

PATENT SPECIFICATION

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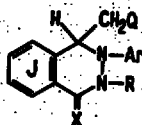
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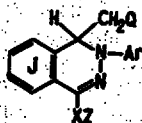


(54) SUBSTITUTED PHTHALAZINES AND THEIR USE AS THERAPEUTIC AGENTS

(71) We, THE BOOTS COMPANY LIMITED, a British Company, of 1 Thane Road West, Nottingham, England, 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:—
 This invention relates to novel compounds having therapeutic properties and to therapeutic compositions containing such compounds.
 The present invention provides compounds of formula I



or their enol or enthiol forms of formula Ia

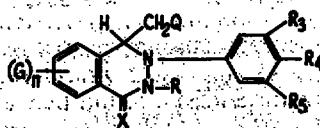


in which Q is COOH, CH₂OH or COOR_e, wherein R_e is an ester forming group; X is oxygen or sulphur; R is hydrogen or alkyl; Z is hydrogen or acyl; Ar is an aryl group and the ring J is substituted, or pharmaceutically acceptable salts with inorganic and organic bases of those compounds which are acids. Ar is unsubstituted in the positions ortho to the point of attachment to the phthalazine ring.

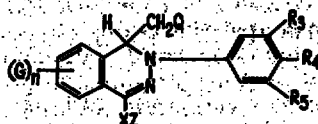
The ring J is preferably substituted by (G)_n, as defined below.

The compounds of the invention have valuable diuretic and saluretic properties in mammals. Accordingly, the invention also provides a method of inducing diuresis and saluresis in mammals which comprises administering to the mammal a pharmaceutically acceptable and effective amount of a compound described above. The invention still further provides a therapeutic composition comprising a compound of the invention in admixture with a pharmaceutically acceptable diluent or carrier.

Preferred compounds are those of formula II



or their enol or enthiol forms of formula IIa



in which Q, X, R and Z are as previously defined; n is 1 to 4; each G may be the same or different and is selected from fluorine; chlorine; bromine; iodine; nitro; amino; substituted amino, e.g. dialkylamino and especially dimethylamino; cyano; alkyl, e.g. of 1 to 4 carbon atoms and especially methyl, ethyl and isopropyl; substituted alkyl, e.g. haloalkyl, especially trifluoromethyl; alkoxy, e.g. of 1 to 4 carbon atoms and especially methoxy; substituted alkoxy, e.g. aralkoxy, especially benzyloxy; alkylthio, e.g. of 1 to 4 carbon atoms and especially methylthio; alkylsulphonyl, e.g. mesyl; alkylsulphinyl, e.g. methylsulphinyl; hydroxy; aryl, e.g. phenyl; and aroyl, e.g. benzoyl and R₃, R₄, and R₅ may be the same or different and are selected from hydrogen; fluorine; chlorine; bromine; iodine; nitro; nitroso; cyano; isocyano; amino; substituted amino e.g. alkylamino, dialkylamino, arylamino, acylamino, hydroxyamino, arylidenamino, alkylidenamino, ureido, carbazoylamino, hydrazino, thioureido, thiocarbazoylamino, alkylsulphinylamino, alkoxycarbonylamino, sulphonamoylamino and sulphonamido, e.g. alkyl-, substituted alkyl- and arylsulphonamido; alkyl, e.g. of 1 to 7 carbons and especially methyl, ethyl, propyl, isopropyl and t-butyl; substituted alkyl, e.g. haloalkyl, especially trifluoromethyl, aralkyl, e.g. benzyl, hydroxyalkyl, e.g. hydroxypropyl and alkoxyalkyl, e.g. methoxymethyl; cycloalkyl, e.g. cyclohexyl and substituted cycloalkyl; alkenyl e.g. allyl; aryl e.g. phenyl and substituted phenyl e.g. tolyl, alkoxyphenyl and halophenyl; cycloalkenyl, e.g. cyclohexenyl; alkoxy, e.g. of 1 to 4 carbons and especially methoxy, ethoxy, n-propoxy, isopropoxy and butoxy; substituted alkoxy, e.g. dialkylaminoalkoxy and aralkoxy, alkenyloxy, e.g. allyloxy and butenyloxy; cycloalkyloxy, e.g. cyclohexyloxy; cycloalkenyloxy, e.g. cyclohexenyloxy; acyloxy, e.g. acetoxy; alkylthio e.g. of 1 to 4 carbons and especially methylthio, ethylthio and propylthio; substituted alkylthio e.g. haloalkylthio, especially trifluoromethylthio, and aralkylthio; alkenylthio; cycloalkylthio; cycloalkenylthio; arylthio, e.g. phenylthio; alkylsulphonyl, e.g. mesyl; alkylsulphinyl, e.g. methylsulphinyl; acyl e.g. acetyl and propionyl; substituted acyl, especially haloacyl, e.g. trifluoroacetyl; aroyl, e.g. benzoyl; heteroaroyl, e.g. 2-thenoyl; hydroxy; mercapto; carbamoyl; thiocarbamoyl; sulphonamoyl; substituted sulphonamoyl, e.g. dialkylsulphonamoyl, especially dimethylsulphonamoyl and diethylsulphonamoyl; substituted and unsubstituted heterocyclic rings, e.g. 2-, 3- and 4-pyridyl, piperidino, morpholino, thiamorpholino, pyrrolin-1-yl, pyrrolidin-1-yl, 1-pyrrolyl, 2-thienyl, 2-thiazolyl, 2-oxopiperidino, 5-oxopyrazolidinyl, optionally, N-alkylated, and 2-oxopyrrolidin-1-yl. R₃ and R₄ may also together form a portion of a carbocyclic or heterocyclic ring fused to the benzene ring, which rings may be substituted, e.g. with one or more lower alkyl groups.

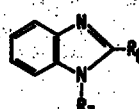
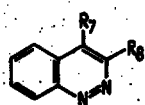
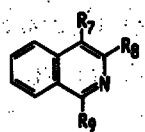
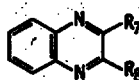
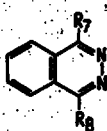
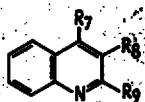
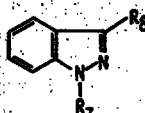
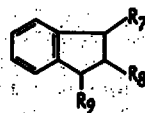
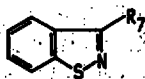
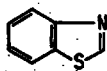
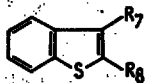
When G, R₃, R₄ or R₅ is substituted amino, the nitrogen of the amino group may be mono or disubstituted, with at least one of the substituents preferably being an alkyl, e.g. methyl, ethyl or isopropyl, or an alkoxy group, e.g. methoxy. Where the substituent on the substituted amino group is itself an amino group or is one containing further amino groups, e.g. ureido, these further amino groups may also be mono- or di-substituted, usually alkyl-, e.g. methyl-, substituted.

Examples of substituted amino groups include methylamino, ethylamino, dimethylamino, diethylamino, methylethylamino, trimethylammonio, anilino, benzylamino, N-methylformamido, N-methylacetamido, methanesulphonamido, N-methylmethanesulphonamido, N-methyl-p-toluenesulphonamido and N-acetyl-N', N'-dimethylhydrazino.

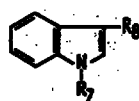
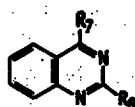
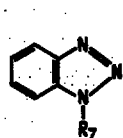
Examples of fused ring systems include the following. Unless otherwise

shown, these are attached to the 2-nitrogen of the phthalazine ring at either the 5 or the 6 position (in the case of 9-membered bicyclic ring systems and usually the 5 position) or at the 6 or the 7 position (in the case of the 10-membered bicyclic ring systems). The first four of these systems are particularly preferred.

