

PATENT SPECIFICATION

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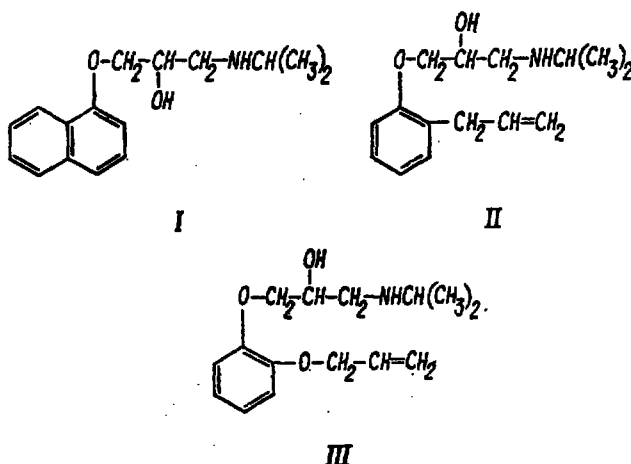


(54) PHENOXY-HYDROXYPROPYLAMINES AND THEIR PREPARATION

(71) We, AKTIEBOLAGET HASSLE, a Swedish Body Corporate of Karragatan 5, 431 33 Molndal, Sweden, 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 phenoxy-hydroxypropylamines and in particular to p-substituted phenoxy-hydroxypropylamines having valuable pharmacological properties, useful in the treatment of heart diseases. The invention also relates to methods for the preparation of the compounds and to pharmaceutical preparations, e.g. in dosage units, containing them:

β -receptor blocking agents such as propranolol (I), alprenolol (II) and oxprenolol (III)



have been shown to possess good therapeutic effects in the treatment of heart diseases and vascular diseases such as angina pectoris, hypertension, vasoregulatoric neurasthenia and certain forms of arrhythmia.

However, these compounds have the disadvantage that they block not only the β -receptors of the heart, which produces the therapeutic effect, but also the β -receptors in blood vessels and bronchi. This may lead to undesired side effects with patients having manifest or latent asthma. Blocking of the β -receptors in the bronchi may, in such cases, lead to bronchospasm and attacks of asthma; for this reason treatment with β -receptor-blocking substances such as the compounds I, II and III above is



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contra-indicated for asthma sufferers. The receptor blocking effect on blood vessels of these compounds means that adrenalin, which is released from the marrow of the suprarenal glands, has a pure pressor effect instead of the balanced pressor-depressor-effect as it does in untreated patients.

5 The compounds of the present invention are useful in the treatment of heart diseases while avoiding complications due to β -blocking in bronchi and blood vessels.

The present invention provides p-substituted phenoxy-hydroxypropylamine derivatives of the general formula:



IV

wherein R^1 is an isopropyl or tertiary butyl radical, A is a straight or branched alkylene group containing 1 to 4 carbon atoms, Z is a member of the group consisting of $-\text{OR}^2$, $-\text{SO}_2\text{R}^2$, $-\text{SOR}^2$, $-\text{SR}^2$, $-\text{NCOR}^2$, $-\text{NSO}_2\text{R}^2$ and $-\text{NCOOR}^2$

15 wherein R^2 is a straight or branched alkyl radical with 1 to 3 carbon atoms and R^3 is a hydrogen atom or a straight or branched alkyl radical with 1 to 3 carbon atoms and pharmaceutically acceptable, non-toxic acid addition salts thereof.

The invention is particularly concerned with compounds of Formula IV wherein A as a straight chain alkylene group containing 1-3 carbon atoms and Z is a OR^2 , SO_2R^2 , SOR^2 , SR^2 , NHCOR^2 or $\text{NH}\text{SO}_2\text{R}^2$ group.

20 Since the new compounds described above contain an asymmetric carbon atom, they exist in the form of optically active forms, which can be resolved into their optical antipodes by well known methods such as by using optically active acids such as tartaric acid, camphor-10-sulphonic acid and dibenzyl tartaric acid.

Examples of compounds according to the invention are:

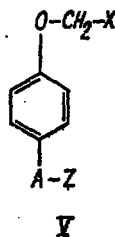
25 1-isopropylamino-3-[p-(β -methoxyethyl)-phenoxy]-propanol-2
 1-isopropylamino-3-[p-(β -acetamidoethyl)-phenoxy]-propanol-2
 1-isopropylamino-3-[p-(β -ethoxyethyl)-phenoxy]-propanol-2
 1-isopropylamino-3-[p-(ethoxymethyl)-phenoxy]-propanol-2
 1-isopropylamino-3-[p-(methylsulfonylmethyl)-phenoxy]-propanol-2
 30 1-isopropylamino-3-[p-(β -ethoxycarbonylamidoethyl)-phenoxy]-propanol-2
 1-isopropylamino-3-[p-(acetamidoethyl)-phenoxy]-propanol-2
 1-isopropylamino-3-[p-(β -methoxycarbonylamidoethyl)-phenoxy]-propanol-2
 1-isopropylamino-3-[p-(β -ethoxycarbonylamidoethyl)-phenoxy]-propanol-2
 1-isopropylamino-3-[p-(α -acetamidoethyl)-phenoxy]-propanol-2

35 The following compounds of the general formula IV are particularly preferred in the form of the racemate and in the form of an optically active isomer:

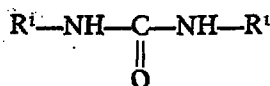
1-isopropylamino-3-[p-(β -methoxyethyl)-phenoxy]-propanol-2
 1-isopropylamino-3-[p-(β -acetamidoethyl)-phenoxy]-propanol-2

40 These p-substituted phenoxy-hydroxypropylamines of the formula IV may be prepared by

A) reacting a compound of the formula

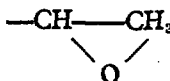


with a compound of the formula



to form a compound of the formula IV, in which formulae A, Z, R¹, R² and R³ have the meaning given above and X represents

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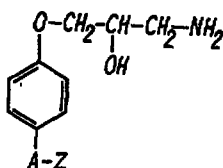
or $\text{---CHOH---CH}_2\text{---Hal}$, where Hal means a halogen atom, preferably chlorine,

B) reacting a compound of the formula V above with an amine of the formula $\text{H}_2\text{N---R}^1$ to form a compound of the formula IV, in which formulae A, Z, R¹, R², R³ and X have the same meaning as above.

