

PATENT SPECIFICATION

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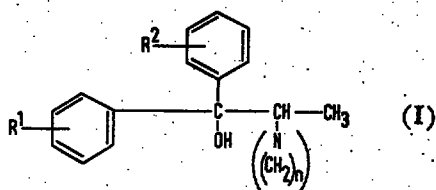
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(54) α,α -DIARYL- β -(TERT-AMINO)-PROPANOLS, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(71) We, TEMMLER AG, a Corporate Body organised and existing under the laws of the Confederation of Switzerland, of Gostenstrasse 85, Basle, Switzerland, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to derivatives of α,α -diaryl- β -(tert-amino)-propanols, processes for their preparation, and also to pharmaceutical compositions containing them.

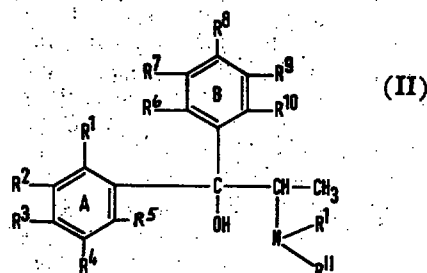
α,α - Diaryl - β - (tert - amino) - propanols of the general formula:



are known, wherein R^1 and R^2 are each independently a halogen atom, a benzyloxy radical, a lower alkyl or a lower alkoxy group and $-N(CH_2)_n$ is a saturated N-heterocyclic radical, which is connected via the ring-stable nitrogen atom. These compounds possess antitussive activity. The compounds of formula (I) may be prepared in known manner by the reaction of (α -tertiary amino)-ethyl aryl ketones with aryl magnesium halides.

Surprisingly, compounds, of the α,α -diaryl- β -(tert-amino)-propanols having saluretic activity have now been found.

Accordingly, the present invention provides α,α -diaryl- β -(tert-amino)-propanols of the general formula:



in which R' and R'' are each independently a straight or branched chain alkyl group having from 1 to 6 carbon atoms, or R' and R'' together with the nitrogen atom, form a 5- or 6-membered ring, and R^1 to R^{10} are each independently a hydrogen or halogen atom, a straight or branched chain alkyl group having from 1 to 6 carbon atoms, an alkenyl group having 2 or 3 carbon atoms, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, or a benzyloxy group or wherein two adjacent substituents together form a 5- or 6-membered heterocyclic ring having one or two hetero-atoms and the other substituents are as defined above, provided that at least one of the rings A and B has more than one substituent group other than hydrogen attached thereto.

These multiple-substituted α,α -diaryl- β -(tert-amino)-propanols of the formula (II) exhibit a diuretic and saluretic effect which differs from that of diuretics found commercially.

Medicaments which result in an increased discharge of urine and produce an increased elimination of sodium and chloride ions via the kidneys (saluretics) are used for example in the treatment of oedema, in widely varying

convalescent conditions and in the therapy of high-pressure conditions.

In addition to eliminating sodium and chloride, saluretics normally also cause at the same time an increase in the excretion of potassium. Such an effect is disadvantageous, since it carries with it the risk, particularly in long-term therapy, of a potassium-depletion of the organism.

Diuretics, in which this side effect is not found, are of particular interest. They are classified pharmacologically as aldosterone-antagonists or as pseudo-antialdosterones or anti-kaliuretic diuretics. Previously known examples of medicaments of this type are the aldosterone antagonist 4',5' - dihydro - 7 α -mercaptospiro - [androst - 4 - ene - 17,2' - (3'H) - furan] - 3 - one acetate which is from the group of spirolactones and the antikaliuretic diuretics 2,4,7 - triamino - 6-phenyl - pteridine and N - amidino - 3,5-diamino - 6 - chloropyrazinecarboxamide. However in patients, in which sodium is retained, these compounds generally only have a slight effect on the sodium elimination. For this reason they are generally only used in combination with a powerful saluretic. This procedure involves disadvantages since the effect of such a combination is frequently quantitatively impossible to anticipate. The effect will depend on the relationship between the primary disease and the simultaneous administration of the saluretic and anti-kaliuretic diuretic, and furthermore gives rise to problems in respect of the possible concurrence of side effects. Furthermore, the previously known anti-kaliuretics may cause potassium congestion in the body, since because of their anti-kaliuretic action potassium is retained in the organism, if its elimination *via* the kidneys is not increased.

For these reasons, new diuretics have been sought which possess both anti-kaliuretic and saluretic activity.

As can be seen from the results of pharmacological tests which are summarised in the following tables, the compounds of the present invention increase the water and sodium chloride elimination beyond that obtained with 2,4,7 - triamino - 6 - phenyl - pteridine, without inhibiting the elimination of potassium, and furthermore do not increase the excretion of potassium, such as is known with the conventional saluretics. It can be seen from Table 2 that the potassium values obtained using the compounds of the invention, by contrast with the reference compositions, are in the range which is considered to be normal.

It is also found that the novel compounds not only possess more favourable properties than 2,4,7 - triamino - 6 - phenyl - pteridine, but that they to some extent also considerably surpass the effect of 6 - chloro - 3,4 - dihydro - 7 - sulphamoyl - 2H - 1,2,4 - benzo-

thiadiazine-1,1-dioxide with respect to their diuretic and saluretic action. The following explanations are given with regard to the tables.

In order to test the saluretic efficiency of the compounds of the invention rats having a weight of 150 to 200 g were used. The animals were kept without food, but not without drinking water, for 15 hours before the beginning of the test. The test substances were administered to groups of four rats, of substantially equal weight, with a rigid stomach probe in a 1% methyl cellulose slime. The dose required per 100 g animal (unit dosage in μ mol/kg body weight) was contained in one ml. Following the administration of the substance the rats were given 5 ml 0.9% sodium chloride solution per 100 g body weight p.o. and placed in a diuresis funnel after manually emptying the bladder. Urine was collected for 6 hours in an air-conditioned chamber at $24 \pm 1^\circ$ C and a relative air humidity of $50 \pm 5\%$. The diuretic effect of a particular dose was tested on at least two, but more frequently however on four to eight groups of rats. Two sodium chloride controls were also used for each test day.

At the end of the collecting periods the volumes of urine discharged per group were noted and the pH value and also the content of sodium and potassium (measured flame-photometrically) and chloride (measured argentometrically with the determination of the end point potentiometrically) were determined.

From the analysis results the quantities of Na^+ , K^+ and Cl^- eliminated were calculated in mol/lg body weight, and the values thus obtained compared with those of the control animals.

Means values and twice the standard deviation were calculated from the data for the sodium chloride controls, in order to determine the normal range. Then, for the values found with the test substances, the percentage variations from the average in respect of these parameters were calculated and tabulated. In this connection, with the results given in Table 1, the upper limit of the normal range, which is defined as the mean value plus twice the standard deviation, was selected as the reference quantity for the variations. In this way relevant hyper-eliminations could clearly be recognised.

In Table 2, the mean percentage variations in potassium elimination after administration of the compounds in accordance with the invention are compared with the mean value of the potassium elimination in the case of the sodium chloride controls. At the same time the Na/K ratio is given which provides conclusive evidence of the effective saluretic property. The larger this quotient is, then the proportionately more sodium than potassium is eliminated.

