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(54) Titre : CANNABIDIOLS ANORMAUX UTILES COMME AGENTS DESTINES A FAIRE BAISSER LA PRESSION
INTRAOCULAIRE
(54) Title: ABNORMAL CANNABIDIOLS AS AGENTS FOR LOWERING INTRAOCULAR PRESSURE

(57) **Abrégé/Abstract:**

The present invention provides a method of treating glaucoma or ocular hypertension which comprises applying to the eye of a person in need thereof an amount sufficient to treat glaucoma or ocular hypertension of a compound of formula (I), wherein Y, Q, Z, R, R¹ and R² are as defined in the specification. The present invention further comprises pharmaceutical compositions, e.g. ophthalmic compositions, including said compound.



Abstract

The present invention provides a method of treating glaucoma or ocular hypertension which comprises applying to the eye of a person in need thereof an amount sufficient to treat glaucoma or ocular hypertension of a compound of formula (I), wherein Y, Q, Z, R, R¹ and R² are as defined in the specification. The present invention further comprises pharmaceutical compositions, e.g. ophthalmic compositions, including said compound.

17909ABC(AP)**ABNORMAL CANNABIDIOLS AS AGENTS FOR LOWERING
INTRAOCULAR PRESSURE****BACKGROUND OF THE INVENTION****1. Field of the Invention**

The present invention relates to the use of Abnormal Cannabidiols to lower the intraocular pressure of mammals and thus are useful in treating glaucoma.

2. Background of the Related Art

Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward

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against the angle, and may produce pupillary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe, and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical α -adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Certain Abnormal Cannabidiols are disclosed in Howlett et al, "International Union of Pharmacology. XXVII. Classification of Cannabinoid Receptors", Pharmacological Reviews 54: 161-202, 2002.

Reference is made to Published U.S. Patent Application Numbers 2005/0282902, 2005/0282912 and 2005/0282913 to Chen et al which were published on December 22, 2005 .

(June Chen is a co-inventor of each of said published patent applications and the present patent application.)

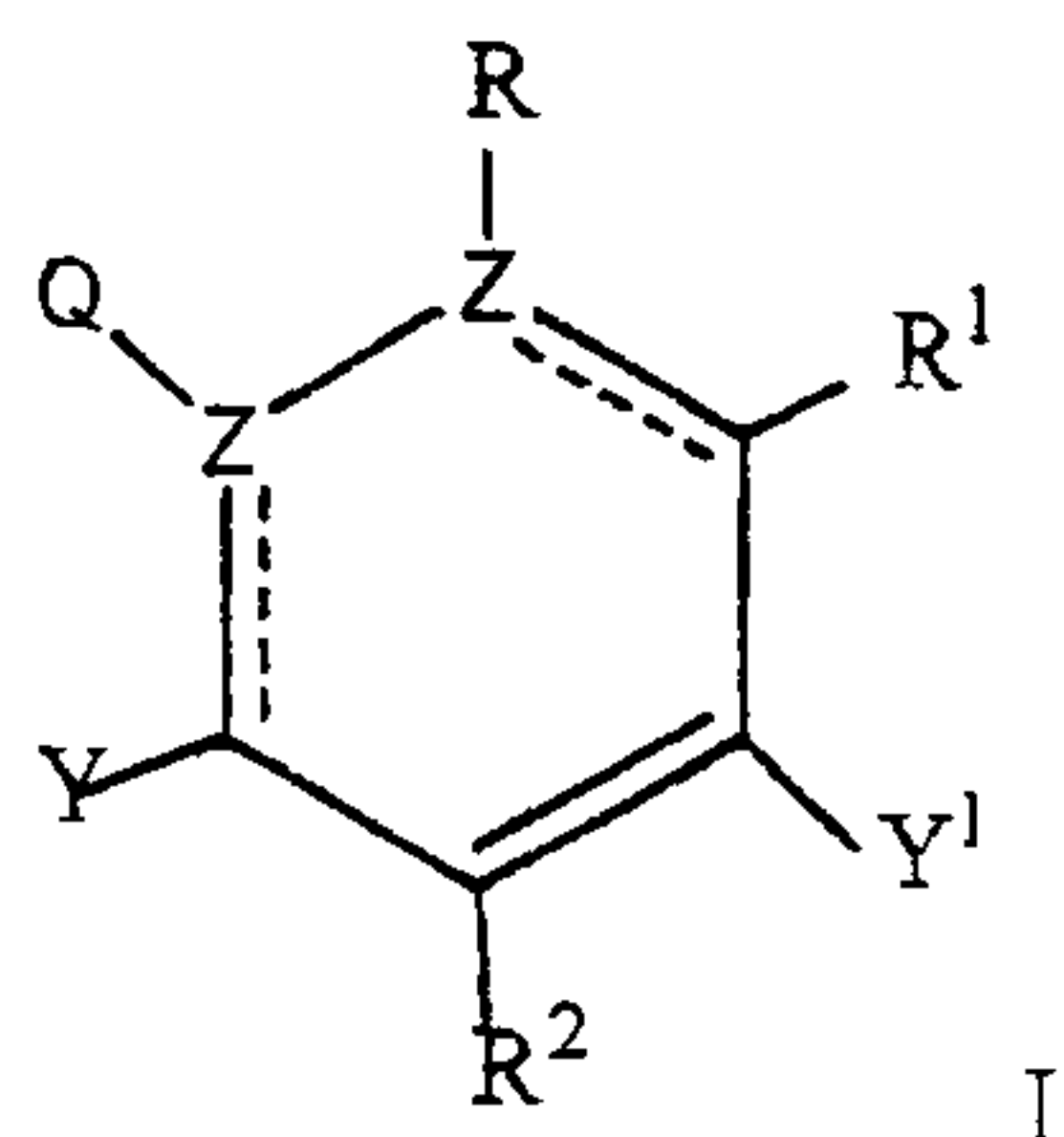
Summary of the Invention

We have found that Abnormal Cannabidiols are potent ocular hypotensive agents. We have further found that Abnormal Cannabidiols and homologues and derivatives thereof, are especially useful in the treatment of glaucoma and surprisingly, cause no or significantly lower ocular surface hyperemia than the

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other compounds that are useful in lowering intraocular pressure, e.g. $\text{PGF}_{2\alpha}$ and lower alkyl esters thereof.

The present invention relates to methods of treating ocular hypertension which comprises administering an effective amount of a compound represented by

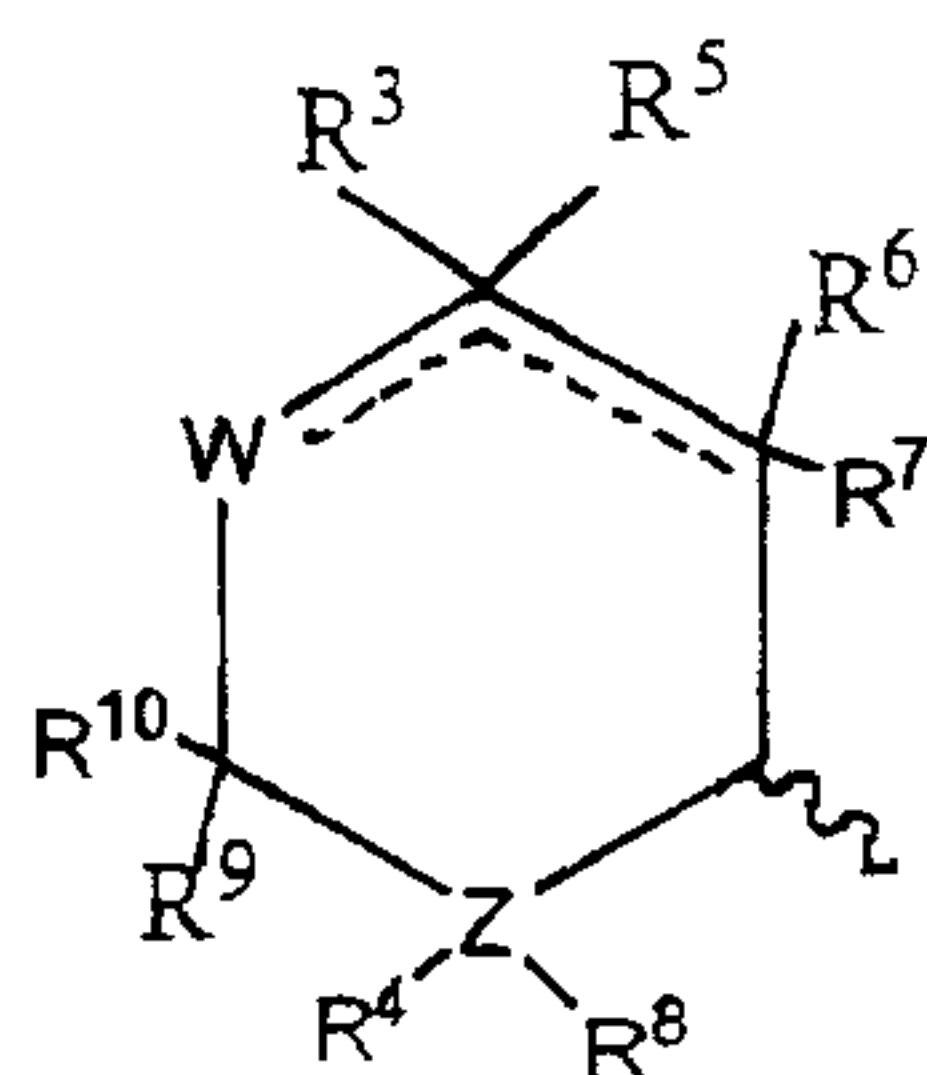


whercin Y is selected from the group consisting of keto and hydroxyl;

Y^1 is selected from the group consisting of hydroxyl, keto, halogen and $\text{C}_1\text{-C}_5$ alkyl;

Z is N or C;

Q is selected from the group consisting of phenyl, halogen-substituted phenyl, 5 or 6 member heterocyclic radicals, wherein the hetero atom is nitrogen, oxygen or sulfur,



wherein W is a direct bond or $\text{C}(\text{R}^{11})(\text{R}^{12})$;

a dotted line represents the presence or absence of a double bond;

the wavy line represents a direct bond;

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Q and Y may form a condensed ring wherein Y is $-\text{C}(\text{O})-\text{NR}_3-$ and Q is $-\text{C}(\text{Q}')-$ wherein Q' is R³ or said C is a spiro atom and Q', together with said C, represents a carbocyclic or heterocyclic ring having from 3 to 6 carbon atoms and said hetero atom is N, O or S;

R is selected from the group consisting of H, halogen and C₁₋₅ alkyl;

R¹ is selected from the group consisting of H and halogen;

R² is selected from the group consisting of H, C₁₋₅ alkyl, halogen, XC₁₋₅ alkyl, C₁₋₅ alkylOR¹³, C₁₋₅ alkylN(R¹³)₂,

N(R¹³)₂, XC₁₋₅ alkylN(R¹³)₂ and XC₁₋₅ alkylOR¹³; wherein

X is O or S(O)_n;

n is 0 or an integer of from 1 to 2;

R³ is selected from the group consisting of H, hydroxyl, oxo, C₁₋₅ alkyl, C₁₋₅ alkylOR¹³ and C₁₋₅ alkylN(R¹³)₂;

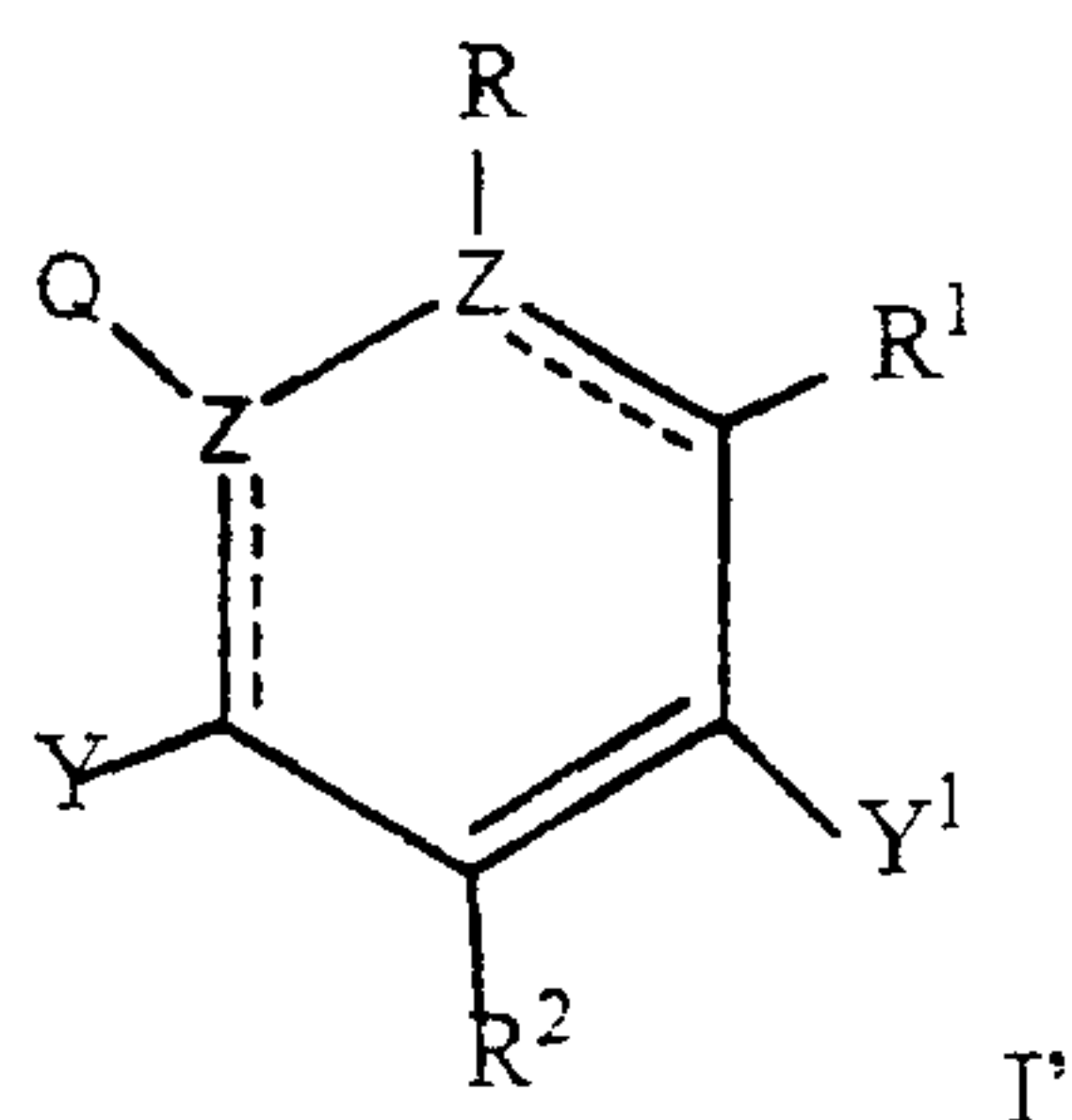
R⁴ is selected from the group consisting of H, C₁₋₅ alkenyl, C₁₋₅ alkyl, C₁₋₅ alkylOR¹³ and C₁₋₅ alkylN(R¹³)₂;

R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² are independently selected from the group consisting of H, C₁₋₅ alkyl, C₁₋₅ alkylOR¹³ and OR¹³; and

R¹³ is selected from the group consisting of H, C₁₋₅ alkyl and C₃₋₈ cyclic alkyl, or two R¹³ groups, together with N, may form a cyclic ring such as a piperidine or morpholine ring; and provided that R⁸ and R¹² may, together, form a cyclic ring, and R³ and R⁵ may, together, represent O, and when Q is menthadiene, R¹ and R² are H and Y is hydroxyl, R may not be H or alkyl.

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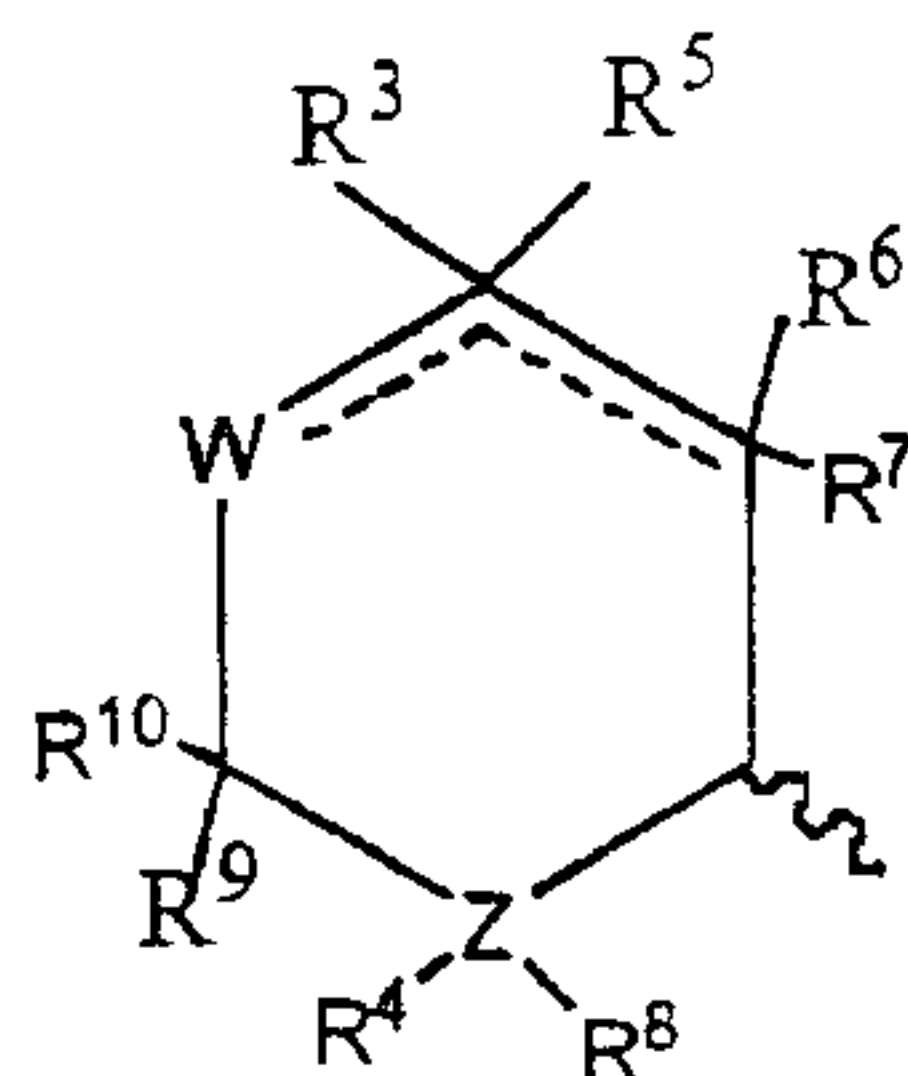
Preferably, the compound of formula I is



wherein Y is selected from the group consisting of keto and hydroxyl;

Z is N or C;

Q is selected from the group consisting of



wherein W is a direct bond or C(R¹¹)(R¹²);

a dotted line represents the presence or absence of a double bond;

wherein R is selected from the group consisting of H, halogen, e.g. bromo or chloro; and C₁₋₅ alkyl; R¹ is selected from the group consisting of H, halogen, e.g. bromo or chloro;

R² is independently selected from the group consisting of H, C₁₋₅ alkyl, halogen, XC₁₋₅ alkyl, C₁₋₅ alkylOR¹³, C₁₋₅ alkylN(R¹³)₂, N(R¹³)₂, XC₁₋₅ alkylN(R¹³)₂ and XC₁₋₅ alkylOR¹³;

X is O or S(O)_n;

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n is 0 or an integer of from 1 to 2;

R^3 is selected from the group consisting of H, hydroxyl, C_{1-5} alkyl, C_{1-5} alkylOR¹³ and C_{1-5} alkylN(R^{13})₂;

R^4 is selected from the group consisting of H, C_{1-5} alkenyl, e.g. isopropenyl, C_{1-5} alkyl, C_{1-5} alkylOR¹³ and C_{1-5} alkylN(R^{13})₂;

R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} are independently selected from the group consisting of H, C_{1-5} alkyl, C_{1-5} alkylOR¹³ and OR¹³; and

R^{13} is selected from the group consisting of H, C_{1-5} alkyl and C_{3-8} cyclic alkyl, or two R^{13} groups, together with N, may form a cyclic ring such as a piperidine or morpholine ring; and provided that any of said alkyl groups may be substituted with a hetero atom containing radical, wherein said heteroatom is R^8 and R^{12} may, together, form a cyclic ring; and R^3 and R^5 may, together, represent O, and when Q is menthadiene, R^1 and R^2 are H and Y is hydroxyl, R may not be H or alkyl.

In a further aspect, the present invention relates to pharmaceutical compositions comprising a therapeutically effective amount of a compound of formulae (I) or (I'), in admixture with a non-toxic, pharmaceutically acceptable liquid vehicle. Such pharmaceutical compositions may be ophthalmic solutions which are useful in treating ocular hypertension and/or glaucoma. Finally, the present invention provides certain novel compounds which are useful in treating ocular hypertension and/or glaucoma.

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Brief Description of the Figures

Figure 1 shows the effect of abnormal cannabidiol on intraocular pressure.

Figure 2 shows the effect of the compound of Example 4 intraocular pressure.

Figure 3 shows the effect of the compound of Example 3 intraocular pressure.