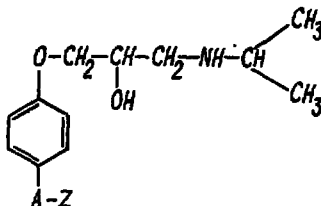
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C) alkylating a compound of the formula

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reductively by using hydrogen and acetone to form a compound of the formula

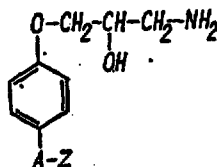


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in which formulae A, Z, R² and R³ have the same meaning as above,

D) alkylating a compound of the formula

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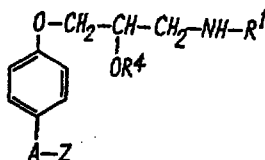


by reaction with a compound of the formula $\text{Hal---CH(CH}_3)_2$ to form a compound of the formula IV, in which formulae A, Z, R², R³ and Hal have the same meaning as above,

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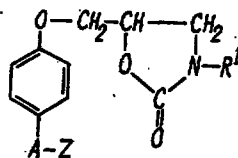
E) hydrolysis of a compound of the formula

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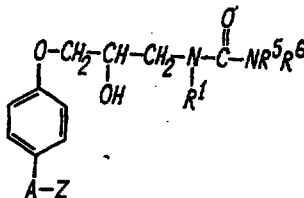
to form a compound of the formula IV, in which formulae A, Z, R¹, R² and R³ have the same meaning as above and R⁴ is a group, which can be removed hydrolytically, preferably an alkyl- or a tetrahydropyranyl group,

F) hydrolysis of a compound of the formula



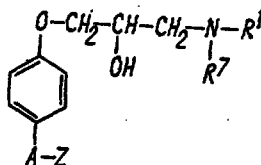
using strong alkali or strong acids to form a compound of the formula IV, in which formulae A, Z, R¹, R² and R³ have the same meaning as above,

G) hydrolysis or pyrolysis of a compound of the formula



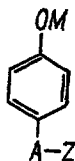
to form a compound of the formula IV, in which formulae A, Z, R¹, R² and R³ have the same meaning as above and R⁵ and R⁶ each represents a hydrogen atom, a lower alkyl- (C₁-C₄), aralkyl- or aryl group,

H) hydrolysis or hydrogenolysis of a compound of the formula

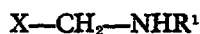


to form a compound of the formula IV, in which formulae A, Z, R¹, R² and R³ have the same meaning as above and R⁷ is an amino protecting group such as benzyl-, acetyl- or carbobenzyloxy group,

I) reacting a phenolate of the formula

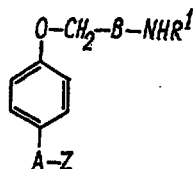


with a compound of the formula



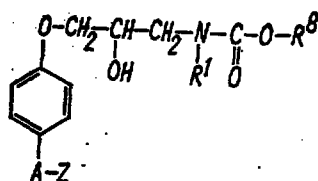
to form a compound of the formula IV, in which formulae A, Z, R¹, R², R³ and X have the same meaning as above and M as a cation, preferably an alkali metal cation, or reacting a phenolate of the above formula with a compound of the formula X-CH₂-NR¹R², in which formula R¹, X and R² are as defined above, and then hydrolysing or hydrogenolysing the product to form a compound of formula IV

J) reducing a compound of the formula



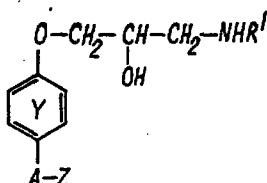
preferably by using a complex alkali metal hydride to form a compound of the formula IV, in which formulae A, Z, R¹, R² and R³ have the same meaning as above and B represents -CHOH-CO- (the C=O group being attached to the NHR¹ group) or -CO-CH₂ (the CH₂ group being attached to the NHR¹ group) or

K) hydrolysis of a compound of the formula



to form a compound of the formula IV, in which formulae A, Z, R¹, R² and R³ have the same meaning as above and R⁸ is a lower alkyl (C₁—C₄), aralkyl- or aryl group, preferably a phenyl group,

L) by hydrolysis of a compound of the formula



where A, Z, R¹, R² and R³ have the same meaning as above and where Y means that the benzene ring is substituted with 1—4 halogen atoms such as chlorine, bromine or iodine.,

whereafter, if desired, the racemate thus obtained is resolved into its optically active antipodes in manner *known per se*, and, when a pharmaceutically acceptable, non-toxic acid addition salt is desired, reacting the compound thus formed with a suitable acid.

The reaction A above is preferably performed in a high boiling, inert, organic solvent such as 1,2,3,4-tetrahydronaphthalene, decahydronaphthalene, benzonitrile, paraffin oil or chlorinated, aromatic compounds or in molten state at a temperature of 150—220°C, preferably 180—200°C.

In clinical practice the compounds of the present invention will normally be administered orally, rectally or by injection, in the form of pharmaceutical preparations comprising the active ingredient either as a free base or as a pharmaceutically acceptable non-toxic, acid addition salt, e.g., the hydrochloride, lactate, acetate and sulfamate, in association with a pharmaceutically acceptable carrier. Accordingly, terms relating to the novel compounds of this invention whether generically or specifically, are intended to include both the free amine base and the acid addition salts of the free base, unless the context in which such terms are used, e.g., in the specific examples would be inconsistent with the broad concept. The carrier may be a solid, semisolid or liquid diluent or capsule. These pharmaceutical preparations constitute a further aspect of this invention. Usually the active substance will constitute between 0.1 and 95 % by weight of the preparation, more specifically between 0.5 and 20 % or between 2 and 50 % by weight for preparations intended for injection and between 2 and 50 % by weight for preparations suitable for oral administration.