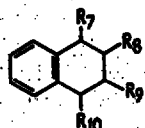
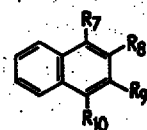
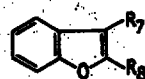
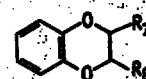
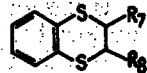
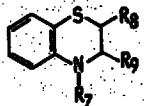
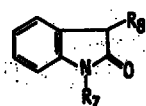
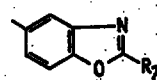
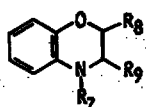
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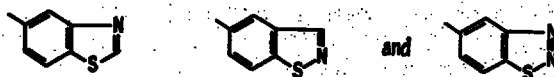


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*R*₁, *R*₂, *R*₃ and *R*₁₀ are the same or different and are hydrogen or alkyl of one to 4 carbon atoms e.g. methyl.

Especially preferred systems are the following:



*R*₁ is preferably hydrogen. *R*₂ is preferably other than hydrogen. *R* may be alkyl of, for example 1 to 7 carbon atoms, preferably 1 to 3 carbon atoms and especially methyl or ethyl. It is generally preferred however that *R* is hydrogen except when one or more of *R*₁, *R*₂ and *R*₃ is a substituted or unsubstituted amino group. *Q* is usually COOH, but when it is COOR₄, *R*₄ is preferably an alkyl group, e.g. methyl or ethyl, although other ester-forming groups, for example alkyloxyalkyl, acyloxyalkyl, e.g. pivaloyloxymethyl, and 6-indanyl may be suitable. *X* is preferably oxygen. Preferably, *n* is 1 or 2, and most preferably 1, in which case *G* is preferably in the 7-position.

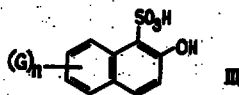
Particularly preferred groups which *G* may include methyl, ethyl and methoxy, as well as isopropyl, fluorine, chlorine and bromine.

A particularly preferred group of compounds are those in which *R*₁ is hydrogen, *n* is 1 and *G* is in the 7-position, *Q* is carboxy, *X* is oxygen, *R*₂ is hydrogen and *R*₃ is other than hydrogen or *R*₂ and *R*₃ together form a portion of a heterocyclic ring fused to the benzene ring, as well as salts thereof.

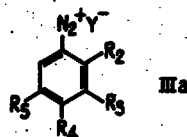
Especially preferred of this group of compounds are those in which *G* is chlorine, fluorine, methyl, ethyl, isopropyl or methoxy and when *R* (or *Z*) is hydrogen, *R*₁ is nitro, trifluoromethyl, methylthio, chloro or bromo or *R*₂ and *R*₃ together with the benzene ring to which they are attached are benzothiazol-5-yl, 1,2,3-benzothiadiazol-5-yl or 1,2-benzisothiazol-5-yl and when *R* is methyl, *R*₃ is *N,N*-dimethylamino.

The preferred compounds of the invention may be prepared by a process which comprises the steps of

(a) reacting a 2-naphthol-1-sulphonic acid of formula III



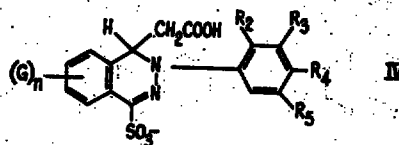
or a salt thereof in which *G* and *n* are as previously defined with a compound of formula IIIa



in which *R*₁, *R*₂ and *R*₃ are as previously defined, *R*₂ is hydrogen, iodine, bromine or chlorine and *Y* is the anion of a mineral acid.

(b) treating the product from (a) with a mild base,

(c) treating the product from (b) with an alkali metal hydroxide, followed by acidification to give a compound of formula IV,



(d) if desired, modifying at least one of the groups *G*, *R*₁, *R*₂ or *R*₃ and/or, if *R*₂ is iodine, bromine or chlorine, converting it to hydrogen, and/or converting the 1-acetic acid group to a hydroxyethyl group,

(e) treating the product from (c) or (d) with an aqueous acid or an alcoholic acid to give a compound of formula II in which *R* is hydrogen and *X* is oxygen,

(f) in the case when R_2 is iodine, bromine or chlorine, converting it to hydrogen,

(g) if desired, modifying at least one of the groups Q, X, Z, G, R, R_3 , R_4 or R_5 in the product obtained from (e) or (f), and

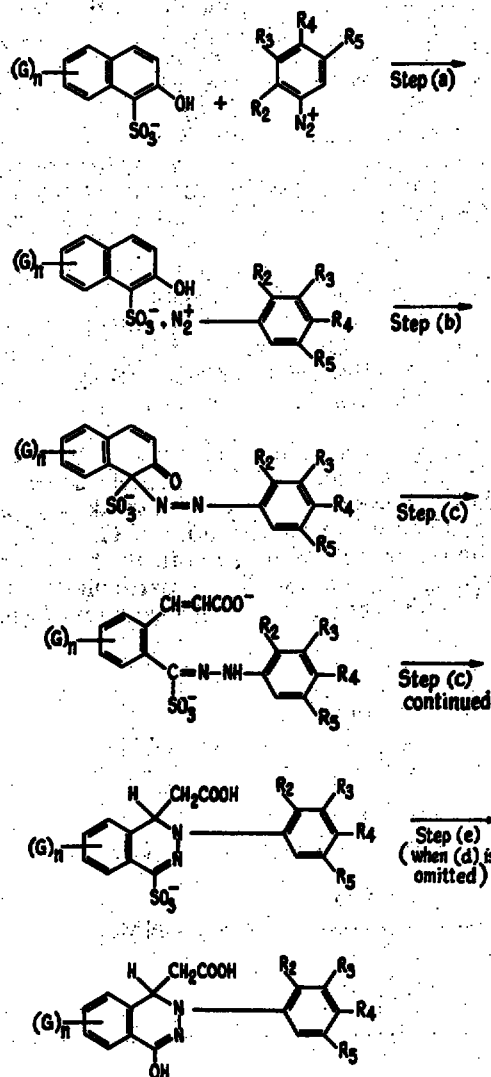
(h) if desired, forming a pharmaceutically acceptable salt with an inorganic or organic base of any compound which is an acid.

Steps (e) to (h) need not always be carried out in the order given. Thus, for example where the R_2 group is halogen it may, in some cases, be converted to hydrogen after modification of one or more of the groups G, R_3 , R_4 , R_5 or Q, or even simultaneously, when, for instance, such a modification includes a hydrogenation step. Similarly, for example, it may be desirable to carry out steps (d) and (e) simultaneously; for instance conversion of the 1-acetic acid group to a hydroxyethyl group may be carried out at the same time as the hydrolysis of the 4-sulphonate group.

It will also be appreciated that it is not necessary to isolate the products from one step before proceeding with the next step.

The compounds of formula III and their salts are novel and may be prepared by sulphonating the substituted 2-naphthol, e.g. by treatment with concentrated sulphuric acid, usually at low temperature, preferably -10 to $+10^\circ\text{C}$. The sulphonate salts may then be obtained by treating the sulphonic acid so obtained with an inorganic salt, e.g. sodium chloride.

Without wishing to be held to any theory we believe that the reaction for preparing the compounds of formula II proceeds by the following sequence:



Step (a) is generally carried out at a temperature below 60°C., preferably from -20 to +50°C., e.g. -10 to +10°C. The salt is preferably an alkali metal salt, e.g. the sodium salt and Y is preferably Cl.