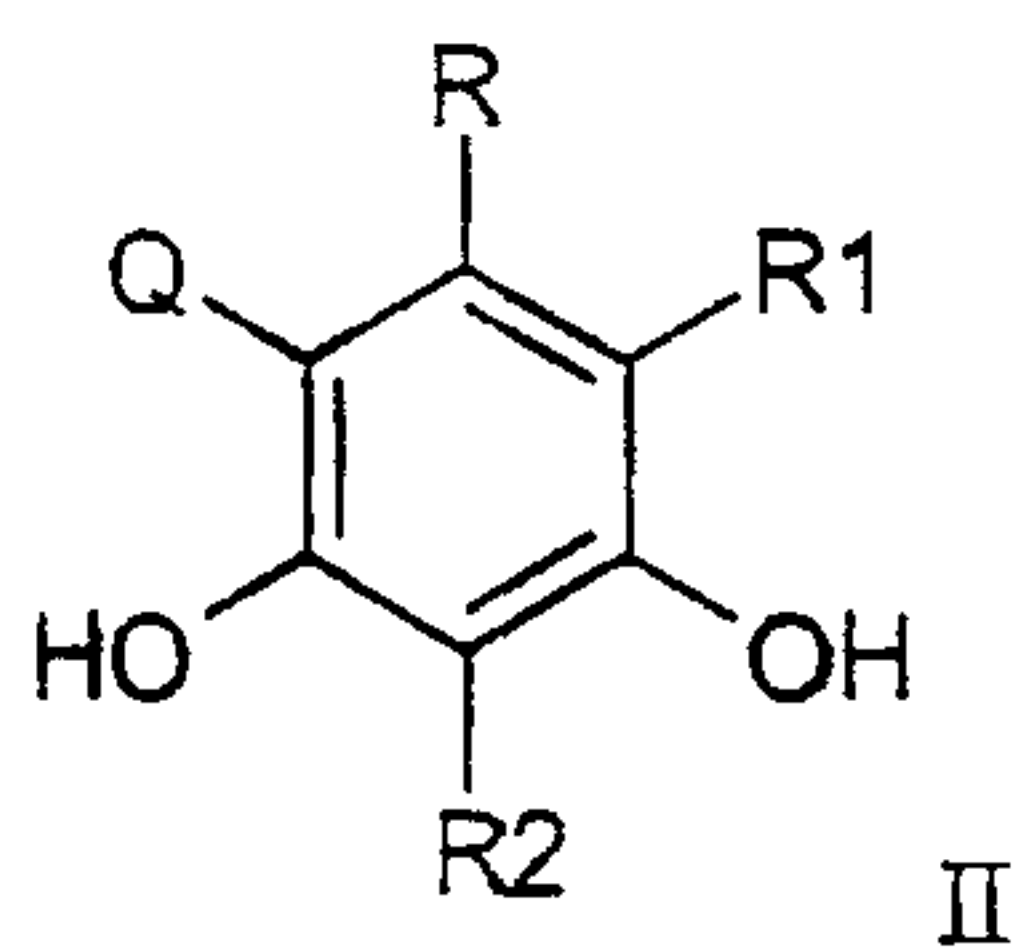
Figure 4 shows the effect of the compound of Example 6 intraocular pressure.

Figure 5 shows the effect of the compound of Example 5 intraocular pressure.

Detailed Description of the Invention

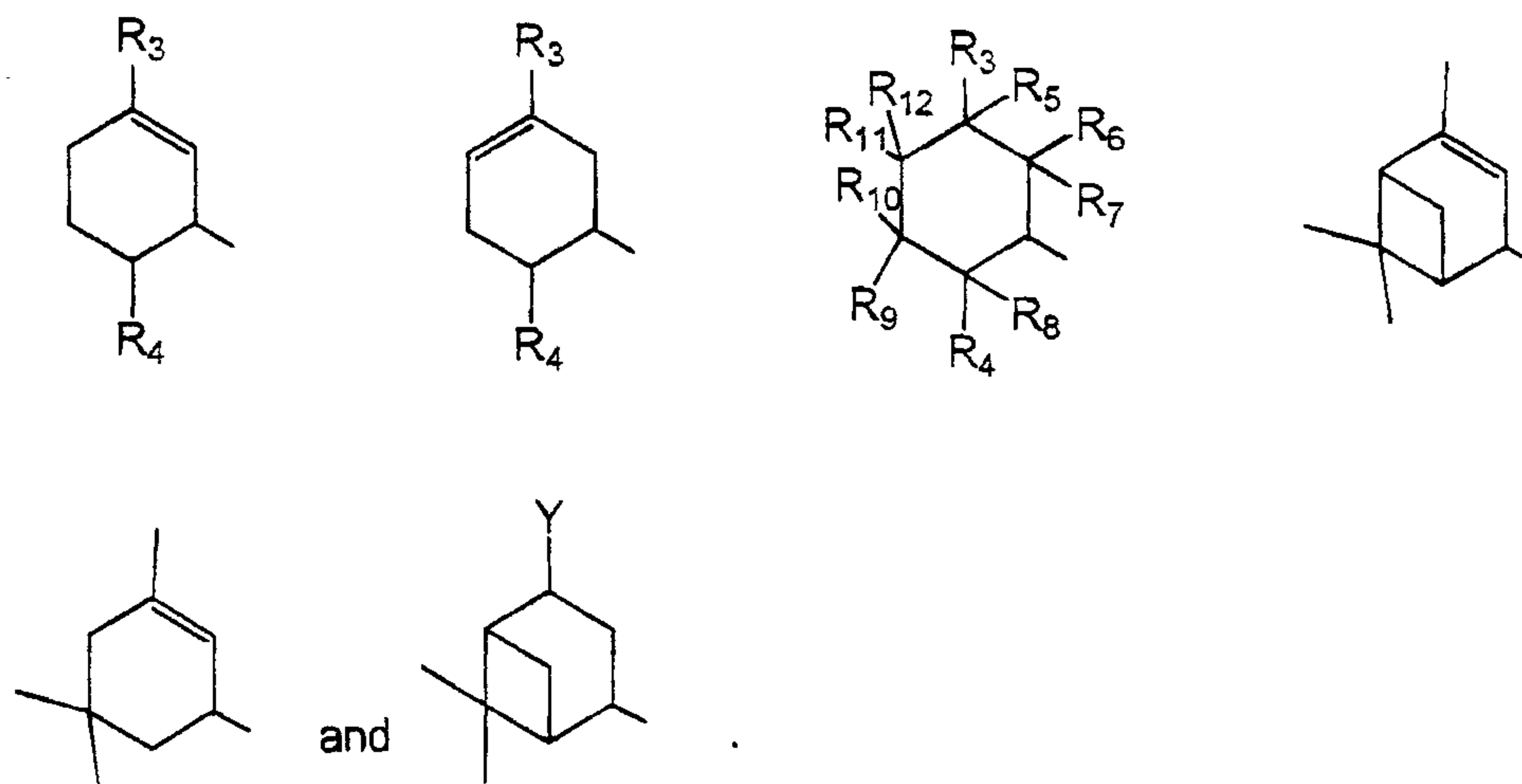
The present invention relates to the use of Abnormal Cannabidiols as ocular hypotensives. These therapeutic agents are represented by compounds having the formula I or I', above.

In one embodiment of the invention, the compound is selected from the group consisting of abnormal Cannabidiols and analogues thereof represented by formula II

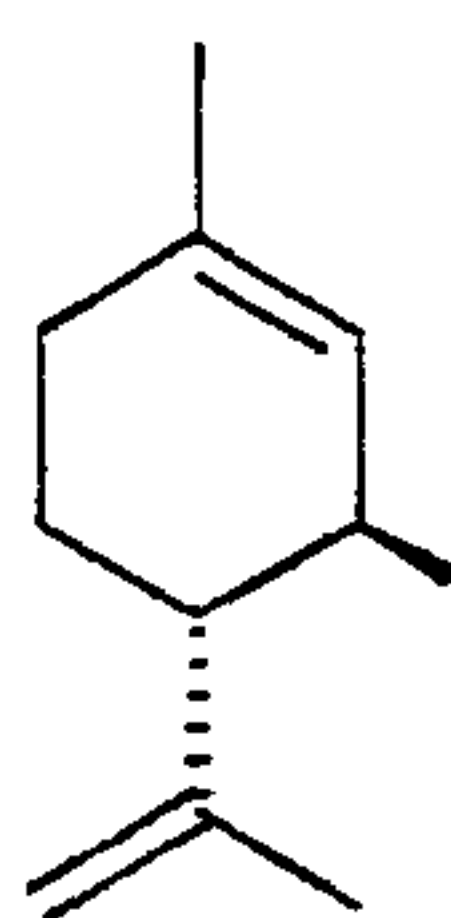


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wherein Q is selected from the group consisting of



A particularly preferred group represented by Q is menthadiene or

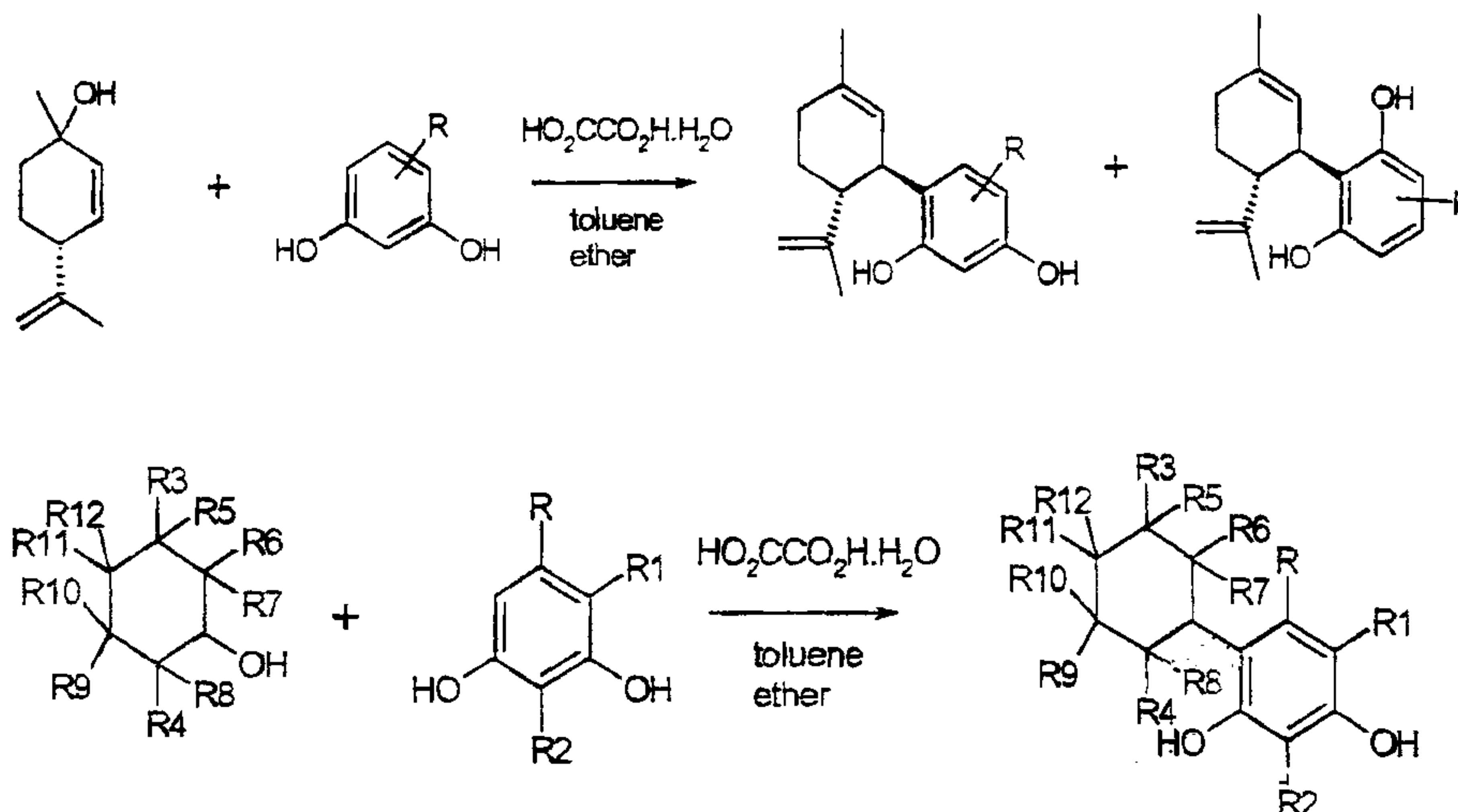


In this class of compounds, preferably, R is selected from the group consisting of hydrogen, methyl, bromo and chloro and R¹ is selected from the group consisting of hydrogen, methyl and chloro.

Compounds of this type may be prepared by condensation of a cyclic alkene or cyclic alcohol with a suitably substituted benzene-1,3-diol. The reaction is catalysed by an acid such as oxalic acid dihydrate or p-toluenesulphonic acid. The reaction is carried out in a solvent or mixture of solvents such as toluene, diethyl ether or dichloromethane. A mixture of the two isomers is obtained and

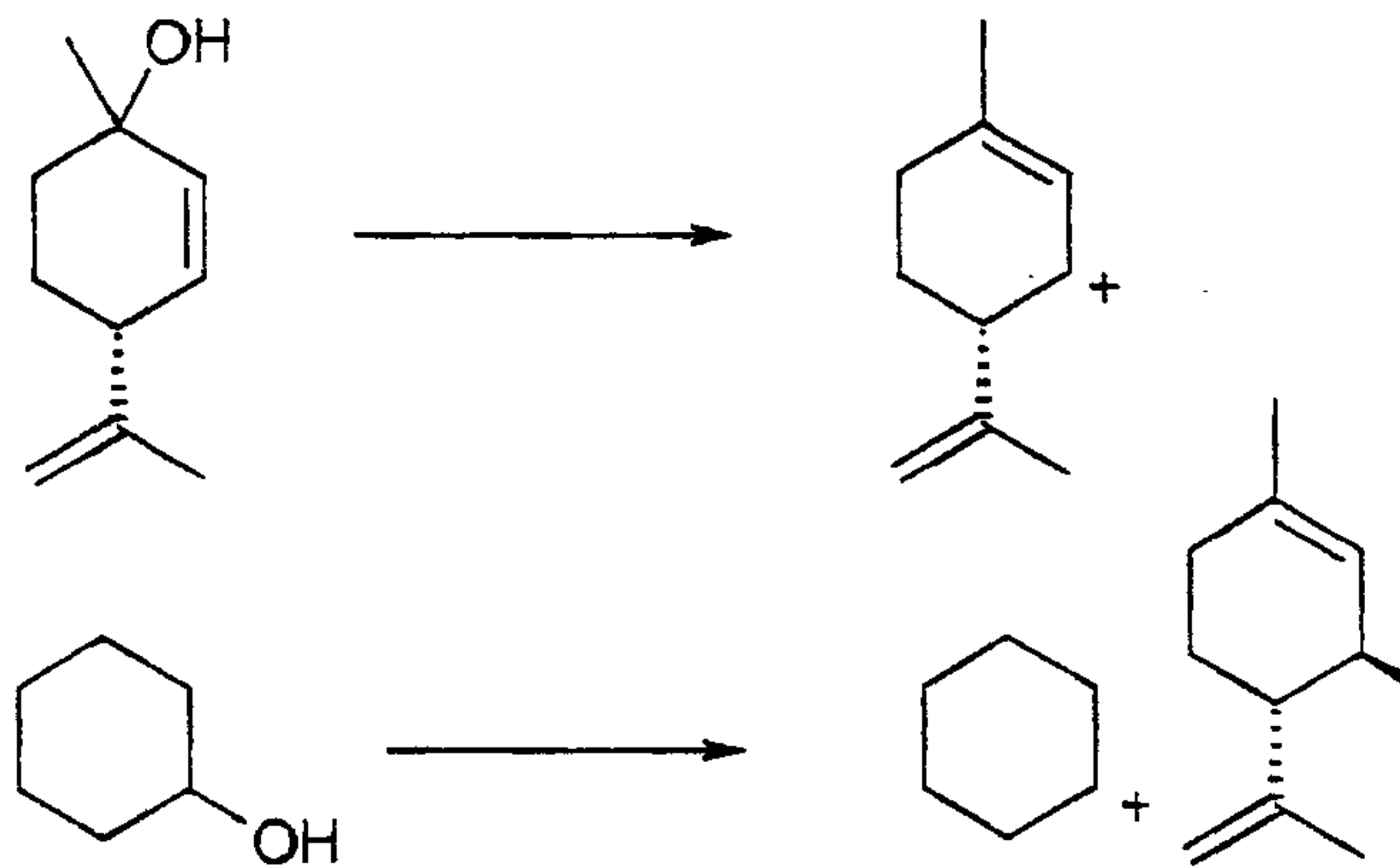
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the desired product is separated by chromatography. The reaction scheme is illustrated below.



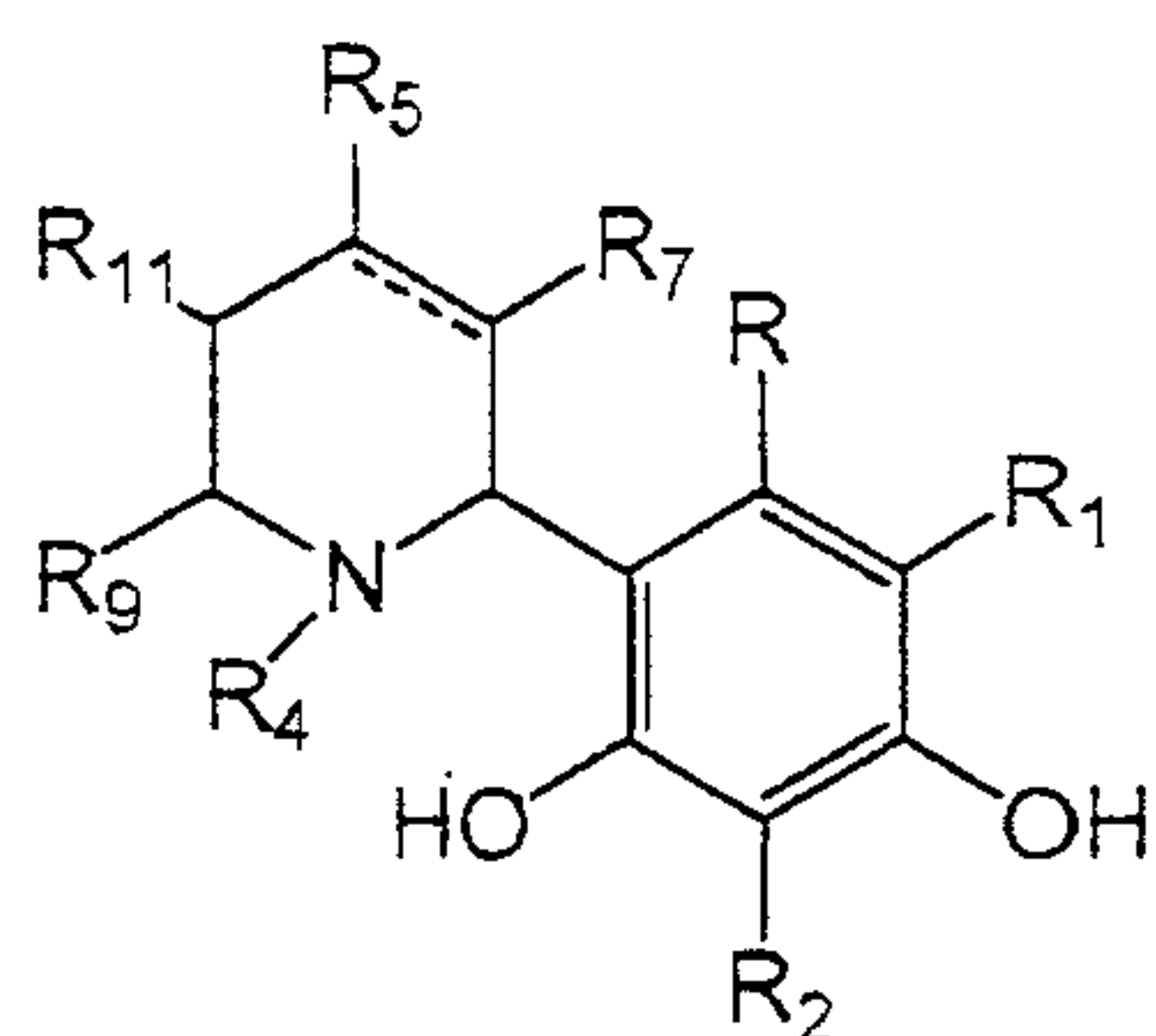
The synthesis of the starting materials is well known.

The mechanism of the reaction is the result of the formation of a carbocation by elimination of OH or a starting material containing a functional group such as acetate which can also be eliminated to give the carbocation can be used.



