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CA 2117892 C 2001/12/18

(11)(21) **2 117 892**

(12) **BREVET CANADIEN
CANADIAN PATENT**

(13) **C**

(86) Date de dépôt PCT/PCT Filing Date: 1993/03/10
(87) Date publication PCT/PCT Publication Date: 1993/10/28
(45) Date de délivrance/Issue Date: 2001/12/18
(85) Entrée phase nationale/National Entry: 1994/10/11
(86) N° demande PCT/PCT Application No.: US 93/02103
(87) N° publication PCT/PCT Publication No.: WO 93/21156
(30) Priorités/Priorities: 1992/04/10 (867,261) US;
1993/02/25 (017,251) US

(51) Cl.Int.⁵/Int.Cl.⁵ C07D 211/22, C07D 211/70,
C07D 409/12, C07F 7/10
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(54) Titre : DERIVES DE LA 4-DIPHENYLMETHYLPIPERIDINE ET METHODE POUR LEUR PREPARATION
(54) Title: 4-DIPHENYLMETHYL PIPERIDINE DERIVATIVES AND PROCESS FOR THEIR PREPARATION

(57) **Abrégé/Abstract:**

The present invention is related to a novel process for preparing certain piperidine derivatives which are useful as antihistamines, antiallergy agents and bronchodilators.



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ABSTRACT OF THE DISCLOSURE

5 The present invention is related to a novel process for
preparing certain piperidine derivatives which are useful
as antihistamines, antiallergy agents and bronchodilators.

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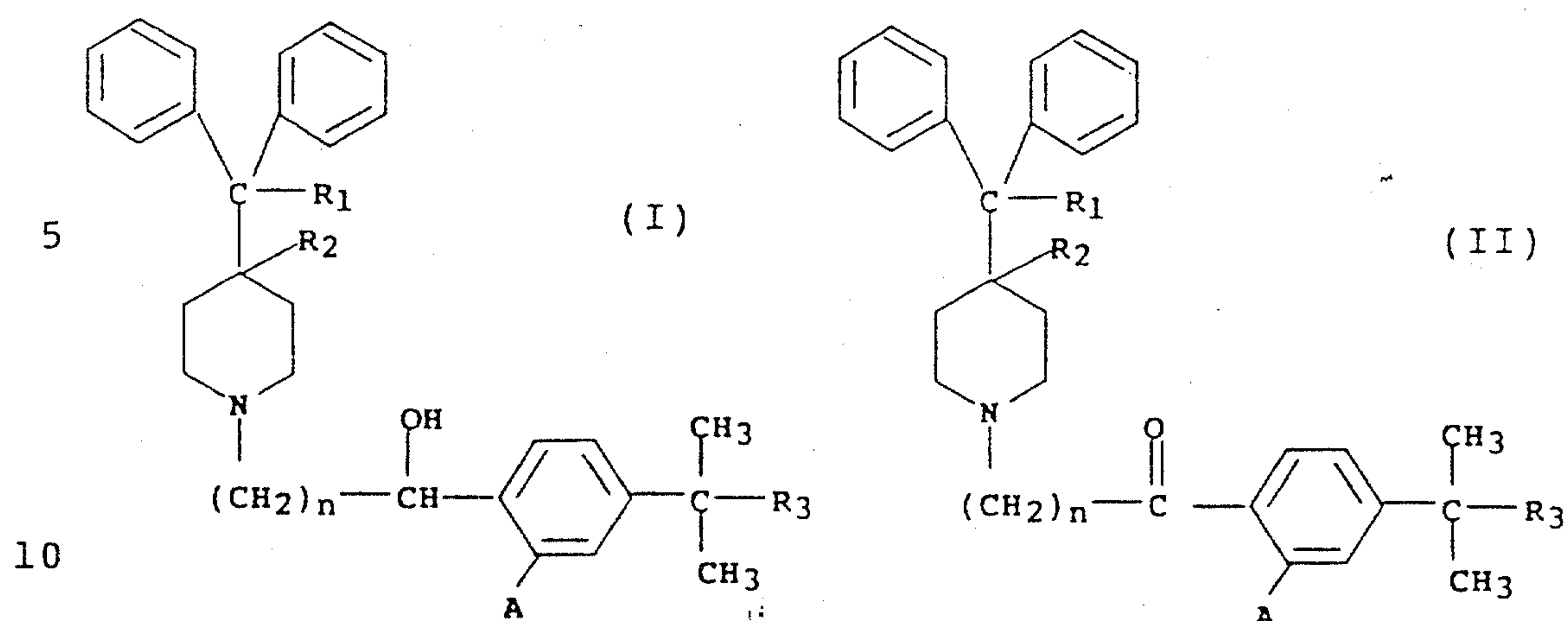
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4-DIPHENYLMETHYL PIPERIDINE DERIVATIVES
AND PROCESS FOR THEIR PREPARATION

5 The present invention is related to a novel process for
preparing certain piperidine derivatives which are useful as
antihistamines, antiallergy agents and bronchodilators [United
States Patent No. 4,254,129, March 3, 1981, United States
Patent No. 4,254,130, March 3, 1981 and United States Patent
10 No. 4,285,958, April 25, 1981].

These piperidine derivatives can be described by the
following formulas:



wherein

- 15 R₁ represents hydrogen or hydroxy;
 R₂ represents hydrogen; or
 R₁ and R₂ taken together form a second bond between the
 carbon atoms bearing R₁ and R₂;
 n is an integer of from 1 to 5;
 R₃ is -CH₂OH, -COOH or -COOalkyl wherein the alkyl
 20 moiety has from 1 to 6 carbon atoms and is straight or
 branched;
 each of A is hydrogen or hydroxy; and
 pharmaceutically acceptable salts and individual optical
 isomers thereof.

25

The novel process for preparing the piperidine
 derivatives of formula (I) and formula (II) of the present
 invention offers high yields and ease of purification.