Step (b) is generally carried out at a temperature of from -20 to +20°C., e.g. -10 to +10°C. The mild base is generally an alkali metal carbonate or ammonium carbonate and is preferably sodium carbonate. The period of the reaction mainly depends on the nature of the substituents in the compounds of formula III. Those compounds in which at least one of R₁, R₂, R₃, R₄ or R₅ is an electron withdrawing substituent, e.g. halogen and trifluoromethyl, generally only require a short reaction time, e.g. 1 to 30 minutes. These compounds in which at least one of R₁, R₂, R₃, R₄ or R₅ is an electron donating substituent, e.g. alkyl, generally require a longer reaction time, e.g. 1 to 24, preferably 1 to 6 hours.

Step (c) is generally carried out at a temperature of from -20 to +50°C., e.g. -5 to +30°C. The alkali metal hydroxide is generally sodium hydroxide. The period of reaction is generally between 1 and 24 hours.

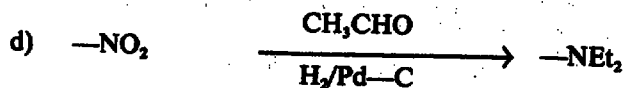
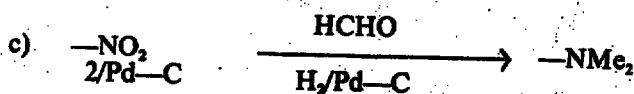
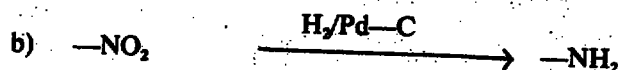
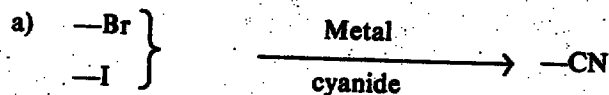
Step (e) is generally carried out at a temperature for example, of from 20 to 200°C., preferably 50 to 120°C., and if desired, under reflux. The acid is usually a mineral acid, for example hydrochloric acid. The time of reaction is usually at least 1/2 an hour e.g. 1 to 6 hours. When the acid is used in conjunction with an alcohol, the acid is usually anhydrous e.g. hydrochloric acid gas, which is dissolved in the alcohol e.g. methanol or ethanol. The product obtained is then one in which Q is COOR.

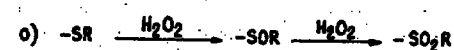
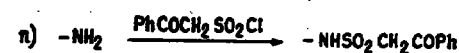
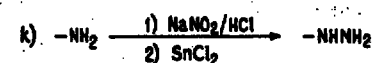
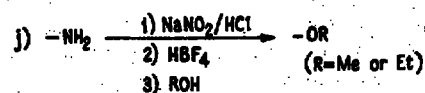
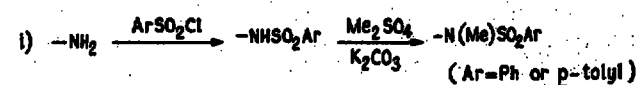
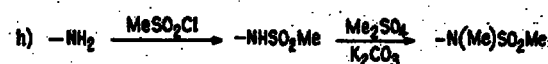
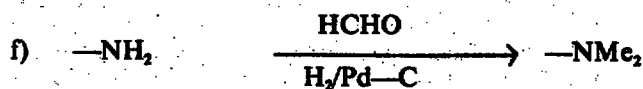
Compounds in which R is alkyl are generally obtained by alkylation of the compounds in which R is hydrogen. Suitable alkylating agents include alkyl halides, e.g. methyl or ethyl iodide or propyl bromide, and dialkyl sulphates, e.g. dimethyl or diethyl sulphate. The alkylation is preferably carried out in the presence of a base, e.g. an alkali metal hydroxide in which case when it is desired to obtain the acid, acidification, e.g. with hydrochloric acid may be carried out. When using an alkyl halide the reaction is generally carried out on a metal derivative which can be preformed, for example by the use of a metal hydride, e.g. sodium hydride. The alkylation may be carried out at a temperature of, for example from 0 to 200°C., preferably in the presence of a solvent, e.g. tetrahydrofuran or diglyme.

To obtain compounds in which X is sulphur, it is usually necessary to sulphurise the compound in which X is oxygen. This may be carried out with a sulphurising agent, for example phosphorus pentasulphide. This reaction may be carried out, for example at a temperature of from 20 to 100°C. Generally the compound of formula II is converted to an ester before sulphurisation. If the free acid is required this can then be obtained from the sulphurised esters by hydrolysis.

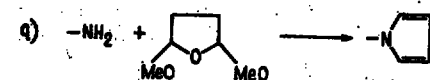
When R₁ is a halogen group it is replaced with hydrogen, generally by hydrogenation in conventional manner, for example using a palladium-charcoal catalyst preferably in the presence of a salt of a weak acid, e.g. sodium acetate.

Examples of modifications to one or more of G, R₁, R₂, R₃ and R₄ that may be carried out include the following, where the radicals shown may be examples of G, where applicable, and of R₁, R₂, R₃ and R₄. A particularly useful modification is reductive alkylation of a nitro or amino group, examples of which are shown under c, d, f and g.

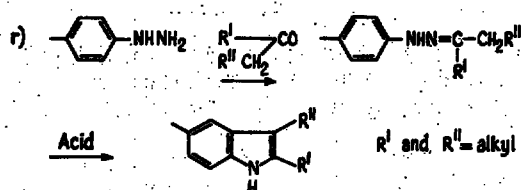


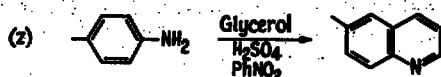
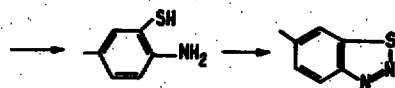
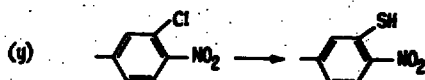
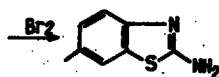
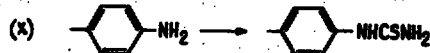
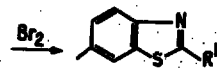
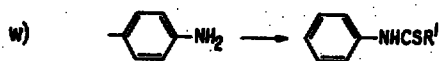
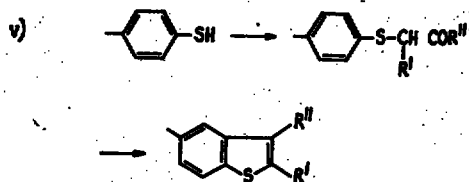
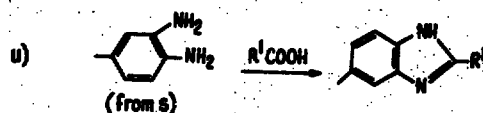
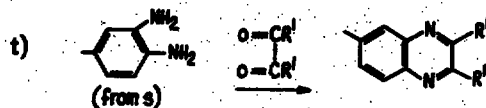
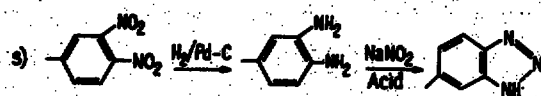


(R = Me or Et)



In some cases fused rings may be obtained by suitable modification of R₁ and R₂ so that they cyclise to form the fused ring. Examples of such reactions include the following:





The conversion of compounds in which Q is COOH to those in which Q is CH₂OH may be carried out by various procedures. When R is alkyl, the compound may be converted to a mixed anhydride e.g. by reacting with an ester of a haloformic acid, usually ethyl chloroformate, in the presence of a tertiary amine, e.g. triethylamine. The mixed anhydride is then reduced with, for example, sodium borohydride. When the group in the 4-position of the phthalazine nucleus is a hydroxy or mercapto group it may be first necessary to protect it before carrying

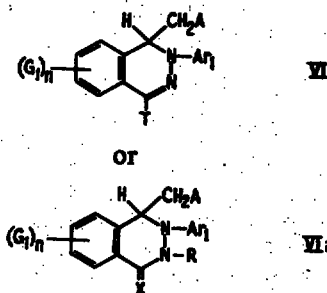
out this procedure, e.g. by acylation, usually acetylation, or by treatment with an agent such as benzyl chloroformate to form the 4-benzyloxycarbonyloxy compound. The protecting group can then be removed by conventional means, e.g. by hydrolysis in the case of the acetyl group or hydrogenation in the case of the benzyloxycarbonyl group. Alternatively when R is hydrogen or alkyl, acids may be converted to the corresponding acid chloride, e.g. by reaction with thionyl chloride, which can then be reduced, for example using lithium aluminium tri-*t*-butoxy hydride. When converting compounds in which the group in the 4-position of the phthalazine nucleus is a sulphonate, i.e. compounds of formula IV, the procedure used is generally the formation and reduction of the mixed anhydride.