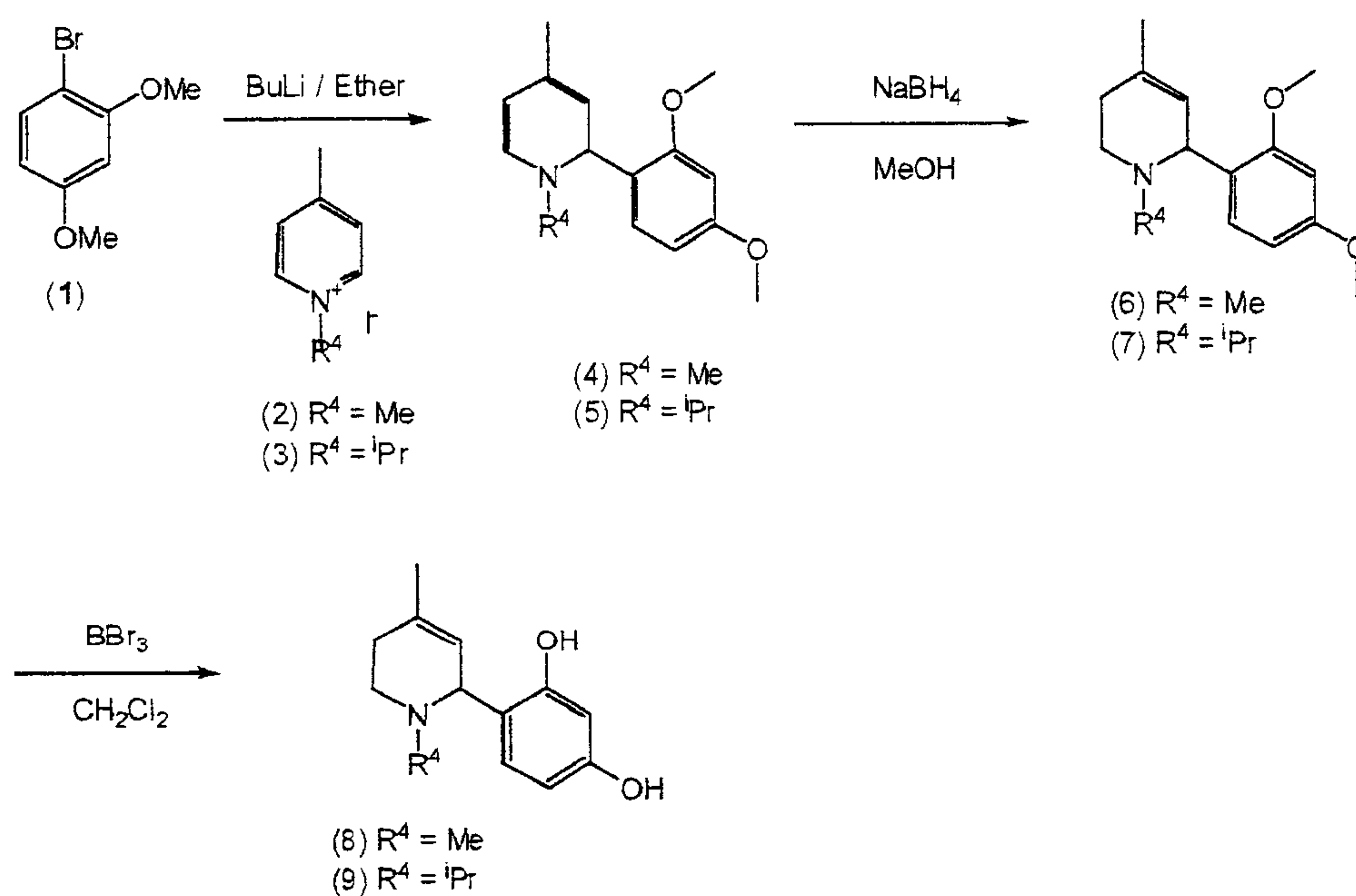
In another embodiment of the invention the compound is tetrahydropyridine represented by formula III

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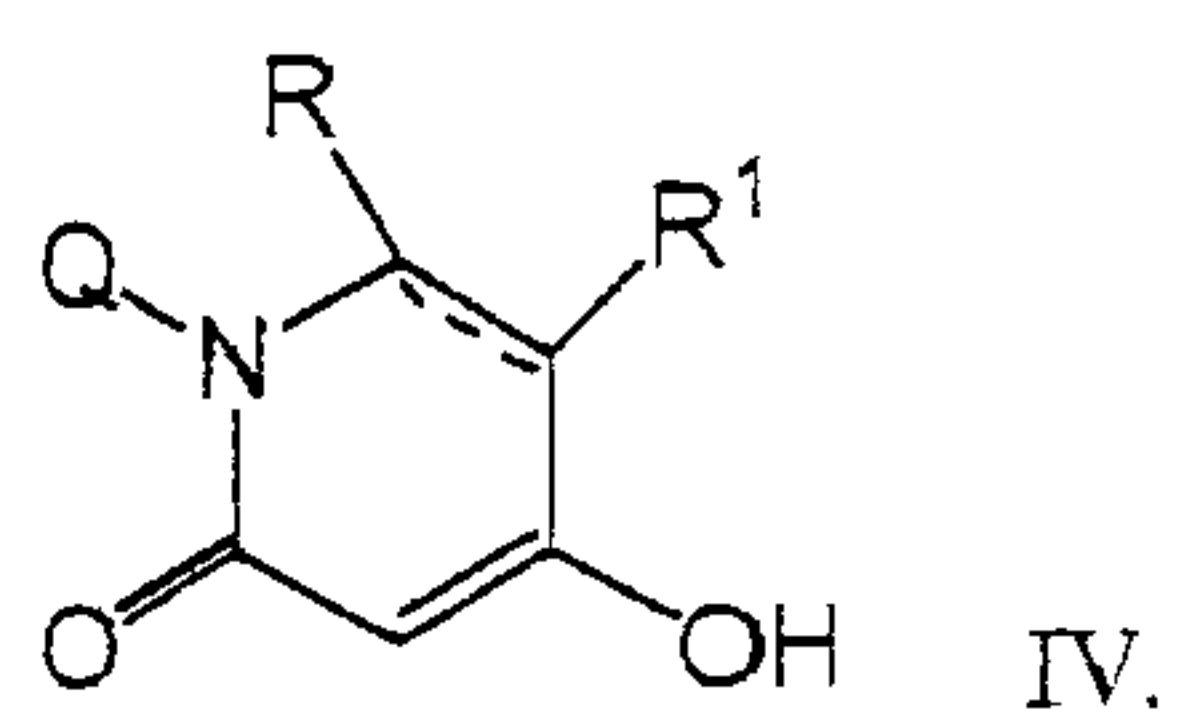
III.

These tetrahydropyridine compounds may be synthesized according to the following reaction scheme wherein Me is methyl, Bu is butyl and iPr is isopropyl.

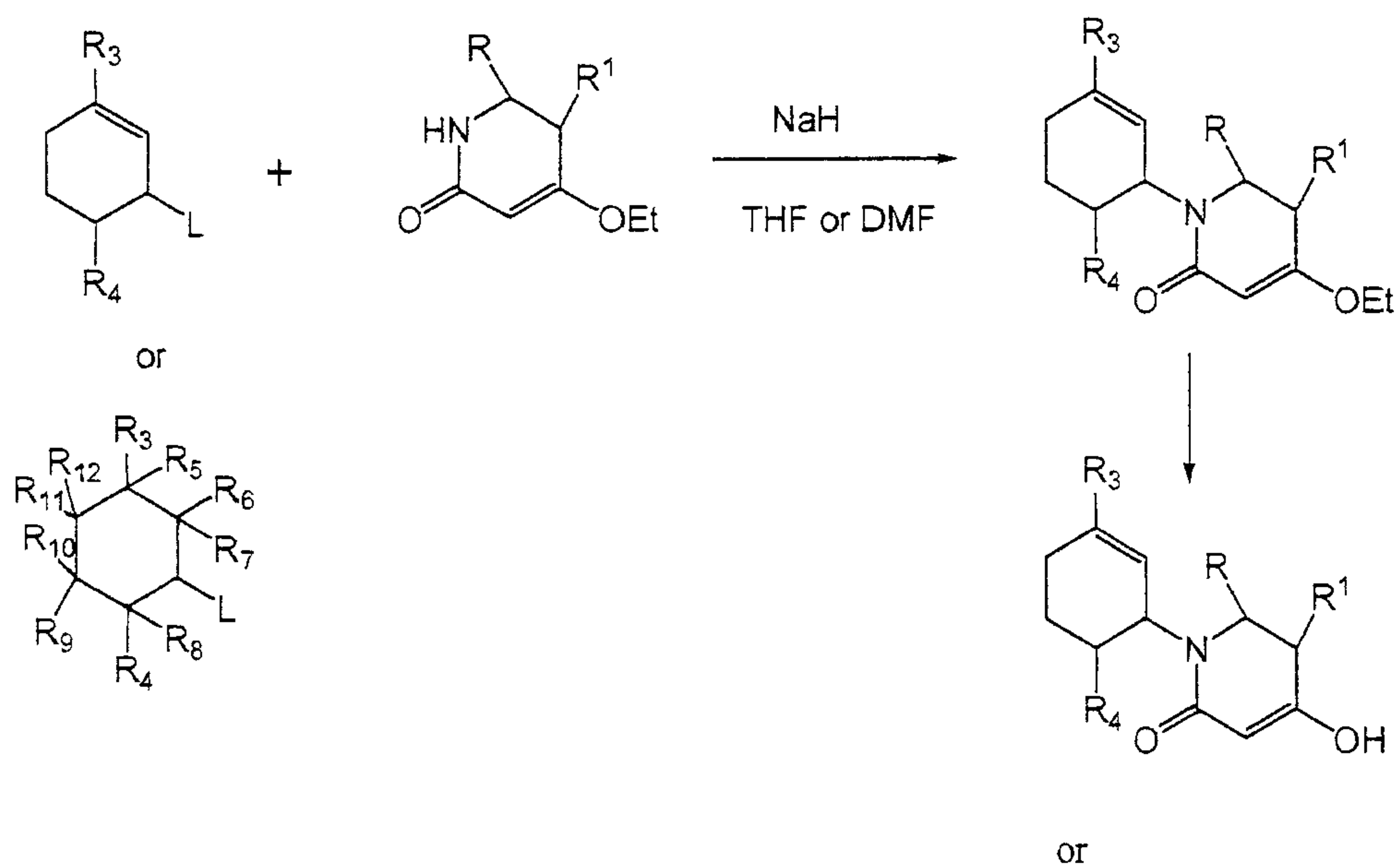


In a further embodiment of the invention, the compound is a piperidinedione represented by the formula IV

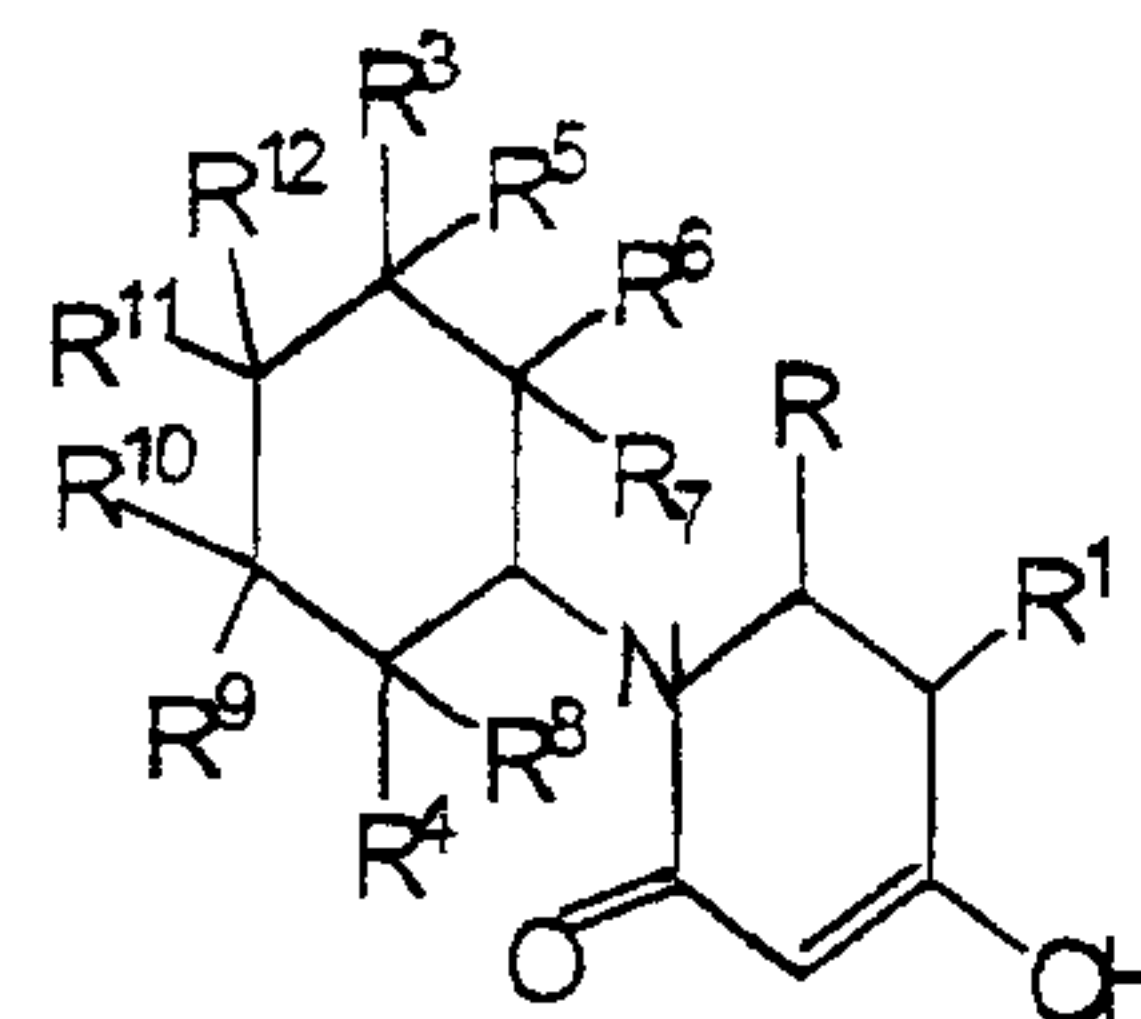
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These compounds may be synthesized according to the following reaction scheme wherein Et is ethyl, THF is tetrahydrofuran and DMF is dimethyl formamide.



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Where L is a leaving group such bromine, iodine or tosyl.

Compounds of formula I' wherein Y and Y¹ are keto are known as piperidine-2, 4-diones and may be synthesized as described by H. Nishino, et al., Tetrahedron 2005, 11107-11124. The corresponding cyclohexane-1, 3 diones may be prepared as described in EP 291114 and EP 310186.

Compounds of formula I' wherein Y is keto and Y¹ is hydroxyl are known as 4-hydroxypyridin-2-ones and may be prepared as described by Castillo, et al. in Bull. Soc. Chim. Fr. 1982, 257-261.

The compounds wherein Y=Y¹=hydroxyl may be prepared by dehydrogenation of the corresponding cyclohexane -1, 3 diones by the method described by E.D. Berymann, et al., JACS, 1953, 3226. Compounds of formula I' wherein both of Z is N, Y is oxo and Y¹ is hydroxyl may be prepared as described in WO 2005/007632 and J. Het. Chem. 1989, 169-176.

In all of the above formulae, as well as in those provided hereinafter, the straight lines represent bonds. Where there is no symbol for the atoms between the bonds, the appropriate carbon-containing radical is to be inferred.

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Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, as an active ingredient, with conventional ophthalmically acceptable pharmaceutical excipients, and by preparation of unit dosage forms suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.0001 and about 5% (w/v), preferably about 0.001 to about 1.0% (w/v) in liquid formulations.

For ophthalmic application, preferably solutions are prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should preferably be maintained between 4.5 and 8.0 with an appropriate buffer system, a neutral pH being preferred but not essential. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A preferred surfactant is, for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium

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thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edentate disodium, although other chelating agents may also be used in place or in conjunction with it.

The ingredients are usually used in the following amounts:

<u>Ingredient</u>	<u>Amount (% w/v)</u>
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	1-10
buffer	0.01-10
pH adjustor	q.s. pH 4.5-7.5
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered application, such as in containers equipped with a dropper, to facilitate application to the eye. Containers suitable for dropwise application are usually made of suitable inert, non-toxic plastic material, and generally contain between about 0.5 and about 15 ml solution. One package may contain one or more unit doses.

Especially preservative-free solutions are often formulated in non-resealable containers containing up to about ten, preferably up to about five unit

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doses, where a typical unit dose is from one to about 8 drops, preferably one to about 3 drops. The volume of one drop usually is about 20-35 μ l.

The compounds disclosed herein for use in the method of this invention, i.e. the treatment of glaucoma or elevated intraocular pressure, may also be used in combination with other drugs useful for the treatment of glaucoma or elevated intraocular pressure.

For the treatment of glaucoma or elevated intraocular pressure, combination treatment with the following classes of drugs are contemplated: β -Blockers (or β -adrenergic antagonists) including carteolol, levobunolol, metipranolol, timolol hemihydrate, timolol maleate, β 1-selective antagonists such as betaxolol, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Adrenergic Agonists including non-selective adrenergic agonists such as epinephrine borate, epinephrine hydrochloride, and dipivefrin, and the like, or pharmaceutically acceptable salts or prodrugs thereof; and

α 2-selective adrenergic agonists such as apraclonidine, brimonidine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Carbonic Anhydrase Inhibitors including acetazolamide, dichlorphenamide, methazolamide, brinzolamide, dorzolamide, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Cholinergic Agonists including direct acting cholinergic agonists such as carbachol, pilocarpine hydrochloride, pilocarpine nitrate, pilocarpine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

cholinesterase inhibitors such as demecarium, echothiophate, physostigmine, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Glutamate Antagonists such as memantine, amantadine, rimantadine, nitroglycerin, dextrophan, detromethorphan, CGS-19755, dihydropyridines, verapamil, emopamil, benzothiazepines, bepridil, diphenylbutylpiperidines, diphenylpiperazines, HOE 166 and related drugs, fluspirilene, eliprodil,

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ifenprodil, CP-101,606, tibalosine, 2309BT, and 840S, flunarizine, nicardipine, nifedimpine, nimodipine, barnidipine, lidoflazine, prenylamine lactate, amiloride, and the like, or pharmaceutically acceptable salts or prodrugs thereof;

Prostamides such as bimatoprost, or pharmaceutically acceptable salts or prodrugs thereof; and

Prostaglandins including travoprost, UFO-21, chloprostenol, fluprostenol, 13,14-dihydro-chloprostenol, isopropyl unoprostone, latanoprost and the like.

The invention is further illustrated by the following non-limiting Examples.

Example 1

Intraocular Pressure

Intraocular pressure was measured by applanation pneumatonometry in conscious animals. The test compound was administered topically to one eye while vehicle was given to the fellow eye in a masked fashion. Ocular normotensive Beagle dogs (males, females) were dosed once daily for five days. Laser-induced unilaterally ocular hypertensive Cynomolgus monkeys (females) were dosed once daily for 4 days. Student's paired *t*-test was used for statistical comparisons. Differences were considered statistically significant if the *P*-value is less than 0.05.

The results are shown in the Figures.

The figures show the change from baseline IOP of Monkey dosed with 0.1% of the active compound versus time.

Example 2

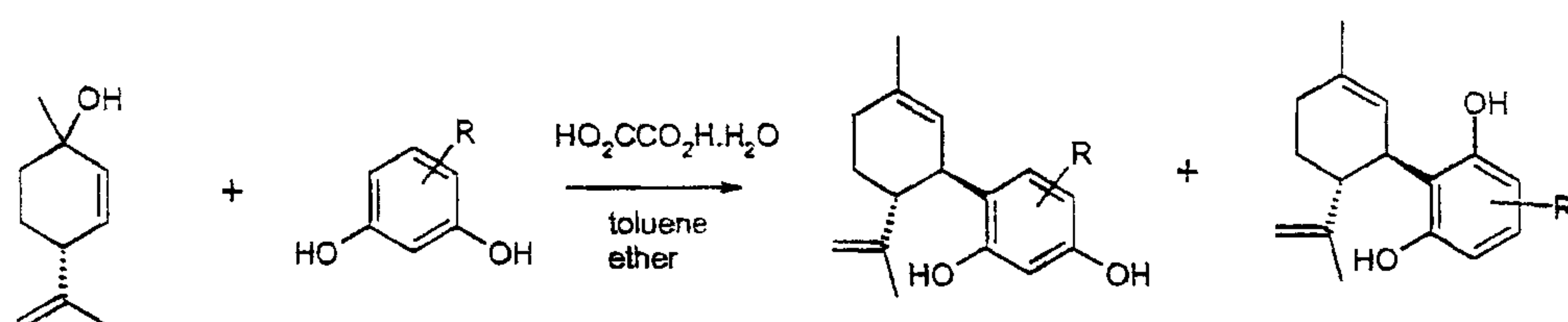
Determination of Abnormal Cannabidiol Activity

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Abnormal Cannabidiol receptor activity may be measured in accordance with the procedure disclosed in (Wagner JA et al., *Hypertension* 33 [part II], 429 (1999); J  rai Z et al., *PNAS* 96, 14136 (1999)).

Experimental Details for Synthesis of Abnormal Cannabidiols

General Route



Example 3

5-methyl-4-(6-Isoprenyl-3-methylcyclohex-2-enyl)benzene-1,3-diol

(4R)-1-Methyl-4-isoprenylcyclohex-2-ene-1-ol (300mg, 2mmoles) was dissolved in toluene (20ml) and 5-methylresorcinol (248mg, 2mmoles) was added in diethyl ether (5ml). Oxalic acid dihydrate (252mg, 2mmoles) was added and the reaction mixture heated with stirring at 80° for 5 hours. The reaction mixture was allowed to cool and diluted with diethyl ether (30ml). The ether solution was washed twice with aqueous sodium bicarbonate and dried over anhydrous magnesium sulphate. The solvents were evaporated under reduced pressure to give the crude product as a brown oil (800mg). The product was purified using a silica column eluted with ethyl acetate : isohexane 1 : 9 going to ethyl acetate : isohexane 2 : 8. The product was isolated as a yellow gum (106mg)

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Example 4**4-(6-Isoprenyl-3-methylcyclohex-2-enyl)benzene-1,3-diol**

The named compound is prepared according to the method described in Example 3 except that resorcinol is substituted for 5-methylresorcinol.

¹H NMR (300MHz, CDCl₃) 6.2 (M, 2H), 6.1 (S, 1H), 5.55 (M, 1H), 4.7 (M, 1H), 4.55 (S, 1H), 4.5 (M, 1H), 3.55 (M, 1H), 2.5 (M, 1H), 2.2 (M, 2H), 2.15 (S, 3H), 1.85 (M, 2H), 1.8 (S, 3H), 1.6 (S, 3H)

Also prepared in a similar manner were

Example 5**5-Chloro-4-(6-Isoprenyl-3-methylcyclohex-2-enyl)benzene-1,3-diol**

¹H NMR (300MHz, CDCl₃) 6.4 (M, 1H), 6.3 (M, 1H), 6.25 (S, 1H), 5.6 (M, 1H), 4.7 (brS, 1H), 4.65 (M, 1H), 4.4 (M, 1H), 4.0 (M, 1H), 2.5 (M, 1H), 2.25 (M, 1H), 2.15 (M, 1H), 1.85 (M, 2H), 1.8 (S, 3H), 1.6 (S, 3H)

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Example 6**4-(6-Isoprenyl-3-methylcyclohex-2-enyl)-5-methoxybenzene-1,3-diol**

¹H NMR (300MHz, CDCl₃) 6.15 (brS, 1H), 6.0 (M, 2H), 5.6 (M, 1H), 4.65 (brS, 1H), 4.5 (M, 1H), 4.35 (M, 1H), 3.95 (M, 1H), 3.7 (S, 3H), 2.4 (M, 1H), 2.25 (1H, M), 2.1 (M, 1H), 1.8 (M, 2H), 1.8 (S, 3H), 1.65 (S, 3H)

Example 7**2-(6-Isoprenyl-3-methylcyclohex-2-enyl)-5-methoxybenzene-1,3-diol**

¹H NMR (300MHz, CDCl₃) 6.0 (brS, 2H), 5.55 (M, 1H), 4.7 (M, 1H), 4.6 (M, 1H), 3.8 (M, 1H), 3.75 (S, 3H), 2.4 (M, 1H), 2.2 (M, 1H), 2.1 (M, 1H), 1.8 (S, 3H), 1.8 (M, 2H)

Example 8**Synthesis of 6-Chloro-4-(6-Isoprenyl-3-methylcyclohex-2-enyl)benzene-1,3-diol**

4-Chlororesorcinol (350mg, 2.4mmoles) was dissolved in toluene (30ml) and diethyl ether (20ml) and p-toluenesulphonic acid (91mg, 0.48mmoles) was added.