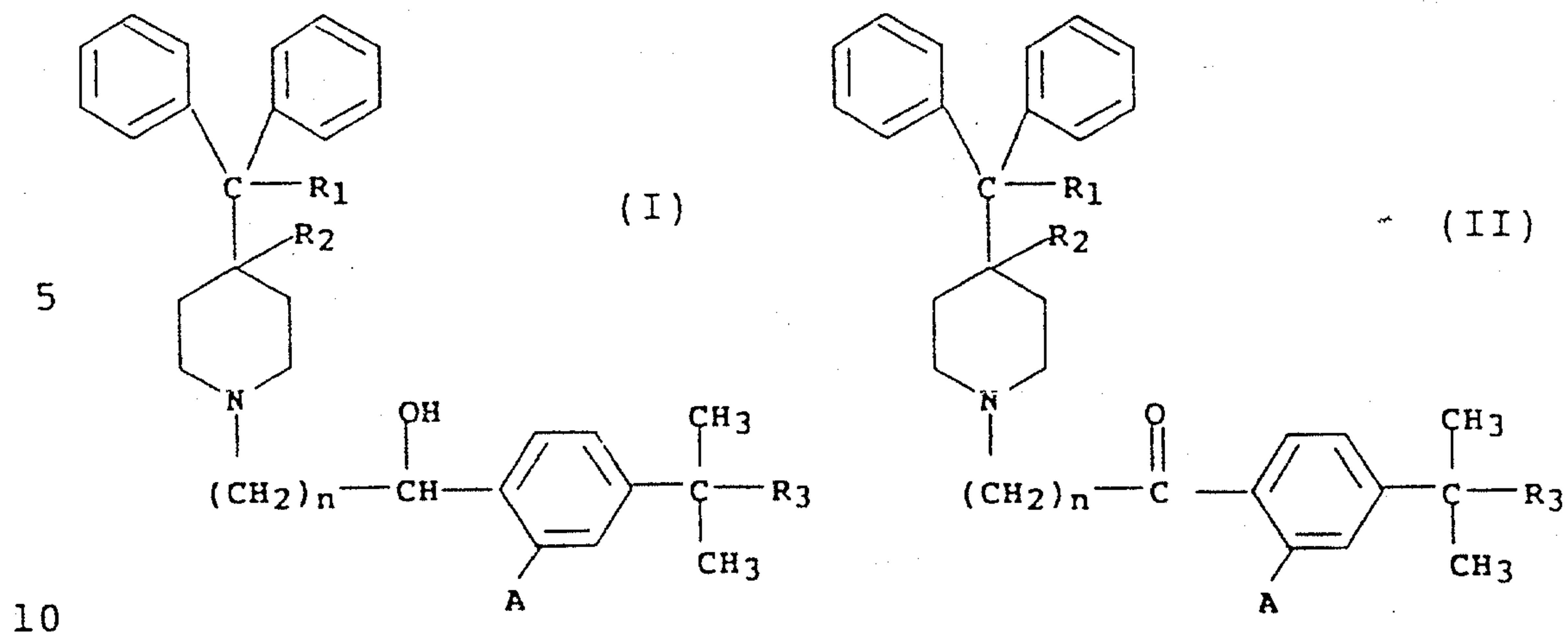
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SUMMARY OF THE INVENTION

The present invention provides a novel process for
 preparing the piperidine derivatives of formula (I) and
 formula (II)

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-3-



wherein

R_1 represents hydrogen or hydroxy;

R_2 represents hydrogen; or

15 R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;

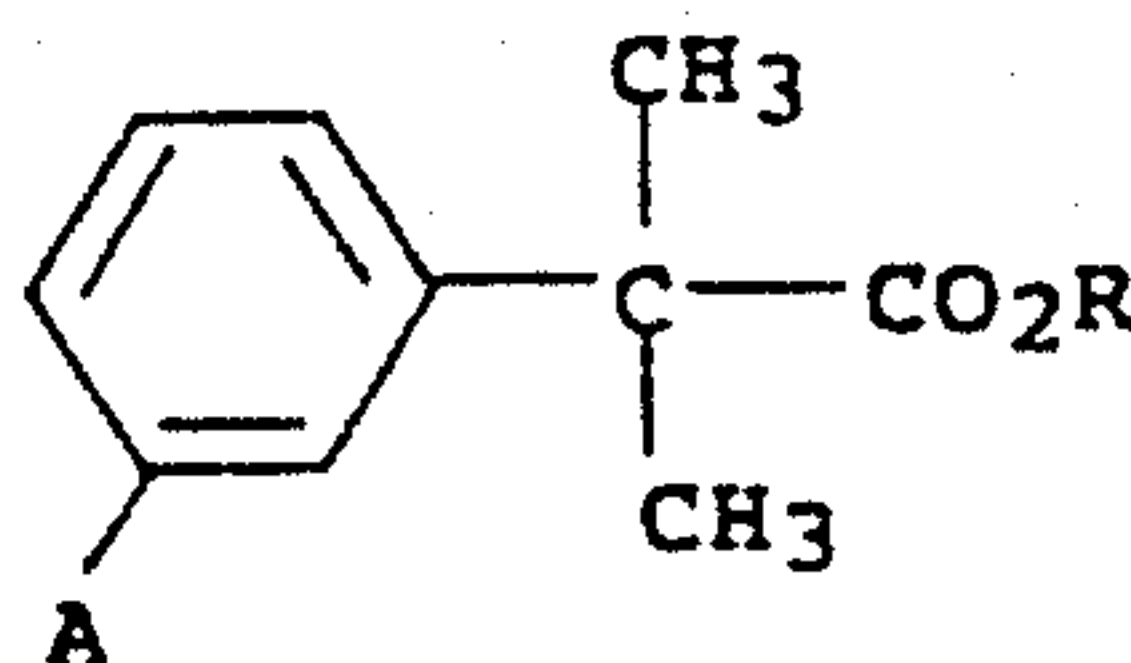
n is an integer of from 1 to 5;