(14)

TABLE 1
Influence on the elimination of water and sodium chloride

Substance	Dose $\mu\text{mol/kg}$ body wt.	Mean percentage variation in the elimination (%)		
	oral	H ₂ O	Sodium	Chloride
T 1523	40	28.9	13.1	-5.1
	80	39.6	28.2	14.2
T 1856	40	41.0	30.6	19.4
	80	59.7	47.6	32.5
T 1857	40	52.0	54.8	32.9
	80	56.5	54.6	36.0
T 1882	40	17.7	24.4	6.3
	80	7.5	9.5	-4.4
T 2111	40	36.8	33.5	9.5
	80	33.8	37.1	23.4
T 2129	40	23.9	32.6	12.4
	80	21.3	19.4	22.0
T 2152	40	22.9	22.7	11.6
	80	22.6	20.4	5.6
T 2237	40	40.8	32.1	24.3
	80	67.9	59.8	57.1
T 2258	40	28.1	22.9	12.8
	80	32.3	24.6	17.3
T 2259	40	46.5	28.7	94.0
	80	76.6	59.8	109.7
T 2266	40	-12.9	-7.7	-13.2
	80	19.7	19.4	12.2
T 2310	40	41.3	27.3	8.9
	80	67.9	42.3	36.3
T 2350	40	24.1	15.5	2.6
	80	49.8	40.5	21.2
2,4,7-triamino-6- phenyl-pteridine	40	-1.0	-4.0	-11.7
	80	-2.0	-0.2	-11.7
T 2378	40	6.7	6.7	-5.6
	80	39.6	45.0	-20.4
T 2453	40	13.4	7.6	6.9
	80	51.7	62.2	31.2
T 2455	40	39.8	31.3	21.4
	80	62.4	55.8	34.8
T 2458	40	30.9	40.4	16.9
	80	83.8	84.2	59.0

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TABLE 1 (Continued)

Influence on the elimination of water and sodium chloride

Substance	Dose $\mu\text{mol/kg}$ body wt.	Mean percentage variation in the elimination (%)		
		H ₂ O	Sodium	Chloride
T 2464	40	49.8	64.4	30.4
	80	65.9	79.0	38.3
T 2481	40	3.0	-2.4	-7.5
	80	34.1	43.8	20.0
T 2493	40	59.2	62.7	41.0
	80	64.4	76.8	41.5

6-chloro-3,4-dihydro-7-sulphamoyl-2H-1,2,4-benzothiadiazine-1,1-dioxide, a typical saluretic, produced with a dose of 10 mol/kg body weight a maximum hyper-elimination amounting on an average for water to 19.9%, sodium 29.6% and chloride 17.3%.

Footnotes

- (¹) Deviations from the limits, defined by the average plus twice the standard deviation ($\bar{x}+2s$), of the control tests.
- (²) Negative prefixes indicate that there is no hyper-elimination by comparison with the sodium chloride controls.

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TABLE 2
Influence on the elimination of potassium

Substance	Dose $\mu\text{mol/kg}$ body wt. oral	Mean percentage variation in the elimination of potassium (%)	Quotient Na/K
T 1523	40	25.5	5.35
	80	13.3	6.72
T 1856	40	25.5	6.18
	80	22.4	7.16
T 1857	40	30.6	7.04
	80	29.6	7.09
T 1882	40	13.3	6.52
	80	-12.2	7.41
T 2111	40	19.4	6.64
	80	-7.1	8.77
T 2129	40	12.3	7.02
	80	35.7	5.23
T 2152	40	9.2	6.67
	80	9.2	6.55
T 2237	40	13.3	6.93
	80	19.4	7.95
T 2258	40	19.4	6.11
	80	1.0	7.32
T 2259	40	19.4	6.40
	80	38.8	6.84
T 2266	40	-2.0	5.59
	80	4.0	6.81
T 2310	40	14.3	6.62
	80	-2.0	8.64
T 2350	40	-2.0	7.00
	80	25.5	6.65
2,4,7-triamino-6- phenyl-pteridine	40	-43.9(*)	10.16(**)
	80	-55.1(*)	13.20(**)
T 2378	40	11.2	5.70
	80	32.7	6.49
T 2453	40	-2.0	6.52
	80	± 0	9.63
T 2455	40	13.3	6.88
	80	-23.5	12.93
T 2458	40	49.0 ⁺	5.60
	80	37.7	8.06

TABLE 2 (Continued)

Influence on the elimination of potassium

Substance	Dose $\mu\text{mol/kg}$ body wt. oral	Mean percentage variation in the elimination of potassium ⁽¹⁾	Quotient Na/K
T 2464	40	9.2	8.94
	80	-1.0	10.74
T 2481	40	-4.1	6.04
	80	16.3	7.34
T 2493	40	35.7	7.74
	80	34.7	7.88

With the maximum effective dose of 6-chloro-3,4-dihydro-7-sulphamoyl-2H-1,2,4-benzothiadiazine-1,1-dioxide (10 mol/kg body wt.) in the case of potassium a hyper-elimination of 58.3% (*) was recorded. The Na/K ratio of the quantities eliminated was 4.86.

Footnotes

- (*) Value lies outside the normal range.
 (**) This extraordinarily high quotient can be explained in that the elimination of sodium remained unaffected while that of potassium was markedly reduced.
 (1) In relation to the mean value of the K^+ elimination of the controls.
 (2) Negative prefixes indicate that there is no hyper-elimination in comparison with the sodium chloride controls.

Furthermore, the compounds in accordance with the invention differ advantageously from the hitherto known anti-kaliuretic diuretics with respect to their toxicity.

In Table 3 the mean lethal doses for mice,

administered orally (LD_{50} determination by the LICHTFEL & WILCOXON method—J. Pharmacol. Exp. Ther. 96,99 (1949)) are compared.

TABLE 3

Comparison of toxicity in mice

Substance	LD ₅₀ mg/kg body wt. oral, observation period 7 days, 95% confidence limit in brackets
T 1523	>3200
T 1856	2200 (1209-4004)
T 1857	3825 (2675-5470)
T 1882	3400 (2656-4352)
T 2111	4450 (3560-5563)
T 2129	>3200
T 2152	
T 2237	>6400
T 2258	>4500
T 2259	560 (444- 706)
T 2266	>3200
T 2310	520 (361- 749)
T 2350	>4500
2,4,7-triamino-6-phenyl-pteridine	ca. 300 (1)
N-Amidino-3,5-diamino-6-chloro-pyrazine carboxamide	70 (2)
T 2378	1600
T 2453	700 (569- 841)
T 2455	4550
T 2458	3200
T 2464	>4550
T 2481	3775 (3341-4266)
T 2493	3610 (2597-5018)
(1) Clarke, D: Identification of Drugs, p. 581, London, Pharmaceutical Press, 1971	
(2) Erhard, G. and H. Ruscipic (Hsg): Arzneimittel 2nd edn. Vol. 2, p. 351 Weinheim/Bergstr., Verlag Chemie. 1972.	

The compounds of the present invention may be used in pharmaceutical compositions both in the free form and in the form of their salts. They may be administered orally

or parenterally, in admixture with the usual pharmaceutical diluents or carriers used in human or veterinary medicine.

The carrier may be one or more inorganic

or organic substance which are suitable for parenteral or oral administration and which do not react with the compounds of the invention. Examples of suitable carriers are water, vegetable oils, polyethylene glycols, gelatin, lactose, starch, magnesium stearate and talc.

For parenteral administration the compositions may be used in the form of aqueous or oily solutions, suspensions, emulsions or implants. The compositions may also take the form of suppositories.

For oral administration tablets or dragees may also be used.

The new compounds listed below are compounds in accordance with the invention.

- 1) 1 - (4' - Methoxy - 2' - methyl - 5' - isopropylphenyl) - 1 - phenyl - 2 - piperidino-propan-1-ol.
- 2) 1 - (4' - Methoxy - 2' - methyl - 5' - tert - butylphenyl) - phenyl - 2 - pyrrolidino-propan-1-ol.
- 3) 1 - (2' - Methoxy - 3' - methyl - 5' - tert - butylphenyl) - 1 - phenyl - 2 - piperidino-propan-1-ol.
- 4) 1 - (4' - Methoxy - 3',5' - diisopropylphenyl) - 1 - (3'',4'' - dimethoxyphenyl) - 2 - piperidino-propan-1-ol.
- 5) 1 - (2' - Methoxy - 3' - methyl - 5' - [3 - methyl - pent - 3 - yl]phenyl) - 1 - phenyl - 2 - pyrrolidino-propan-1-ol.
- 6) 1 - (7',8' - Dimethylchroman - 6' - yl) - 1-phenyl-2-piperidino-propan-1-ol.
- 7) 1 - (4' - Methoxy - 2',3',5',6' - tetramethylphenyl) - 1 - phenyl - 2 - piperidino-propan-1-ol.
- 8) 1 - (4' - Methoxy - 3',5' - diisopropylphenyl) - 1 - (4'' - methoxyphenyl) - 2 - piperidino-propan-1-ol.
- 9) 1 - (4' - Methoxy - 3',5' - diisopropylphenyl) - 1 - (4'' - ethoxyphenyl) - 2 - piperidino-propan-1-ol.
- 10) 1 - (2' - Methoxy - 5' - tert - butylphenyl) - 1 - phenyl - 2 - piperidino - propan-1-ol.
- 11) 1 - (4' - Methoxy - 3',4' - diisopropylphenyl) - 1 - (4'' - methoxy - 3'',5'' - dimethylphenyl) - 2 - piperidino-propan - 1-ol.
- 12) 1 - (4' - Ethoxy - 3',5' - diisopropylphenyl) - 1 - (4'' - methoxyphenyl) - 2 - piperidino-propan-1-ol.
- 13) 1 - (3' - Chloro - 6' - methoxy - 2' - methyl - 5' - isopropylphenyl) - 1 - phenyl - 2 - pyrrolidino-propan-1-ol.
- 14) 1 - (4',5' - Methylene - dioxy - 5' - allylphenyl) - 1 - (4'' - methoxyphenyl) - 2 - piperidino-propan-1-ol.
- 15) 1 - (4' - Ethoxy - 3',5' - diisopropylphenyl) - 1 - (4'' - ethoxyphenyl) - 2 - piperidino-propan-1-ol.
- 16) 1 - (2' - Methoxy - 3' - methyl - 5' - tert - butylphenyl) - 1 - (2'',4'' - dimethoxyphenyl) - 2 - piperidino-propan-1-ol.
- 17) 1 - (2' - Methoxy - 3' - methyl - 5' - tert - butylphenyl) - 1 - (2'' - (or 4'')