(4R)-1-Methyl-4-isoprenylcyclohex-2-ene-1-ol (500mg, 3mmoles) in toluene (10ml) was added and the reaction mixture was stirred at room temperature for 6 hours. Diluted with diethyl ether (30ml) and washed twice with aqueous sodium bicarbonate. Dried over anhydrous magnesium sulphate and the solvent was evaporated under reduced pressure to give a yellow gum (800mg).

Purified using a silica column eluted with ethyl acetate : isohexane 9:1 going to ethyl acetate : isohexane 8:2. The product was isolated as a yellow gum (95mg)

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^1H NMR (300MHz, CDCl_3) 6.9 (S, 1H), 6.5 (S, 1H), 5.5 (S, 1H), 5.45 (M, 1H), 5.35 (S, 1H), 4.7 (M, 1H), 4.6 (M, 1H), 3.35 (M, 1H), 2.2 (M, 3H), 1.8 (M, 3H), 1.75 (M, 2H), 1.6 (S, 3H)

Example 9

Synthesis of 4-Cyclohexylbenzene-1,3-diol

This compound was prepared as described in JACS, 1953, 2341.

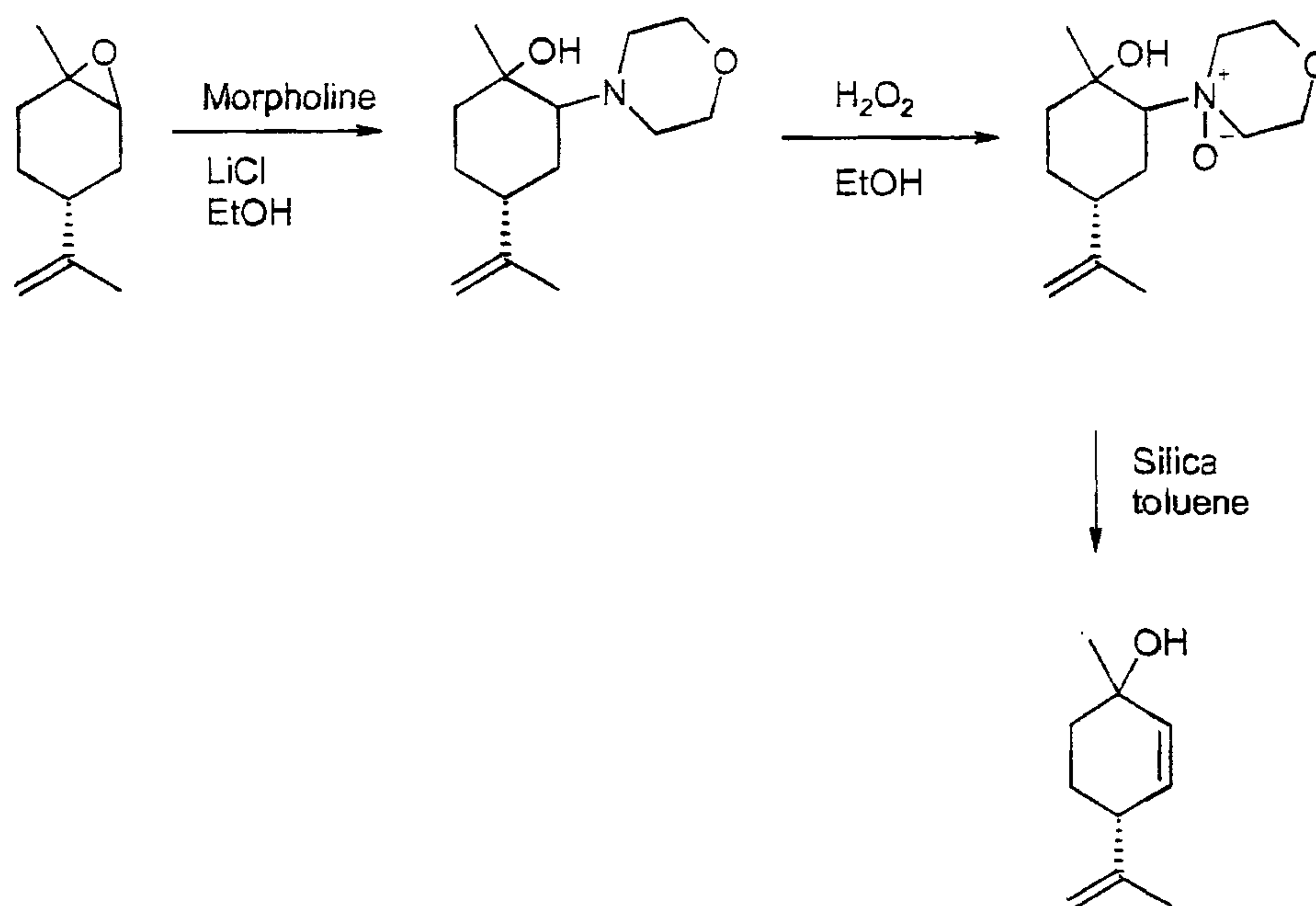
Resorcinol (2.2g, 0.02 moles) was mixed with cyclohexanol (1g, 0.01moles) and zinc (II) chloride (0.48g, 0.0035moles) and the reaction mixture heated to 150° with stirring. After heating 2 hours, the reaction mixture was allowed to cool and then dissolved in ethyl acetate. Washed with water and dried over anhydrous magnesium sulphate. The solvent was evaporated to give a brown oil (3.0g). Excess resorcinol was evaporated by heating in a Kugelrohr oven under reduced pressure (200° , 2mmHg). Purified using a silica column eluted with ethyl acetate : isohexane 2:8 to give the product as a yellow oil (0.5g). Trituration with isohexane gave the product as a white solid (0.2g).

^1H NMR (300MHz, CDCl_3) 7.0 (D, 1H $J = 8\text{Hz}$), 6.4 (M, 1H), 6.3 (M, 1H), 4.7 (S, 1H), 4.55 (S, 1H), 2.7 (M, 1H), 1.8 (M, 5H), 1.4 (M, 5H)

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Example 10**Synthesis of 4R-Isoprenyl-1-methylcyclohex-2-enol**

The synthesis of 4R-Isoprenyl-1-methylcyclohex-2-enol was carried out as described in WO2004096740.

**Example 11****4-Isoprenyl-1-methyl-2-morpholin-4-yl-cyclohexanol**

(+)-Limonene oxide (13.2g, 0.087moles) was dissolved in ethanol (40ml) and lithium chloride (5.9g, 0.14moles) was added with stirring. Morpholine (11.4g, 0.13moles) was added and the reaction mixture was heated at 60° for 48hours. The solvent was evaporated under reduced pressure and the residue taken up in dichloromethane. Washed with water. Extracted into 2M hydrochloric acid and washed with dichloromethane. Basified to pH 10 by addition of 2M sodium hydroxide. Extracted with diethyl ether and washed with

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water. Dried over anhydrous magnesium sulphate and evaporated the solvent under reduced pressure to give the product as a yellow oil (10.3g)

¹H NMR (300MHz, CDCl₃) 4.95 (M, 1H), 4.85 (M, 1H), 3.7 (M, 4H), 2.75 (M, 2H), 2.5 (M, 4H), 2.1 (M, 1H), 1.95 (M, 1H), 1.75 (S, 3H), 1.6 (M, 4H), 1.2 (S, 3H)

Example 12

4-Isoprenyl-1-methyl-2-(4-oxy-morpholin-4-yl)-cyclohexanol

4-Isoprenyl-1-methyl-2-morpholin-4-yl-cyclohexanol (17.7g, 0.074 moles) was dissolved in ethanol (100ml) and 35% hydrogen peroxide (37ml, 0.325moles) was added. Heated with stirring at 50° for 6 hours. 5% palladium on carbon (100mg) was added in order to decompose the excess peroxide. Stirred at room temperature for 3 hours. (Peroxide test papers gave a negative result.)

Filtered through a pad of HiFlo to remove the palladium on carbon and the solvent was evaporated under reduced pressure to give the product as a yellow oil (22.2g).

¹H NMR (300MHz, CDCl₃) 5.5 (M, 1H), 4.85 (M, 1H), 4.5 (M, 2H), 3.7 (M, 4H), 3.4 (M, 3H), 2.95 (M, 1H), 2.65 (M, 1H), 2.25 (M, 1H), 2.0 (M, 1H), 1.85 (M, 1H), 1.75 (M, 1H), 1.75 (S, 3H), 1.55 (M, 1H), 1.55 (S, 3H)

Example 13

4R-Isoprenyl-1-methylcyclohex-2-enol

4-Isoprenyl-1-methyl-2-morpholin-4-yl-cyclohexanol (4.6g, 0.018

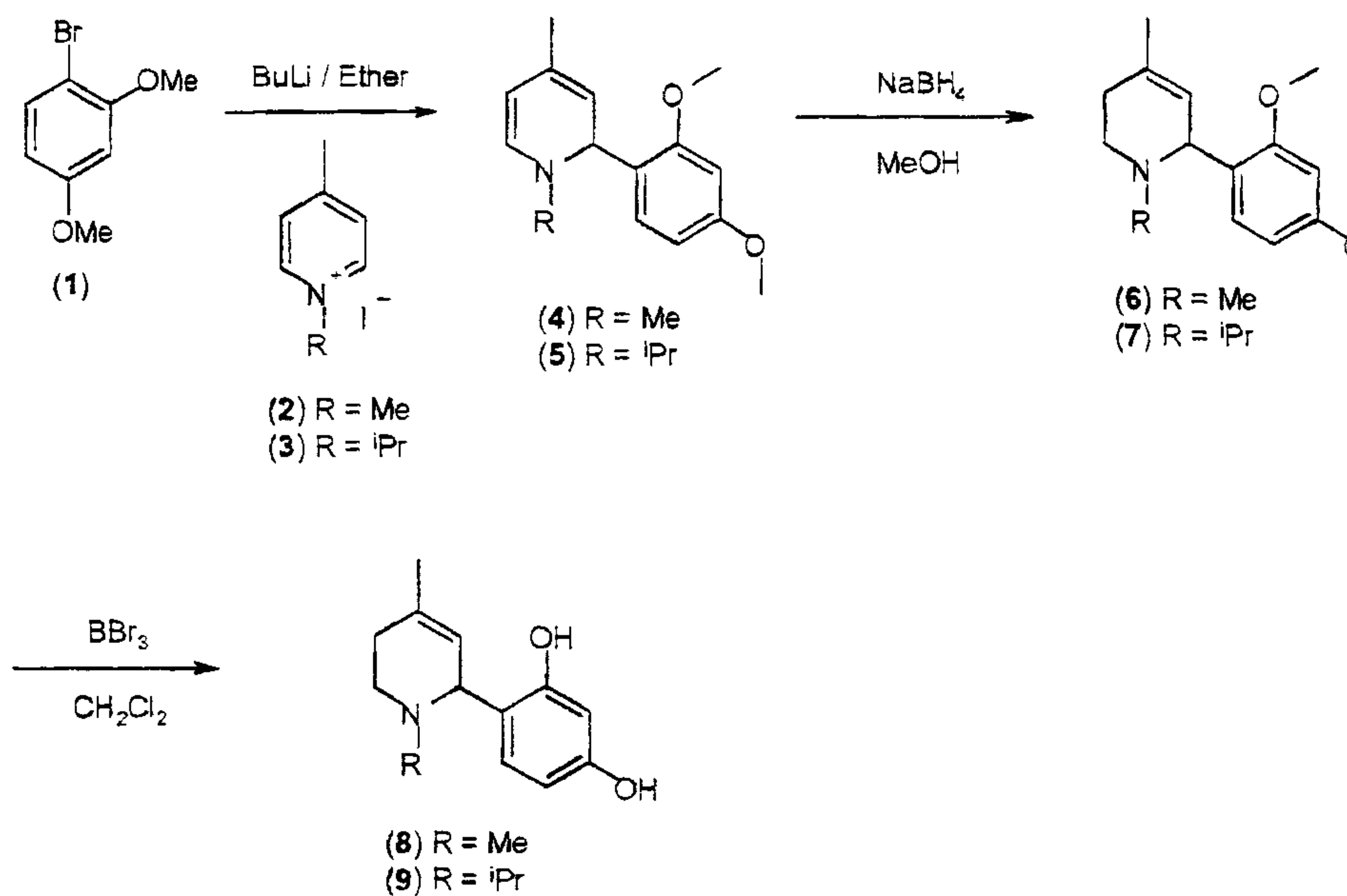
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moles) was dissolved in toluene (80ml) and silica (1.1g) was added. The reaction mixture was heated to reflux with stirring. Water generated in the reaction was removed using Dean and Stark apparatus. After refluxing overnight, the silica was removed by filtration and the filtrate evaporated under reduced pressure to give a brown oil (4.0g). Dissolved in dichloromethane and washed with 2M hydrochloric acid. Washed with water and dried over anhydrous magnesium sulphate. The solvent was removed by evaporation under reduced pressure to give the product as a brown oil (1.3g).

^1H NMR (300MHz, CDCl_3) 5.7 (M, 2H), 4.8 (M, 2H), 2.7 (M, 1H), 1.8 (M, 2H), 1.75 (S, 3H), 1.65 (M, 2H), 1.3 (S, 3H)

Experimental details for Synthesis of Tetrahydropyridines

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Scheme 1

Example 14

Preparation of 2-(2,4-Dimethoxyphenyl)-1,4-dimethyl-1,2-dihydropyridine.

To a stirred solution of 2,4-dimethoxybromobenzene (1) (0.5g, 2.3mmol) in diethyl ether (10ml) cooled at -78°C under nitrogen was added a solution of n-butyl lithium (1.0ml, 2.5mmol of 2.5M solution in hexane) drop wise. The mixture was stirred at -78°C for 2 hours and then 1,4-dimethyl pyridinium iodide (2) (0.54g, 2.5mmol) was added as a solid. The resultant mixture was allowed to warm to room temperature and stirred at room temperature for 18 hours. The mixture was diluted with water (20ml) and extracted with diethyl ether (2 x 15ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated to yield 2-(2,4-dimethoxyphenyl)-1,4-dimethyl-1,2-dihydropyridine (4) (0.5g, 93%) as a brown oil, ^1H NMR

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CDCl_3 δ 1.7 (s, 3H), 2.7 (s, 3H), 3.8 (s, 6H), 4.45 (dd, 1H, $J = 2, 7$), 4.85 (m, 1H), 5.4 (d, 1H, $J = 4$), 6.05 (d, 1H, $J = 7$), 6.45 (d, 1H, $J = 3$), 6.55 (m, 1H), 7.5 (d, 1H, $J = 9$).

By proceeding in a similar manner starting from 2,4-dimethoxybromobenzene (1) and 1-isopropyl-4-methyl pyridinium iodide (3), 2-(2,4-dimethoxyphenyl)-1-isopropyl-4-methyl-1,2-dihydropyridine (5) was prepared, ^1H NMR CDCl_3 δ (d, 6H $J = 7$), 1.7 (s, 3H), 3.15 (m, 1H), 3.7 (s, 6H), 4.5 (d, 1H $J = 8$), 4.8 (m, 1H), 5.5 (s, 1H $J = 5$), 6.3 (d, 1H $J = 7$), 6.45 (d, 1H $J = 2$), 6.55 (m, 1H), 7.55 (d, 1H $J = 8$).

Example 15

Preparation of 6-(2,4-Dimethoxyphenyl)-1,4-dimethyl-1,2,3,6-tetrahydropyridine (6).

To a stirred solution of 2-(2,4-dimethoxyphenyl)-1,4-dimethyl-1,2-dihydropyridine (4) (0.48g, 2.06mmol) in methanol (5ml) at room temperature was added sodium borohydride (98mg, 2.51mmol), gas evolution commenced immediately, the resulting mixture was stirred for 3 hours. At this time the solvent was evaporated and the residue suspended in water (5ml) and extracted with ethyl acetate (2 x 10ml). The organic extract was then extracted with 2M hydrochloric acid (2 x 15ml). The aqueous layer was basified with 2M sodium hydroxide and extracted with ethyl acetate (2 x 20ml), the organic extract was dried over anhydrous magnesium sulphate, filtered and evaporated to yield 6-(2,4-dimethoxyphenyl)-1,4-dimethyl-1,2,3,6-tetrahydropyridine (6) (350mg, 73%) as a yellow oil, ^1H NMR CDCl_3 δ 1.55 (s, 3H), 1.9 (m, 1H), 2.2 (s, 3H), 2.5 (m, 2H), 2.95 (m, 1H), 3.8 (s, 6H), 4.1 (m, 1H), 5.2 (m, 1H), 6.5 (m, 2H), 7.3 (d, 1H $J = 4$).

By proceeding in a similar manner starting from 2-(2,4-dimethoxyphenyl)-1-isopropyl-4-methyl-1,2-dihydropyridine (5), 6-(2,4-dimethoxyphenyl)-1-

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isopropyl-4-methyl-1,2,3,6-tetrahydropyridine (7) was prepared, ^1H NMR CDCl_3 δ 0.95 (d, 3H J = 6), 1.05 (d, 3H J = 6), 1.7 (s, 3H), 1.9 (m, 1H), 2.5 (m, 1H), 2.85 (m, 1H), 3.0 (m, 1H), 3.8 (s, 6H), 4.6 (s, 1H), 5.2 (s, 1H), 6.45 (d, 1H J = 3), 6.5 (dd, 1H J = 3, 8), 7.4 (d, 1H J = 8).

Example 16

Preparation 4-(1,4-Dimethyl-1,2,5,6-tetrahydropyridin-2-yl)-benzene-1,3-diol (8)

To a stirred solution of 6-(2,4-dimethoxyphenyl)-1,4-dimethyl-1,2,3,6-tetrahydro-pyridine (6) (300mg, 1.27mmol) in dichloromethane (20ml) cooled at 0°C under nitrogen was added boron tribromide (3.1ml, 3.18mmol of 1.0M solution in dichloromethane), the resultant dark solution was allowed to warm to room temperature and stirred for 1 hour. The solution was poured onto ice and basified with sodium bicarbonate. The layers were separated and the aqueous layer was extracted with dichloromethane (20ml), the combined organic layers were dried over anhydrous magnesium sulphate, filtered and evaporated to a gum (200mg). The material was purified on a 10g silica cartridge eluting with methanol/dichloromethane/ammonia (7:92:1) to yield 4-(1,4-dimethyl-1,2,5,6-tetrahydropyridin-2-yl)-benzene-1,3-diol (8) (93mg, 35%) as a gum, ^1H NMR D_6 -acetone δ 1.67 (s, 3H), 1.97 (m, 1H), 2.3 (s, 3H), 2.42 (m, 1H), 2.74 (m, 1H), 3.08 (m, 1H), 3.74 (s, 1H), 5.15 (s, 1H), 6.2 (d, 1H J = 2), 6.27 (dd, 1H J = 2, 8), 6.82 (d, 1H J = 8), 9.4 (bs, 2H).

By proceeding in a similar manner starting from 6-(2,4-dimethoxyphenyl)-1-isopropyl-4-methyl-1,2,3,6-tetrahydropyridine (7), 4-(1-isopropyl-4-methyl-1,2,5,6-tetra-hydropyridin-2-yl)-benzene-1,3-diol (9) was prepared, NMR D_6 -acetone δ 0.81 (d, 3H J = 7), 0.98 (d, 3H J = 7), 1.52 (s, 3H), 1.84 (m, 1H), 2.15(m, 1H), 2.29(m, 1H), 2.94 (m, 2H), 4.09 (s, 1H), 4.97 (s, 1H), 6.05 (d, 1H J = 3), 6.11(dd, J = 3, 8), 6.68 (d, J = 8), 9.6 (bs, 2H).