To produce pharmaceutical preparations containing a compound of the invention in the form of dosage units for oral application, the selected compound may be mixed with a solid pulverulent carrier, e.g., lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, or gelatin, and a lubricant such as magnesium stearate, calcium stearate and polyethylene glycol waxes, and then compressed to form tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, e.g., gum arabic, gelatin, talcum and titanium dioxide. Alternatively, the tablet can be coated with a lacquer dissolved in a readily volatile organic solvent or mixture of organic solvents. Dyestuffs may be added to these coatings in order to distinguish readily between tablets containing different active substances of different amounts of the active compound.

For the preparation of soft gelatin capsules (pearl-shaped closed capsules) consisting of gelatin and, for example, glycerol, or similar closed capsules, the active substance may be admixed with a vegetable oil. Hard gelatin capsules may contain granulates of the active substance in combination with solid, pulverulent carries such

as lactose, saccharose, sorbitol, mannitol, starches (e.g. potato starch, corn starch or amylopectin), cellulose derivatives or gelatin.

5 Dosage units for rectal application can be prepared in the form of suppositories comprising the active substance in admixture with a neutral fatty base, or gelatin rectal capsules comprising the active substance in admixture with vegetable oil or paraffin oil.

10 Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing from about 0.2 % to about 20 % by weight of the active substance herein described, the balance being sugar and a mixture of ethanol, water, glycerol, and propyleneglycol. Optionally such liquid preparations may contain coloring agents, flavoring agents, saccharine and carboxymethyl-cellulose as a thickening agent.

15 Solutions for parenteral applications by injection can be prepared as an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance preferably in a concentration of from about 0.5 % to about 10 % by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

The following Examples illustrate the invention.

Example 1

20 1,2-Epoxy-3-[p-(β -methoxyethyl)-phenyl]-propane (16.7 g) was dissolved in 50 ml isopropanol and mixed with 20 ml isopropylamine. The mixture was heated in an autoclave on boiling water-bath over night, whereafter it was evaporated and the residue dissolved in 2 N HCl. The solution was extracted first with ether and thereafter with methylene chloride. After evaporation of the methylene chloride phase, the hydrochloride of 1-isopropylamino-3-[p-(β -methoxyethyl)-phenoxy]-propanol-2 was obtained, which, after recrystallization from ethyl acetate, weighed 10.4 g. Melting point 83°C. Equiv. weight: found 304.0, calculated 303.8. The starting material 1,2-epoxy-3-[p-(β -methoxyethyl)-phenoxy]-propane was obtained from p-(β -methoxyethyl)-phenol, which was reacted with epichlorohydrin, whereafter the reaction product was distilled at 118—128°C at a pressure of 0.35 mm Hg.

Examples 2—9

According to the method described in Example 1 the following compounds were prepared as hydrochlorides:

Example 2

35 1-isopropylamino-3-[p-(β -ethoxyethyl)-phenoxy]-propanol-2; melting point 102°C. Equiv. weight: found 323.0, calculated 317.8.

Example 3

1-isopropylamino-3-(p-ethoxymethyl-phenoxy)-propanol-2; melting point 94°C. Equiv. weight: found 304.0, calculated 303.8.

Example 4

40 1-isopropylamino-3-[p-(N-ethyl- β -methoxycarbonylamidoethyl)-phenoxy]-propanol-2; an oil (the base). Equiv. weight (base): found 339.0, calculated 338.0.

Example 5

45 1-isopropylamino-3-[p-(methyl-sulfonylmethyl)phenoxy]-propanol-2; melting point 98°C. Equiv. weight: found 341.0, calculated 337.8.

Example 6

1-isopropylamino-3-[p-(β -acetamidoethyl)-phenoxy]-propanol-2; melting point 112°C (base). Equiv. weight (base): found 290.0, calculated 294.0.

Example 7

50 1-isopropylamino-3-[p-(β -methoxycarbonylamidoethyl)-phenoxy]-propanol-2. Melting point 106°C; Equiv. weight: found, 349, calc. 347.

Example 8

1-isopropylamino-3-[p-(β -ethoxycarbonylamidoethyl)-phenoxy]-propanol-2. Melting point 120°C; Eq. weight: found 364, calc. 361.

Example 9

1-isopropylamino-3-[p-(α -acetamidoethyl)-phenoxy]-propanol-2. Melting point (base) 112—14°C.

The parasubstituted phenylglycidyl ethers used in Examples 2—5 and 7—9 were obtained from the corresponding phenols and epichlorohydrin according to the process given in Example 1. These glycidylethers were used without isolation until the last step.

The phenyl-glycidylether used as starting material in Example 6 was prepared as follows:

1.8 g p-(β -acetamidoethyl)-phenol was dissolved in 25 ml acetone. To the solution was added 1.86 g epichlorohydrin and 2 g powdered K_2CO_3 . The mixture was boiled under reflux overnight while stirring. Thereafter the mixture was filtered and evaporated and the remainder, which was an oil, was used without purification.