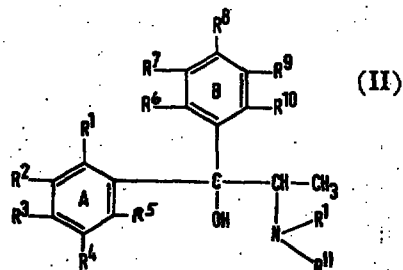
hydroxy - 4'' (or 2'') - methoxyphenyl) - 2 - piperidino-propan-1-ol.

18) 1 - (2' - Methoxy - 3' - methyl - 5' - tert - butylphenyl) - 1 - (3'',4'' - dimethoxyphenyl) - 2 - piperidino-propan-1-ol.

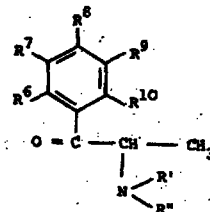
19) 1 - (2' - Methoxy - 5' - methylphenyl) - 1 - (4'' - benzyloxy - 3'',5'' - diisopropylphenyl) - 2 - piperidino-propan-1-ol.

20) 1 - (3' - Chloro - 6' - methoxy - 5' - methylphenyl) - 1 - (4'' - methoxy - 3'',5'' - dimethylphenyl) - 2 - (N - methyl - N - tert-butylamino)-propan-1-ol.

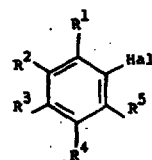
The present invention also includes within its scope a process for the preparation of a compound of Formula (II) as hereinbefore defined which comprises a process for the preparation of an α,α -diaryl- β -(tert-amino)-propanol of the general formula:



as hereinbefore defined, which process comprises adding a compound of the general formula:



wherein R' R'', R⁶, R⁷, R⁸, R⁹ and R¹⁰ are as hereinbefore defined, if desired, dissolved in diethyl ether, to a Grignard solution in diethyl ether, of magnesium and a compound of the general formula:



wherein R¹, R², R³, R⁴ and R⁵ are as hereinbefore defined but do not represent an alkenyl group containing 2 or 3 carbon atoms but may represent a dibromoalkyl group containing 2 or 3 carbon atoms in which the bromine atoms are on adjacent carbon atoms and Hal is a halogen atom, optionally in the presence of 1,2-dibromoethane, and thereafter treating the reaction mixture so obtained in order to

isolate a compound of Formula II as hereinbefore defined.

The following Examples illustrate the preparation of compounds in accordance with the invention.

Example 1. (T 1523).

26 g of α -piperidinopropiophenone were added to a Grignard solution of 4 g of magnesium and 40 g of 4-bromothymol methyl ether in 200 ml of diethyl ether. After boiling for 4 hours under reflux, the reaction mixture was poured on to ice, immediately acidified with hydrochloric acid and the crystals precipitated from the mixture were filtered off by suction. The crystals were then washed with diethyl ether and were added, while still moist, to a mixture of concentrated ammonia solution and petroleum ether. After brief agitation, the crystals dissolved. The petroleum ether extract was separated, dried with potash and then the petroleum ether was removed by evaporation. 23.7 g of 1-(4'-methoxy-2'-methyl-5'-isopropylphenyl)-1-phenyl-2-piperidino-propan-1-ol, having a melting point of 134° C to 135° C were obtained.

Example 2. (T 1856).

22 g of α -pyrrolidinopropiophenone were added to a Grignard solution of 7.3 g of magnesium, 38.5 g of 4-bromo-5-methyl-2-tert-butylanisole and 28.2 g of 1,2-dibromoethane in 300 ml of diethyl ether. After boiling for 4 hours under reflux, the reaction mixture was poured onto ice and acidified with hydrochloric acid. The crystals which precipitated from the water-ether mixture were filtered off by suction, washed with diethyl ether and added to a mixture of concentrated ammonia solution with diethyl ether. After brief agitation the crystals dissolved. The ether extract was separated, dried with potash and the ether was removed by evaporation. The remaining viscous brown oil was dissolved in a little isopropanol. After a short time, 28.2 g of 1-(4'-methoxy-2'-methyl-5'-tert-butylphenyl)-1-phenyl-2-pyrrolidino-propan-1-ol, having a melting point of 112° C to 113° C, crystallized out. This product was recrystallized from isopropanol and then had a melting point of 113° C to 114° C.

Example 3. (T 1857).

15 g of α -piperidinopropiophenone were added to a Grignard solution of 7.3 g of magnesium, 38.5 g of 6-bromo-2-methyl-4-tert-butylanisole and 28.2 g of 1,2-dibromethane in 300 ml of diethyl ether. After boiling for 4 hours under reflux, the reaction mixture was poured on to ice and acidified with hydrochloric acid. The acidic aqueous solution and the oily intermediate layer were both separated, together made alkaline with

concentrated aqueous ammonia solution, and the base which separated therefrom was dissolved in diethyl ether. After evaporation of the diethyl ether, 26.5 g of a viscous brown oil were obtained from which, upon trituration or dilution with isopropanol, 21.5 g of 1-(2'-methoxy-3'-methyl-5'-tert-butylphenyl)-1-phenyl-2-piperidino-propan-1-ol, having a melting point of 86° C to 87° C, crystallized out. The product was recrystallized from isopropanol and then had a melting point of 87° C to 88° C.

Example 4. (T 1882).

12 g of 1-(3',4'-dimethoxyphenyl)-2-piperidino-propan-1-one were added to a Grignard solution of 7.3 g of magnesium, 40.6 g of 4-bromo-2,6-diisopropylanisole and 28.2 g of 1,2-dibromoethane in 300 ml of diethyl ether. After boiling for 4 hours under reflux, the reaction mixture was poured onto ice and acidified with hydrochloric acid. The acidic aqueous solution and the oily intermediate layer were both separated, together made alkaline with concentrated aqueous ammonia solution and the base which precipitated therefrom was dissolved in diethyl ether. After drying the diethyl ether extract over potash and evaporation of the diethyl ether, 24.7 g of a yellowish-brown oil were obtained. On dilution with isopropanol, 14.8 g of crude 1-(4'-methoxy-3',5'-diisopropylphenyl)-1-(3'',4''-dimethoxyphenyl)-2-piperidino-propan-1-ol, having a melting point of 118° C to 119° C crystallized out. After recrystallization from isopropanol the pure compound melted at 120 to 121° C.

Example 5. (T 2111).

7.5 g α -pyrrolidinopropiophenone were added to a Grignard solution, of 3.6 g of magnesium, 21.5 g of 2-methyl-4-(3-methylpent-3-yl)-6-bromoanisole, 14.1 g of 1,2-dibromoethane and 200 ml of diethyl ether. After boiling for 4 hours under reflux, the reaction mixture was poured onto ice and acidified with hydrochloric acid. The acidic aqueous solution and the oil intermediate layer were both separated, together made alkaline with concentrated aqueous ammonia solution and the base which precipitated therefrom was dissolved in diethyl ether. After drying the diethyl ether extract over potash and evaporation of the diethyl ether, 14.8 g of a brown oil were obtained. On dilution with isopropanol, 8.3 g of crude 1-(2'-methoxy-3'-methyl-5'-[3-methylpent-3-yl]phenyl)-1-phenyl-2-pyrrolidino-propan-1-ol, having a melting point of 96° C to 97° C, were obtained. After recrystallization from isopropanol the compound melted at 97° C to 98° C.

Example 6. (T 2129).

