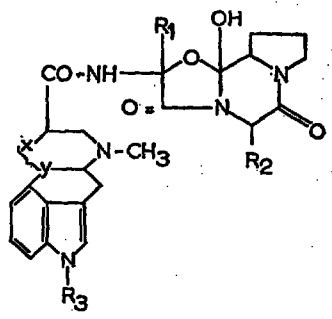
320 mg (1 millimol) of 2-amino-2-methyl-5 - isopropyl - 10b - hydroxy - 3,6 - dioxo-octahydro - oxazolo[3,2 - a]pyrrolo[2,1 - c]-pyrazine hydrochloride and 980 mg (3 millimols) of 9,10 - dihydro - d - lysergic acid chloride hydrochloride are suspended in 50 cc of absolute methylene chloride. 25 cc of pyridine are added to this suspension at 0°, a dark solution resulting quickly. This solution is stirred for half an hour at 0° and subsequently for 1½ hours at room temperature. 200 cc of a diluted sodium carbonate solution are added to the reaction solution and the mixture is extracted thrice with chloroform. The combined chloroform extracts are dried over sodium sulphate and the solvent is evaporated in a vacuum. So as to remove as much pyridine as possible the mixture is evaporated a further three times with benzene.

The purification of the crude product is best effected by chromatography on an aluminium oxide column. The crude product is dissolved in chloroform and adsorbed onto a 30-fold quantity of aluminium oxide (Merck activity 1). Elution with methylene chloride containing 1 to 2% of methanol, evaporation

of the solvent and recrystallization of the residue from ethanol/ethyl acetate (1:1) results in 9,10 - dihydro - ergovaline of melting point 221—222°, $[\alpha]_D^{20} = -5.8°$ ($c=1$ in chloroform), Keller's colour reaction blue-violet, UV spectrum: $\lambda_{max}=223$ mμ (log $\epsilon=4.51$), 280 mμ (log $\epsilon=3.84$) and 291 mμ (log $\epsilon=3.75$). Minima at 244.5 and 288.5 mμ.

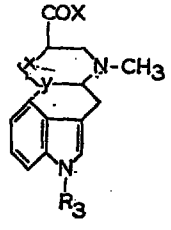
WHAT WE CLAIM IS:—

1. Process for the production of compounds of general formula I,



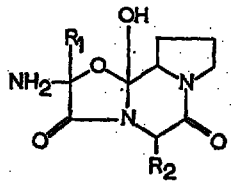
I

in which each of R_1 and R_3 signifies a hydrogen atom or an alkyl radical containing from 1 to 3 carbon atoms inclusive
and R_2 signifies a hydrogen atom, an alkyl radical containing from 1 to 5 carbon atoms inclusive or the benzyl radical
and $\overset{\frown}{x\ y}$ signifies the radical $-CH=C<$ or $-CH_2-CH<$,
and their acid addition salts, characterized in that a compound of general formula II,



II

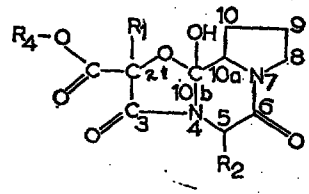
in which R_3 and $\overset{\frown}{x\ y}$ have the above significance and X signifies a chlorine or bromine atom or the radical $-OSO_3H$,
is reacted with a salt of a compound of general formula III,



III

in which R_1 and R_2 have the above significance,
in the presence of a tertiary base and, when an acid addition salt is required, salification is effected with an organic or inorganic acid.

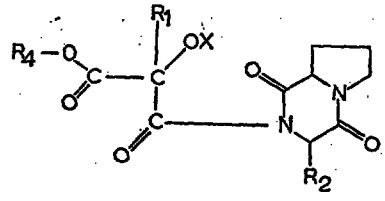
2. Process according to claim 1, in which the compound III is produced in that the ester radical of the compound of general formula VII,



VII

in which R_1 and R_2 have the significance stated in claim 1
and R_4 signifies an alkyl radical containing from 1 to 4 carbon atoms inclusive,
is saponified to form the corresponding free acid which is converted to the corresponding acid chloride and subsequently to the corresponding azide in manner known *per se*, the azide is heated in a non-polar solvent to produce the isocyanate which is reacted with benzyl alcohol to give the corresponding benzyl urethane which is then hydrogenated in solution in the presence of a mineral acid to produce the desired amine salt III.