Salts of acids may be obtained by reacting the acids with organic or inorganic bases.

O- or *S*-acylated derivatives may be obtained by treating the compounds in which R is hydrogen with an acylating agent e.g. acetyl chloride or acetic anhydride.

If desired, compounds in which Q is CH₂OH may be oxidised, in conventional manner, to give compounds in which Q is COOH. Also compounds in which Q is COOR, may be hydrolysed, in conventional manner, to give compounds in which Q is COOH or salts of such compounds.

It will thus be appreciated that compounds of the invention may be prepared by a process in which a compound of formula VI or VIa



in which A is the group Q as previously defined or a group convertible to Q; G₁ is the group G as previously defined or a group convertible to G; Ar₁ is aryl; T is the group XZ as previously defined, or is SO₂⁻, and R and Z are as previously defined; is treated to modify at least one of the groups A, G₁, Ar₁, R, X, T or Z to give a novel compound of the invention.

Examples of groups convertible to Q include an aldehyde group which may be oxidised to give COOH or a cyano or carbamoyl group which may be hydrolysed to give COOH.

It will be appreciated that, since the compounds of the invention possess an asymmetric carbon atom, they are ordinarily present in the form of a racemic mixture. The resolution of such racemates may be carried out by conventional means and the separated optically active stereoisomers form part of the present invention.

The therapeutic activity of compounds of the invention can be assessed in various species, by administering the drug to the animal and measuring the amount of sodium ions in the urine excreted after a given time (usually expressed as milliequivalents of sodium ions/kg. of body weight of the animal). In rats, the drug was administered orally in suspension in distilled water containing 0.25% hydroxyethyl cellulose and the amount of sodium ions in the urine was compared with the amount in control rats given the same amount of liquid without any drug. In this test 4-hydroxy-7-methyl-2-(3-methylthiophenyl)-1,2-dihydrophthalazine-1-acetic acid (or in its "keto" form, 7-methyl-2-(3-methylthiophenyl)-4-oxo-1,2,3,4-tetrahydrophthalazine-1-acetic acid) promoted sodium ion loss and had a potency based on sodium ion diuresis better than that of frusemide.

The compounds may be administered in conventional manner for example, orally, rectally or parenterally, preferably orally. The optimum dosage rate varies *inter alia* with the route of administration and the condition being treated, but normally lies within the range 0.003—100, e.g. 0.1—100 mg./kg./day. The unit dose may vary from 0.1 mg.—500 mg., e.g. 3 mg. to 500 mg.; for oral administration the dosage rate is preferably 0.1 mg.—2 g. e.g. 3 mg.—2 g. per subject per day.

For ease of administration the compounds are preferably formulated as therapeutic compositions which comprise the active compound in association with pharmaceutical excipients for the production of compositions for oral, rectal or parenteral administration. These compositions preferably contain 0.1—90% by weight of a compound of the invention.

Preferred compositions of the invention are compositions for oral administration, and these are the conventional pharmaceutical forms for such administration, such as for example tablets, capsules, lozenges, powders, effervescent granules, syrups and aqueous and oily suspensions. The excipients used in the preparation of these compositions are the excipients of the pharmacist's art. Thus in the preparation of tablets, typical excipients include disintegrating agents, e.g. maize starch and lubricating agents, e.g. magnesium stearate. In the preparation of capsules, standard gelatin capsules may be used containing the active ingredient alone or admixed with a diluent. The liquid compositions may comprise as excipients water and sucrose to provide syrups, water, dispersing agents and suspending agents, e.g. sodium carboxymethyl-cellulose to provide aqueous suspensions, and a non-toxic oil, e.g. a vegetable oil such as arachis oil and a suspending agent to provide oily suspensions.

Other compositions of the invention are compositions for rectal administration, and these are the conventional pharmaceutical forms for such administration, such as for example suppositories with fatty glyceride or polyethylene glycol bases.

Compositions for parenteral administration are the conventional pharmaceutical forms for such administration, for example a sterile solution of the sodium salt in water.

In some formulations it may be beneficial to use the compounds of the invention in the form of particles of very small size, such as for example, as obtained by fluid energy milling, e.g. micronizing.

The active compounds may be mixed with or used in conjunction with other therapeutic agents, for example other diuretic agents, especially those which reduce potassium ion excretion e.g. amiloride, spironolactone or triamterene; and antihypertensive agents, such as reserpine or adrenergic neurone blocking agents, such as guanethidine or methyldopa. The compounds may additionally or alternatively be mixed or used in conjunction with a potassium salt, such as potassium chloride, to replace excess potassium loss that may result from the use of the diuretic compound. Generally the potassium salt is enterically coated.

The invention is illustrated in the following Examples in which "parts" and "percentages" are by weight unless otherwise stated. In the examples the following abbreviations are used:

"TPA" = 1,2,3,4-tetrahydrophthalazine-1-acetic acid
"TPAE" = 1,2,3,4-tetrahydrophthalazine-1-acetate
"DPA" = 1,2-dihydrophthalazine-1-acetic acid
"DPAE" = 1,2-dihydrophthalazine-1-acetate
"IMS" = Industrial methylated spirits

The products of the examples gave satisfactory elemental analyses.

Example 1.

6-Bromo-2-naphthol (44 g.) was added portionwise, with stirring, to concentrated sulphuric acid, cooled to 0°C. When the mixture had solidified, it was allowed to stand overnight at room temperature. Water (250 ml.) was added and the mixture stirred and filtered. Sodium chloride (40 g.) was added to the filtrate with stirring, the mixture allowed to stand overnight and then filtered. The solid which was collected was washed with saturated brine (350 ml.), dried, and extracted with boiling absolute ethanol. The extract was filtered, the ethanol evaporated and the residue stirred with ether (500 ml.) for two hours. The mixture was filtered leaving sodium 6-bromo-2-naphthol-1-sulphonate. A portion (6.3 g.) of this was dissolved in water (250 ml.) filtered and cooled. This was then added slowly to a diazonium salt, obtained by slowly adding ice-cold aqueous sodium nitrite (1.7 g. in 5 ml. water) to a cooled solution of *m*-trifluoromethylaniline (3.22 g.) in concentrated hydrochloric acid (8 ml.) and water (30 ml.). A yellow precipitate formed which was filtered off, washed with cold saturated brine (250 ml.) and made into a paste with cold water (100 ml.). The paste was cooled to 0°C. and sodium carbonate (6 g.) added with stirring. After 1½ mins. cold aqueous

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sodium hydroxide (12 g. in 30 ml. water) was added and after a red solution had formed, the mixture was stirred on an ice-bath for 3 hours and then at room temperature overnight. The mixture was acidified to pH 2—3 with concentrated hydrochloric acid and then brought to pH 8 with saturated aqueous sodium carbonate. The mixture was filtered and the filtrate acidified to pH 1 with concentrated hydrochloric acid, whilst stirring. The solid was filtered off and dissolved in warm water (250 ml.) and the solution refluxed for two hours during which time concentrated hydrochloric acid (15 ml.) was added. The mixture was then cooled, the solid filtered off and recrystallised from a 2:1 by volume mixture of acetic acid and water to give 7-bromo-4-hydroxy-2-(3-trifluoromethylphenyl)-DPA, mp 217—9°C.