15 g of α -piperidinopropiophenone in 20

ml of diethyl ether were added to a Grignard solution of 5.4 g of magnesium, 26.5 g of 6-bromo-7,8-dimethylchromane and 20.7 g of 1,2-dibromoethane in 80 ml diethyl ether. After boiling for 4 hours under reflux, the reaction mixture was poured onto ice and acidified with hydrochloric acid. The crystals which precipitated from the mixture were filtered by suction. The crystals were mixed, while still moist, with concentrated aqueous ammonia solution and the mixture was extracted with diethyl ether several times. After drying the combined diethyl ether extracts over potash and evaporation of the diethyl ether, an oil was obtained which crystallized out after a short time. After recrystallization from methanol 5.2 g of pure 1-(7',8'-dimethylchroman-6'-yl)-1-phenyl-2-piperidino-propan-1-ol, having a melting point of 125° C to 128° C were obtained.

Example 7. (T 2152).

18.0 g of α -piperidinopropiophenone were added to a Grignard solution of 7.3 g magnesium, 36.4 g of 4-bromo-2,3,5,6-tetramethylanisole, 28.2 g of 1,2-dibromoethane and 300 ml of diethyl ether. After boiling for 4 hours under reflux, the reaction mixture was poured onto ice and acidified with hydrochloric acid. The acidic aqueous solution and the oily intermediate layer were both separated, together made alkaline with concentrated aqueous ammonia solution and the base which precipitated therefrom was dissolved in diethyl ether. After evaporation of the diethyl ether, a brown oil was obtained. On dilution with methanol, 10.5 g of 1-(4'-methoxy-2',3',5',6'-tetramethylphenyl)-1-phenyl-2-piperidino-propan-1-ol, having a melting point of 148° C to 150° C, were obtained. After recrystallization from isopropanol, the pure compound melted at 151° C to 152° C.

Example 8. (T 2237).

10 g of p-methoxy- α -piperidino-propio-phenone were added to a Grignard solution of 4.8 g of magnesium, 27.1 g of 4-bromo-2,6-diisopropylanisole, 18.8 g of 1,2-dibromoethane and 200 ml of diethyl ether. After boiling for 4 hours under reflux, the reaction mixture was poured onto ice and acidified with hydrochloric acid. The aqueous acidic solution and the oily intermediate layer were both separated, together made alkaline with concentrated aqueous ammonia solution and the base which separated therefrom was dissolved in diethyl ether. After evaporation of the diethyl ether, 18.2 g of a brown oil were obtained. On dilution with methanol, 12.9 g of 1-(4'-methoxy-3',5'-diisopropylphenyl)-1-(4''-methoxyphenyl)-2-piperidino-propan-1-ol, having a melting point of 62 to 64° C, were obtained. After recrystallization the pure compound melted at 64° C to 65° C.

Example 9. (T 2258).

8 g of p-ethoxy- α -piperidino-propiophenone were added to a Grignard solution of 4.8 g of magnesium, 27.1 g of 4-bromo-2,6-diisopropylanisole, 18.8 g of 1,2-dibromoethane and 200 ml of diethyl ether. After boiling for 4 hours under reflux, the mixture was poured onto ice and acidified with hydrochloric acid. The aqueous acidic layer and the oily intermediate layer, were both separated together made alkaline with concentrated aqueous ammonia solution and extracted with diethyl ether several times. The combined diethyl ether extracts were dried over potash, the diethyl ether was evaporated therefrom and the residue was diluted with isopropanol. The resultant crude crystalline 1-(4'-methoxy-3',5'-diisopropylphenyl)-(4''-ethoxyphenyl)-2-piperidino-propan-1-ol had a melting point of 81° C to 83° C (8.5 g) and melted at 84° C to 85° C, after recrystallization from isopropanol.

Example 10. (T 2259).

21 g of α -piperidino-propiophenone were added to a Grignard solution of 7.3 g of magnesium, 36.4 g of 2-bromo-4-tertiary-butylanisole, 28.2 g of 1,2-dibromoethane and 300 ml of diethyl ether. After boiling for 4 hours under reflux, the reaction mixture was poured onto ice and acidified with hydrochloric acid. The crystals, so precipitated, were filtered by suction, covered with a layer of diethyl ether and mixed with concentrated aqueous ammonia solution until the crystals dissolved upon stirring or agitating. After evaporation of the diethyl ether, 33.3 g of a partly crystalline compound were obtained and dissolved in the necessary quantity of hot methanol. Upon cooling, 25.8 g of 1-(2'-methoxy-5'-tertiary-butylphenyl)-1-phenyl-2-piperidino-propan-1-ol having a melting point of 139 to 140° C crystallized out.

Example 11. (T 2266)

10 g of 1-(4'-methoxy-3',5'-dimethyl)-2-piperidino-propan-1-one were added to a Grignard solution of 4.8 g of magnesium, 27.1 g of 4-bromo-2,6-diisopropylanisole, 18.8 g of 1,2-dibromoethane and 200 ml of diethyl ether. After boiling for 4 hours under reflux, the reaction mixture was poured onto ice and acidified with hydrochloric acid. The precipitated crystals were filtered by suction, covered with a layer of diethyl ether and mixed with a concentrated aqueous ammonia solution until all the crystals had dissolved upon agitation. The diethyl ether portion was separated and dried over potash. After evaporation of the diethyl ether 16.0 g of a partly crystalline compound were obtained. After recrystallization from isopropanol 10.0 g of 1-(4'-methoxy-3',5'-diisopropylphenyl)-1-(4''-methoxy-3'',5''-dimethylphenyl)-2-

piperidinopropan-1-ol having a melting point of 118 to 119° C were obtained.

Example 12. (T 2310).

12 g of p-methoxy- α -piperidino-propio-
phenone were added to a Grignard solution,
of 6.1 g of magnesium, 35.7 g of 4-bromo-2,6-
diisopropyl-phenetole, 23.5 g of 1,2-dibromo
ethane and 200 ml of diethyl ether. After boiling
for 4 hours under reflux, the reaction mixture
was poured onto ice and acidified with
hydrochloric acid. The aqueous acid solution
and the oily intermediate layer were both
separated and together made alkaline with
concentrated aqueous ammonia solution. The
precipitated base was dissolved in diethyl
ether. After evaporation of the diethyl ether,
21.7 g of a brown oil was obtained which was
dissolved in a small amount of isopropanol
and then immediately acidified with aqueous
70% perchloric acid. Upon dilution, 18.9 g of
1-(4'-ethoxy-3',5'-diisopropylphenyl)-
1-(4''-methoxyphenyl)-2-piperidino-
propan-1-ol perchlorate precipitated which,
after recrystallization from isopropanol,
melted at 147° C to 148° C.

Example 13. (T 2350).

10 g of α -pyrrolidino-propio-phenone were
added to a Grignard solution of 7.3 g of
magnesium, 41.5 g of 4-chloro-6-bromo-
thymol methyl ether, 28.2 g of 1,2-dibromo-
ethane and 300 ml of diethyl ether. After
boiling for 6 hours under reflux, the reaction
mixture was poured onto ice and acidified with
hydrochloric acid. The precipitated crystals
were filtered by suction, covered with a layer
of diethyl ether and mixed with concentrated
aqueous ammonia solution until they dissolved
upon agitation. The diethyl ether portion was
separated and dried with potash. After
evaporation of the diethyl ether, 11.1 g of
1-(3'-chlor-6'-methoxy-2'-methyl-
5'-isopropylphenyl)-1-phenyl-2-pyrro-
lidino-propan-1-ol having a crude m.p. of
108 to 109° C. After recrystallization from
methanol the pure compound melted at 112°
C to 113° C.

Example 14. (T 2378).

12 g of p-methoxy- α -piperidino-propio-
phenone were added to a Grignard solution
of 12.2 g of magnesium, 80.0 g of 2-(2',3'-
dibromopropyl)-4,5-methylenedioxy-
bromobenzene, 18.8 g of 1,2-dibromoethane
and 300 ml of diethyl ether. After boiling for
6 hours under reflux, the reaction mixture
was poured onto ice and acidified with
hydrochloric acid. After a certain amount of
time the precipitated dark oil partially
crystallized. The crystals were filtered by
suction, washed with diethyl ether and sub-
sequently decomposed with concentrated
aqueous ammonia solution. The free base was
dissolved in diethyl ether and the diethyl

ether extract was dried over potash. After
evaporation of the diethyl ether, 4.8 g 1-(4',5'-
methylene dioxy-2'-allylphenyl)-1-(4''-
methoxyphenyl)-2-piperidino-propan-
1-ol, having a crude melting point of 117 to
130° C, were obtained. After treatment with
activated carbon and recrystallization from
isopropanol the pure compound had a melting
point of 132 to 133.5° C.