3. Process according to claim 2, in which the compound VII is produced by hydrogenating a compound of general formula VI,



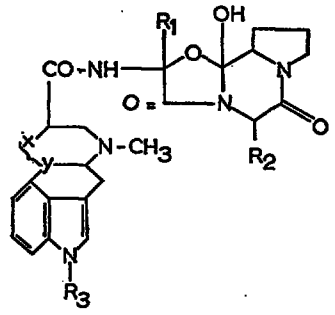
VI

In which R_1, R_2 and X have the significance stated in claim 1

of the solvent and recrystallization of the residue from ethanol/ethyl acetate (1:1) results in 9,10 - dihydro - ergovaline of melting point 221—222°, $[\alpha]_D^{20} = -5.8°$ (c=1 in chloroform), Keller's colour reaction blue-violet, UV spectrum: λ_{max}=223 mμ (log ε=4.51), 280 mμ (log ε=3.84) and 291 mμ (log ε=3.75). Minima at 244.5 and 288.5 mμ.

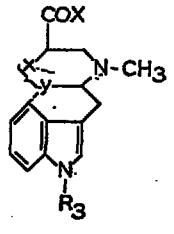
WHAT WE CLAIM IS:—

1. Process for the production of compounds of general formula I,



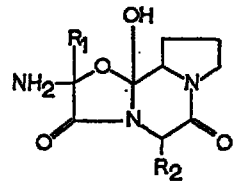
I

in which each of R_1 and R_3 signifies a hydrogen atom or an alkyl radical containing from 1 to 3 carbon atoms inclusive
and R_2 signifies a hydrogen atom, an alkyl radical containing from 1 to 5 carbon atoms inclusive or the benzyl radical
and $\widetilde{x\ y}$ signifies the radical $-CH=C\langle$ or $-CH_2-CH\langle$
and their acid addition salts, characterized in that a compound of general formula II,



II

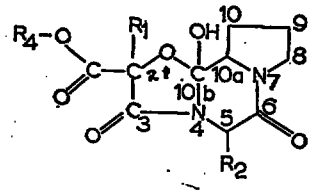
in which R_3 and $\widetilde{x\ y}$ have the above significance and X signifies a chlorine or bromine atom or the radical $-OSO_3H$,
is reacted with a salt of a compound of general formula III,



III

in which R_1 and R_2 have the above significance,
in the presence of a tertiary base and, when an acid addition salt is required, salification is effected with an organic or inorganic acid.

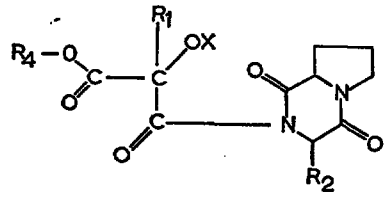
2. Process according to claim 1, in which the compound III is produced in that the ester radical of the compound of general formula VII,



VII

in which R_1 and R_2 have the significance stated in claim 1
and R_4 signifies an alkyl radical containing from 1 to 4 carbon atoms inclusive,
is saponified to form the corresponding free acid which is converted to the corresponding acid chloride and subsequently to the corresponding azide in manner known *per se*, the azide is heated in a non-polar solvent to produce the isocyanate which is reacted with benzyl alcohol to give the corresponding benzyl urethane which is then hydrogenated in solution in the presence of a mineral acid to produce the desired amine salt III.

3. Process according to claim 2, in which the compound VII is produced by hydrogenating a compound of general formula VI,

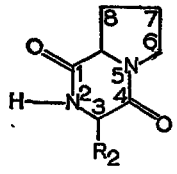


VI

In which R_1, R_2 and X have the significance stated in claim 1

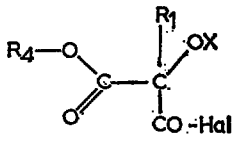
and R_4 has the significance stated in claim 2, so as to split off the protective radical whereupon spontaneous cyclization occurs to form the desired compound VII.

4. Process according to claim 3, in which the compound VI is produced by acylating a compound of general formula V,



V

in which R_2 has the significance stated in claim 1,
with a compound of general formula VIII,



VIII

in which R_1 and X have the significance stated in claim 1, R_4 has the significance stated in claim 2 and Hal signifies a chlorine, bromine or iodine atom.

5. Process for the production of compounds of general formula I stated in claim 1 and their acid addition salts substantially as herein described with reference to the example.

6. Compounds of the general formula I stated in claim 1 and their acid addition salts whenever produced by a process claimed in any one of claims 1 to 5.

7. Ergovaline.

8. Ergovalinine.

9. 9,10-dihydro-ergovaline.

10. The acid addition salts of the compounds claimed in Claims 7, 8 and 9.

11. Pharmaceutical compositions containing, in addition to a physiologically acceptable carrier, a compound of the general formula I stated in claim 1 whenever produced by the process claimed in any of claims 1 to 5, ergovaline, ergovalinine and/or 9,10 - dihydroergovaline, and/or a physiologically acceptable acid addition salt thereof.

12. Pharmaceutical compositions according to claim 11, in which the compound of formula I is ergotamine, ergosine or ergosinine or a physiologically acceptable acid addition salt thereof.

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* C L M S *