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Examples 2—36.

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In a similar manner to that described in Example 1 there was obtained from the appropriate 2-naphthol and aniline, the corresponding acetic acid. The compounds obtained are set out in Table I. In some cases the diluted reaction mixture from the sulphonation of the 2-naphthol or a solution of the crude sodium naphthol sulphonate was reacted with the diazonium salt solution without purification. In some case also, neutral and phenolic impurities from the final acetic acid were removed by partition between a water immiscible solvent, usually ether, and aqueous sodium hydrogen carbonate. The product was then recovered from the aqueous phase by acidification.

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TABLE I

Compounds obtained

Ex. No.	Aniline	2-naphthol	R ₃	R ₄	G ₁	G ₂	G ₃	m.p. (°C)
2	3-methylthio	6-bromo	MeS	H	H	Br	H	232-233
3	3-nitro	6-bromo	NO ₂	H	H	Br	H	228-230
4	3-chloro	6-bromo	Cl	H	H	Br	H	166-168
5	3-nitro	6-methoxy	NO ₂	H	H	MeO	H	217-218
6	3-methylthio	6-methoxy	MeS	H	H	MeO	H	233-235
7	3-nitro	6- <i>t</i> -butyl	NO ₂	H	H	But ^t	H	244-245
8	3-trifluoromethyl	6-ethyl	CF ₃	H	H	Et	H	202-206
9	3-nitro	6-ethyl	NO ₂	H	H	Et	H	220-222
10	3-methylthio	6-ethyl	MeS	H	H	Et	H	195-196
11	3-trifluoromethyl	6-methyl	CF ₃	H	H	Me	H	219
12	3-nitro	6-methyl	NO ₂	H	H	Me	H	233-233.5
13	3-chloro	6-methyl	Cl	H	H	Me	H	210-211
14	4-chloro	6-methyl	H	Cl	H	Me	H	215-216
15	3-methylthio	6-methyl	MeS	H	H	Me	H	208-209
16	3-bromo	6-methyl	Br	H	H	Me	H	231-232

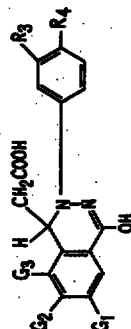


TABLE I (Continued)

Ex. No.	Aniline	2-naphthol	Compounds obtained						m.p. (°C)
			R ₁	R ₂	R ₃	G ₁	G ₂	G ₃	
17	3-nitro	6-chloro	H	NO ₂	H	H	Cl	H	227-229
18	3-methylthio	6-chloro	H	MeS	H	H	Cl	H	218
19	3-nitro	6-fluoro	H	NO ₂	H	H	F	H	242-243
20	3-nitro	7-fluoro	H	NO ₂	H	F	H	H	232-235
21	3-nitro	6,7-dichloro	H	NO ₂	H	Cl	Cl	H	234-235
22	3-chloro	6-ethyl	H	Cl	H	H	Et	H	215-220
23	3-trifluoromethyl	6-chloro	H	CF ₃	H	H	Cl	H	197-198
24	3-nitro	6-isopropyl	H	NO ₂	H	H	Pr ⁱ	H	226-227
25	3-trifluoromethyl	6-fluoro	H	CF ₃	H	H	F	H	123-124
26	3-trifluoromethyl	7-fluoro	H	CF ₃	H	F	H	H	228-229
27	4-methylthio	6-methyl	MeS	H	H	H	Me	H	182-186
28	3-nitro	5-chloro	H	NO ₂	H	H	Cl	Cl	230-231
29	3-nitro	5,6-dimethyl	H	NO ₂	H	H	Me	Me	268-270
30	3-nitro	7-ethyl	H	NO ₂	H	Et	H	H	138-140
31	3-nitro	5-fluoro	H	NO ₂	H	H	H	F	211-213
32	3-fluoro	6-methyl	H	F	H	H	Me	H	207-209
33	3-iodo	6-methyl	H	I	H	H	Me	H	228-230
34	3-acetyl	6-methyl	H	CH ₃ CO	H	H	Me	H	195-196

TABLE I (Continued)

Ex. No.	Aniline	2-naphthol	Compounds obtained						m.p. (°C)
			R ₁	R ₂	R ₃	G ₁	G ₂	G ₃	
35	3-nitro	6-methylthio		NO ₂	H	H	MeS	H	238
36	4-methyl-3-nitro	6-methyl		NO ₂	Me	H	Me	H	138-140
37	3-trifluoroacetyl	6-chloro		CF ₃ CO	H	H	H	Cl	130-140

Examples 38—47.

In a similar manner as described in Example 1 starting from 1,2,3-benzothiadiazol-5-ylamine and the appropriate naphthol, the acids set out in Table II were obtained.

TABLE II

Ex. No.	2-Naphthol	Compounds obtained			
		G ₁	G ₂	G ₃	m.p. (°C)
38	6-methyl	H	Me	H	234
39	6-chloro	H	Cl	H	*233
40	6-fluoro	H	F	H	254—255
41	7-fluoro	F	H	H	274—275
42	6-isopropyl	H	Pr ⁱ	H	230—231
43	5,6-dimethyl	H	Me	Me	210—212
44	6- <i>t</i> -butyl	H	Bu ^t	H	232—234
45	6-ethyl	H	Et	H	235
46	7-chloro	Cl	H	H	265
47	6-benzoyl	H	PhCO	H	164—166

* This product is obtained in two forms, having different infra-red spectra. Recrystallisation from acetic acid gives a product having $\nu_{\max}$ 1710, 1680 cm^{-1} , whereas recrystallisation from ethyl acetate gives a product having $\nu_{\max}$ 1700, 1635 cm^{-1} (KBr disc).

Examples 48—50.

The product of Example 12 (2.8 g.) was dissolved in aqueous potassium hydroxide (6.3 g. in 63 ml. of water). Dimethyl sulphate (3.2 g.) was added and the mixture stirred at room temperature for $\frac{1}{2}$ hour. The solution was cooled to 0°C and acidified with concentrated hydrochloric acid. The yellow precipitate, which formed, was filtered off and recrystallised from a mixture of acetic acid and water (2:1) to give 3,7-dimethyl-2-(3-nitrophenyl)-4-oxo-TPA, m.p. 217—219°C. (Example 48).

In a similar manner, the product of Example 39 gave 2-(1,2,3-benzothiadiazol-5-yl)-7-chloro-3-methyl-4-oxo TPA, m.p. 260—261°C, (Example 49) and the product of Example 36 gave 3,7-dimethyl-2-(4-methyl-3-nitrophenyl)-4-oxo-TPA, m.p. 201—202°C (Example 50).

Examples 51—56.

The product of Example 48 (19 g.) was esterified by refluxing with methanol (700 ml.) containing concentrated sulphuric acid (15 ml.) for 6 hours. The mixture was evaporated to 150 ml., cooled and poured into ice-water. The solid was collected, washed with saturated aqueous sodium hydrogen carbonate, followed by water, dried and recrystallised from methanol to give methyl 3,7-dimethyl-2-(3-nitrophenyl)-4-oxo-TPAE, m.p. 179—180°C (Example 51).