Example 15. (T 2453).

10 g of p-ethoxy- α -piperidino-propio-
phenone, dissolved in 100 ml of diethyl ether,
were added to a Grignard solution of 7.3 g of
magnesium, 42.8 g of 4-bromo-2,6-diisopropyl
phenetole and 28.2 g of 1,2-dibromoethane
in 100 ml of diethyl ether. After boiling for 4
hours under reflux, the reaction mixture was
poured onto ice and the mixture acidified with
hydrochloric acid. The oily intermediate layer
and the aqueous acidic layer were both
separated, together made alkaline with con-
centrated aqueous ammonia solution and the
base which precipitated therefrom was dis-
solved in diethyl ether. After drying over
potash and evaporation of the diethyl ether,
a brown oil remained (23 g) which was dis-
solved in 20 ml of isopropanol. The solution
was acidified by drop-by-drop addition of
aqueous 70 percent perchloric acid during
which 17.4 g of 1-(4'-ethoxy-3',5'-diisopropyl-
phenyl)-1-(4''-methoxy-3'',5''-dimethyl-
phenyl)-2-piperidino-propan-1-ol
perchlorate having a melting point of 160 to
161° C (decomposition), crystallized out.
After recrystallization from isopropanol the
pure perchlorate melted at 161 to 162° C. The
free base was liberated from the perchlorate
with dilute caustic soda solution dissolved in
diethyl ether and dried over potash. After
evaporation of the diethyl ether, 1-(4'-
ethoxy-3',5'-diisopropylphenyl)-1-(4''-
ethoxyphenyl)-2-piperidino-propan-1-
ol was obtained as a colourless viscous oil
(14.0 g). By adding a calculated quantity of
aqueous hydrochloric acid, the free base
could be converted into the corresponding
hydrochloride which was chosen as the form
for administration in the pharmacological
tests.

Example 16. (T 2455).

7 g of 2,4-dimethoxy- α -piperidino-propio-
phenone in 100 ml of diethyl ether were
added to a Grignard solution of 7.3 g of
magnesium, 38.6 g of 6-bromo-2-methyl-4-
tert.butyl anisole, 28.2 g of 1,2-dibromo-
ethane and 200 ml of diethyl ether.
After boiling for 6 hours under reflux, the
reaction mixture was poured onto ice and
acidified with hydrochloric acid. The diethyl
ether layer was separated and discarded,
whilst the aqueous acidic layer was made
alkaline with concentrated aqueous ammonia
solution and was extracted several times with

diethyl ether. The combined ether extracts were dried over potash and then the diethyl ether was evaporated. The residual brownish oil (13.4 g) crystallized on diluted with a little isopropanol. The pure 1-(2'-methoxy-3'-methyl-5'-tertiary-butylphenyl)-1-(2'',4''-dimethoxyphenyl)-2-piperidino-propan-1-ol, having a melting point of 133.5 to 135° C, was obtained after two recrystallizations from about 200 ml of isopropanol in each case.

Example 17. (T 2458).

5 g of 2 (or 4) - methoxy - 4 (or 2) - hydroxy - α - piperidinopropiophenone (obtained from 2,4-dimethoxy-propio-phenone, which is a by-product from the preliminary stage of the production of 2,4-dimethoxy- α -piperidinopropiophenone) dissolved in 100 ml of diethyl ether were added to a Grignard solution of 7.3 g of magnesium, 38.6 g of 6 - bromo - 2 - methyl - 4 - tert. - butyl anisole, 28.2 g of 1,2-dibromoethane and 150 ml diethyl ether. The reaction mixture was boiled for 4 hours under reflux, was then poured onto ice and acidified with hydrochloric acid. The mixture was vigorously agitated and then the diethyl ether was separated. The separated ether layer was then thoroughly agitated several times with semi-concentrated hydrochloric acid. The combined aqueous and hydrochloric acid extracts were then covered with a layer of 200 ml of diethyl ether and concentrated aqueous ammonia solution was then added dropwise thereto until the pH-value of the mixture reached 8. The diethyl ether layer was then separated, the aqueous alkaline solution was extracted several times with diethyl ether and the combined ether extracts of the ammoniacal solution were dried over sodium sulphate. After evaporation of the diethyl ether 14.5 g of a brown oil remained. On dilution with a little isopropanol the oil crystallized out. The crystals (5.2 g having a crude melting point of 146 to 148° C) were filtered by suction and recrystallized several times from isopropanol. The melting point of the pure 1-(2'-methoxy-3'-methyl-5'-tertiary-butylphenyl)-2-(2'' (or 4'')-methoxy-4'' (or 2'')-hydroxyphenyl)-2-piperidino-propan-1-ol was then 153.5 to 155° C.

Example 18. (T 2464).

7.9 g of 3,4-dimethoxy- α -piperidinopropiophenone, dissolved in 100 ml diethyl ether, were added to a Grignard solution of 7.3 g of magnesium, 38.6 g of 2-methyl-6-bromo-4-tertiary-butyl anisole, 28.2 g of 1,2-dibromoethane and 100 ml diethyl ether. The reaction mixture was heated to boiling for 4 hours under reflux and then poured onto ice. After acidification with hydrochloric acid and after stirring, three layers were formed. The upper diethyl ether layer was separated and

discarded, the lower, aqueous layer and the oily central layer together were covered with a layer of fresh diethyl ether and, subsequently, were made alkaline with concentrated aqueous ammonia solution. The diethyl ether layer above the alkaline solution was separated, dried within potash and evaporated. 13.4 g of a light-brown oil remained, which was dissolved in 100 ml of hot methanol. Upon cooling 8.3 g of 1-(2'-methoxy-3'-methyl-5'-tertiary-butylphenyl)-1-(3'',4''-dimethoxyphenyl)-2-piperidino-propan-1-ol, having a melting point of 125 to 126° C, crystallized out. The melting point of the pure compound, after treatment with activated carbon and two recrystallizations from methanol, was 127 to 128° C.

Example 19. (T 2481).

6.0 g of 4-benzyloxy-3,5-diisopropyl- α -piperidino-propio-phenone in 100 ml of diethyl ether were added to a Grignard solution of 7.3 g of magnesium, 30.2 g of 2-bromo-methyl anisole, 28. g of 1,2-dibromoethane and 100 ml of diethyl ether. After boiling for 4 hours under reflux, the mixture was poured onto ice and acidified with hydrochloric acid. The resultant oily intermediate layer and the aqueous phase were both separated, together mixed with diethyl ether and concentrated aqueous ammonia solution and agitated thoroughly. The diethyl ether extract so obtained was separated, dried over potash and the ether evaporated. The residual brown oil (12.1 g) was dissolved in 40 ml of isopropanol and was acidified with saturated solution of picric acid in isopropanol. 12.2 g of the picrate, having a crude melting point of 95 to 100° C, crystallized out. After recrystallization from isopropanol, the pure picrate melted at 99 to 101° C. The 1-(2'-methoxy-5'-methylphenyl)-1-(4''-benzyloxy-3'',5''-diisopropylphenyl)-2-piperidino-propan-1-ol was obtained as a colourless oil by decomposition of the pure picrate with ethanolamine, in accordance with the directions of I. A. Kaye *et al* (J. Amer. Chem. Soc. 72, 5752 (1950)). By adding a calculated amount of aqueous hydrochloric acid, the free base could be converted into the corresponding hydrochloride which was chosen as the form for administration in the pharmacological tests.

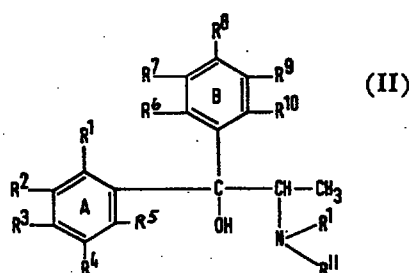
Example 20. (T 2493).