R_3 is $-\text{CH}_2\text{OH}$, $-\text{COOH}$ or $-\text{COOalkyl}$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

20 each of A is hydrogen or hydroxy; and

pharmaceutically acceptable salts and individual optical isomers thereof comprising the steps of:

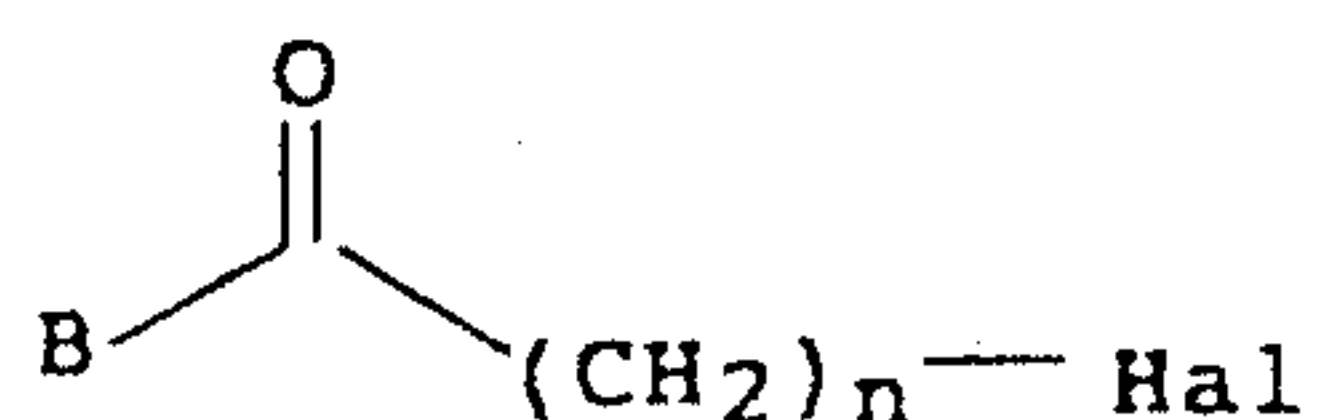
(a) reacting a benzeneacetic acid compound of the
25 formula



wherein A is as defined above and R is hydrogen or $\text{C}_1\text{-C}_6$ alkyl with a suitable reducing agent to give a phenethyl alcohol;

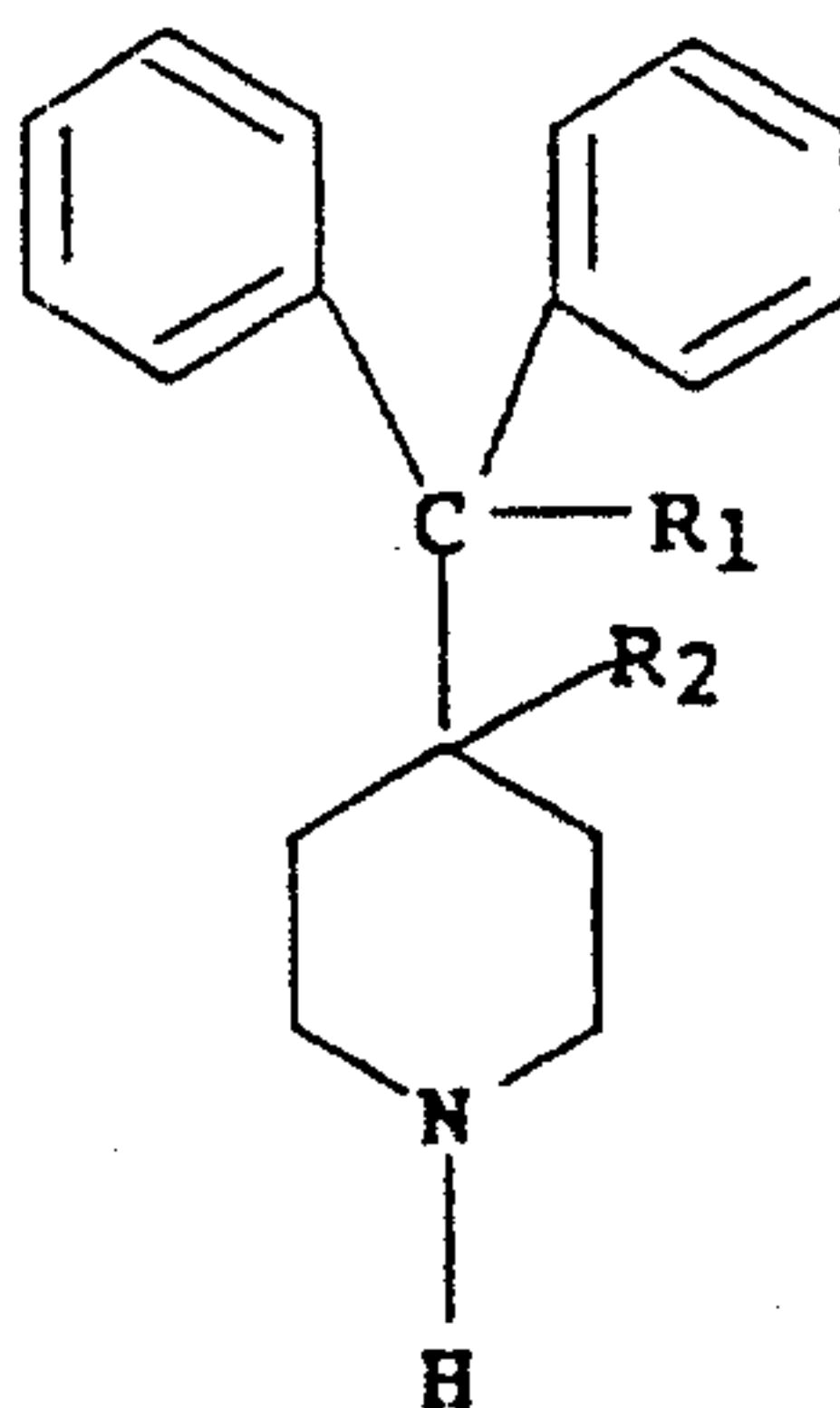
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(b) reacting the phenethyl alcohol with a ω -halo compound of the formula



wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of a suitable Lewis acid to produce a ω -halo hydroxyethylphenylketone; and