Example 10 (Illustrating method B)

5 g of p-(β -methoxyethyl)-phenol, 100 ml of epichlorohydrin and 0.5 ml of piperidine were heated on a boiling water bath for 10 hours. The mixture was thereafter evaporated at reduced pressure and the residue was dissolved in chloroform and was thereupon extracted with hydrochloric acid. The chloroform phase was washed with water, dried and evaporated at reduced pressure. The residue consisting of 3-[p-(β -methoxyethyl)-phenoxy]-1-chloropropanol-2 was dissolved in 20 ml of isopropyl alcohol, to which was added 10 ml of isopropylamine and the mixture was heated in an autoclave on a water bath with boiling water for 10 hours. Thereafter the mixture was evaporated and the residue was shaken with a mixture of 2 N NaOH and ether. The ether phase was dried and evaporated at reduced pressure. The residue so obtained crystallized from petroleum ether and there was thus obtained 1-isopropylamino-3-[p-(β -methoxyethyl)-phenoxy]-propanol-2, which was converted to the hydrochloride in accordance with the process given in Example 1. The melting point of the hydrochloride was 83°C.

Example 11 (Illustrating method C)

A solution of 20 g of p-(β -methoxyethyl)-phenyl glycidyl ether in 200 ml of ethanol saturated with ammonia was heated in an autoclave on a water bath with boiling water for 4 hours. The mixture was thereupon evaporated and the residue was dissolved in ethyl acetate whereupon gaseous HCl was introduced into the solution. The hydrochloride of the amine, which then crystallized, was removed by filtration and 5 g was dissolved in 50 ml of ethanol and 10 ml of acetone. The solution was cooled to 0°C and 5 g of sodium borohydride was added in portions during 1 hour to form hydrogen *in situ*. Then 2.5 ml of acetone and 0.8 g of sodium borohydride were added and the solution was kept at room temperature for 1 hour whereupon 150 ml of H_2O was added. The mixture was extracted with ether whereupon the ether phase was dried over potassium carbonate and evaporated. The residue was transformed to the hydrochloride by dissolving the base in ethyl acetate and introducing gaseous HCl into the solution. In this way the hydrochloride of 1-isopropylamino-3-[p-(β -methoxyethyl)-phenoxy]-propanol-2 was obtained having a melting point of 83°C.

Example 12 (Illustrating method D)

A solution of 10 g of p-(β -ethoxyethyl)-phenyl glycidyl ether in 100 ml of ethanol was saturated with ammonia whereupon the mixture was heated upon a water bath containing boiling water for 4 hours. Thereafter the reaction mixture was evaporated and the residue dissolved in ethyl acetate. HCl in gaseous form was introduced causing the amine hydrochloride to crystallize. The crystals were removed by filtration and dissolved in 70 ml of ethanol whereupon 10 ml of isopropylbromide and 12 g of potassium carbonate were added. The mixture was heated in an autoclave at 120°C for 10 hours whereupon the ethanol was removed by evaporation. To the residue was added 100 ml of 2 N HCl and 100 ml of ether. The water phase was separated and made alkaline with 2 N NaOH and thereupon extracted with ethyl acetate. The ethyl acetate phase was dried by means of potassium carbonate whereupon gaseous HCl was introduced. This caused crystallization of the hydrochloride which was separated by filtration and recrystallized from methylethylketone. There was thus obtained the hydrochloride of 1-isopropylamino-3-[p-(β -ethoxyethyl)-phenoxy]-propanol-2 having a melting point of 102°C.

Example 13 (Illustrating method E)

A solution of 8 g of 3-[p-(β -ethoxyethyl)-phenoxy]-1-chloro-propanol-2 (prepared for instance according to method B) in 15 ml of 3,4-dihydropyran was mixed with a small amount of p-toluenesulphonic acid. This caused an increase of the temperature to 50°C and, after having been kept at this temperature for 30 minutes, the mixture was dissolved in 100 ml of ethanol whereupon 10 ml of isopropylamine was added. The reaction was heated in an autoclave for 10 hours on steam bath and was thereafter evaporated. The residue was dissolved in ethyl acetate to which was added oxalic acid and was thereupon diluted with ether. The crystallized oxalate was separated and recrystallized from ethanol/ether. To the oxalate was added 30 ml of 2 N HCl and the mixture was heated on water bath for 15 minutes. After cooling the mixture was made alkaline by addition of NaOH and the base was extracted with ether. The ether phase was dried and evaporated whereafter the residue was dissolved in ethyl acetate followed by introduction of gaseous HCl. The precipitate thus obtained was recrystallized from methylethylketone which gave the hydrochloride of 1-isopropylamino-3-[p-(β -ethoxyethyl)-phenoxy]-propanol-2 having a melting point of 103°C.

Example 14 (Illustrating method F)

5.5 g of 3-isopropyl-5-[p-(β -methoxyethyl)-phenoxy]methyl-oxazolidinone-2 was dissolved in 60 ml of ethanol to which was added a solution of 9 g of KOH in 15 ml of H₂O. The mixture was refluxed and then evaporated and the residue dissolved in 2 N HCl and extracted with ether. The water phase was made alkaline with NaOH and extracted with ether. After drying by means of potassium carbonate, gaseous HCl was introduced, causing the hydrochloride of 1-isopropylamino-3-[p-(β -methoxyethyl)-phenoxy]-propanol-2 to crystallize. The hydrochloride gave after recrystallization from methylethylketone, a melting point of 83°C.

Example 15 (Illustrating method A and G)

4.5 g of p-(β -ethoxyethyl)-phenyl glycidyl ether was dissolved in 50 ml of tetralin to which was added 5.7 g of N,N'-diisopropylurea and 20 g of lithium hydroxide whereupon the mixture was heated at 200° C. for 3 hours. The reaction mixture was, after cooling, diluted with 50 ml of ether and shaken with 100 ml of 2 N HCl. The water phase was extracted with ether and thereupon made alkaline by addition of NaOH and was finally shaken with ether. The ether phase was washed with water, dried and evaporated. The residue was dissolved in ethyl acetate and the hydrochloride precipitated by addition of a solution of gaseous HCl in ether. The hydrochloride of 1-isopropylamino-3-[p-(β -ethoxyethyl)-phenoxy]-propanol-2 with a melting point of 102°C was obtained after recrystallization from methylethylketone.