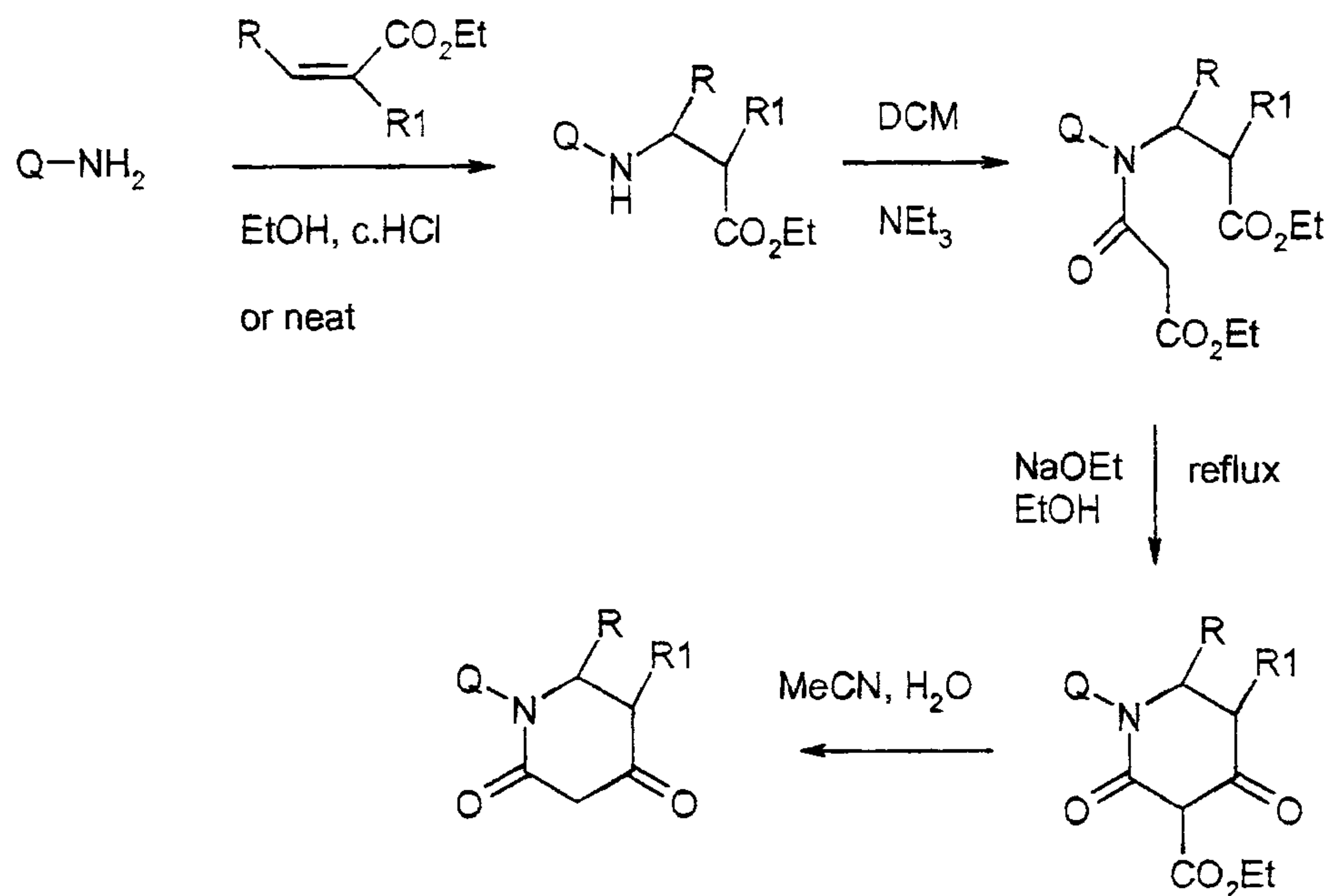
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Example 17**Preparation of 1- Isopropyl-4-methyl pyridinium iodide (3).**

To a stirred solution of 4-picoline (2.5g, 26.8mmol) in acetonitrile (50ml) was added isopropyl iodide (9.1g, 53.6mmol) drop wise, the resultant mixture was heated at 90°C for 24 hours. After cooling the solvent was evaporated to give a red solid which on trituration with ethyl acetate yielded 1- isopropyl-4-methyl pyridinium iodide (6.01g, 85%) as a cream solid, ^1H NMR D6-DMSO δ ?1.6 (d, 6H, $J = 7$), 2.6 (s, 3H), 4.95 (m, 1H), 8.0 (d, 2H $J = 6$), 9.05 (d, 2H $J = 6$).

Preparation of 1-Aryl-piperidine2,4-diones

Scheme



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Example 18**Preparation of Ethyl 3-(3-Chlorophenylamino)propionate**

3-Chloroaniline (3.8g, 0.03moles) was dissolved in ethanol (5ml) and ethyl acrylate (3.3g, 0.033moles) was added in ethanol (5ml). Concentrated hydrochloric acid (1ml) was added and the reaction mixture was heated at reflux for 48 hours. Evaporated to a low bulk and dissolved the residue in dichloromethane and water. Basified to pH 9 with aqueous ammonia and separated. Evaporated off the dichloromethane under reduced pressure to give the crude product as a yellow oil (5.4g) Purified using a silica column eluted with isohexane:ethyl acetate 9:1 to give the required product (3.5g, 51%) as a colourless oil.

^1H NMR CDCl_3 δ 1.30 (t, 3H, $J = 6.5\text{Hz}$), 2.65 (t, 2H, $J = 6\text{Hz}$), 3.45 (q, 2H $J = 6\text{Hz}$), 4.20 (q, 2H, $J = 6.5\text{Hz}$), 6.50 (m, 1H), 6.60 (m, 1H), 6.70 (m, 1H), 7.10 (m, 1H)

Example 19**Preparation of *N*-(3-Chlorophenyl)-*N*-(2-ethoxycarbonyl-ethyl)-malonamic acid ethyl ester**

Ethyl 3-(3-Chlorophenylamino)propionate (3.5g, 0.0154moles) was dissolved in dichloromethane (40ml) and ethyl malonyl chloride (2.55g, 0.017moles) was added dropwise in dichloromethane (10ml) with stirring and cooling in order to keep the reaction temperature below 20° . Triethylamine (1.72g, 0.017moles) was added dropwise in dichloromethane (10ml). The reaction temperature was kept below 20° by ice bath cooling. The reaction mixture was allowed to warm to room temperature and stirred at room temperature overnight. Washed with 2M hydrochloric acid, water and sodium bicarbonate solution. Dried over

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anhydrous magnesium sulphate, filtered and evaporated to give the required product as an orange oil. (4.5g, 86%)

^1H NMR CDCl_3 δ 1.25 (m, 6H), 2.65 (t, 2H, $J = 7\text{Hz}$), 3.20 (s, 2H), 4.10 (m, 4H), 7.15 (m, 1H), 7.30 (m, 1H), 7.40 (m, 2H)

Example 20

Preparation of Ethyl 1-(3-chlorophenyl)piperidine-2,4-dione carboxylate

Sodium (0.7g, 0.029moles) was dissolved in ethanol (90ml) and *N*-(3-Chlorophenyl)-*N*-(2-ethoxycarbonyl-ethyl)-malonamic acid ethyl ester (4.5g, 0.0132moles) was added in ethanol (30ml). The reaction mixture was heated at reflux overnight. The ethanol was evaporated off and the residue dissolved in water. Washed with diethyl ether and acidified to pH2 with concentrated sulphuric acid. Extracted with dichloromethane and the combined dichloromethane extracts were combined. Washed with water and dried over anhydrous magnesium sulphate. Filtered and evaporated to give the product as an orange oil (2.8g, 72%)

^1H NMR CDCl_3 δ 1.40 (t, 3H, $J = 5\text{Hz}$), 2.85 (t, 2H, $J = 6\text{Hz}$), 3.85 (t, 2H, $J = 6\text{Hz}$), 4.40 (q, 2H, $J = 5\text{Hz}$), 7.20 (m, 2H), 7.30 (m, 1H), 7.35 (m, 1H)

Example 21

Preparation of 1-(3-Chlorophenyl)piperidine-2,4-dione

Ethyl 1-(3-chlorophenyl)piperidine-2,4-dione carboxylate (2.8g, 0.0095moles) was dissolved in acetonitrile (100ml)/water (10ml) and refluxed for 2 hours. Evaporated to a low bulk and dissolved in dichloromethane. Washed with water and dried over anhydrous magnesium sulphate. Filtered and evaporated to give the product as an orange oil (2.2g). Purified using a silica column eluted with

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dichloromethane:ethyl acetate 9:1 to give the required product as a pale yellow gum (1.2g, 59%)

^1H NMR CDCl_3 δ 2.80 (t, 2H, $J = 6\text{Hz}$), 3.55 (s, 2H), 4.05 (t, 2H, $J = 6\text{Hz}$), 7.20 (m, 1H), 7.30 (m, 1H), 7.35 (m, 1H), 7.40 (m, 1H)

Also prepared in a similar manner were

1-Phenylpiperidine-2,4-dione

^1H NMR CDCl_3 , ppm) δ 2.80 (t, 2H, $J = 6\text{Hz}$), 3.6 (s, 2H), 4.05 (t, 2H, $J = 6\text{Hz}$), 7.30 (m, 3H), 7.45 (m, 2H)

1-(3-Methylphenyl)piperidine-2,4-dione

^1H NMR (CDCl_3 , ppm) δ 2.40 (s, 3H), 2.80(t, 2H, $J = 6.5\text{Hz}$), 3.6 (s, 2H), 4.05 (t, 2H, $J = 6.5\text{Hz}$), 7.30 (m, 3H), 7.45 (m, 2H)

1-(4-Fluorophenyl)piperidine-2,4-dione

^1H NMR CDCl_3 , ppm) δ 2.80 (t, 2H, $J = 6\text{Hz}$), 3.55 (s, 2H), 4.0 (t, 2H, $J = 6\text{Hz}$), 7.1 (m, 2H), 7.25 (m, 2H)

1-(3,5-Difluorophenyl)piperidine-2,4-dione

^1H NMR (CDCl_3 , ppm) δ 2.80 (t, 2H, $J = 6\text{Hz}$), 3.58 (s, 2H), 4.04 (t, 2H, $J = 6\text{Hz}$), 6.68-6.83 (m, 1H), 6.84-6.99 (m, 2H).

1-(3,5-Dichlorophenyl)piperidine-2,4-dione

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^1H NMR (CDCl_3 , ppm) δ 2.80 (t, 2H, $J = 6\text{Hz}$), 3.58 (s, 2H), 4.02 (t, 2H, $J = 6\text{Hz}$), 7.20-7.36 (m, 3H).

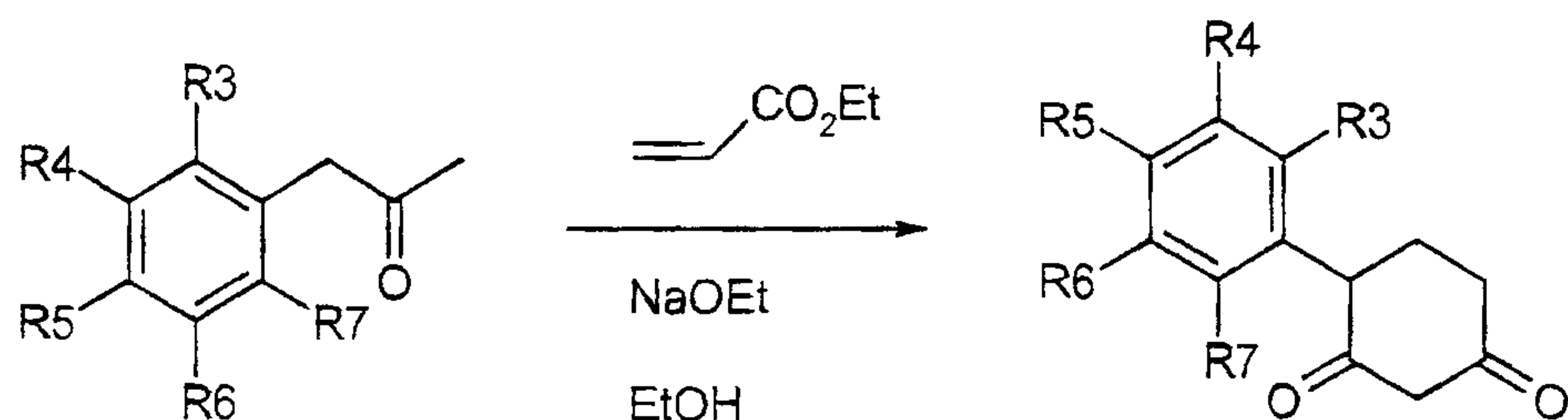
1-(4-Methylpyrid-2-yl)piperidine-2,4-dione

^1H NMR (CDCl_3 , ppm) δ 2.41 (s, 3H), 2.75 (t, 2H, $J = 6\text{Hz}$), 3.62 (s, 2H), 4.44 (t, 2H, $J = 6\text{Hz}$), 6.94-7.02 (m, 1H), 7.72-7.79 (m, 1H), 8.25-8.36 (m, 1H).

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Preparation of Cyclohexane-1,3-diones

Scheme

**Example 22****Preparation of 4-(4-Fluorophenyl)cyclohexane-1,3-dione**

Sodium (0.3g, 0.013moles) was dissolved in ethanol (50ml) and 4-Fluorophenylacetone (2.0g, 0.013moles) was added in ethanol (10ml). Ethyl acrylate (1.3g, 0.013moles) was and the reaction mixture was heated at reflux overnight. The reaction mixture was allowed to cool and evaporated under reduced pressure to give a brown gum. Dissolved in water and washed with diethyl ether. The aqueous layer was acidified to pH2 with conc. Hydrochloric acid and extracted with dichloromethane. The extracts were combined and washed with water. Dried over anhydrous magnesium sulphate and filtered. The filtrate was evaporated to give an orange oil. (1.7g) This was purified using a silica column eluted with dichloromethane:ethyl acetate 8:2 and then dichloromethane:ethyl acetate 2:1 to give a colorless gum. (0.428g) This was triturated with diethyl ether/isohexane to give 4-(4-Fluorophenyl)cyclohexane-1,3-dione (0.28g) as a white solid.

^1H NMR (CD_3OD , ppm) δ 2.1 (m, 1H), 2.3 (m, 1H), 2.4 (m, 2H), 3.7 (m, 1H), 4.9 (s, 2H), 7.1 (m, 2H), 7.2 (m, 2H).

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Also prepared in a similar manner

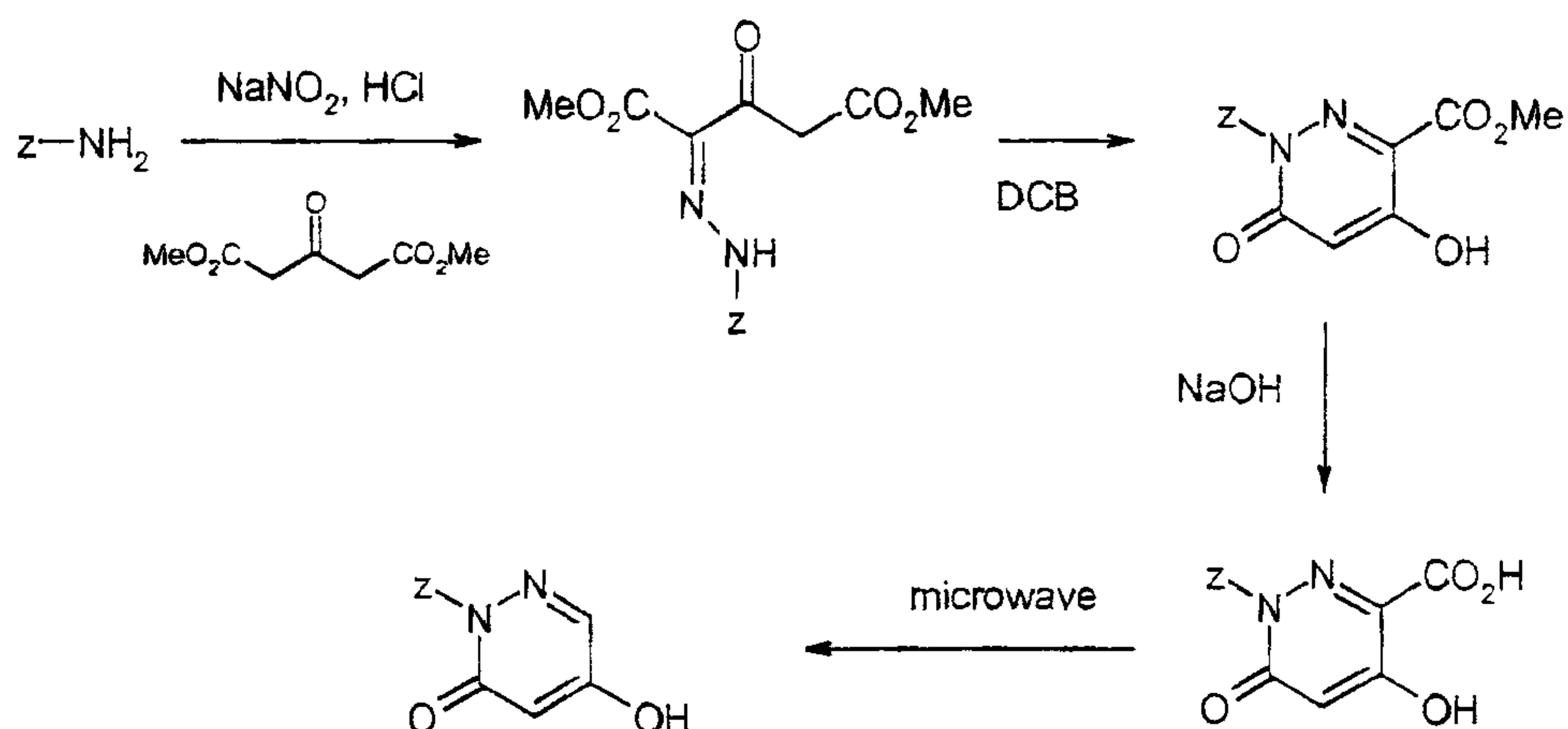
4-Phenylcyclohexane-1,3-dione

^1H NMR (CD_3OD , ppm) δ 2.15 (m, 1H), 2.3 (m, 3H), 3.7 (m, 1H), 4.9 (s, 2H), 7.2 (m, 3H), 7.3 (m, 2H).

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Preparation of Pyridazin-3-ones

Scheme

**Example 23****3-Oxo-2-phenylhydrazono)pentanedioic acid dimethylester**

To a mixture of aniline (1.86g, 20mmol) in concentrated hydrochloric acid (10ml) and water (20ml) at a temperature below $5^\circ C$ was added a solution of sodium nitrite (1.38g, 20mmol) in water (15ml) drop wise. The resultant mixture was stirred for 15 minutes and then it was poured into a solution of dimethylacetonedicarboxylate (3.48g, 20mmol) and sodium acetate (12g, 0.146mol) in ethanol (12ml) and water (40ml) causing an immediate precipitation. The suspension was stirred for 1 hour and then extracted with ethyl acetate (3 x 125ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated to yield 3-oxo-2-phenylhydrazono)pentanedioic acid dimethyl ester as a red oil (5.58g, quantitative) consisting of a mixture of *E* and *Z* isomers about the hydrazone

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^1H NMR CDCl_3 δ 7.8-8.0 (singlets, 8H), 7.1-7.5 (m, 5H), 12.8 (s, 1H).

Example 24

Methyl 4-hydroxy-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylate

3-Oxo-2-phenylhydrazono)pentanedioic acid dimethyl ester (12.5mmol) was dissolved in dichlorobenzene and heated at reflux for 24 hours and then allowed to cool to room temperature. The solvent was evaporated and the residue triturated with ether to give methyl 4-hydroxy-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylate a beige solid (2.4g, 78%)

^1H NMR CDCl_3 δ 4.0 (s, 3H), 6.4 (s, 1H), 7.4-7.6 (m, 5H), 10.3 (s, 1H).

Example 25

4-Hydroxy-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylic acid

Methyl 4-hydroxy-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylate (0.8g, 3.24mmol) was suspended in sodium hydroxide solution (20ml of 2.0M) and heated at reflux for 1 hour. The mixture was allowed to cool to room temperature, acidified with 2M hydrochloric acid and extracted with ethyl acetate (3 x 15ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated to yield 4-hydroxy-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylic acid as a yellow solid (0.6g, 80%)

^1H NMR CDCl_3 δ 6.3 (s, 1H), 7.35-7.7 (m, 5H).

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Example 26**5-Hydroxy-2-phenyl-2H-pyridazin-3-one**

4-Hydroxy-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylic acid (400mg, 1.72mmol) was heated at 270°C in a microwave for 3 minutes. The resultant black mixture was extracted into saturated sodium bicarbonate (15ml). The sodium bicarbonate solution was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3 x 15ml). The combined organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated to a crude solid (300mg). This was purified on a 10g SPE cartridge eluting with dichloromethane/ ethyl acetate (80:20 to 60:40) to yield 5-hydroxy-2-phenyl-2H-pyridazin-3-one (60mg) as a beige solid

¹H NMR D6 DMSO δ 6.05 (d, 1H, J = 2.7 Hz), 7.4-7.6 (m, 5H), 7.85 (d, 1H, J = 2.7 Hz), 11.6 (s, 1H).