10 (c) reacting the ω -halo hydroxyethylphenylketone with a piperidine compound of the formula



wherein R₁ and R₂ are as defined above in the presence of a suitable non-nucleophilic base to produce a piperidine hydroxyethylphenylketone derivative of formula (II) wherein R₃ is -CH₂OH;

(d) optionally reacting the piperidine hydroxyethylphenylketone derivative of formula (II) wherein R₃ is -CH₂OH with a suitable oxidizing agent to produce a piperidine carboxyphenylketone derivative of formula (II) wherein R₃ is -COOH;

(e) optionally reacting the piperidine carboxyphenylketone derivative of formula (II) wherein R₃ is

-COOH to produce a piperidine carboxyphenylketone ester derivative of formula (II) wherein R₃ is -COOalkyl.

(f) optionally reacting the piperidine
5 carboxyphenylketone derivative of formula (II) wherein R₃ is -COOH or the piperidine carboxyphenylketone ester derivative of formula (II) wherein R₃ is -COOalkyl with a suitable reducing agent to produce a piperidine carboxyphenylalcohol derivative of formula (I) wherein R₃ is -COOH or the
10 piperidine carboxyphenylalcohol ester of formula (I) wherein R₃ is -COOalkyl;

(g) optionally reacting the piperidine
carboxyphenylalcohol derivative of formula (I) wherein R₃ is
15 -COOH to produce a piperidine carboxyphenylalcohol ester derivative of formula (I) wherein R₃ is -COOalkyl; and

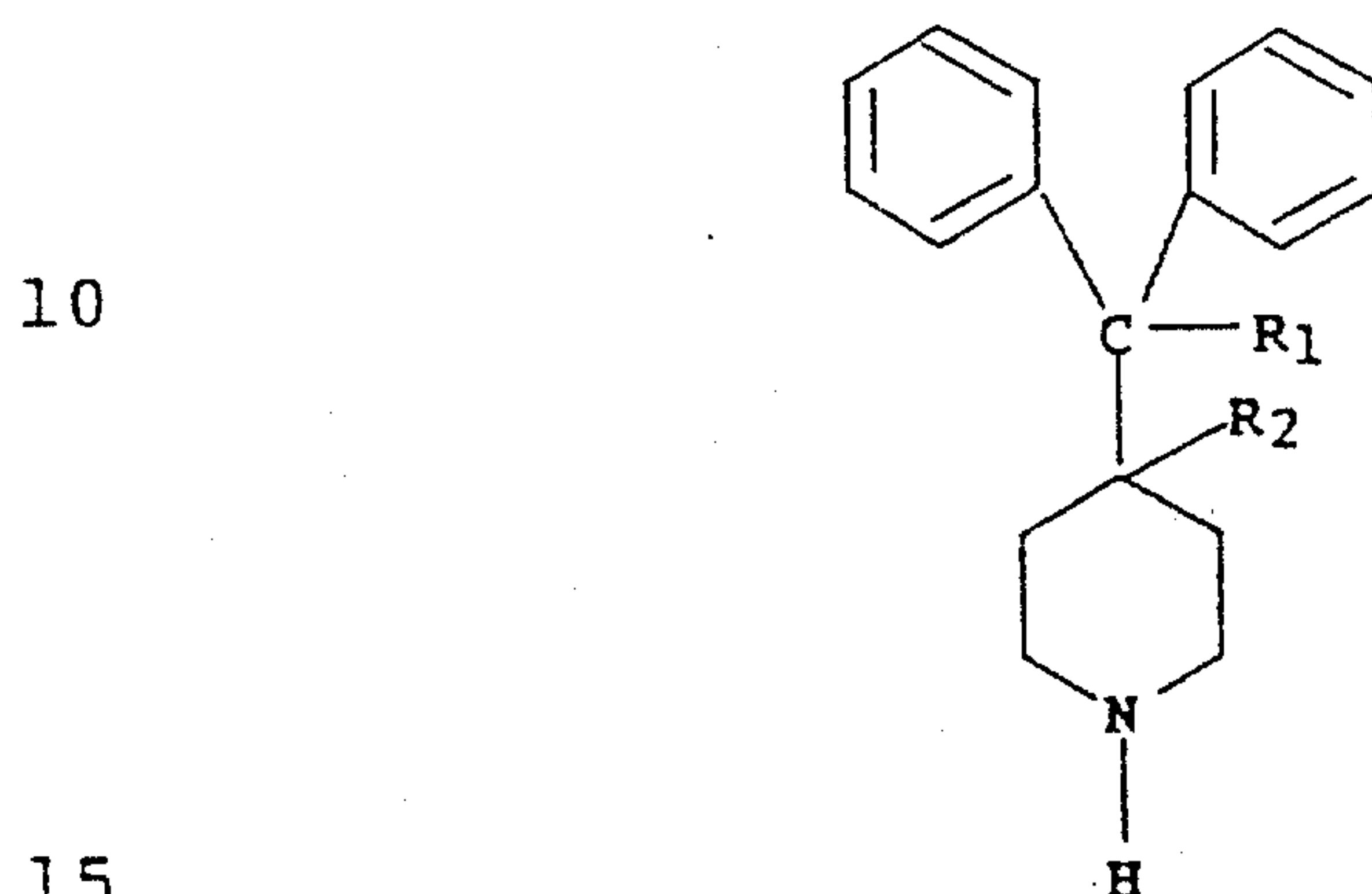
(h) optionally reacting the piperidine
hydroxyethylphenylketone derivative of formula (II) wherein
20 R₃ is -CH₂OH, the piperidine carboxyphenylketone derivative of formula (II) wherein R₃ is -COOH, the piperidine carboxyphenylketone ester derivative of formula (II) wherein R₃ is -COOalkyl, the piperidine carboxyphenylalcohol derivative of formula (I) wherein R₃ is -COOH or the
25 piperidine carboxyphenylalcohol ester of formula (I) wherein R₃ is -COOalkyl with an appropriate deprotecting reagent,

with the proviso that each of the hydroxy groups present in the compounds described in steps a-g are optionally
30 protected or unprotected.