Example 16 (Illustrating method H and I)

0.92 g of Na was dissolved in 50 ml of alcohol and to the solution was added 6.1 g of p-(β -methoxyethyl)-phenol 9.6 g of 3-(N-benzyl-N-isopropylamino)-1-chloropropanol-2. The mixture was heated in an autoclave on steam bath overnight and was thereupon filtered and evaporated to dryness. To the residue was added 100 ml of 2 N HCl and the mixture was extracted with ether whereupon the water phase was made alkaline by addition of NaOH and thereupon shaken with ether. The ether phase was dried and evaporated and the residue obtained dissolved in 200 ml of alcohol and neutralized with concentrated HCl. To this solution was added 0.5 g of Pd/C catalyst and the reaction mixture was hydrogenated at atmospheric pressure until the calculated amount of H₂ had been consumed. After filtration, the reaction mixture was evaporated to dryness and the residue thereupon recrystallized from methylethylketone giving the hydrochloride of 1-isopropylamino-3-[p-(β -methoxyethyl)-phenoxy]-propanol-2 having a melting point of 83°C.

Example 17 (Illustrating method J)

15.2 g of p-(β -methoxyethyl)-phenol was dissolved in a solution of 4.6 g of Na in 100 ml of ethanol. To the solution was added 12.5 g of 2-hydroxy-3-chloropropionic acid and the mixture was refluxed for 3 hours. The mixture was thereupon evaporated and to the residue was added 100 ml of 2 N HCl and the resulting mixture was thereupon extracted with benzene. The benzene phase was shaken with sodium bicarbonate solution which was thereupon acidified by addition of HCl followed by an extraction with benzene. After evaporation 2-hydroxy-3-[p-(methoxy-

ethyl)-phenoxy]-propionic acid was obtained which was converted to the N-isopropylamide by dissolving the acid in tetrahydrofuran followed by an addition of isopropylamine and dicyclohexyldicarbodiimide and heating the reaction mixture at 40°C for 5 hours. To the solution, after filtering, was added 5 g of lithium aluminum hydride and the mixture was refluxed overnight. After the application of conventional separation methods, 1-isopropylamino-3-[p-(β-methoxyethyl)-phenoxy]-propanol-2 was obtained, which was converted to the hydrochloride of melting point 82°C.

Example 18 (Illustrating method K)

To 5 g of N-isopropyl-N-[3-[p-(β-methoxyethyl)-phenoxy]-2-hydroxypropyl] carbamic acid ethyl ester was added 25 ml of 2 N HCl and the mixture was heated on water bath for 2 hours. After cooling, the mixture was extracted with ether and the water phase was made alkaline by addition of NaOH, followed by an extraction with ether. After drying and evaporation and recrystallization from petroleum ether, 1-isopropylamino-3-[p-(β-methoxyethyl)-phenoxy]-propanol-2 was obtained having a melting point of 83°C hydrochloride).

Example 19 (Illustrating method L)

15.2 g of p-(β-methoxyethyl)-phenol was dissolved in 100 ml of carbon tetrachloride whereupon 16 g of Br₂ was added dropwise with simultaneous cooling of the reaction mixture. When the bromine had reacted, the mixture was shaken with water, dried and evaporated whereupon a residue consisting of a bromo-(p-(β-methoxyethyl)-phenol) was obtained. This product was reacted with epichlorohydrin for the formation of the corresponding chlorohydrin and was thereupon reacted with isopropylamine according to the process given in Example 10 illustrating method B which gave a 1-isopropylamino-3-[bromo-p-(β-methoxyethyl)-phenoxy]-propanol-2. This product was converted to the hydrochloride and dissolved in 200 ml of ethanol and thereupon hydrogenated in the presence of Pd/C-catalyst at atmospheric pressure. When the calculated amount of H₂ had been consumed, the reaction mixture was filtered and evaporated. The residue was dissolved in H₂O and made alkaline by addition of NaOH and thereupon extracted with ether. 1-isopropylamino-3-[p-(β-methoxyethyl)-phenoxy]-propanol-2 was obtained after drying and evaporating, and recrystallization from petroleum ether.

Example 20

A syrup containing 2% (weight per volume) of the active substance was produced from the following ingredients:

35	1-isopropylamino-3-(p-methoxyethyl-phenoxy)-propanol-2-HCl	2.0 g	35
	Saccharin	0.6 g	
	Sugar	30.0 g	
	Glycerol	5.0 g	
	Flavoring agent	0.1 g	
40	Ethanol 96%	10.0 ml	40
	Distilled water	to 100.0 ml	

The sugar, saccharin and the ether salt were dissolved in 60 grams of hot water. After cooling, the glycerol was added and a solution of the flavouring agent in ethanol was added. The mixture was then made up to a volume of 100 milliliters with water.

The active substance shown above may be replaced by other pharmaceutically acceptable acid addition salts.

Example 21

1-isopropylamino-3-(p-ethoxyethylphenoxy)-propanol-2 hydrochloride (250 g) was mixed with lactose (175.8 g), potato starch (169.7 g) and colloidal silica (32 g). The mixture was moistened with a 10 % gelatin solution and granulated through a 12 mesh sieve. After drying, potato starch (160 g), talc (50 g) and magnesium stearate (2.5 g) were mixed in and the resulting mixture was pressed into tablets (10,000) containing 25 milligrams of active substance which were suitable for use as tablets. The tablets were marked with break lines to enable a dose other than 25 milligrams or multiples thereof to be administered.