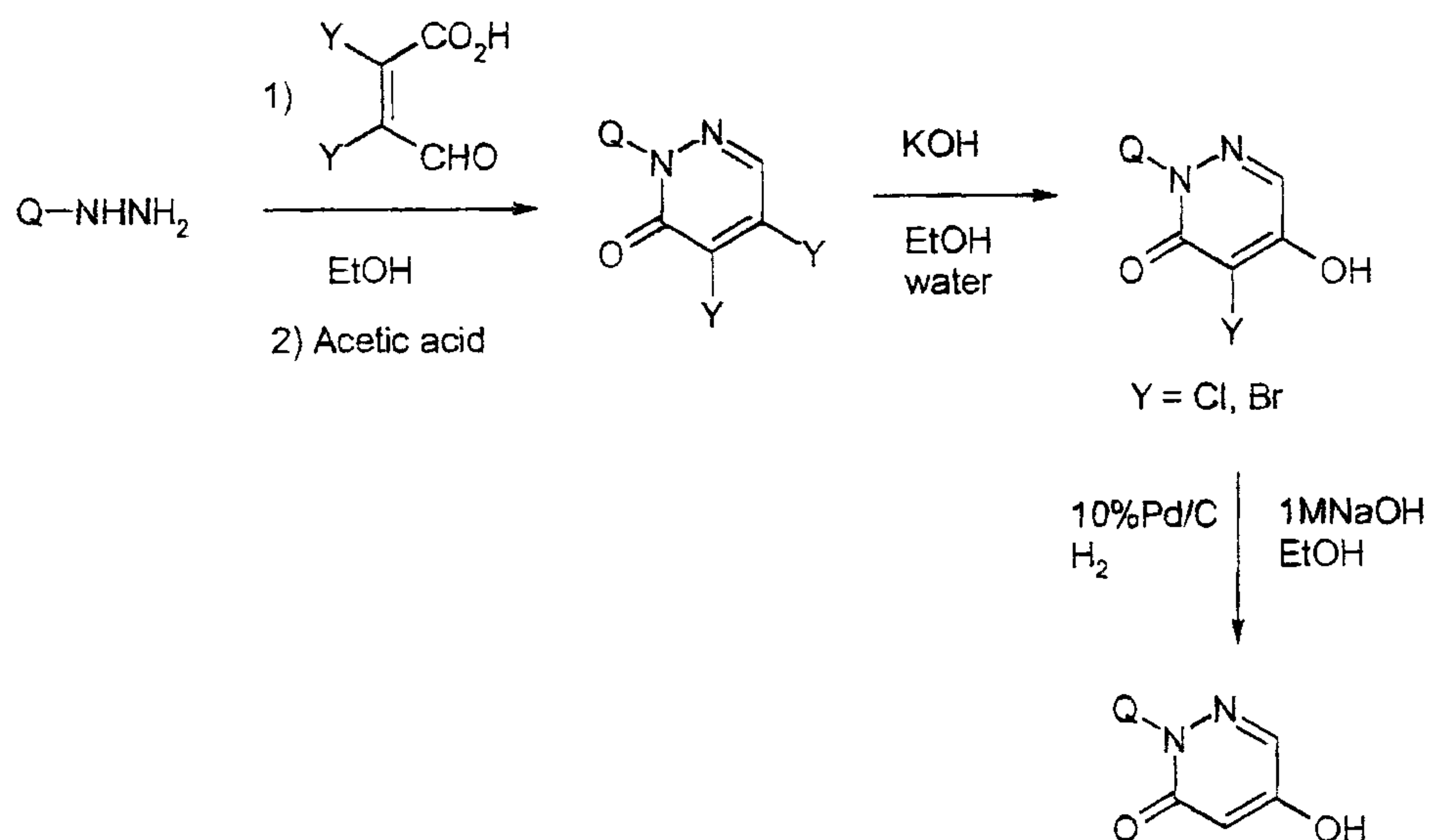
The following compounds are also active in the method of the present invention:

2-(4-Chlorophenyl)-5-hydroxy-2H-pyridazin-3-one**5-Hydroxy-2-(3-trifluoromethylphenyl)-2H-pyridazin-3-one**

The following synthesis is described in J. Het. Chem. 1989, 26, 169-176

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Scheme

**Example 27****2-(3,5-Difluorophenyl)-5-hydroxypyridazin-3-one**

4-Bromo-2-(3,5-difluorophenyl)-5-hydroxypyridazin-3-one (0.6g, 1.98mmoles) was dissolved in ethanol (50ml) and 1M sodium hydroxide (4ml) was added. 10% Palladium on carbon (0.15g) was added and the flask was placed under an atmosphere of hydrogen (balloon) with stirring. The reaction mixture was stirred overnight at room temperature. Filtered off the catalyst using Hyflo and evaporated to dryness. Added 2M hydrochloric acid and extracted into ethyl acetate. Washed with water and dried over anhydrous magnesium sulphate. Filtered and evaporated the filtrate to give a white solid. Triturated with diethyl ether to give the product as a white solid. (0.32g, 72%)

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¹H NMR DMSO-d₆ δ 12.2 (br s, 1H), 7.9 (d, 1H, J = 3Hz), 7.3 (m, 5H), 6.1 (d, 1H, J = 3Hz)

Also prepared in a similar manner

2-(2,5-Difluorophenyl)-5-hydroxypyridazin-3-one

¹H NMR DMSO-d₆ δ 11.8 (br s, 1H), 7.85 (d, 1H, J = 2.5Hz), 7.4 (m, 4H), 6.1 (d, 1H, J = 2.5Hz)

Example 28

4-Bromo-2-(3,5-difluorophenyl)-5-hydroxypyridazin-3-one

4,5-Dibromo-2-(3,5-difluorophenyl)pyridazin-3-one (1.5g, 0.0041 moles) was suspended in ethanol (50ml) and potassium hydroxide (0.8g, 0.0123 moles) was added in water (8ml). Refluxed for 4 hours with stirring. Evaporated to a low bulk and diluted with water. Acidified to pH2 with conc. hydrochloric acid and extracted with ethyl acetate. Washed with water and dried with anhydrous magnesium sulphate. Filtered and evaporated the filtrate to give an orange solid. Triturated with diethyl ether and dried in a desiccator to give the product as a cream solid. (0.7g, 56%)

¹H NMR DMSO-d₆ δ 12.5 (br s, 1H), 7.9 (s, 1H), 7.35 (m, 3H); ¹⁹F NMR δ 110

Also prepared in a similar manner

4-Bromo-2-(2,5-difluorophenyl)-5-hydroxypyridazin-3-one

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^1H NMR DMSO-d₆ δ 7.9 (s, 1H), 7.5 (m, 3H); ^{19}F NMR δ 117, 126

4-Bromo-2-(2,5-dichlorophenyl)-5-hydroxypyridazin-3-one

^1H NMR DMSO-d₆ δ 7.9 (s, 1H), 7.8 (d, 1H, $J = 2.5\text{Hz}$), 7.7 (d, 1H, $J = 8.5\text{Hz}$), 7.6 (d, 1H, $J = 2.5, 8.5\text{Hz}$)

Example 29

4,5-Dibromo-2-(3,5-difluorophenyl)pyridazin-3-one

Mucobromic acid (2.8g, 0.011moles) was dissolved in ethanol (75ml) and 3,5-difluorophenyl hydrazine hydrochloride (1.8g, 0.01moles) was added. After 30 minutes, triethylamine (1.4ml, 0.01moles) was added. The reaction mixture was stirred at room temperature for 3 hours. Evaporated to a low bulk and the residue was suspended in glacial acetic acid (80ml). Refluxed with stirring overnight to give a brown solution. Evaporated to dryness and triturated with methanol to give the required product as a pale brown solid. (3.4g, 93%)

^1H NMR DMSO-d₆ δ 8.3 (s, 1H), 7.4 (m, 3H); ^{19}F NMR δ 109

Also prepared in a similar manner

4,5-Dibromo-2-(2,5-dichlorophenyl)pyridazin-3-one

^1H NMR DMSO-d₆ δ 7.9 (s, 1H), 7.45 (m, 1H), 7.4 (m, 2H)

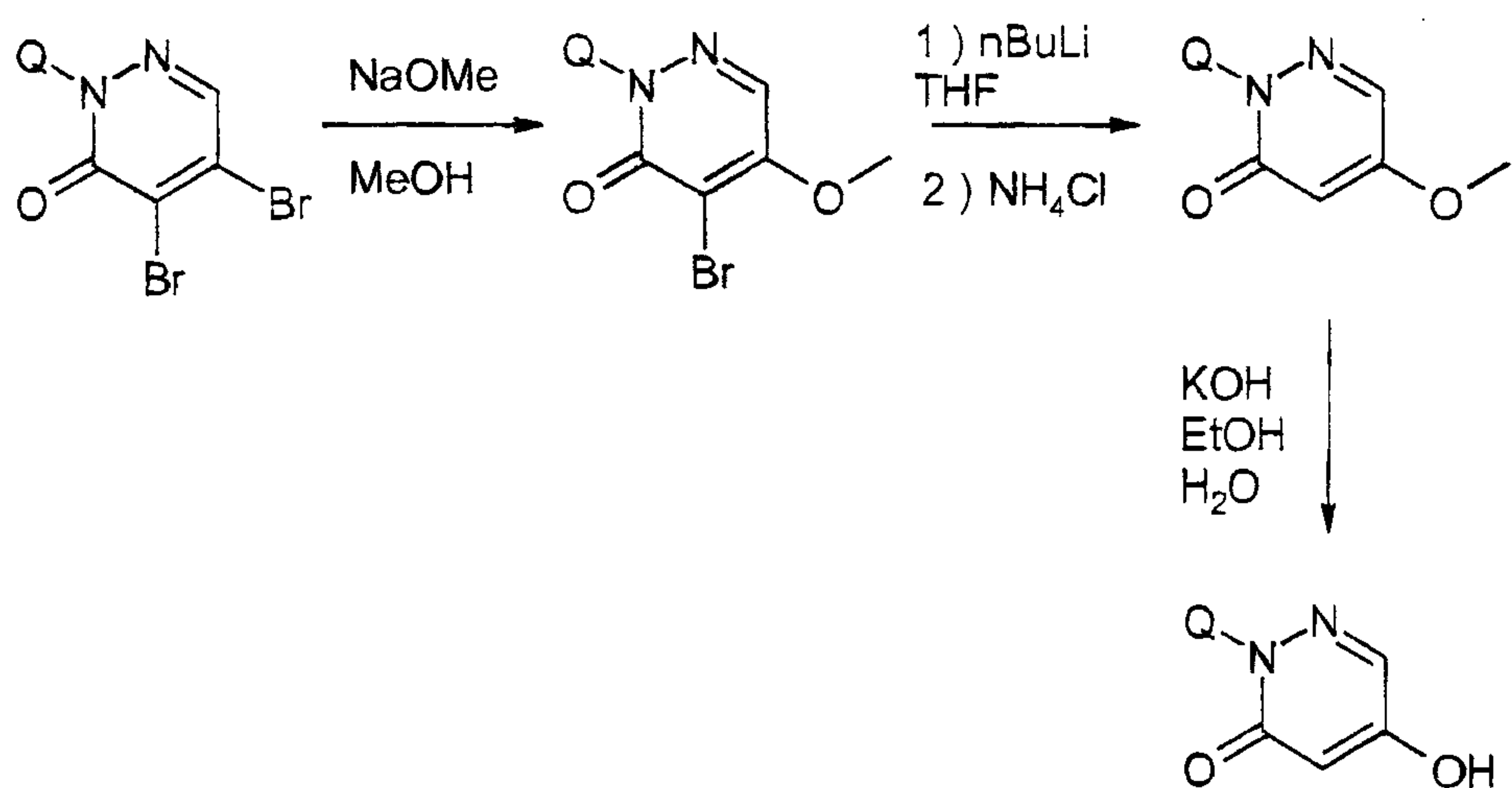
4,5-Dibromo-2-(3,5-dichlorophenyl)pyridazin-3-one

^1H NMR DMSO-d₆ δ 8.35 (s, 1H), 7.8 (m, 1H), 7.7 (m, 2H)

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4,5-Dibromo-2-(2,5-difluorophenyl)pyridazin-3-one¹H NMR DMSO-d₆ δ 8.35 (s, 1H), 7.5 (m, 3H)

Scheme

**Example 30****2-(3,5-Dichlorophenyl)-5-hydroxypyridazin-3-one**

2-(3,5-Dichlorophenyl)-5-methoxypyridazin-3-one (0.25g, 0.92mmoles) was suspended in ethanol (40ml) and potassium hydroxide (0.12g, 1.8mmoles) was added in water (5ml). Refluxed overnight with stirring to give a yellow solution. Evaporated to dryness and added 2M hydrochloric acid. Extracted with ethyl acetate (x2) and washed with water and dried over anhydrous magnesium sulphate. Filtered and evaporated to give a yellow solid. Triturated with dichloromethane to give a pale yellow solid. (0.1g, 42%)

-41-

¹H NMR DMSOd6 δ 7.75 (d, 1H, J = 3Hz), 7.6 (m, 2H), 7.5 (m, 1H), 6.25 (d, 1H, J = 3Hz)

Also prepared in a similar manner

2-(2,5-Dichlorophenyl)-5-hydroxypyridazin-3-one

¹H NMR DMSOd6 δ 10.9 (br s, 1H), 7.7 (d, 1H, J = 3Hz), 7.4 (m, 1H), 7.35 (m, 1H), 7.3 (m, 1H), 6.2 (d, 1H, J = 3Hz)

Example 31

2-(3,5-Dichlorophenyl)-5-methoxypyridazin-3-one

4-Bromo-2-(3,5-dichlorophenyl)-5-methoxypyridazin-3-one (2.5g, 0.0071 moles) was dissolved in THF (250ml) and cooled to -50° under nitrogen. 1.6M n-Butyl lithium (6.7ml, 0.011 moles) was added dropwise with stirring. Allowed to warm to -20° over 1 hour. Added 1 equivalent of 1.6M n-Butyl lithium (4.4ml, 0.0071 moles) dropwise. Stirred at -20° for 30 minutes. Poured into ammonium chloride solution and stirred for 15 minutes. Extracted with EtOAc (x2) and washed with water. Dried over anhydrous magnesium sulphate, filtered and evaporated to give a brown solid. (3.0g) Purified using MPLC (silica, eluted with dichloromethane: EtOAc 9:1) to give a yellow solid. (0.25g, 13%) Not pure used directly in the next reaction.

¹H NMR DMSOd6 δ 7.7 (d, 1H, J = 3Hz), 7.6 (d, 2H, J = 2Hz), 7.5 (d, 1H, J = 2Hz), 6.2 (d, 1H, J = 3Hz)

Also prepared in a similar manner

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2-(2,5-Dichlorophenyl)-5-methoxypyridazin-3-one

¹H NMR DMSO-d₆ δ 7.95 (d, 1H, J = 3Hz), 7.75 (d, 1H, J = 2.5Hz), 7.7 (d, 1H, J = 8Hz), 7.6 (d, d, 1H, J = 2.5, 8Hz), 6.45 (d, 1H, J = 3Hz)

Example 32**4-Bromo-2-(3,5-dichlorophenyl)-5-methoxypyridazin-3-one**

Sodium (0.28g, 0.012moles) was dissolved in methanol (100ml) and a suspension of 4,5-Dibromo-2-(3,5-dichlorophenyl)pyridazin-3-one (4.0g, 0.01moles) in methanol (60ml) was added. Refluxed overnight. Evaporated to dryness and added water. Filtered off the solid and dried in a dessicator. Triturated with ether and dried in a dessicator. (3.1g, 89%)

¹H NMR DMSO-d₆ δ 8.35 (s, 1H), 7.75 (m, 1H), 7.7 (m, 2H), 4.15 (s, 3H)

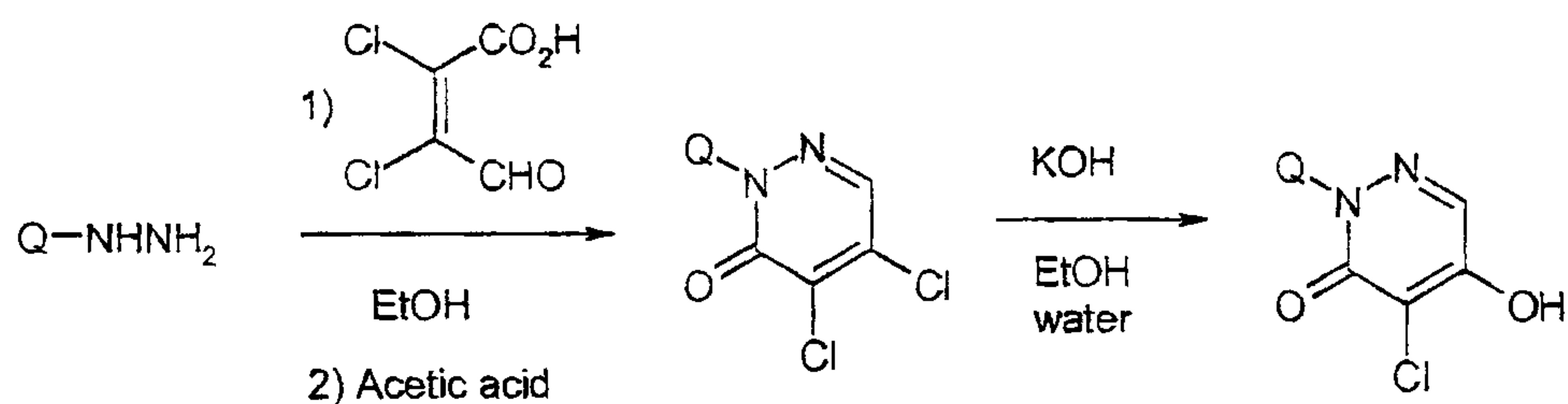
Also prepared in a similar manner

4-Bromo-2-(2,5-dichlorophenyl)-5-methoxypyridazin-3-one

¹H NMR DMSO-d₆ δ 8.35 (s, 1H), 7.8 (d, 1H, J = 2.5Hz), 7.7 (d, 1H, J = 8.5Hz), 7.65 (d of d, 1H, J = 2.5, 8Hz), 4.15 (s, 3H)

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Scheme

**Example 33****4-Chloro-2-phenyl-5-hydroxypyridazin-3-one**

4,5-Dichloro-2-phenylpyridazin-3-one (2.4g, 0.01moles) was suspended in ethanol (50ml) and potassium hydroxide (2.0g, 0.03moles) was added in water (20ml). Refluxed for 4 hours. Evaporated to dryness and added water. Acidified to pH2 with c. hydrochloric acid. Filtered off the product as a buff solid and dried in a desiccator. (2.1g) Took 0.5g and dissolved in methanol, filtered and evaporated. Triturated with ether to give the product as a cream solid. (0.4g, 76%)

^1H NMR DMSO-d₆ δ 7.9, (s, 1H), 7.5 (m, 4H), 7.4 (m, 1H)

Example 34**4,5-Dichloro-2-phenylpyridazin-3-one**

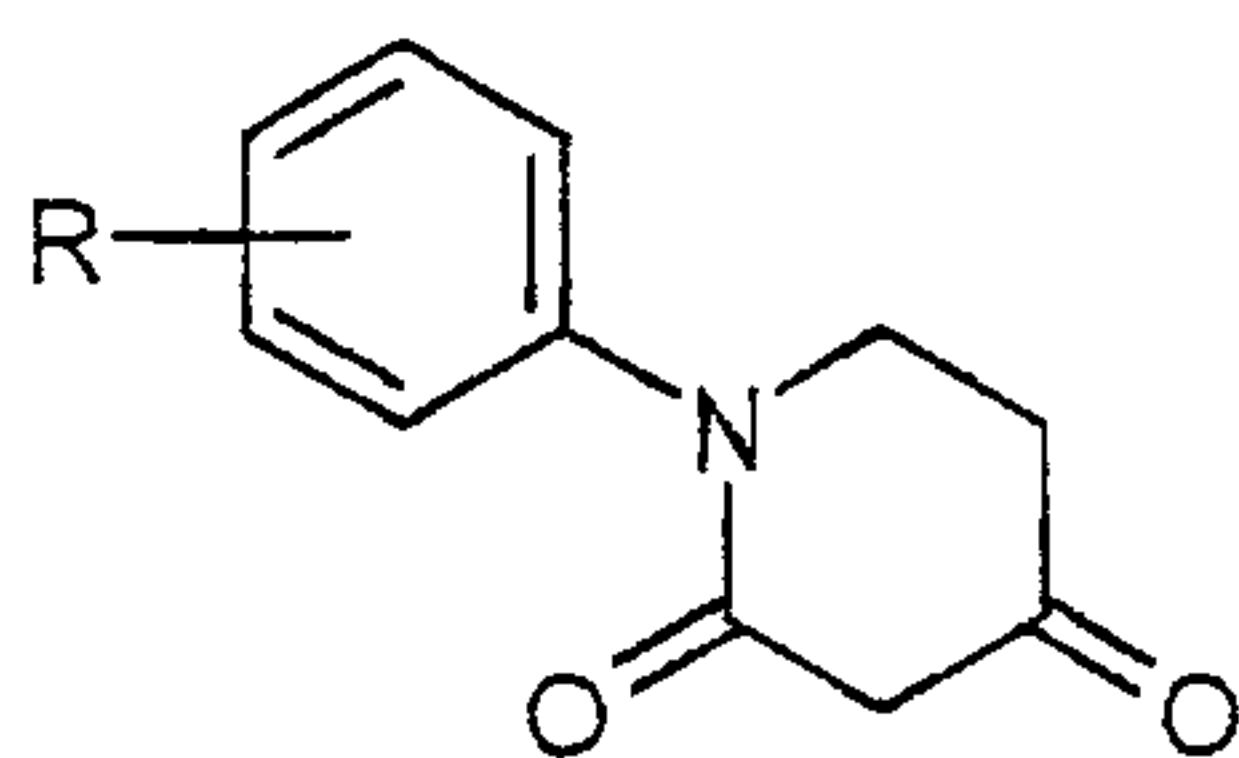
Muconchloric acid (9.3g, 0.055moles) was dissolved in ethanol (60ml) and phenyl hydrazine (5.4g, 0.05moles) was added. The reaction mixture was stirred at room temperature for 2 hours. Evaporated to a low bulk and the residue was suspended in glacial acetic acid (60ml). Refluxed with stirring for 3 hours.

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Evaporated to dryness and triturated with methanol to give the required product as a pale brown solid. (11.0g, 91%)

^1H NMR DMSO-d₆ δ 7.95 (s, 1H), 7.5 (m, 4H), 7.4 (m, 1H)

The following compounds have also been found to be effective in treating glaucoma or ocular hypertension according to the method of the present invention.