Alternatively, the present invention provides a novel process for preparing the piperidine derivatives of formula (I) comprising the steps of:

(a) reacting the ω -halo hydroxyethylphenylketone with a suitable reducing agent to produce a ω -halo hydroxyethylphenylalcohol;

5 (b) reacting the ω -halo hydroxyethylphenylalcohol with a piperidine compound of the formula



wherein R_1 and R_2 are as defined above, in the presence of a suitable non-nucleophilic base to produce a piperidine hydroxyethylphenylalcohol derivative of formula (I) wherein

20 R_3 is $-\text{CH}_2\text{OH}$;

(c) optionally reacting the piperidine hydroxyethylphenylalcohol derivative of formula (I) wherein R_3 is $-\text{CH}_2\text{OH}$ with a suitable oxidizing agent to produce a

25 piperidine carboxyphenylalcohol derivative of formula (I) wherein R_3 is $-\text{COOH}$; and

(d) optionally reacting the piperidine carboxyphenylalcohol derivative of formula (I) wherein R_3 is

30 $-\text{COOH}$ to produce the piperidine carboxyphenylalcohol ester derivative of formula (I) wherein R_3 is $-\text{COOalkyl}$.

(e) optionally reacting the piperidine hydroxyethylphenylalcohol derivative of formula (I) wherein

35

R₃ is -CH₂OH, the piperidine carboxyphenylalcohol derivative of formula (I) wherein R₃ is -COOH or the piperidine carboxyphenylalcohol ester derivative of formula (I) wherein R₃ is -COOalkyl with an appropriate deprotecting reagent,

5

with the proviso that each of the hydroxy groups present in the compounds described in steps a-d are optionally protected or unprotected.

10 In addition, the present invention provides a novel process for preparing the piperidine derivatives of formula (I) comprising the steps of:

(a) reacting the piperidine hydroxyethylphenylketone
15 derivative of formula (II) wherein R₃ is -CH₂OH with a suitable reducing agent to produce a piperidine hydroxyethylphenylalcohol derivative of formula (I) wherein R₃ is -CH₂OH;

20 (b) optionally reacting the piperidine hydroxyethylphenylalcohol derivative of formula (I) wherein R₃ is -CH₂OH with a suitable oxidizing agent to produce a piperidine carboxyphenylalcohol derivative of formula (I) wherein R₃ is -COOH; and

25

(c) optionally reacting the piperidine carboxyphenylalcohol derivative of formula (I) wherein R₃ is -COOH to produce the piperidine carboxyphenylalcohol ester derivative of formula (I) wherein R₃ is -COOalkyl.

30

(d) optionally reacting the piperidine hydroxyethylphenylketone derivative of formula (II) wherein R₃ is -CH₂OH, the piperidine hydroxyethylphenylalcohol derivative of formula (I) wherein R₃ is -CH₂OH, the
35 piperidine carboxyphenylalcohol derivative of formula (I)

wherein R₃ is -COOH or the piperidine carboxyphenylalcohol ester derivative of formula (I) wherein R₃ is -COOalkyl with an appropriate deprotecting reagent, with the proviso that each of the hydroxy groups present in the compounds described in steps a-c are optionally protected or unprotected.

As used herein, straight or branched alkyl groups having from 1 to 6 carbon atoms as referred to herein are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, neopentyl and n-hexyl.

The piperidine derivatives of the formula (I) and formula (II) can form pharmaceutically acceptable salts. Pharmaceutically acceptable acid addition salts of the compounds of this invention are those of any suitable inorganic or organic acid. Suitable inorganic acids are, for example, hydrochloric, hydrobromic, sulfuric, and phosphoric acids. Suitable organic acids include carboxylic acids, such as, acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, fumaric, malic, tartaric, citric, cyclamic, ascorbic, maleic, hydroxymaleic, and dihydroxymaleic, benzoic, phenylacetic, 4-aminobenzoic, 4-hydroxybenzoic, anthranillic, cinnamic, salicyclic, 4-aminosalicyclic, 2-phenoxybenzoic, 2-acetoxybenzoic, and mandelic acid, sulfonic acids, such as, methanesulfonic, ethanesulfonic and 8-hydroxyethanesulfonic acid. Non-toxic salts of the compounds of the above-identified formula formed with inorganic or organic bases are also included within the scope of this invention and include, for example, those of alkali metals, such as, sodium, potassium and lithium, alkaline earth metals, for example, calcium and magnesium, light metals of group IIIA, for example, aluminum, organic amines, such as, primary, secondary or tertiary amines, for example, cyclohexylamine, ethylamine,

pyridine, methylaminoethanol and piperazine. The salts are prepared by conventional means as, for example, by treating a piperidine derivative of formula (I) or formula (II) with an appropriate acid or base.

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The novel process for preparing the piperidine derivatives of formula (I) and formula (II) is outlined in Scheme A. In Scheme A, all substituents are as previously defined unless otherwise indicated.