Example 22

5 A granulate was prepared from 1-isopropylamino-3-(p-ethoxymethylphenoxy)-propanol-2 hydrochloride (250 g), lactose (175.9 g) and an alcoholic solution of polyvinyl pyrrolidone (25 g). After drying, the granulate was mixed with talc (25 g), potato starch (40 g) and magnesium stearate (2.50 g) and pressed into 10,000 biconvex tablets. These tablets were first coated with a 10 % alcoholic shellac solution and then with a water solution containing saccharose (45 %), gum arabic (5 %), gelatin (4 %) and dyestuff (0.2 %). Talc and sugar powder were used as dusting powders after the first 15 applications. The coating was then finished with a 66 % sugar syrup and polished with a 10 % carnauba wax solution in carbon tetrachloride.

Example 23

15 1-isopropylamino-3-(p-methoxyethylphenoxy)-propanol-2 hydrochloride (1 g), sodium chloride (0.8 g) and ascorbic acid (0.1 g) were dissolved in sufficient distilled water to make 100 milliliters of solution. This solution, each milliliter of which contained 10 milligrams of the active substance, was used to fill ampoules which were sterilized by heating for 20 minutes at 120°C.

Pharmacological evaluation

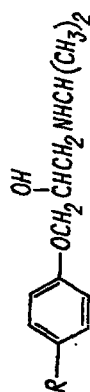
20 The compounds prepared according to Examples 1—19 were evaluated for intrinsic activity and blocking effect on heart rate and for peripheral vasodilator response to isoprenaline in the cat. The acute LD₅₀ in mice was evaluated. Alprenolol was used as a reference substance.

25 Cats weighing between 1.8 and 2.8 kg were anaesthetized with 30 mg/kg pentobarbital sodium i.p. The cats had been pretreated with reserpine, 5 mg/kg i.m. about 18 hours before the start of the experiment. Bilateral vagotomy was performed before the start of the experiment.

30 The heart rate was recorded on an Offner cardi tachometer triggered by the EKG-complex. Mean intraarterial blood pressure was recorded from a carotid artery. The peripheral resistance was measured in one of the legs of the cat in the following way: The femoral artery was opened in the inguinal region and the leg was perfused by blood delivered through a sigma motor pump at constant rate. The flow resistance (the pressure) was recorded via a strain gauge transducer connected to the catheter distally to the pump. The paw was excluded from the circulation by a tight ligature around the ankle. Intravenously injected isoprenaline increased the heart rate and reduced the perfusion pressure. An isoprenaline dose giving 70—80 % of the maximal chronotropic response was determined. This dose (usually 0.1 µg/kg) was then repeated with 20 minute intervals. Ten minutes before each isoprenaline injection, the tested substances were administered intravenously for two minutes, starting with a dose of 0.01 mg/kg and increasing each subsequent dose fourfold. The intrinsic effects of the test substances were determined. The dose producing 50% blockade of the isoprenaline responses were evaluated from the plotted log dose per cent blockade diagrams.

TABLE

Intrinsic stimulating activity on heart rate in cats, betablocking activity on heart rate and peripheral vascular resistance in cat; LD₅₀ after i.p. administration in mice.



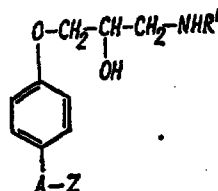
Compound	Reserpinized cat			Mouse	
	Intrinsic activity % of isoprenaline heart rate response	β-blockade Heart rate ED ₅₀ mg/kg	β-blockade Peripheral vascular resistance ED ₅₀ mg/kg	LD ₅₀ i.p. mg/kg	
R					
o-allyl(alprenolol)	20	0.1	0.5	100	
CH ₃ OCH ₂ CH ₂ —(H 93/26)	0	0.4	3	200	
C ₂ H ₅ OCH ₂ —(H 87/31)	0	0.4	6	175	
C ₂ H ₅ OCH ₂ CH ₂ —(H 93/47)	0	0.3	4	150	
CH ₃ CONHCH ₂ CH ₂ —(H 95/22)	0	0.4	20	>200	
CH ₃ OC—NHCH ₂ CH ₂ — O (H 104/08)	0	0.4	19	125	
C ₂ H ₅ OC—NHCH ₂ CH ₂ — O (H 93/93)	0	0.3	25	200	
CH ₃ CONHCH— CH ₃ (H 95/36)	0	0.2	5	300	

As is evident from the Table the eight test substances were 2—10 times less active than alprenolol as regards blockage of the β -receptors of the heart. The peripheral vascular β -blocking activity for the eight test substances was 60—500 times lower than the activity of alprenolol.

The results demonstrate that the eight test substances developed a relatively stronger blockage of the β -receptors of the heart than of the receptors in smooth muscles. Due to their cardioselectivity the test substances may be expected to give therapeutic effect in heart diseases without developing complications due to β -blockage in bronchi and blood vessels.

WHAT WE CLAIM IS:—

1. A compound of the formula



IV

wherein R^1 is an isopropyl or tertiary butyl radical, A is a straight or branched alkylene group containing 1 to 4 carbon atoms, Z is a $-\text{OR}^2$, $-\text{SO}_2\text{R}^2$, $-\text{SOR}^2$, $-\text{SR}^2$, $-\text{NCOR}^2$, $-\text{NSO}_2\text{R}^2$ and $-\text{NCOOR}^2$ radical wherein R^2 is a straight or branched

alkyl radical with 1 to 3 carbon atoms and R^3 is a hydrogen atom or a straight or branched alkyl radical and pharmaceutically acceptable, non-toxic acid addition salts thereof.

2. A compound according to claim 1 in racemic form and pharmaceutically acceptable, non-toxic acid addition salts thereof.

3. A compound according to claim 1 in form of the optically active levo-rotatory isomer and pharmaceutically acceptable, non-toxic acid addition salts thereof.

4. A compound according to claim 1 in form of the optically active, dextro-rotatory isomer and pharmaceutically acceptable, non-toxic acid addition salts thereof.

5. A compound according to any one of the preceding claims wherein A is a straight chain alkylene group containing 1—3 carbon atoms and Z is an OR^2 , SO_2R^2 , SOR^2 , SR^2 , NHCOR^2 or NHSO_2R^2 radical where R^2 is as defined in claim 1.