5 g of 4-methoxy-3,5-dimethyl- α -(N-methyl-N-tertiary-butylamino)-propio-phenone in 100 ml of diethyl ether were added to a Grignard solution of 7.3 g of magnesium, 35.3 g of 6-bromo-4-chloro-2-methyl-anisole, 28.2 g of 1,2-dibromoethane and 100 ml diethyl ether. The mixture was boiled for 4 hours under reflux. Subsequently, the mixture was poured onto ice and acidified with hydrochloric acid. The resultant mixture was

thoroughly agitated in a separating funnel, the diethyl ether layer being separated and discarded. The aqueous layer and the oily intermediate layer together were rendered alkaline with aqueous concentrated ammonia solution and were then extracted with diethyl ether. This diethyl ether extract was dried over potash and the ether was evaporated. 10.1 g of a brown alkaline oil remained which was dissolved in 20 ml of methanol and was mixed with a saturated solution of picric acid in methanol until the solution reacted acidically over the crystals precipitated therefrom. The resultant crude 1-(6'-methoxy-5'-methyl-3'-chlorophenyl) - 1 - (4'' - methoxy - 3'',5'' - dimethylphenyl) - 2 - (N - methyl - N - tertiary - butylamino) - propan - 1 - ol picrate (9.4 g) had a melting point of 179 to 180° C. The pure picrate, which melted at 185 to 186° C after two recrystallizations from methanol, was decomposed with ethanolamine in accordance with the directions of I. A. Kaye *et al* (J. Amer. Chem. Soc. 72, 5752 (1950)). The resultant colourless, oily 1 - (3' - chloro - 6' - chloro - 6' - methoxy - 5' - methylphenyl) - 1 - (4'' - methoxy - 3'',5'' - dimethylphenyl) - 2 - (N - methyl - N - tertiary - butylamino) - propan - 1 - ol could be converted, by the addition of a calculated quantity of aqueous hydrochloric acid, into the corresponding hydrochloride which was chosen as the form for administration in the pharmacological tests.

WHAT WE CLAIM IS:—

1. A compound of the general formula:—



wherein R' and R'' are each independently a straight or branched chain alkyl group having from 1 to 6 carbon atoms, or R' and R'' together with the nitrogen atom form a 5- or 6-membered ring, and R¹ to R¹⁰ are each independently a hydrogen or halogen atom, a straight or branched chain alkyl group having from 1 to 6 carbon atoms, an alkenyl group having 2 or 3 carbon atoms, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, or a benzyloxy group, or two adjacent substituents together form a 5- or 6-membered heterocyclic ring having one or two hetero atoms and the other substituents are as defined above, provided that at least one of the rings A and B has more than one sub-

stituent group other than hydrogen attached thereto.

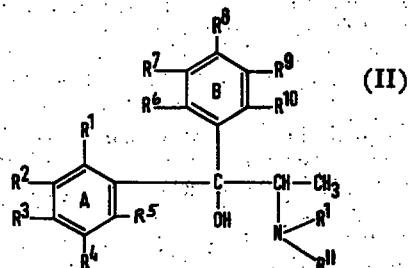
2. 1 - (4' - Methoxy - 2' - methyl - 5' - isopropylphenyl) - 1 - phenyl - 2 - piperidino-propan-1-ol. 55
3. 1 - (4' - Methoxy - 2' - methyl - 5' - tert - butylphenyl) - 1 - phenyl - 2 - pyrrolidino-propan-1-ol. 60
4. 1 - (2' - Methoxy - 3' - methyl - 5' - tert - butylphenyl) - 1 - phenyl - 2 - piperidino-propan-1-ol.
5. 1 - (4' - Methoxy - 3',5' - diisopropylphenyl) - 1 - (3'',4'' - dimethoxyphenyl) - 2 - piperidino-propan-1-ol. 65
6. 1 - (2' - Methoxy - 3' - methyl - 5' - [3 - methyl - pert - 3 - yl]phenyl) - 1 - phenyl-2-pyrrolidino-propan-1-ol.
7. 1 - (7',8' - Dimethylchroman - 6' - yl) - 1-phenyl-2-piperidino-propan-1-ol. 70
8. 1 - (4' - Methoxy - 2',3',5',6' - tetramethylphenyl) - 1 - phenyl - 2 - piperidino-propan-1-ol.
9. 1 - (4' - Methoxy - 3',5' - diisopropylphenyl) - 1 - (4'' - methoxyphenyl) - 2 - piperidino-propan-1-ol. 75
10. 1 - (4' - Methoxy - 3',5' - diisopropylphenyl) - 1 - (4'' - ethoxyphenyl) - 2 - piperidino-propan-1-ol. 80
11. 1 - (2' - Methoxy - 5' - tert - butylphenyl) - 1 - phenyl - 2 - piperidino - propan-1-ol.
12. 1 - (4' - Methoxy - 3',5' - diisopropylphenyl) - 1 - (4'' - methoxy - 3'',5'' - dimethylphenyl)-2-piperidino-propan-1-ol. 85
13. 1 - (4' - Ethoxy - 3',5' - diisopropylphenyl) - (4'' - methoxyphenyl) - 2 - piperidino-propan-1-ol.
14. 1 - (3' - Chloro - 6' - methoxy - 2' - methyl - 5' - isopropylphenyl) - 1 - phenyl-2-pyrrolidino-propan-1-ol. 90
15. 1 - (4',5' - Methylene dioxy - 2' - allylphenyl) - (4'' - methoxyphenyl) - 2 - piperidino-propan-1-ol. 95
16. 1 - (4' - Ethoxy - 3',5' - diisopropylphenyl) - 1 - (4'' - ethoxyphenyl) - 2 - piperidino-propan-1-ol.
17. 1 - (2' - Methoxy - 3' - methyl - 5' - tert - butylphenyl) - 1 - (2'',4'' - dimethoxyphenyl)-2-piperidino-propan-1-ol. 100
18. 1 - (2' - Methoxy - 3' - methyl - 5' - tert - butylphenyl) - 1 - (2'' (or 4'') - hydroxy - 4'' (or 2'') - methoxyphenyl - 2 - piperidino-propan-1-ol. 105
19. 1 - (2' - Methoxy - 3' - methyl - 5' - tert - butylphenyl) - 1 (3'',4'' - dimethoxyphenyl)-2-piperidino-propan-1-ol.
20. 1 - (2' - Methoxy - 5' - methylphenyl) - 1 - (4'' - benzyloxy - 3'',5'' - diisopropylphenyl) - 2 - piperidino - propan - 1 - ol. 110
21. 1 - (3' - Chloro - 6' - methoxy - 5' - methylphenyl) - 1 - (4'' - methoxy - 3'',5'' - dimethylphenyl) - 2 - (N - methyl - N - tert-butylamino)-propan-1-ol. 115
22. A pharmaceutically acceptable salt of



thoroughly agitated in a separating funnel, the diethyl ether layer being separated and discarded. The aqueous layer and the oily intermediate layer together were rendered alkaline with aqueous concentrated ammonia solution and were then extracted with diethyl ether. This diethyl ether extract was dried over potash and the ether was evaporated. 10.1 g of a brown alkaline oil remained which was dissolved in 20 ml of methanol and was mixed with a saturated solution of picric acid in methanol until the solution reacted acidically over the crystals precipitated therefrom. The resultant crude 1-(6'-methoxy-5'-methyl-3'-chlorophenyl) - 1 - (4'' - methoxy - 3'',5'' - dimethylphenyl) - 2 - (N - methyl - N - tertiary - butylamino) - propan - 1 - ol picrate (9.4 g) had a melting point of 179 to 180° C. The pure picrate, which melted at 185 to 186° C after two recrystallizations from methanol, was decomposed with ethanolamine in accordance with the directions of I. A. Kaye *et al* (J. Amer. Chem. Soc. 72, 5752 (1950)). The resultant colourless, oily 1 - (3' - chloro - 6' - chloro - 6' - methoxy - 5' - methylphenyl) - 1 - (4'' - methoxy - 3'',5'' - dimethylphenyl) - 2 - (N - methyl - N - tertiary - butylamino) - propan - 1 - ol could be converted, by the addition of a calculated quantity of aqueous hydrochloric acid, into the corresponding hydrochloride which was chosen as the form for administration in the pharmacological tests.

WHAT WE CLAIM IS:—

1. A compound of the general formula:—



wherein R' and R'' are each independently a straight or branched chain alkyl group having from 1 to 6 carbon atoms, or R' and R'' together with the nitrogen atom form a 5- or 6-membered ring, and R¹ to R¹⁰ are each independently a hydrogen or halogen atom, a straight or branched chain alkyl group having from 1 to 6 carbon atoms, an alkenyl group having 2 or 3 carbon atoms, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, or a benzyloxy group, or two adjacent substituents together form a 5- or 6-membered heterocyclic ring having one or two hetero atoms and the other substituents are as defined above, provided that at least one of the rings A and B has more than one sub-

stituent group other than hydrogen attached thereto.