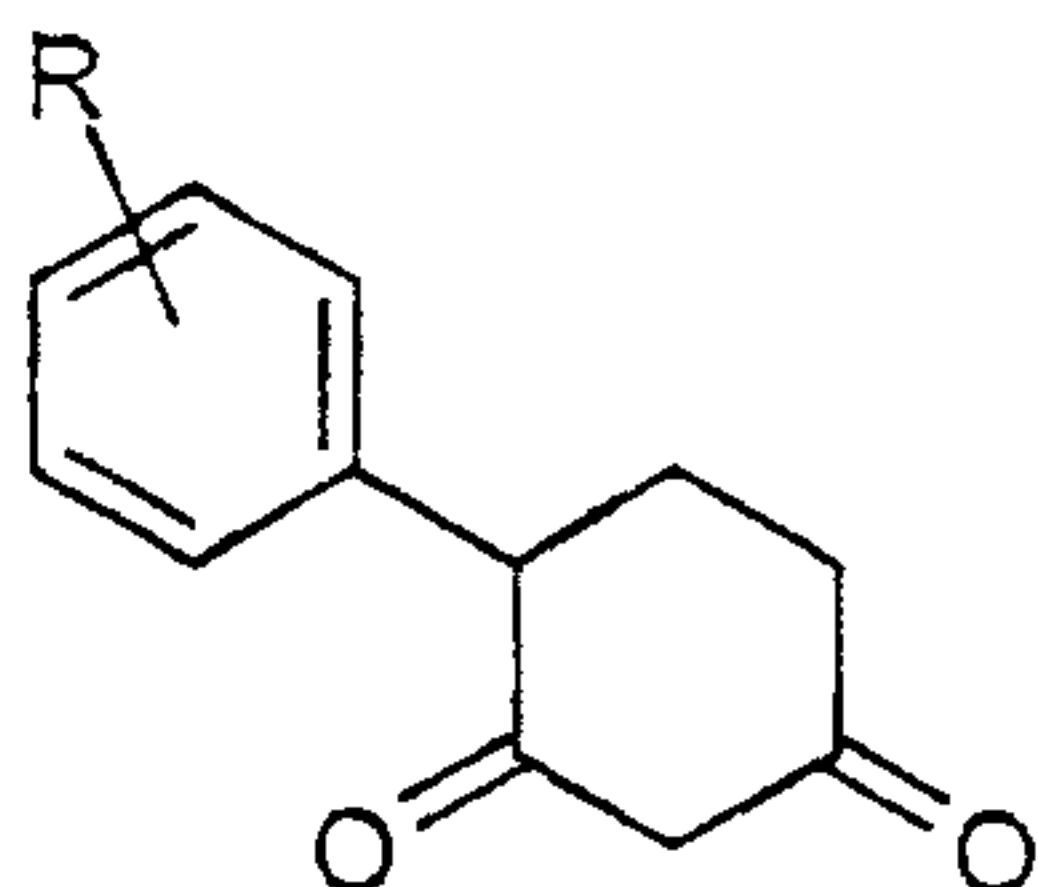
R = H; 2-CO₂H, 5-Cl

H Nishino et al. Tetrahedron, 2005, 11107-11124

H Nishino et al. Heterocyclic Comm. 2005, 11, 379-384

Bekhli et al. Chem. Heterocyclic Compds. Engl. Trans. 1970, 6, 814

-45-

Cyclohexane-1,3-diones

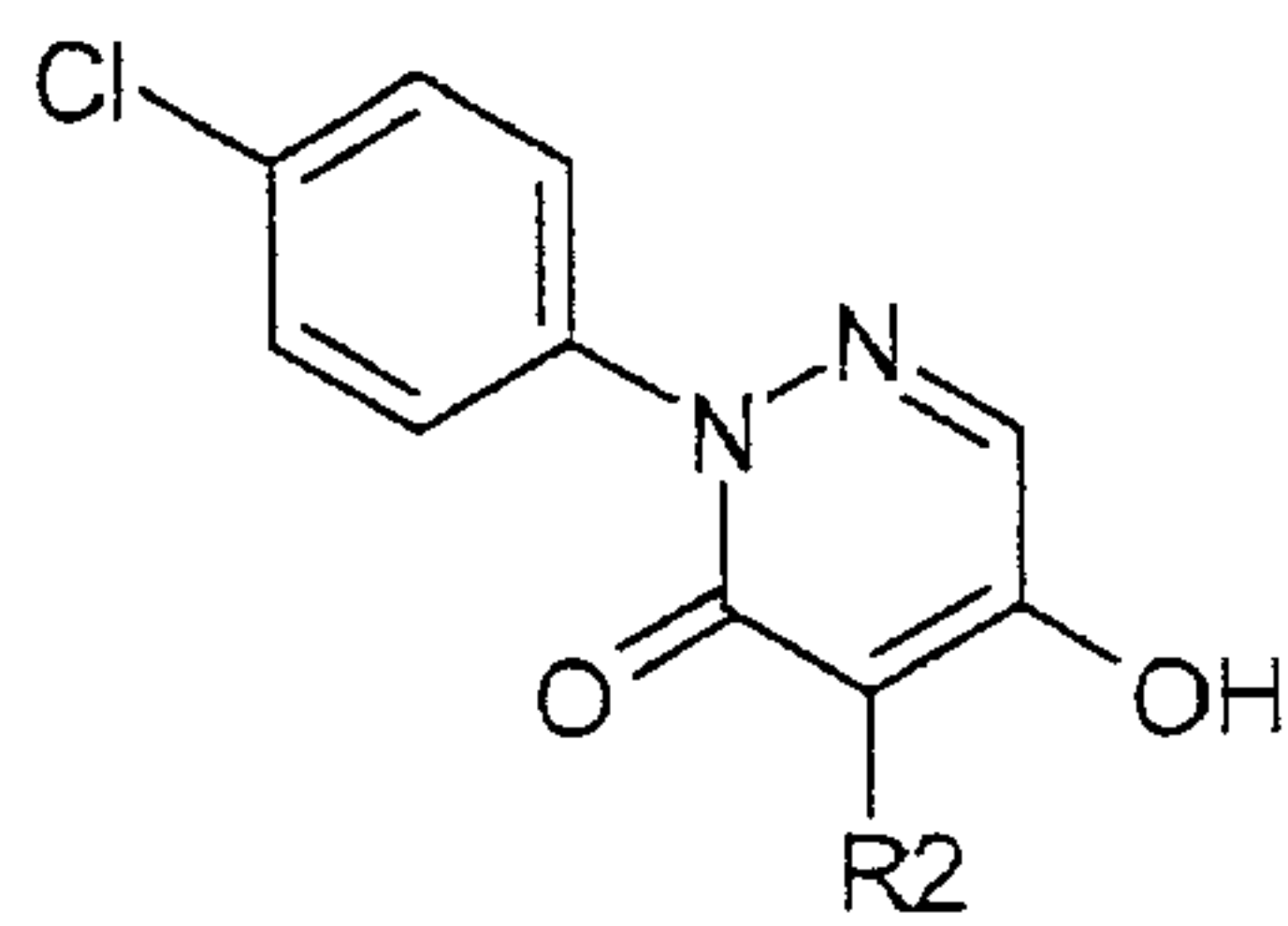
R = H, 4-OMe See EP 291114 (R = H, 4-OMe), US 4546104, US
4795488 (R = 2-F)

Bergmann et al. J. Am. Chem. Soc. 1953, 3226

R = 3,4-DiOMe See Synthesis 1980, 394-397

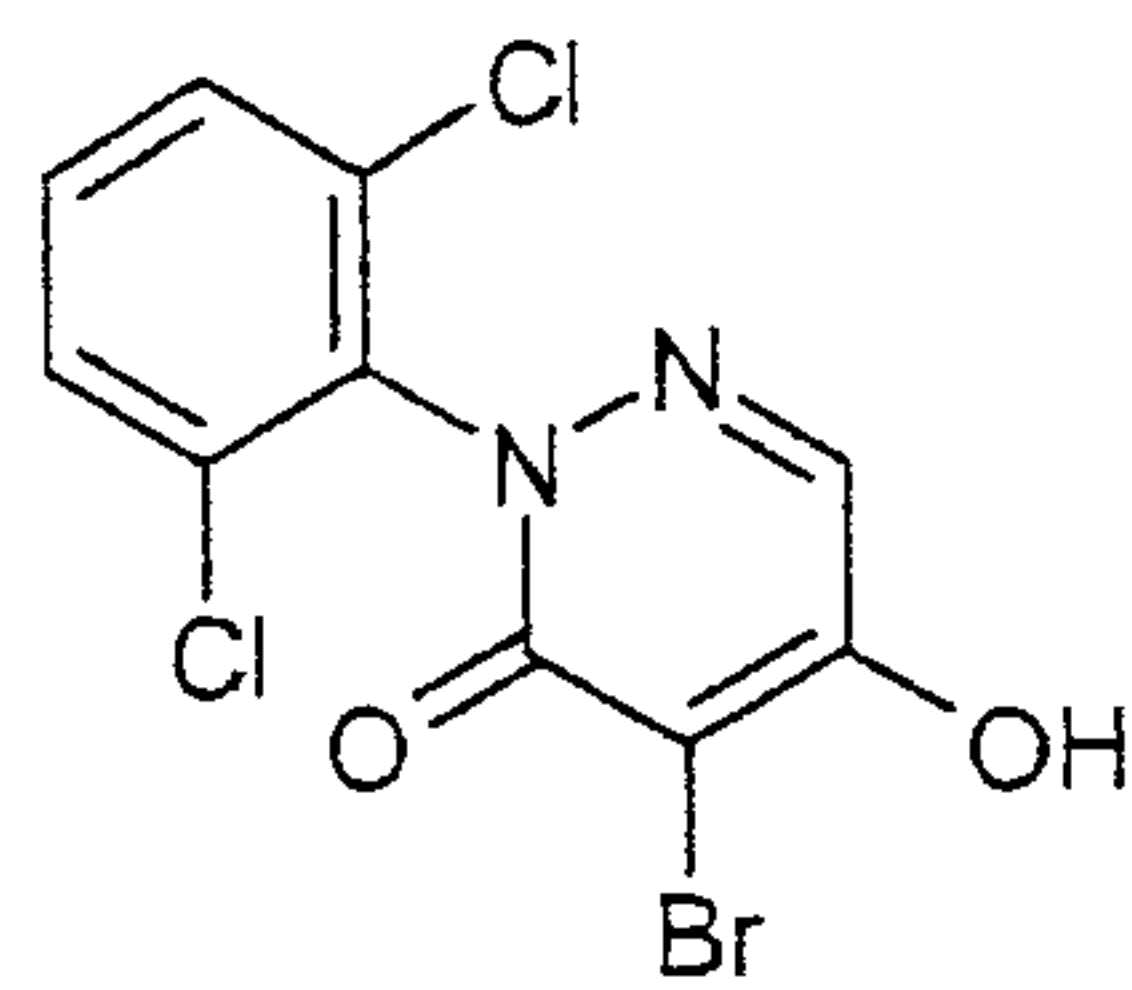
R = 4-Cl See J. Med. Chem. 1981, 1006-1010

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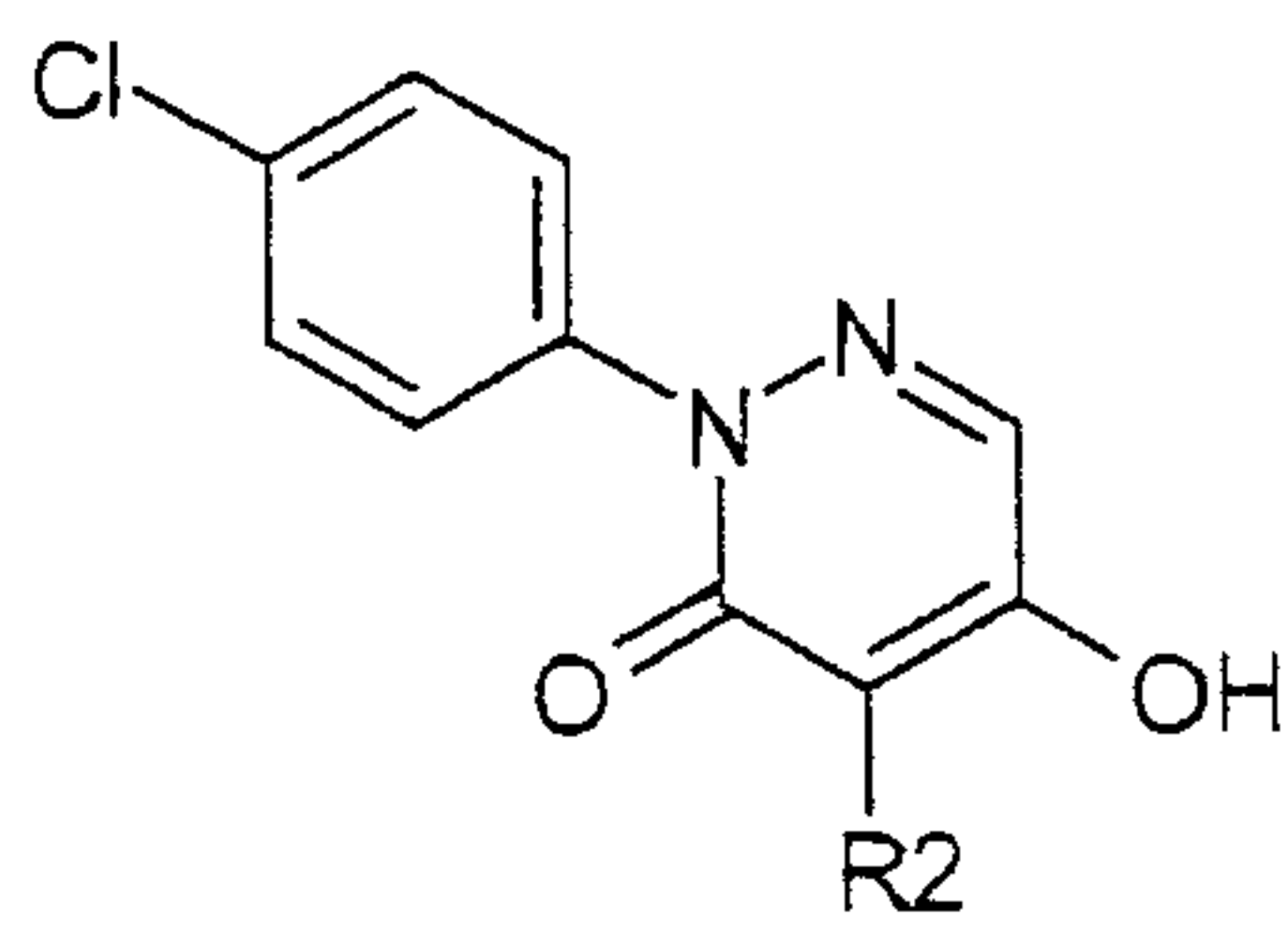
Pyridazin-3-ones

Nissan, EP 210647

R2 = H, Cl

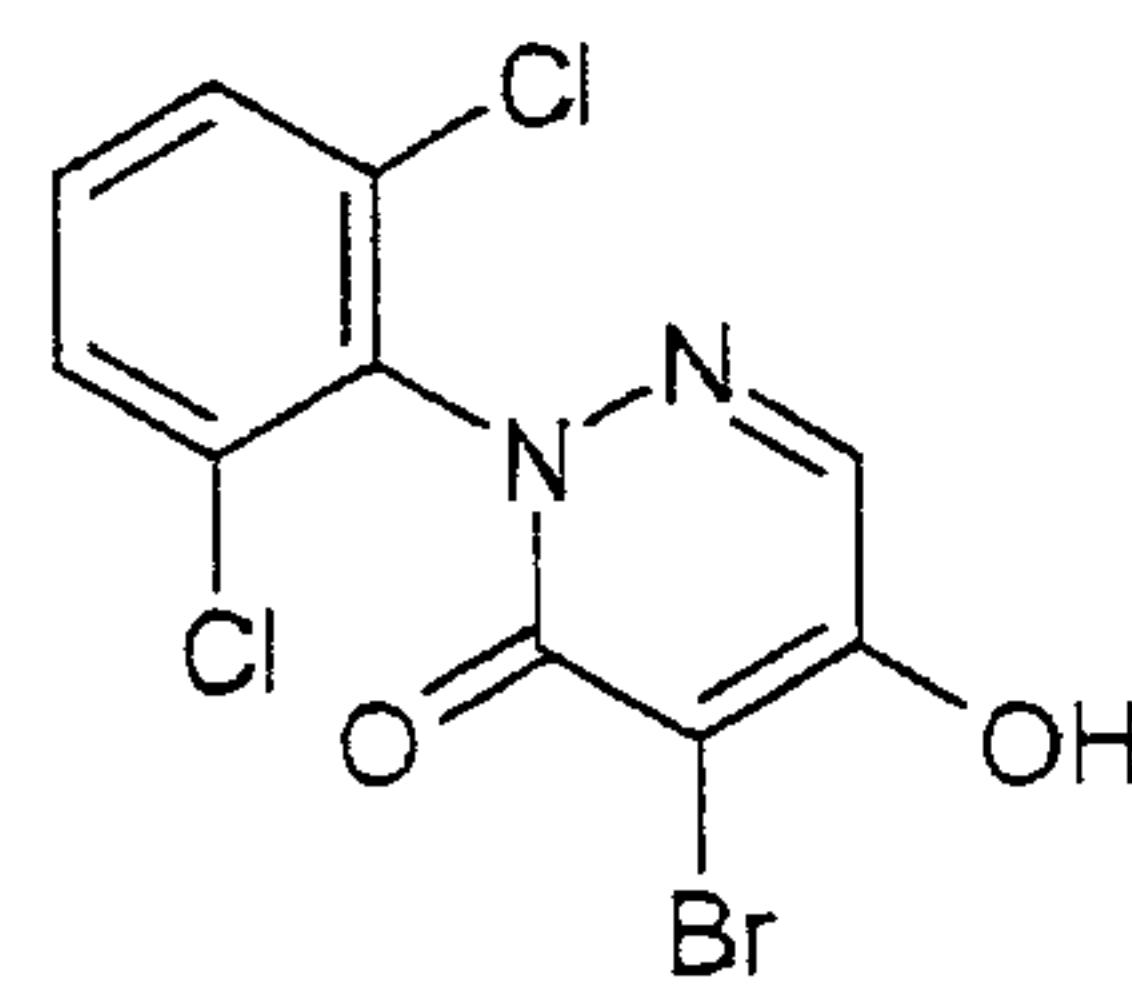


Pharmacia, WO2005007632

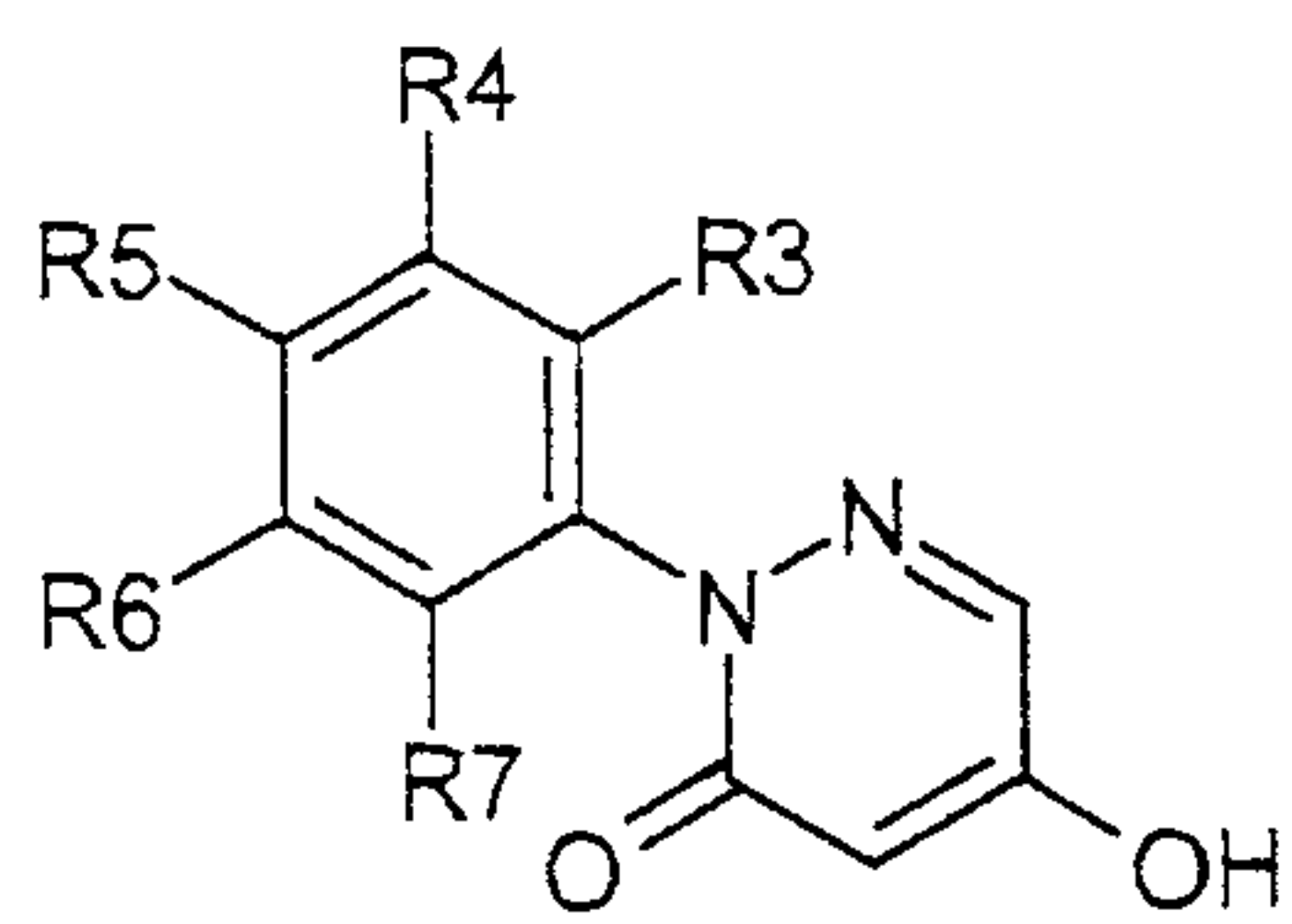


Nissan, EP 210647

R2 = H, Cl

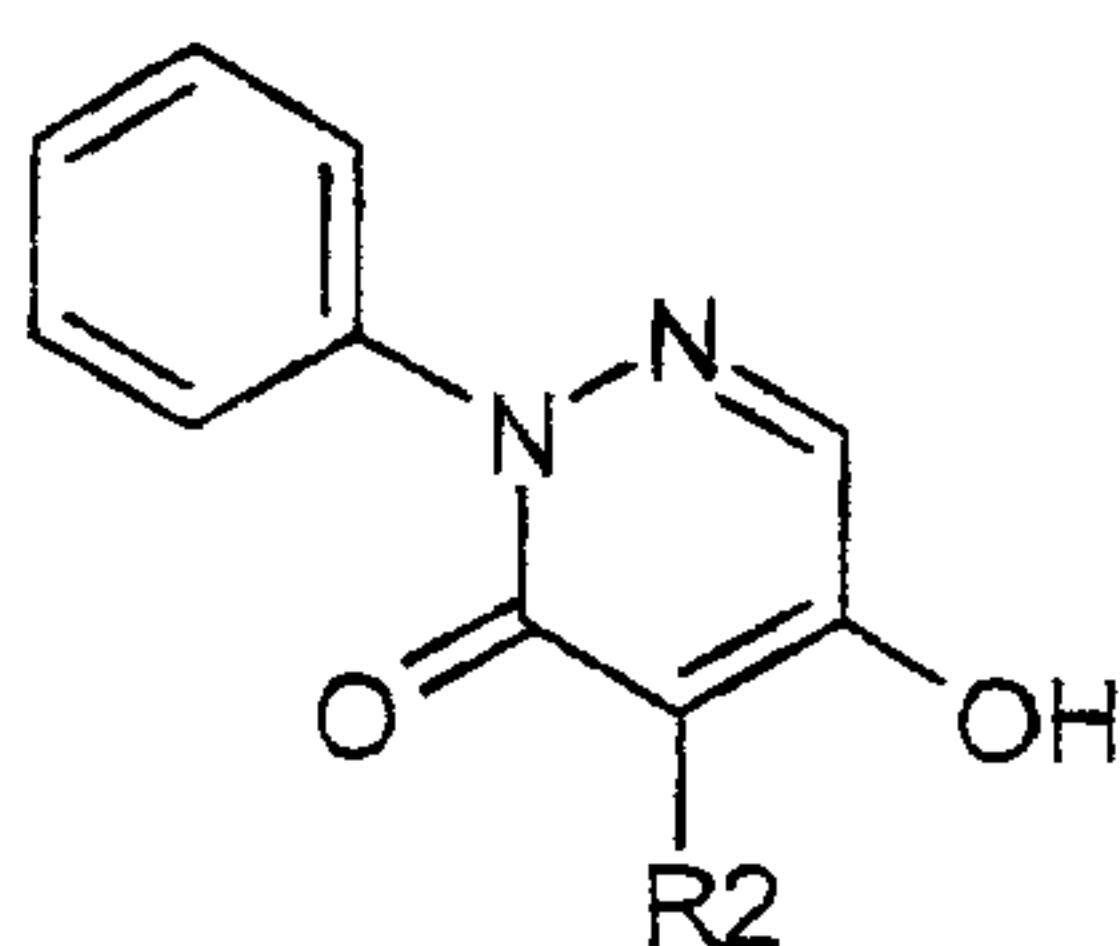


Pharmacia, WO2005007632



i) R3, R4, R5, R6, R7 = H

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ii) $R_3 = CF_3$, $R_4-R_7 = H$ iii) $R_4 = CF_3$, $R_3, R_5-R_7 = H$ iv) $R_5 = Cl$, $R_3, R_4, R_6, R_7 = H$ i) Maier et al. *Helv. Chim. Acta.* 1954, 37, 523ii),iii),iv) *J. Het. Chem.* 1989, 26, 169-176; *J. Het. Chem.* 1990, 27, 471-477i) $R_3, R_4, R_5, R_6, R_7 = H$ iii) $R_4 = CF_3$, $R_3, R_5-R_7 = H$ ii) $R_4 = CF_3$, $R_3, R_5-R_7 = H$; iv) $R_5 = Cl$, $R_3, R_4, R_6, R_7 = H$  $R_2 = OMe$ *Chem. Pharm. Bull.* 1971, 1635