6. $(\pm)$ -1-isopropylamino-3-[p-(β -methoxyethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

7. $(-)$ -1-isopropylamino-3-[p-(β -methoxyethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid additions salts thereof.

8. $(+)$ -1-isopropylamino-3-[p-(β -methoxyethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

9. $(\pm)$ -1-isopropylamino-3-[p-(β -acetamidoethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

10. $(-)$ -1-isopropylamino-3-[p-(β -acetamidoethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

11. $(+)$ -1-isopropylamino-3-[p-(β -acetamidoethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

12. $(\pm)$ -1-isopropylamino-3-[p-(β -ethoxyethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

13. $(-)$ -1-isopropylamino-3-[p-(β -ethoxyethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

14. $(+)$ -1-isopropylamino-3-[p-(β -ethoxyethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

15. $(\pm)$ -1-isopropylamino-3-([p-(ethoxymethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

16. $(-)$ -1-isopropylamino-3-[p-(ethoxymethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

17. $(+)$ -1-isopropylamino-3-[p-(ethoxymethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

18. ($\pm$)-1-isopropylamino-3-[p-(methyl-sulfonylmethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

19. (-)-1-isopropylamino-3-[p-(methyl-sulfonylmethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

20. (+)-1-isopropylamino-3-[p-(methyl-sulfonylmethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

21. ($\pm$)-1-isopropylamino-3-[p-(β -methylsulfonylamidoethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

22. (-)-1-isopropylamino-3-[p-(β -methyl sulfonylamidoethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

23. (+)-1-isopropylamino-3-[p-(β -methylsulfonylamidoethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

24. ($\pm$)-1-isopropylamino-3-[p-(acetamidomethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

25. (-)-1-isopropylamino-3-[p-(acetamidomethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

26. (+)-1-isopropylamino-3-[p-(acetamidomethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

27. ($\pm$)-1-isopropylamino-3-[p-(β -methoxycarbonylamidoethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

28. (-)-1-isopropylamino-3-[p-(β -methoxycarbonylamidoethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

29. (+)-1-isopropylamino-3-[p-(β -methoxycarbonylamidoethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

30. ($\pm$)-1-isopropylamino-3-[p-(β -ethoxycarbonylamidoethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

31. (-)-1-isopropylamino-3-[p-(β -ethoxycarbonylamidoethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

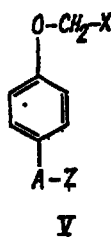
32. (+)-1-isopropylamino-3-[p-(β -ethoxycarbonylamidoethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

33. ($\pm$)-1-isopropylamino-3-[p-(α -acetamidoethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

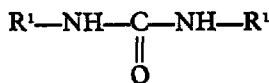
34. (-)-1-isopropylamino-3-[p-(α -acetamidoethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

35. (+)-1-isopropylamino-3-[p-(α -acetamidoethyl)-phenoxy]-propanol-2 and pharmaceutically acceptable, non-toxic acid addition salts thereof.

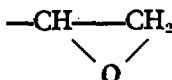
36. A process for the preparation of a compound as defined in claim 1 which comprises reacting a compound of the formula



40 with a compound of the formula

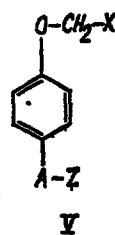


where A, Z, R¹, R² and R³ are as defined in claim 1 and X represents



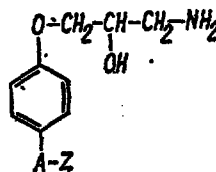
or —CHOH—CH₂—Hal, (Hal is a halogen atom).

37. A process for the preparation of a compound as defined in claim 1 which comprises reacting a compound of the formula V



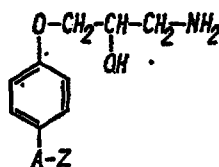
5 with an amine of the formula H_2N-R^1 where A, Z, R^1 , R^2 and R^3 are as defined in claim 1 and X is as defined in claim 36. 5

38. A process for the preparation of a compound as defined in claim 1 where R^1 is isopropyl which comprises reductively alkylating a compound of the formula



10 using hydrogen and acetone where A, Z, R^2 and R^3 are as defined in claim 1. 10

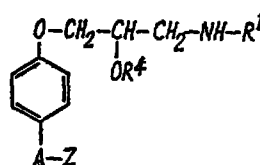
39. A process for the preparation of a compound as defined in claim 1 where R^1 is isopropyl which comprises alkylating a compound of the formula



15 by reaction with a compound of the formula $Hal-CH(CH_3)_2$ where A, Z, R^2 and R^3 are as defined in claim 1 and Hal is a halogen atom. 15

40. A process according to claim 36, 37 or 39 wherein Hal is a chlorine atom.

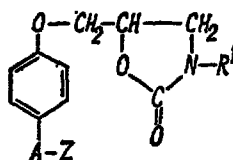
41. A process for the preparation of a compound as defined in claim 1 which comprises hydrolysing a compound of the formula



20 where A, Z, R^1 , R^2 , and R^3 are as defined in claim 1 and R^4 is a group, which can be removed hydrolytically. 20

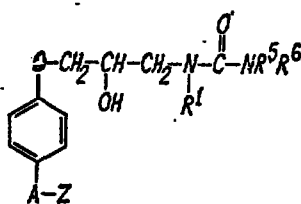
42. A process according to claim 41 wherein R^4 is an alkyl or tetrahydropyranyl group.