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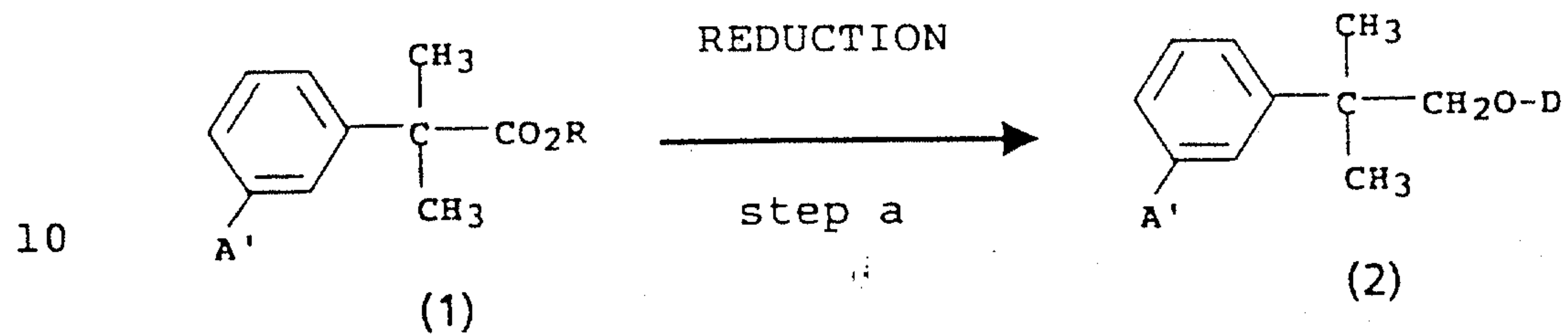
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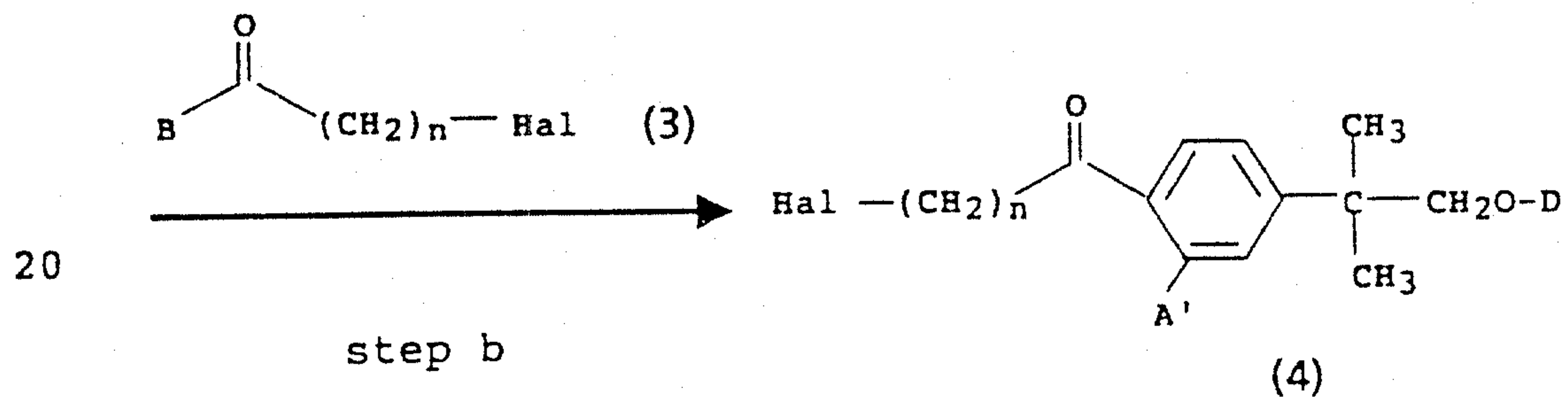
Scheme A

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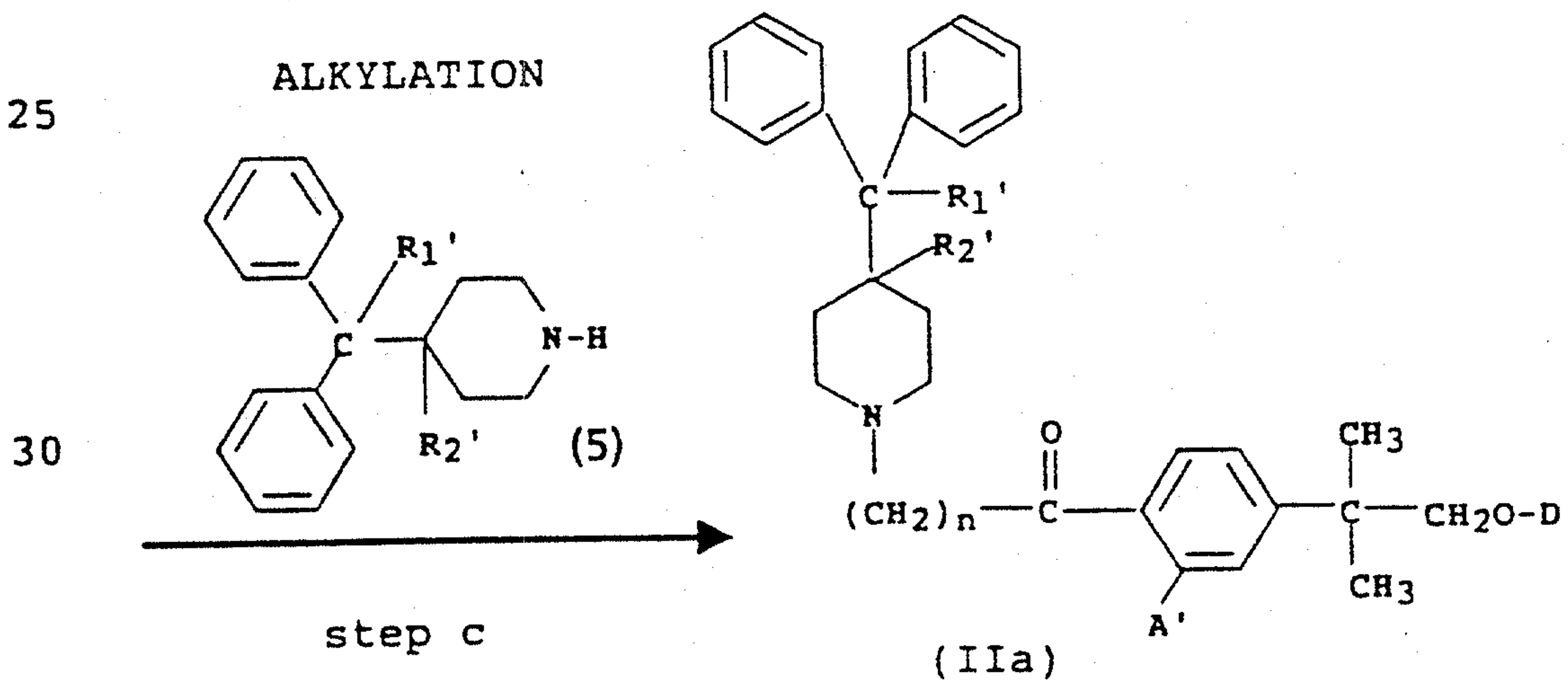
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ACYLATION