2. 1 - (4' - Methoxy - 2' - methyl - 5' - isopropylphenyl) - 1 - phenyl - 2 - piperidino-propan-1-ol. 55
3. 1 - (4' - Methoxy - 2' - methyl - 5' - tert - butylphenyl) - 1 - phenyl - 2 - pyrrolidino-propan-1-ol. 60
4. 1 - (2' - Methoxy - 3' - methyl - 5' - tert - butylphenyl) - 1 - phenyl - 2 - piperidino-propan-1-ol. 60
5. 1 - (4' - Methoxy - 3',5' - diisopropylphenyl) - 1 - (3'',4'' - dimethoxyphenyl) - 2 - piperidino-propan-1-ol. 65
6. 1 - (2' - Methoxy - 3' - methyl - 5' - [3 - methyl - pert - 3 - yl]phenyl) - 1 - phenyl-2-pyrrolidino-propan-1-ol.
7. 1 - (7',8' - Dimethylchroman - 6' - yl) - 1-phenyl-2-piperidino-propan-1-ol. 70
8. 1 - (4' - Methoxy - 2',3',5',6' - tetramethylphenyl) - 1 - phenyl - 2 - piperidino-propan-1-ol.
9. 1 - (4' - Methoxy - 3',5' - diisopropylphenyl) - 1 - (4'' - methoxyphenyl) - 2 - piperidino-propan-1-ol. 75
10. 1 - (4' - Methoxy - 3',5' - diisopropylphenyl) - 1 - (4'' - ethoxyphenyl) - 2 - piperidino-propan-1-ol. 80
11. 1 - (2' - Methoxy - 5' - tert - butylphenyl) - 1 - phenyl - 2 - piperidino - propan-1-ol.
12. 1 - (4' - Methoxy - 3',5' - diisopropylphenyl) - 1 - (4'' - methoxy - 3'',5'' - dimethylphenyl)-2-piperidino-propan-1-ol. 85
13. 1 - (4' - Ethoxy - 3',5' - diisopropylphenyl) - (4'' - methoxyphenyl) - 2 - piperidino-propan-1-ol.
14. 1 - (3' - Chloro - 6' - methoxy - 2' - methyl - 5' - isopropylphenyl) - 1 - phenyl-2-pyrrolidino-propan-1-ol. 90
15. 1 - (4',5' - Methylene dioxy - 2' - allylphenyl) - (4'' - methoxyphenyl) - 2 - piperidino-propan-1-ol. 95
16. 1 - (4' - Ethoxy - 3',5' - diisopropylphenyl) - 1 - (4'' - ethoxyphenyl) - 2 - piperidino-propan-1-ol.
17. 1 - (2' - Methoxy - 3' - methyl - 5' - tert - butylphenyl) - 1 - (2'',4'' - dimethoxyphenyl)-2-piperidino-propan-1-ol. 100
18. 1 - (2' - Methoxy - 3' - methyl - 5' - tert - butylphenyl) - 1 - (2'' (or 4'') - hydroxy - 4'' (or 2'') - methoxyphenyl) - 2 - piperidino-propan-1-ol. 105
19. 1 - (2' - Methoxy - 3' - methyl - 5' - tert - butylphenyl) - 1 (3'',4'' - dimethoxyphenyl)-2-piperidino-propan-1-ol.
20. 1 - (2' - Methoxy - 5' - methylphenyl) - 1 - (4'' - benzyloxy - 3'',5'' - diisopropylphenyl) - 2 - piperidino - propan - 1 - ol. 110
21. 1 - (3' - Chloro - 6' - methoxy - 5' - methylphenyl) - 1 - (4'' - methoxy - 3'',5'' - dimethylphenyl) - 2 - (N - methyl - N - tert-butylamino)-propan-1-ol. 115
22. A pharmaceutically acceptable salt of



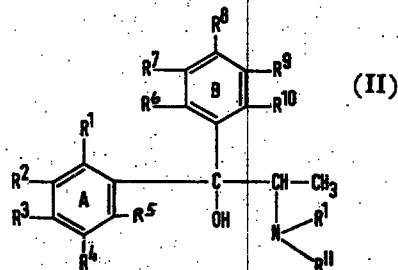
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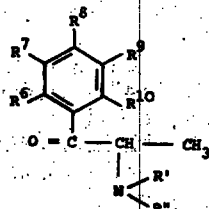
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a compound as claimed in any one of claims 1 to 21.

23. A process for the preparation of an α,α -diaryl- β -(tert-amino)propanol of the general formula:



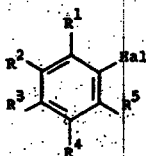
as defined in claim 1, which process comprises adding a compound of the general formula:



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wherein R^1, R^2, R^3, R^4, R^5 and R^{10} are as defined in claim 1, if desired dissolved in diethyl ether, to a Grignard solution in diethyl ether of magnesium and a compound of the general formula:



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wherein R^1, R^2, R^3, R^4 and R^5 are as claimed in claim 1 but do not represent an alkenyl group containing 2 or 3 carbon atoms but may represent a dibromoalkyl group containing 2 or 3 carbon atoms in which the bromine atoms are on adjacent carbon atoms and Hal is a halogen atom, optionally in the presence of 1,2-dibromoethane, and thereafter treating the reaction mixture so obtained in order to isolate a compound of Formula II as defined in claim 1.

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24. A process for the preparation of 1-(4'-methoxy-2'-methyl-5'-isopropylphenyl)-1-phenyl-2-piperidino-propan-1-ol as claimed in claim 23 which comprises adding α -piperidinopropiophenone to a Grignard solution of magnesium and 4-bromothymol methyl ether in diethyl ether and recovering the crystals precipitated from the reaction mixture.

25. A process for the preparation of 1-(4'-methoxy-2'-methyl-5'-tert-butyl-

phenyl)-1-phenyl-2-pyrrolidino-propan-1-ol as claimed in claim 23 which comprises adding α -pyrrolidino-propio-phenone to a Grignard solution of magnesium, 4-bromo-5-methyl-2-tert-butylanisole and 1,2-dibromoethane in diethyl ether and recovering the crystals precipitated from the reaction mixture.

26. A process for the preparation of 1-(2'-methoxy-3'-methyl-5'-tert-butylphenyl)-1-phenyl-2-piperidino-propan-1-ol as claimed in claim 23 which comprises adding α -piperidinopropiophenone to a Grignard solution of magnesium, 6-bromo-2-methyl-4-tert-butylanisole and 1,2-dibromoethane in diethyl ether and processing the liquid phase obtained from the reaction mixture.

27. A process for the preparation of 1-(4'-methoxy-3',5'-diisopropylphenyl)-1-(3'',4''-dimethoxyphenyl)-2-piperidino-propan-1-ol as claimed in claim 23 which comprises adding 1-(3',4'-dimethoxyphenyl)-2-piperidino-propan-1-one to a Grignard solution of magnesium, 4-bromo-2,6-diisopropylanisole and 1,2-dibromoethane on diethyl ether and processing the liquid phase obtained from the reaction mixture.

28. A process for the preparation of 1-(2'-methoxy-3'-methyl-5'-[3-methylpiper-3-yl]phenyl)-1-phenyl-2-pyrrolidino-propan-1-ol as claimed in claim 23 which comprises adding α -pyrrolidino-propio-phenone to a Grignard solution of magnesium, 2-methyl-4-(3-methyl-piper-3-yl)-6-bromoanisole, 1,2-dibromoethane and diethyl ether and processing the liquid phase obtained from the reaction mixture.

29. A process for the preparation of 1-(7',8'-dimethyl-chroman-6'-yl)-1-phenyl-2-piperidino-propan-1-ol as claimed in claim 23 which comprises adding α -piperidinopropiophenone in diethyl ether to a Grignard solution of magnesium, 6-bromo-7,8-dimethyl-chroman and 1,2-dibromoethane in diethyl ether and recovering the crystals precipitated from the reaction mixture.

30. A process for the preparation of 1-(4'-(methoxy-2',3',5',6'-tetramethylphenyl)-1-phenyl-2-piperidino-propan-1-ol as claimed in claim 23 which comprises adding α -piperidinopropiophenone to a Grignard solution of magnesium, 4-bromo-2,3,5,6-tetramethyl-anisole, 1,2-dibromoethane and diethyl ether and processing the liquid phase obtained from the reaction mixture.