In a similar manner the product of Example 38 gave methyl 2-(1,2,3-benzothiadiazol-5-yl)-4-hydroxy-7-methyl-DPAE, m.p. 202—3°C (Example 52); the product of Example 39 gave methyl 2-(1,2,3-benzothiadiazol-5-yl)-7-chloro-4-

hydroxy-DPAE, m.p. 220—222°C (Example 53); the product of Example 50 gave methyl 3,7-dimethyl-2-(4-methyl-3-nitrophenyl)-4-oxo-TPAE, m.p. 177—178°C (Example 54); the product of Example 71 gave methyl 2-(1,2-benzisothiazol-5-yl)-4-hydroxy-7-methyl-DPAE, m.p. 120—127°C (Example 55) and the product of Example 36 gave methyl 4-hydroxy-7-methyl-2-(4-methyl-3-nitrophenyl)-DPAE, m.p. 188—189°C (Example 56).

Example 57.

The product of Example 48 (1.4 g.) was dissolved in IMS (200 ml.), mixed with palladium-charcoal (10% Pd; 0.5 g.) and formaldehyde (40%; 1.0 ml.) and the mixture hydrogenated with hydrogen (440 ml.) with shaking. The mixture was filtered, evaporated under reduced pressure and the residue allowed to stand to 0°C. White crystals, which formed, were filtered off, washed with and recrystallised from IMS and dried *in vacuo* to give 2-(3-*N,N*-dimethylamino-phenyl)-3,7-dimethyl-4-oxo-TPA, m.p. 202—204°C.

Examples 58—60.

The product of Example 51 (14 g.) was dissolved as in methanol (1 litre) and hydrogenated at room temperature using a palladium-charcoal catalyst (10%; 1 g.). The mixture was filtered and the filtrate concentrated to give crystals of methyl 2-(3-aminophenyl)-3,7-dimethyl-4-oxo-TPAE, m.p. 184—185°C (Example 58).

In a similar manner the product of Example 12 gave 2-(3-aminophenyl)-4-hydroxy-7-methyl-DPA, m.p. 191°C (Example 59) and the product of Example 48 gave 2-(3-aminophenyl)-3,7-dimethyl-4-oxo-TPA, m.p. 216—217°C (Example 60).

Example 61.

A solution of *p*-toluene sulphonyl chloride (3.1 g.) in pyridine (11 ml.) was added to a solution of the product of Example 58 (5.6 g.) in pyridine (33 ml.). The mixture was refluxed for 1 hour, cooled and poured onto ice-water. The aqueous layer was removed and the remaining gum stirred with light petroleum (b.p. 80—100°C). The solid product was filtered and recrystallised from IMS to give methyl 3,7-dimethyl-4-oxo-2-(3-*p*-toluenesulphonamidophenyl)-TPAE, m.p. 205—206°C. This was mixed with sodium carbonate (3.65 g.), dimethyl sulphate (2.5 ml.) and acetone and the mixture stirred and refluxed for 2 hours. The acetone was evaporated and the residue treated with a mixture of ethyl acetate and water. The organic layer was washed with water, dried and evaporated and the product recrystallised from IMS to give methyl 3,7-dimethyl-2-(3-*N*-methyl-*p*-toluenesulphonamidophenyl)-4-oxo-TPAE, m.p. 172—173°C. This was dissolved in IMS and hydrolysed by treatment with aqueous sodium hydroxide, followed by evaporation. The residue was dissolved in water, filtered and acidified and the product filtered, washed with water and recrystallised from aqueous acetic acid to give 3,7-dimethyl-2-(3-*N*-methyl-*p*-toluenesulphonamidophenyl)-4-oxo-TPA, m.p. 214—5°C.

Example 62.

The product of Example 58 (11 g.) was refluxed with glacial acetic acid (100 ml.) for 18 hours. The mixture was then evaporated to give an oil which was triturated with methanol. The solid product was recrystallised from methanol to give methyl 2-(3-acetamidophenyl)-3,7-dimethyl-4-oxo-TPAE, m.p. 224—225°C. 3 g. of this was dissolved in dioxan (75 ml.), sodium hydride (0.6 g.) added and the mixture refluxed for 2 hours. It was then cooled and dimethylsulphate (1.2 ml.) added and refluxed for a further 4 hours. The mixture was evaporated and the remaining gum washed with water and extracted with dichloromethane. The extract was washed with aqueous sodium hydrogen carbonate and water, dried, evaporated and the residue recrystallised from ethyl acetate to give methyl 3,7-dimethyl-2-[3-(*N*-methylacetamido)phenyl]-4-oxo-TPAE, m.p. 190°C.

Example 63.

The product of Example 62 was hydrolysed in a similar manner to that described in Example 61 to give 3,7-dimethyl-2-[3-(*N*-methylacetamido)phenyl]-4-oxo-TPA, m.p. 228—230°C.

Example 64.

To a cooled solution of the product of Example 48 (5 g.) in dry tetrahydrofuran (25 ml.) and triethylamine (2 ml.) was added, dropwise, a solution

of methyl chloroformate (1.1 ml.) in dry tetrahydrofuran (5 ml.). The mixture was stirred at -5°C for 30 mins. and then filtered. The filtrate was added dropwise with stirring to a solution of sodium borohydride (1.6 g.) in water. The mixture was stirred for 3 hours and then acidified with hydrochloric acid (2N: 50 ml.). The solid was extracted with dichloromethane and the extract washed with aqueous sodium hydrogen carbonate, dried and evaporated to give a gum which was triturated with ether. The solid, which separated, was recrystallised from methanol to give 3,7-dimethyl-1-(2-hydroxyethyl)-2-(3-nitrophenyl)-4-oxo-1,2,3,4-tetrahydrophthalazine, m.p. $169-170^{\circ}\text{C}$.

Example 65.

The product of Example 58 (3 g.) was diazotised using sodium nitrite and hydrochloric acid. Aqueous fluoroboric acid (42%; 24 ml.) was added and the yellow precipitate of the diazonium fluoroborate was filtered, washed with an ether/methanol mixture (4:1) and then mixed with methanol (50 ml.). The mixture was heated to 50°C . Nitrogen was evolved and the solid dissolved. The red solution was poured into water (200 ml.) and the solid which separated was extracted with chloroform. The extract was dried and evaporated and the residue recrystallised from methanol to give methyl 2(3-methoxyphenyl)-3,7-dimethyl-4-oxo-TPAE, m.p. $120-1^{\circ}\text{C}$.

Example 66.

The product of Example 58 (1 g.) was diazotised and treated with fluoroboric acid as described in Example 65 to give the diazonium fluoroborate which was filtered, washed with aqueous ice-cold fluoroboric acid (10%, 5 ml.), ice-cold methanol (10 ml.), an ice-cold methanol/ether mixture (1:1; 10 ml.) and ice-cold ether (10 ml.). The solid was dried *in vacuo* and then added to an ice-cold solution of potassium carbonate (205 mg.) in trifluoroacetic acid (6.3 ml.). The mixture was refluxed for 45 mins, cooled and poured into water (30 ml.). The solid was dissolved in dichloromethane and the solution extracted with aqueous sodium hydroxide (2 N; 30 ml.). The extract was treated with charcoal, filtered and the filtrate acidified with hydrochloric acid (5 N). The precipitate was filtered, dried *in vacuo* and recrystallised from a mixture of ethyl acetate and light petroleum (b.p. $60-80^{\circ}\text{C}$) to give 2-(3-hydroxyphenyl)-3,7-dimethyl-4-oxo-TPA, m.p. $150-152^{\circ}\text{C}$.