43. A process for the preparation of a compound as defined in claim 1 which comprises hydrolysing a compound of the formula



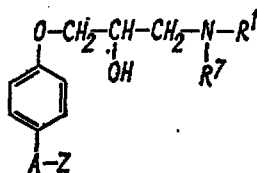
25 using strong alkali or strong acid where A, Z, R^1 , R^2 and R^3 are as defined in claim 1. 25

44. A process for the preparation of a compound as defined in claim 1 which comprises hydrolysing or pyrolysing a compound of the formula



where A, Z, R¹, R² and R³ are as defined in claim 1 and R⁵ and R⁶ each represent a hydrogen atom, or a lower alkyl- (C₁-C₄), aralkyl- or aryl group.

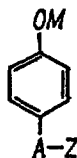
45. A process for the preparation of a compound as defined in claim 1 which comprises hydrolysing or hydrogenolysing a compound of the formula



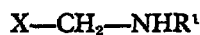
where A, Z, R¹, R² and R³ are as defined in claim 1 and R⁷ is an amino protecting group.

46. A process according to claim 45 wherein R⁷ is a benzyl, acetyl or carbobenzoxy group.

47. A process for the preparation of a compound as defined in claim 1 which comprises reacting a phenolate of the formula



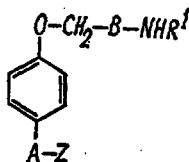
with a compound of the formula



where A, Z, R¹, R² and R³ are as defined in claim 1, X is as defined in claim 36, and M is a cation, or reacting a phenolate of the above formula with a compound of the formula X-CH₂NR¹R², in which formula R¹ and X are as defined in claim 1 and 36 respectively and R² is as defined in claim 45 or 46, and then hydrolysing or hydrogenolysing the product to form a compound of formula IV in claim 1.

48. A process according to claim 47 wherein M is an alkali metal cation.

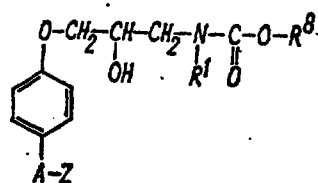
49. A process for the preparation of a compound as defined in claim 1 which comprises reducing a compound of the formula



where A, Z, R¹, R², and R³ are defined in claim 1 and B represents —CHOH—CO— (the C=O group being attached to the NHR¹ group) or —CO—CH₂— (the CH₂ group being attached to the NHR¹ group).

50. A process according to claim 49 wherein the reduction is performed with a complex alkali metal hydride.

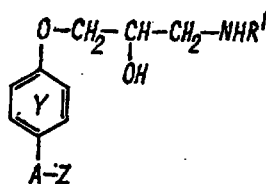
51. A process for the preparation of a compound as defined in claim 1 which comprises hydrolysing a compound of the formula



where A, Z, R¹, R² and R are as defined in claim 1 and R⁸ is a lower alkyl- (C₁—C₄), aralkyl- or aryl group.

52. A process according to claim 51 wherein the aryl group represented by R⁸ is a phenyl group.

53. A process for the preparation of a compound as defined in claim 1 which comprises hydrogenolysing a compound of the formula



where A, Z, R¹, R² and R³ are as defined in claim 1 and Y means that the benzene ring is substituted with 1—4 halogen atoms.

54. A process according to claim 53 wherein the halogen is chlorine, bromine or iodine.

55. A process according to any one of claims 36—54 wherein the resulting racemate is resolved into an optically active antipode.

56. A process according to any one of claims 36—55 wherein the free base is reacted with an acid to give a pharmaceutically acceptable non-toxic acid addition salt.

57. A process according to any one of claims 36—56 wherein A and Z are as defined in claim 5.

58. A process for the production of a compound as defined in claim 1 according to any one of claims 36—57, substantially as hereinbefore described.

59. A compound as defined in claim 1 obtained by a process according to any one of claims 36—58.

60. A pharmaceutical preparation which comprises 0.1 to 95 per cent by weight of a compound according to any one of claims 1—35 or 59, together with a pharmaceutically acceptable carrier.

61. An injectable pharmaceutical preparation which comprises 2 to 50 per cent by weight of a compound according to any one of claims 1—35 or 59 together with a pharmaceutically acceptable injectable carrier.

62. A pharmaceutical preparation for parenteral application which comprises an aqueous solution containing a water-soluble salt of a compound according to any one of claims 1—35 or 59 in an amount of 0.5 to 10 per cent by weight.

63. A pharmaceutical preparation for oral application containing 2 to 50 per cent by weight of a compound according to any one of claims 1—35 or 59 in combination with a solid, pharmaceutically acceptable diluent.

64. A preparation according to any one of claims 60—63 wherein A and Z are as defined in claim 5.

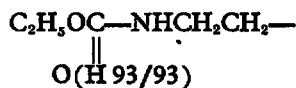
65. A pharmaceutical preparation according to any one of claims 60—64 substantially as hereinbefore described.

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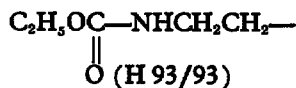
ERRATA

SPECIFICATION No. 1,308,106

Page 2, line 18, *for as read is*
Page 2, line 23, *for dibenzyl read dibenzoyl*
Page 2, line 31, *for acetamidoethyl read*
acetamidomethyl
Page 4, line 20, *for as (second occurrence)*
read is
Page 5, line 6, *for hydrolysis read hydrogenolysis*
Page 5, line 49, *for carries read carriers*
Page 7, line 30, *for p(-βmethoxyethyl) read*
p-(β-methoxyethyl)
Page 7, line 35, *for ethanol read methanol*
Page 9, line 20, *for -(p- read -p-*
Page 11, Table, Column 4, line 1, *for 0.5*
read 0.05
Page 11, Table, Column 1, line 7, *for*



read



Page 12, line 13, *for isoproyl read isopropyl*
Page 12, line 15, *for and read or*
Page 12, lines 35, 37 and 39, *for acceptable*
read acceptable
Page 12, line 46, *for -(lp- read -lp-*
Page 13, lines 10 and 12, *for addition read*
addition

THE PATENT OFFICE
28th July, 1975