31. A process for the preparation of 1-(4'-methoxy-3',5'-diisopropylphenyl)-1-(4''-methoxyphenyl)-2-piperidino-propan-1-ol as claimed in claim 23 which comprises adding p-methoxy- α -piperidino-propio-phenone to a Grignard solution of magnesium, 4-bromo-2,6-diisopropylanisole, 1,2-dibromoethane and diethyl ether



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and processing the liquid phase obtained from the reaction mixture.

32. A process for the preparation of 1-(4'-methoxy - 3',5' - diisopropylphenyl) - 1-(4'' - ethoxyphenyl) - 2 - piperidino - propan-1-ol as claimed in claim 23 which comprises adding to p-ethoxy- α -piperidino-propio-phenone to a Grignard solution of magnesium, 4 - bromo - 2,6 - diisopropylanisole, 1,2-dibromoethane and diethyl ether and processing the liquid phase obtained from the reaction mixture.

33. A process for the preparation of 1-(2'-methoxy - 5' - tert - butylphenyl) - 1-phenyl-2-piperidino-propan-1-ol as claimed in claim 23 which comprises adding α -piperidino-propio-phenone to a Grignard solution of magnesium, 2 - bromo - 4 - tert - butyl-anisole, 1,2-dibromoethane and diethyl ether and recovering the crystals precipitated from the reaction mixture.

34. A process for the preparation of 1-(4'-methoxy - 3',5' - diisopropylphenyl) - 1-(4'' - methoxy - 3'',5'' - dimethylphenyl) - 2-piperidino-propan-1-ol as claimed in claim 23 which comprises adding 1-(4'-methoxy-3',5'-dimethylphenyl)-2-piperidino-propan-1-one to a Grignard solution of magnesium, 4-bromo-2,6-diisopropyl-anisole, 1,2-dibromoethane and diethyl ether and recovering the crystals precipitated from the reaction mixture.

35. A process for the preparation of 1-(4'-ethoxy - 3',5' - diisopropylphenyl) - 1 - (4'' - methoxyphenyl) - 2 - piperidino - propan - 1-ol as claimed in claim 23 which comprises adding p - methoxy - α - piperidino-propio-phenone to a Grignard solution of magnesium, 4 - bromo - 2,6 - diisopropyl-phenetole, 1,2-dibromoethane and diethyl ether and processing the liquid phase obtained from the reaction mixture.

36. A process for the manufacture of 1-(3'-chloro - 6' - methoxy - 2' - methyl - 5' - isopropylphenyl) - 1 - phenyl - 2 - pyrrolidino-propan-1-ol as claimed in claim 23 which comprises adding α -pyrrolidino-propio-phenone to a Grignard solution of magnesium, 4-chloro-6-bromo-thymol methyl ether, 1,2-dibromoethane and diethyl ether and recovering the crystals precipitated from the reaction mixture.

37. A process for the preparation of 1-(4',5' - methylene - dioxy - 2' - allylphenyl) - 1 - (4'' - methoxyphenyl) - 2 - piperidino-propan-1-ol as claimed in claim 23 which comprises adding p-methoxy- α -piperidino-propio-phenone to a Grignard solution of magnesium, 2 - (2',3' - dibromopropyl) - 4,5 - methylenedioxy - bromobenzene, 1,2-dibromoethane and diethyl ether and recovering the crystals precipitated from the reaction mixture.

38. A process for the preparation of 1-(4'-ethoxy - 3',5' - diisopropylphenyl) - 1-(4'' - ethoxyphenyl) - 2 - piperidino - pro-

pan-1-ol as claimed in claim 23 which comprises adding p-ethoxy- α -piperidino-propio-phenone in diethyl ether to a Grignard solution of magnesium, 4-bromo-2,6-diisopropyl-phenetole, 1,2-bromoethane and diethyl ether and processing the liquid phase obtained from the reaction mixture.

39. A process for the preparation of 1-(2'-methoxy - 3' - methyl - 5' - tert - butylphenyl) - 1 - (2'',4'' - dimethoxyphenyl) - 2-piperidino-propan-1-ol as claimed in claim 23 which comprises adding 2,4-dimethoxy- α -piperidino-propio-phenone in diethyl ether to a Grignard solution of magnesium, 6-bromo-2 - methyl - 4 - tert - butyl anisole, 1,2 - dibromoethane and diethyl ether and processing the liquid phase obtained from the reaction mixture.

40. A process for the preparation of 1-(2'-methoxy - 3' - methyl - 5' - tert - butylphenyl) - 1 - (2'' (or 4'') - methoxy - 4'' (or 2'') - hydroxyphenyl) - 2 - piperidino - propan-1-ol as claimed in claim 23 which comprises adding 2 (or 4)-methoxy-4 (or 2)-hydroxy- α -piperidinopropio-phenone dissolved in diethyl ether to a Grignard solution of magnesium, 6 - bromo - 2 - methyl - 4-tert-butyl anisole, 1,2-dibromoethane and diethyl ether and processing the liquid phase obtained from the reaction mixture.

41. A process for the preparation of 1-(2'-methoxy - 3' - methyl - 5' - tert - butylphenyl) - 1 - (3'',4'' - dimethoxyphenyl) - 2-piperidino-propan-1-ol as claimed in claim 23, which comprises adding 3,4-dimethoxy- α -piperidino-propio-phenone dissolved in diethyl ether to a Grignard solution of magnesium, 2 - methyl - 6 - bromo - 4 - tert - butyl-anisole, 1,2-dibromoethane and diethyl ether, and processing the liquid phase obtained from the reaction mixture.

42. A process for the preparation of 1-(2'-methoxy - 5' - methylphenyl) - 1 - (4'' - benzyloxy - 3'',5'' - diisopropylphenyl) - 2-piperidino-propan-1-ol as claimed in claim 23 which comprises adding 4-benzyloxy-3,5-diisopropyl - α - piperidino - propio-phenone in diethyl ether to a Grignard solution of magnesium, 2 - bromo - 4 - methyl - anisole, 1,2-dibromoethane and diethyl ether and processing the liquid phase obtained from the reaction mixture.

43. A process for the preparation of 1-(3'-chloro - 6' - methoxy - 5' - methylphenyl) - 1 - (4'' - methoxy - 3'',5'' - dimethylphenyl) - 2 - (N - methyl - N - tert - butylamino)-propan-1-ol as claimed in claim 23, which comprises adding 4 - methoxy - 3,5 - dimethyl - α - (N - methyl - N - tert - butyl-amino)-propio-phenone in diethyl ether to a Grignard solution of magnesium 6-bromo-4-chloro - 2 - methylanisole, 1,2 - dibromoethane and diethyl ether and processing the liquid phase obtained from the reaction mixture.



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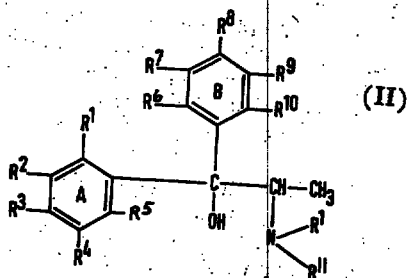
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44. A process as claimed in claim 23 substantially as hereinbefore described with reference to any one of the foregoing Examples.

5 45. A compound of Formula II as defined in claim 1 whenever prepared by a process as claimed in any one of claims 23 to 44.

10 46. A pharmaceutical composition which comprises as the active ingredient at least one α, α -diaryl- β -(tert-amino)-propanol of the general formula:—



wherein R', R'' and R¹ to R¹⁰ are as defined in claim 1 or a pharmaceutically acceptable

salt thereof, together with a pharmaceutically acceptable diluent or carrier.

47. A pharmaceutical composition as claimed in claim 46 wherein the active ingredient is a compound as claimed in any one of claims 2 to 22 or claim 45.

48. A pharmaceutical composition as claimed in claim 46 or claim 47 which is in the form of a solution suspension, emulsion, implant or suppository.

49. A pharmaceutical composition as claimed in claim 46 or claim 47 which is in the form of a tablet or dragee.

50. A method of treating a non-human mammal to increase the elimination of sodium and chloride via the kidneys, which method comprises administering to the animal a diuretically effective amount of a compound as claimed in any one of claims 1 to 22 or claim 45, or of a pharmaceutical composition as claimed in any one of claims 46 to 49.

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