Example 67.

In a similar manner to that described in Example 48 but replacing the dimethyl sulphate with diethyl sulphate, the product of Example 12 gave 3-ethyl-7-methyl-2-(3-nitrophenyl)-4-oxo-TPA, m.p. $232-3^{\circ}\text{C}$.

Example 68.

The product of Example 12 (1 g.) was mixed with acetic anhydride (5 ml.) and the mixture heated on a steam bath for 1 hour. Excess acetic anhydride was evaporated under reduced pressure and the residue triturated with light petroleum (b.p. $40-60^{\circ}\text{C}$) to give a yellow solid which was recrystallised from a mixture of ether and light petroleum (b.p. $40-60^{\circ}\text{C}$) to give 4-acetoxy-7-methyl-2-(3-nitrophenyl)-DPA, m.p. $204-205^{\circ}\text{C}$.

Example 69.

The product of Example 51 (1.5 g.) dissolved in xylene (65 ml.) was mixed with phosphorus pentasulphide (0.81 g.) and the mixture boiled under reflux for 1 hour and filtered. The filtrate was evaporated under reduced pressure and the residue recrystallised from light petroleum (b.p. $80-100^{\circ}\text{C}$) to give methyl 3,7-dimethyl-2-(3-nitrophenyl)-4-thioxo-TPAE, m.p. $160-161^{\circ}\text{C}$.

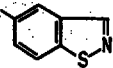
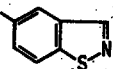
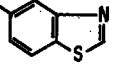
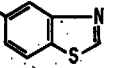
Example 70.

The product of Example 59 (5 g.) was diazotised using sodium nitrite and hydrochloric acid. Mercuric bromide (2.3 g.) was added and the red precipitate collected, washed with ice-cold water and acetone, dried and added to hexamethylphosphoric triamide (40 ml.). The mixture was heated at 40°C until gas evolution ceased, cooled, poured into water and the solid produced, collected, washed with water and recrystallised from aqueous IMS to give 4-hydroxy-7-methyl-2-phenyl-DPA, m.p. $223-224^{\circ}\text{C}$.

Examples 71—74.

In a similar manner as described in Example 1 starting from the appropriate naphthol and aromatic amine, the acids set out in Table III were obtained.

TABLE III

Ex. No.	Amine	2-naphthol	Compounds obtained		
			Ar	G ₂	m.p. (°C)
71	1,2-benzisothiazol-5-ylamine	6-methyl		Me	150—200
72	1,2-benzisothiazol-5-ylamine	6-chloro		Cl	165—170
73	benzothiazol-5-ylamine	6-ethyl		Et	229—231
74	benzothiazol-5-ylamine	6-methyl		Me	251—253

Example 75.

The product of Example 15 (2 g.) was dissolved in glacial acetic acid and aqueous hydrogen peroxide (1.4 ml. of 100 vol diluted to 5 ml.) added. The mixture was stirred at 30°C for 30 minutes, then concentrated by evaporation and diluted with water, filtered and the filtrate allowed to stand to give 4-hydroxy-7-methyl-2-(3-methylsulphinyphenyl)-DPA, m.p. 188—191°C.

Example 76.

In a similar manner as Example 75 the product of Example 35 gave 4-hydroxy-7-methylsulphiny-2-(3-nitrophenyl)-DPA, m.p. 150—153°C.

Example 77.

The product of Example 39 (100 mg.) was added to saturated aqueous sodium hydrogen carbonate (100 ml.) and the mixture evaporated to reduced volume. The solid, which crystallised, was recrystallised from ethanol to give sodium 2-(1,2,3-benzothiadiazol-5-yl)-7-chloro-4-hydroxy-DPAE, m.p. above 300°C.

Example 78.

The following mixture is formed into tablets in conventional manner, each tablet containing 2 mg. of active ingredient.

4-Hydroxy-7-methyl-2-(3-methylthiophenyl)-1,2-dihydrophthalazine-1-acetic acid
maize starch
lactose
stearic acid

Parts

50
30
163
1

Compositions similar to that described above are prepared containing as active ingredient the final products of Examples 1—14 and 16—77.

The substituted 2-naphthol-1-sulphonic acids and their sodium salts which are intermediates in the Examples are novel compounds.

Example 79.

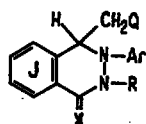
The product of Example 75 was oxidised with further hydrogen peroxide at 100°C to give 4-hydroxy-7-methyl-2-(3-methylsulphonylphenyl)-DPA, m.p. 139—145°C.

Example 80.

In a similar manner to that described in Example 51, the product of Example 15 gave methyl 4-hydroxy-7-methyl-2-(3-methylthiophenyl)-DPAE, m.p. 148.5—149°C.

WHAT WE CLAIM IS:—

1. Compounds of formula I

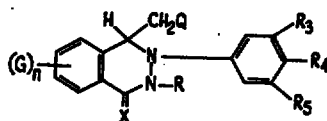


or their enol or enthiol forms of formula Ia

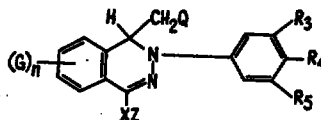


in which Q is COOH, CH₂OH or COOR₆, wherein R₆ is an ester forming group; X is oxygen or sulphur; R is hydrogen or alkyl; Z is hydrogen or acyl; Ar is an aryl group unsubstituted in the positions ortho to the point of attachment to the phthalazine ring and the ring J is substituted, or a pharmaceutically acceptable salt with an inorganic or organic base of any compound which is an acid.

2. Compounds according to Claim 1 of formula II



or their enol or enthiol forms of formula IIa



in which Q, X, R and Z are as defined in claim 1; n is 1 to 4; each G may be the same or different and is selected from fluorine; chlorine; bromine; iodine; amino; substituted amino; nitro; cyano; alkyl; substituted alkyl; alkoxy; substituted alkoxy; alkylthio; alkylsulphonyl; alkylsulphinyl; hydroxy, aroyl and aryl; and R₃, R₄, and R₅ may be the same or different and are selected from hydrogen; fluorine; chlorine; bromine; iodine; nitro; nitroso; cyano; isocyano; amino; substituted amino; alkyl; substituted alkyl; cycloalkyl; substituted cycloalkyl; alkenyl; aryl;



* C L M S *

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4-Hydroxy-7-methyl-2-(3-methylthiophenyl)-1,2-dihydrophthalazine-1-acetic acid

Parts

maize starch
lactose
stearic acid

50
30
163
1

Compositions similar to that described above are prepared containing as active ingredient the final products of Examples 1—14 and 16—77.

The substituted 2-naphthol-1-sulphonic acids and their sodium salts which are intermediates in the Examples are novel compounds.

Example 79.

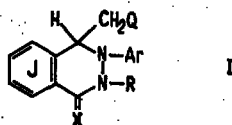
The product of Example 75 was oxidised with further hydrogen peroxide at 100°C to give 4-hydroxy-7-methyl-2-(3-methylsulphonylphenyl)-DPA, m.p. 139—145°C.

Example 80.

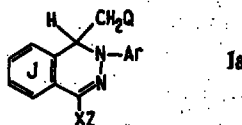
In a similar manner to that described in Example 51, the product of Example 15 gave methyl 4-hydroxy-7-methyl-2-(3-methylthiophenyl)-DPAE, m.p. 148.5—149°C.