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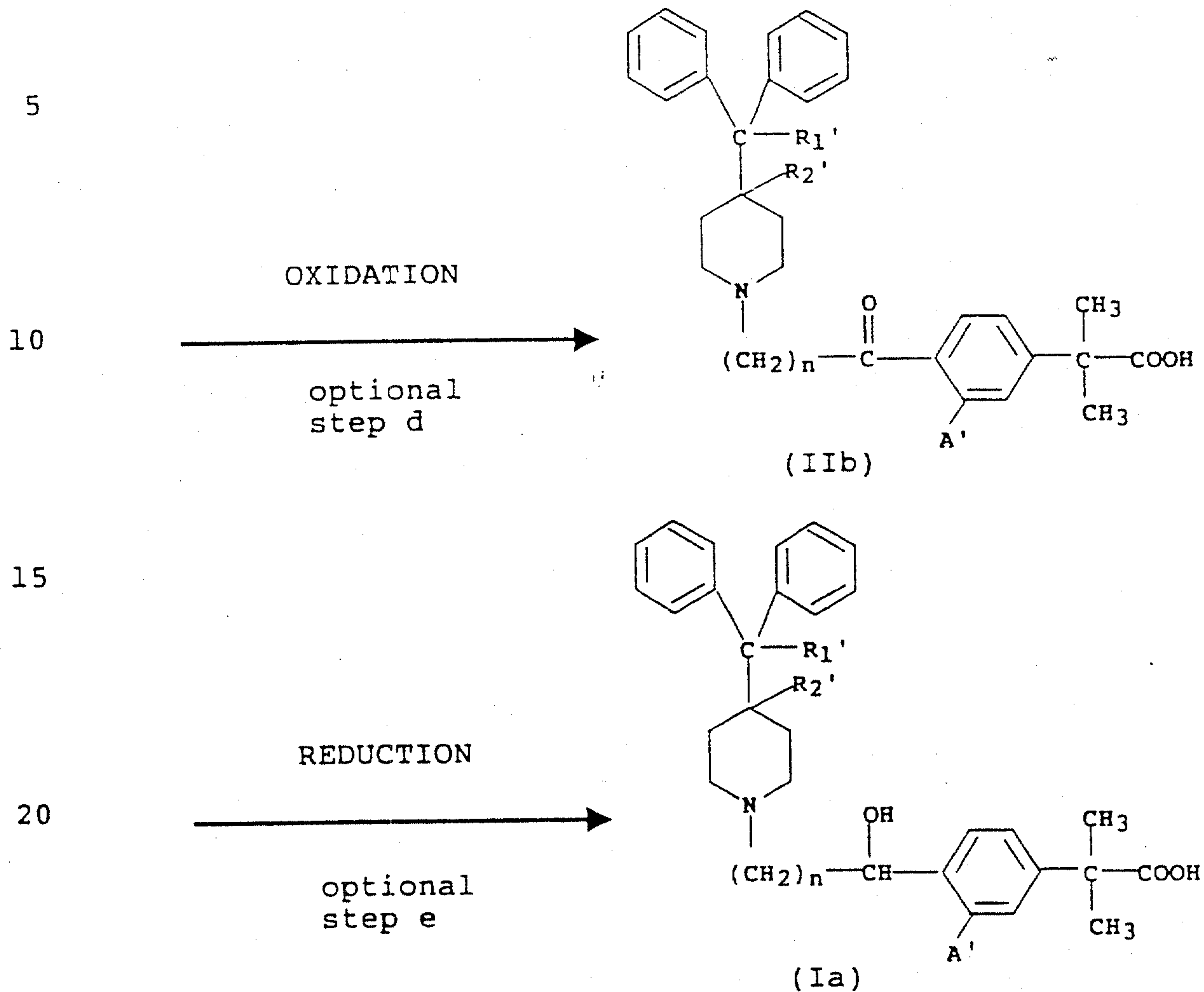
ALKYLATION



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Scheme A Cont.



A' = hydrogen, protected hydroxy or hydroxy
 B = Halo or OH
 D = hydrogen or a suitable protecting group
 R₁' and R₂' = hydrogen, protected hydroxy, hydroxy or
 taken together to form a second bond
 between the carbon atoms bearing R₁' and
 R₂'
 R = C₁-C₆ alkyl or hydrogen

Scheme A provides a general synthetic procedure for preparing the piperidine derivatives of formula (I) and formula (II).

5 In step a, the carboxy functionality of an appropriate benzeneacetic acid compound of structure (1), wherein R is hydrogen or C₁-C₆ alkyl, is reduced to give the corresponding phenethyl alcohol of structure (2), wherein D is hydrogen.

10

For example, reduction of the appropriate benzeneacetic acid of structure (1), wherein R is hydrogen, using, for example, sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, diborane or aluminum hydride with
15 diborane being preferred. Reduction of the appropriate benzeneacetic acid of structure (1), wherein R is C₁-C₆ alkyl, using, for example, lithium aluminum hydride, lithium borohydride, sodium bis(2-methoxyethoxy)aluminum hydride, aluminum hydride, lithium triethylborohydride and
20 lithium tri-sec-butylborohydride with lithium aluminum hydride being preferred. Suitable solvents are ethers, for example, diethyl ether, tetrahydrofuran or dioxane. These reduction reactions are carried out at temperatures ranging from about 0°C to the reflux temperature of the solvent,
25 and the reaction time varies from about 1/2 hour to 8 hours.