1972, 747

 $R_2 = SEt$ *Collect. Czech. Chem. Comm.* 1980, 45,

127

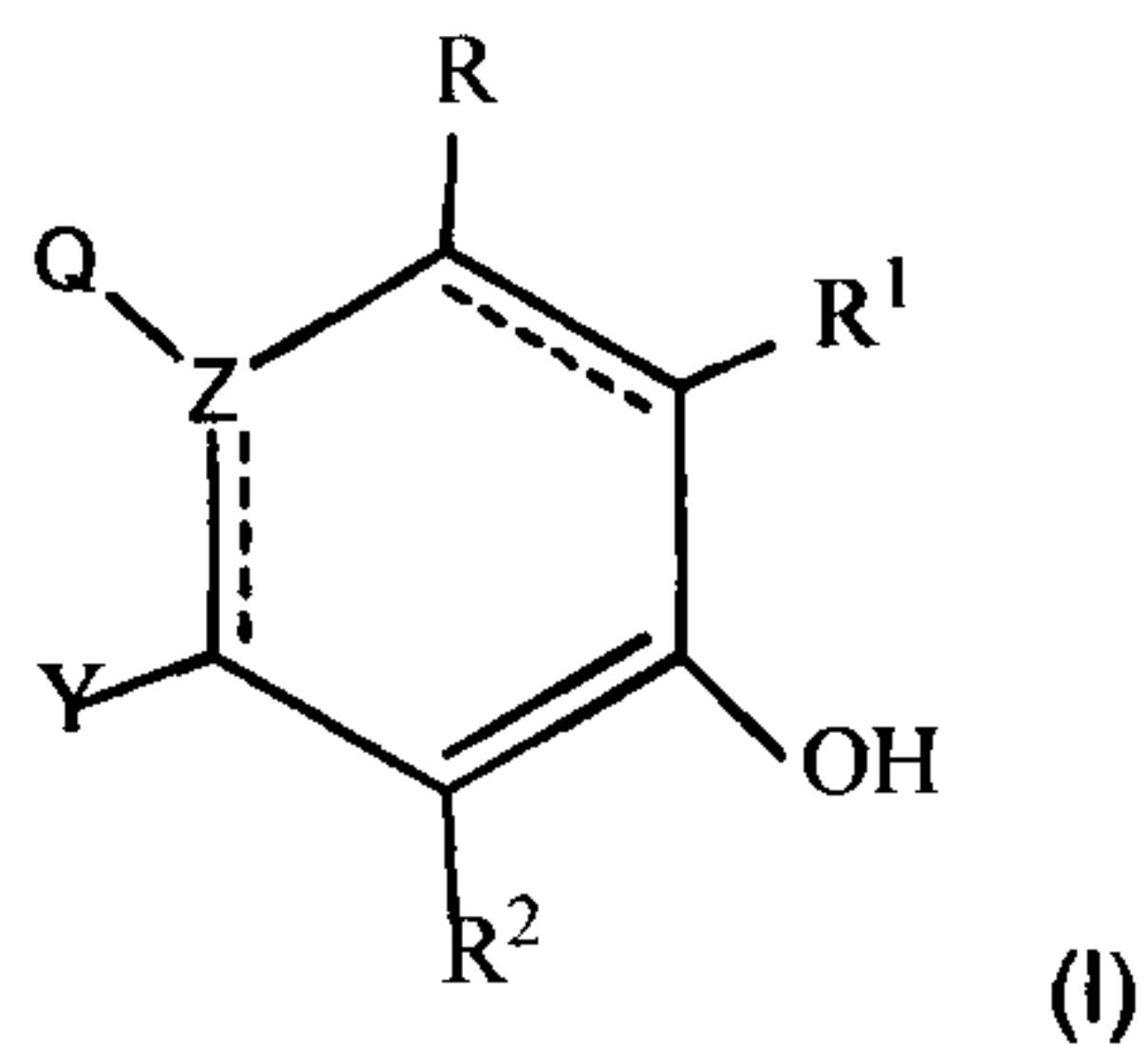
-48-

It is apparent to one of ordinary skill in the art that different pharmaceutical compositions may be prepared and used with substantially the same results. That is, other Abnormal Cannabidiols will effectively lower intraocular pressure in animals and are within the scope of the present invention. Also, the novel compounds of the present invention may be used in a method of providing neuroprotection to the eye of a mammal in a similar manner to the abnormal Cannabidiols of Published U.S. Patent Application 2005/0282912.

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CLAIMS:

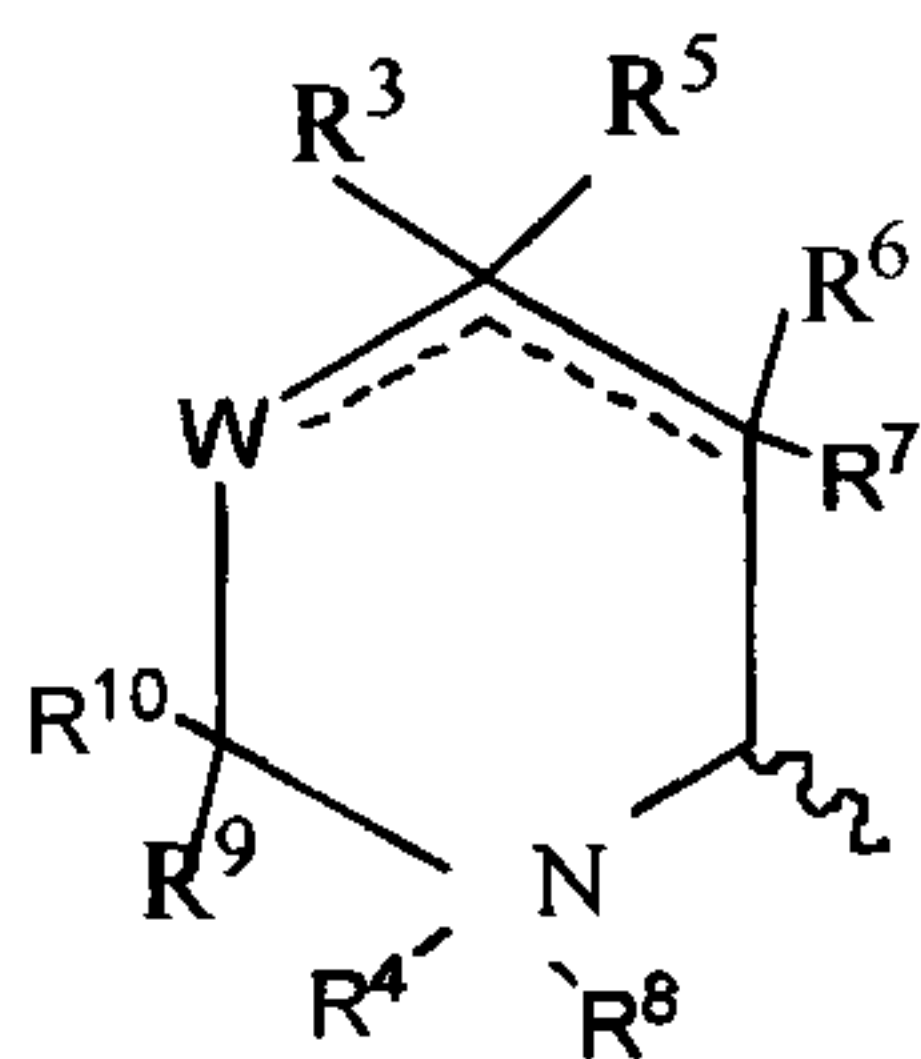
1. A compound of formula I useful for treating glaucoma or ocular hypertension



wherein Y is selected from the group consisting of O and OH;

Z is N or C;

Q is



wherein W is a direct bond or $C(R^{11})(R^{12})$; a dotted line represents the presence or absence of a double bond; the wavy line represents a direct bond;

R is selected from the group consisting of H, halogen and C_{1-5} alkyl;

R^1 is selected from the group consisting of H and halogen;

R^2 is independently selected from the group consisting of H, C_{1-5} alkyl, halogen, XC_{1-5} alkyl, C_{1-5} alkylOR¹³, C_{1-5} alkylN(R^{13})₂,

N(R^{13})₂, XC_{1-5} alkylN(R^{13})₂ and XC_{1-5} alkylOR¹³;

X is O or S(O)_n;

n is 0 or an integer of from 1 to 2;

R^3 is selected from the group consisting of H, hydroxyl C_{1-5} alkyl, C_{1-5} alkylOR¹³ and C_{1-5} alkylN(R^{13})₂;

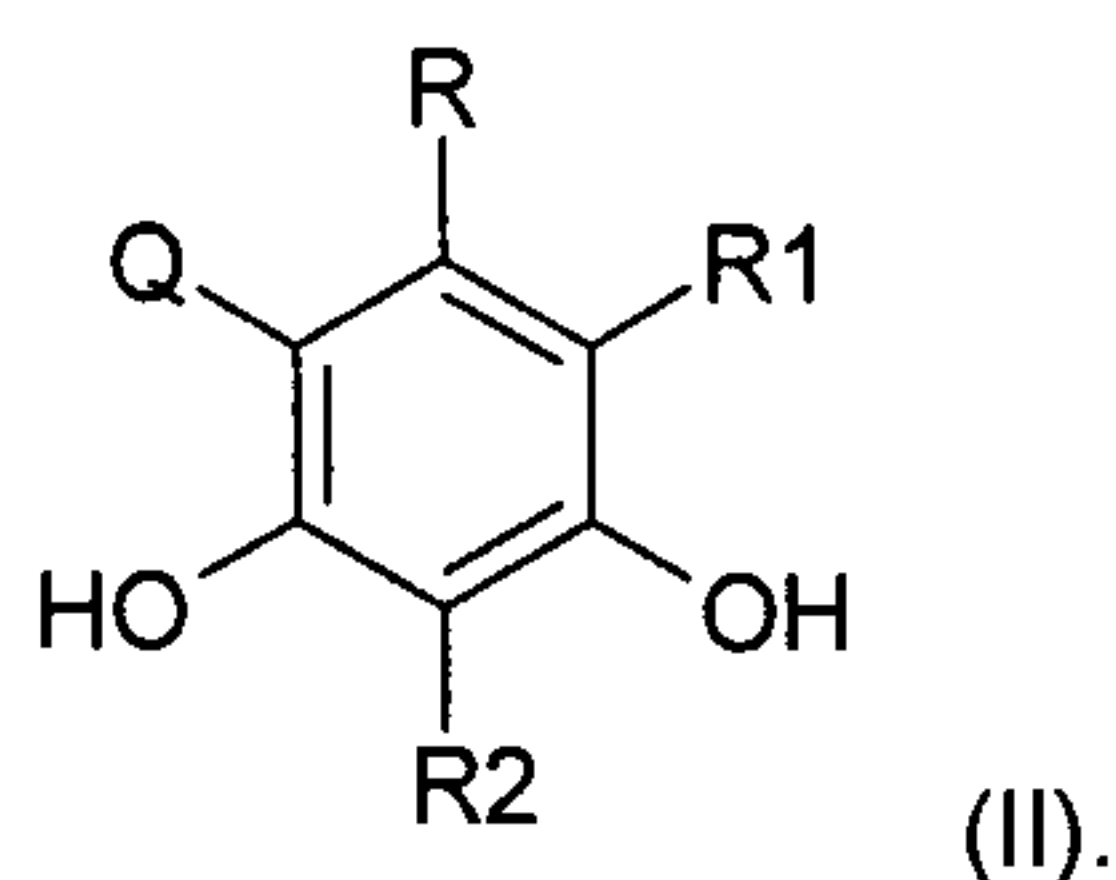
R^4 is selected from the group consisting of H, C_{1-5} alkenyl, C_{2-5} alkyl, C_{1-5} alkylOR¹³ and C_{1-5} alkylN(R^{13})₂;

R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} are independently selected from the group consisting of H, C_{1-5} alkyl, C_{1-5} alkylOR¹³ and OR¹³; and

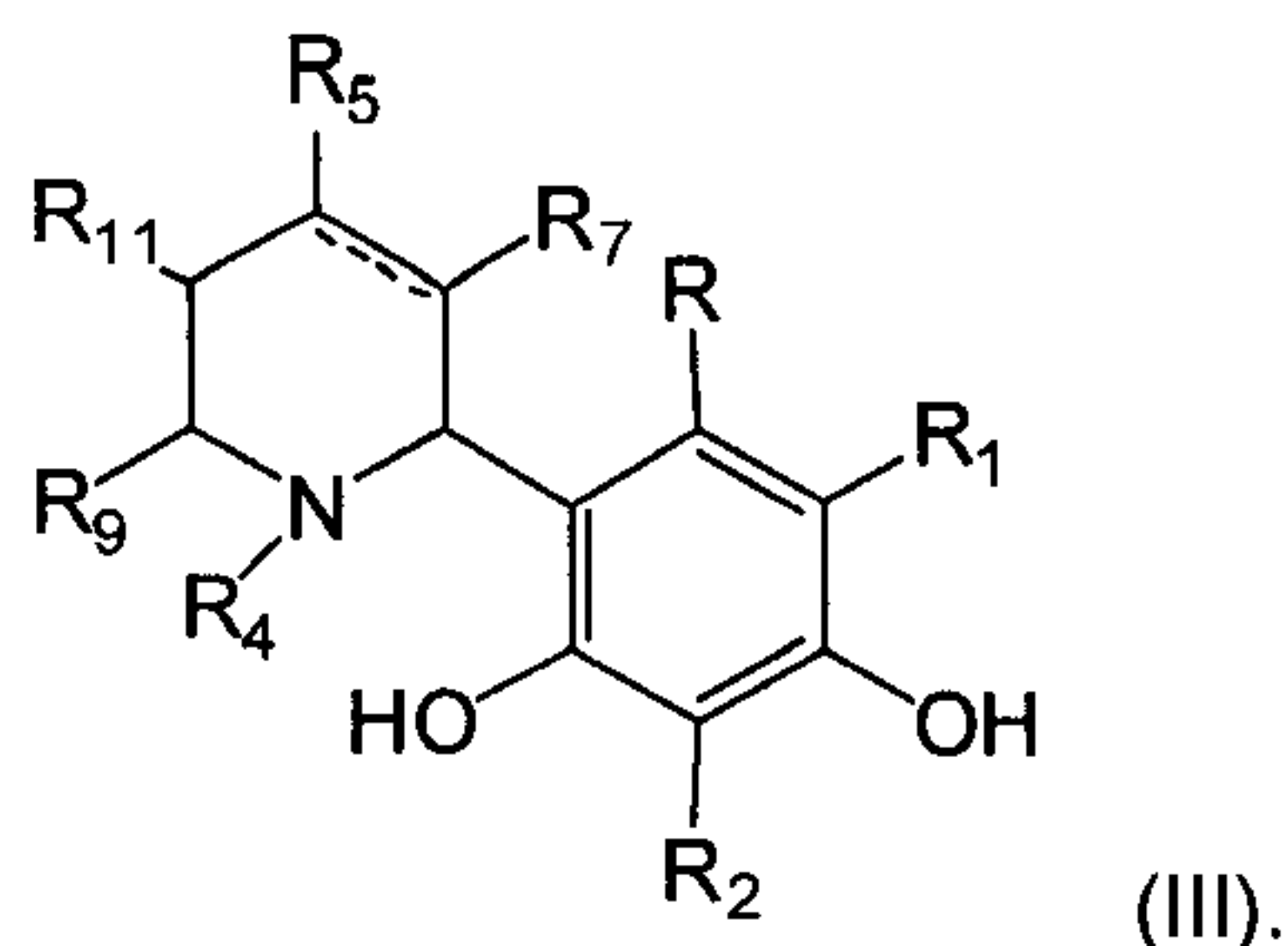
R^{13} is selected from the group consisting of H, C_{1-5} alkyl and C_{3-8} cyclic alkyl, or two R^{13} groups, together with N or O, may form a cyclic ring such as a piperidine or morpholine ring; and provided that any of said alkyl groups may be substituted with a hetero atom containing radical, wherein said heteroatom is selected from the group consisting of halogen, oxygen, nitrogen and sulfur, R^8 and R^{12} may, together, form a cyclic ring, and R^3 and R^5 may, together, represent O, and

when Q is menthadiene, R^1 and R^2 are H and Y is hydroxyl, R may not be H or alkyl.

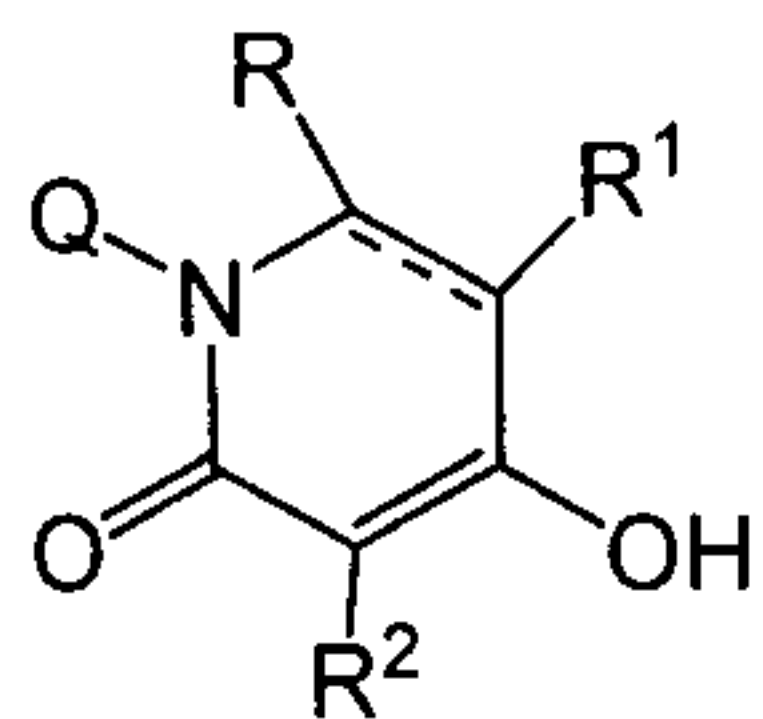
2. The compound of Claim 1 wherein said compound is a compound of formula II



3. The compound of claim 2 wherein R is selected from the group consisting of hydrogen, methyl, bromo and ethyl and R^2 is selected from the group consisting of hydrogen, methyl and chloro.
4. The compound of claim 1 wherein said compound is a compound of formula III



5. The compound of claim 1 wherein said compound is a compound of formula IV



(IV).

6. The compound of claim 2 wherein R is selected from the group consisting of hydrogen, methyl, bromo and chloro; R¹ is selected from the group consisting of hydrogen, methyl and chloro, R² is hydrogen, R³ is methyl, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹ and R¹² are hydrogen and R⁴ is isopropenyl.
7. The compound of claim 1 wherein said compound is 4-(1-isopropyl-4-methyl-1,2,5,6-tetrahydropyridin-2-yl)-5-methylbenzene-1,3-diol.
8. A pharmaceutical composition which is an ophthalmic solution comprising the compound according to any one of claims 1-7 and an ophthalmically acceptable liquid.
9. A pharmaceutical product, comprising a container adapted to dispense its contents in metered form, and the composition as defined in claim 8.
10. Use of the compound according to any one of claims 1 to 7 for topical administration to the eye for treating glaucoma or ocular hypertension.
11. Use of the compound according to any one of claims 1 to 7 for the production of a medicament for topical administration to the eye for treating glaucoma or ocular hypertension.
12. Use of the compound according to any one of claims 1 to 7 for topical administration to the eye for treating glaucoma or ocular hypertension, wherein said use is in combination with a second drug selected from the group consisting of β -blockers, adrenergic agonists, carbonic anhydrase inhibitors, cholinergic agonists, cholinesterase inhibitors, glutamate antagonists, prostamides and prostaglandins.
13. Use of the compound according to any one of claims 1 to 7 for the production of a medicament for topical administration to the eye for treating glaucoma or ocular hypertension, wherein said use is in combination with a second drug selected from the group consisting of β -blockers, adrenergic agonists, carbonic anhydrase inhibitors, cholinergic agonists, cholinesterase inhibitors, glutamate antagonists, prostamides and prostaglandins.