WHAT WE CLAIM IS:—

1. Compounds of formula I

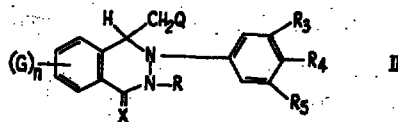


or their enol or enthiol forms of formula Ia

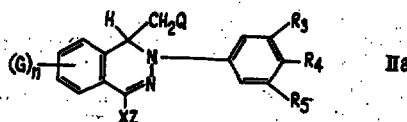


in which Q is COOH, CH₂OH or COOR₆, wherein R₆ is an ester forming group; X is oxygen or sulphur; R is hydrogen or alkyl; Z is hydrogen or acyl; Ar is an aryl group unsubstituted in the positions ortho to the point of attachment to the phthalazine ring and the ring J is substituted, or a pharmaceutically acceptable salt with an inorganic or organic base of any compound which is an acid.

2. Compounds according to Claim 1 of formula II



or their enol or enthiol forms of formula IIa



in which Q, X, R and Z are as defined in claim 1; n is 1 to 4; each G may be the same or different and is selected from fluorine; chlorine; bromine; iodine; amino; substituted amino; nitro; cyano; alkyl; substituted alkyl; alkoxy; substituted alkoxy; alkylthio; alkylsulphonyl; alkylsulphinyl; hydroxy, aroyl and aryl; and R₃, R₄, and R₅ may be the same or different and are selected from hydrogen; fluorine; chlorine; bromine; iodine; nitro; nitroso; cyano; isocyano; amino; substituted amino; alkyl; substituted alkyl; cycloalkyl; substituted cycloalkyl; alkenyl; aryl;



cycloalkenyl; alkoxy; substituted alkoxy; alkenyloxy; cycloalkyloxy; cycloalkenyloxy; acyloxy; alkylthio; substituted alkylthio; alkenylthio; cycloalkylthio; cycloalkenylthio; arylthio; alkylsulphonyl; alkylsulphinyl; acyl; substituted acyl; aroyl; heteroaroyl; hydroxy; mercapto; carbamoyl; thiocarbamoyl; sulphamoyl; substituted sulphamoyl; substituted and unsubstituted heterocyclic rings; or R_3 and R_4 together form a portion of a carbocyclic or heterocyclic ring fused to the benzene ring, which rings may be substituted, together with pharmaceutically acceptable salts with inorganic and organic bases of those compounds which are acids.

3. Compounds according to claim 1 or 2 in which Q is COOH.

4. Compounds according to any one of claims 1, 2 and 3 in which R or Z is hydrogen.

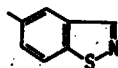
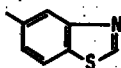
5. Compounds according to any one of claims 1 to 4 in which X is oxygen.

6. Compounds according to any one of claims 2 to 5 in which R_3 is hydrogen.

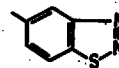
7. Compounds according to any one of claims 2 to 6 in which R_3 is other than hydrogen.

8. Compounds according to any one of claims 2 to 7 in which R_3 and/or R_4 is selected from trifluoromethyl, methylthio, ethylthio, methyl, ethyl, chlorine, iodine, bromine, methoxy, ethoxy, isopropoxy, acetyl, dimethylsulphamoyl, diethylsulphamoyl and nitro.

9. Compounds according to any one of claims 2 to 6 in which R_3 and/or R_4 together with the benzene ring to which they are attached form one of the groups selected from



and



10. Compounds according to any one of claims 1 to 3 or 5 to 10 in which R is methyl or ethyl.

11. Compounds according to claims 2 or 4 to 7 in which R_3 and/or R_4 is *N,N*-dimethylamino, *N*-methyl-*p*-toluenesulphonamido or *N*-methylacetamido and R is methyl or ethyl.

12. Compounds according to any one of claims 2 to 11 in which n is 1.

13. Compounds according to claim 12 in which G is in the 7 position.

14. Compounds according to any one of claims 2 to 13 in which G is selected from methyl, ethyl and methoxy.

15. Compounds according to any one of claims 2 to 13 in which G is selected from isopropyl, fluorine, chlorine and bromine.

16. Compounds according to claim 2 in which R_3 is hydrogen, n is 1 and G is in the 7 position, Q is carboxy, X is oxygen, R_4 is hydrogen and R_3 is other than hydrogen or R_3 and R_4 together form a portion of a heterocyclic ring fused to the benzene ring as well as salts thereof.

17. Compounds according to claim 16 in which G is chlorine, fluorine, methyl, ethyl, isopropyl or methoxy and when R or Z is hydrogen, R_3 is nitro, trifluoromethyl, methylthio, chloro or bromo or R_3 and R_4 together with the benzene ring to which they are attached are benzothiazol-5-yl, 1,2,3-benzothiadiazol-5-yl or 1,2-benzoisothiazol-5-yl and when R is methyl R_3 is *N,N*-dimethylamino.

18. 4 - Hydroxy - 7 - methyl - 2 - (3 - methylthiophenyl) - 1,2 - dihydrophthalazine - 1 - acetic acid.

19. 4 - Hydroxy - 7 - methoxy - 2 - (3 - methylthiophenyl) - 1,2 - dihydrophthalazine - 1 - acetic acid.

20. 2 - (1,2,3 - Benzothiadiazol - 5 - yl) - 4 - hydroxy - 7 - methyl - 1,2 - dihydrophthalazine - 1 - acetic acid.

21. 2 - (1,2 - Benzoisothiazol - 5 - yl) - 4 - hydroxy - 7 - methyl - 1,2 - dihydrophthalazine - 1 - acetic acid.

22. 2 - (1,2,3 - Benzothiadiazol - 5 - yl) - 7 - chloro - 4 - hydroxy - 1,2 - dihydrophthalazine - 1 - acetic acid.

23. 2 - (Benzothiazol - 5 - yl) - 7 - ethyl - 4 - hydroxy - 1,2 - dihydrophthalazine - 1 - acetic acid.

24. 2 - (Benzothiazol - 5 - yl) - 7 - methyl - 4 - hydroxy - 1,2 - dihydrophthalazine - 1 - acetic acid.

25. 2 - (1,2 - Benzoisothiazol - 5 - yl) - 7 - chloro - 4 - hydroxy - 1,2 - dihydrophthalazine - 1 - acetic acid.

26. 4 - Hydroxy - 7 - methyl - 2 - (3 - trifluoromethylphenyl) - 1,2 - dihydrophthalazine - 1 - acetic acid.



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27. 2 - (1,2,3 - Benzothiadiazol - 5 - yl) - 7 - fluoro - 4 - hydroxy - 1,2 - dihydro-
phthalazine - 1 - acetic acid.
28. 2 - (1,2,3 - Benzothiadiazol - 5 - yl) - 4 - hydroxy - 7 - isopropyl - 1,2 - di-
hydrophthalazine - 1 - acetic acid.
29. 2 - (3 - *N,N* - dimethylaminophenyl) - 3,7 - dimethyl - 4 - oxo - 1,2,3,4-
tetrahydrophthalazine - 1 - acetic acid.
30. Compounds according to claim 1 as described in any one of the Examples.
31. Therapeutic compositions comprising a compound claimed in any one of
the preceding claims in admixture with a pharmaceutically acceptable diluent.
32. Compositions according to claim 31 suitable for oral administration and in
the form of tablets, capsules, lozenges, powders, effervescent granules, syrups or
aqueous or oily suspensions.
33. Compositions according to claim 31 suitable for rectal administration and
in the form of a suppository.
34. Compositions according to any one of claims 31 to 33 comprising 0.1 to
90% by weight of the compound.
35. Compositions according to any one of claims 31 to 34 in unit dose form
comprising 0.1 mg. to 500 mg. of the compound.
36. Compositions according to any one of claims 31 to 35 additionally
comprising one or more of a diuretic which reduces potassium ion excretion, an
antihypertensive agent and a potassium salt.

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