The starting benzeneacetic acid compounds of structure (1) are known in the art or are prepared by procedures well
30 known in the art. For example, the benzeneacetic acid compound of structure (1) wherein R is C₁-C₆ alkyl and A' is hydroxy may be prepared by treating a hot solution of 1 equivalent of an appropriate straight or branched alkyl C₁-6 ester of 3-trifluoroacetoxyphenylacetic acid in
35 dimethoxyethane with a base, such as, sodium hydride under

a nitrogen atmosphere followed by the addition of 2.1 equivalents of methyl iodide in dimethoxyethane to the mixture over about a 20 minute period. The mixture is refluxed for about 3 hours then concentrated to remove most
5 of the solvent after which diethyl ether, then water are added cautiously. The organic layer is separated, extracted with ether, dried over magnesium sulfate and distilled to give the appropriate ester of the benzeneacetic acid compound of structure (1) wherein A' is
10 a trifluoroacetoxy protected hydroxy and R is C₁-C₆ alkyl. To a solution of the methylated ester in 50% alcohol/water is added 3X molar amount of potassium carbonate. The solution is stirred at about 25°C for about 8 hours then concentrated to a semisolid at reduced pressure at about
15 50°C and upon cooling water is added and the mixture is neutralized with dilute hydrochloric acid then extracted with ether. The ether extract is dried over magnesium sulfate, filtered and concentrated to give the appropriate ester of the benzeneacetic acid compound of structure (1)
20 wherein A' is hydroxy and R is C₁-C₆ alkyl. The esters of the benzeneacetic acid compounds of structure (1) wherein A' is a trifluoroacetoxy protected hydroxy and R is C₁-C₆ alkyl are known in the art, for example, from ethyl m-hydroxyphenylacetate by treatment with trifluoroacetic
25 anhydride.

Alternatively, the phenethyl alcohol compounds of structure (2) may be prepared by Friedel-Crafts acylation of an appropriate benzene compound with a suitable
30 protected 2-methyl-2-propenyl alcohol compound. For example, the phenethyl alcohol compound of structure (2) wherein A' is hydrogen, hydroxy or a suitably protected hydroxy may be prepared by reacting an appropriate 2-methyl-2-propenyl alcohol compound with an appropriate
35 benzene compound in the presence of AlCl₃.

In step b, the appropriate phenethyl alcohol of structure (2), wherein A' is hydrogen, hydroxy or a suitably protected hydroxy, is acylated with the ω -halo compound of structure (3) wherein B is halo under Freidel-Crafts conditions to give the corresponding ω -halo hydroxyethylphenylketone of structure (4) wherein A' is described as above.

10 For example, the ω -halo hydroxyethylphenylketone of structure (4), wherein A' is hydrogen, hydroxy or a protected hydroxy, may be prepared by reacting an appropriate phenethyl alcohol of structure (2), wherein A' is hydrogen, hydroxy or a protected hydroxy, with a
15 appropriate ω -halo compound of structure (3) wherein B is halo, which are known in the art or are prepared by procedures well known in the art, under the general conditions of a Friedel-Crafts acylation using a suitable Lewis acid. The reaction is carried out in a solvent, such
20 as carbon disulfide, methylene chloride, tetrachloroethane or nitrobenzene with methylene chloride being the preferred solvent. The reaction time varies from about 1/2 hour to 8 hours, preferably 1 to 5 hours and the reaction temperature varies from about 0°C to 25°C. The ω -halo
25 hydroxyethylphenylketone of structure (4) wherein A' is hydrogen, hydroxy or a protected hydroxy is recovered from the reaction zone by an aqueous quench followed by extraction as is known in the art. The ω -halo hydroxyethylphenylketone of structure (4) wherein A' is
30 hydrogen, hydroxy or a protected hydroxy may be purified by procedures well known in the art, such as crystallization.

Alternatively, the appropriate phenethyl alcohol of structure (2) wherein A' is hydroxy may be acylated with
35 the ω -halo compound of structure (3) wherein B is hydroxy

in the presence of a Lewis acid to give the corresponding halo hydroxyethylphenylketone of structure (4) as described in *Arch. Pharm.* 306, 807 1973. In general, an appropriate phenethyl alcohol of structure (2), wherein A' is hydroxy, and the ω -halo compound of structure (3), wherein B is hydroxy, are melted together at about 50°C, then cooled to about 10°C after which a Lewis acid is added in an amount about 2.2 times the molar amount of the appropriate phenethyl alcohol of structure (2), wherein A' is hydroxy, employed. The mixture is heated at about 70°C for about 2 hours after which a 30% sodium acetate solution is added and extracted with ether. The organic layer is dried and the solvent evaporated to give the ω -halo hydroxyethylphenylketone of structure (4) wherein A' is hydroxy. The ω -halo hydroxyethylphenylketone of structure (4) may be purified by procedures well known in the art, such as crystallization.

Suitable Lewis acids for the acylation reaction described in step b are well known and appreciated in the art. Examples of suitable Lewis acids are boron trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride. The selection and utilization of suitable Lewis acids for the acylation reaction of step b is well known and appreciated by one of ordinary skill in the art.

The starting ω -halo compounds of (3) are commercially available or easily prepared by generally known methods.

30

While not necessary for utilization in the acylation reaction of step b, the hydroxyethyl functionality of those phenethyl alcohols of structure (2) may be protected with a suitable protecting group. The selection and utilization of suitable protecting groups for the phenethyl alcohols of

structure (2) is well known by one of ordinary skill in the art and is described in "Protective Groups in Organic Syntheses", Theodora W. Greene, Wiley (1981). For example, suitable protecting groups for the hydroxyethyl

5 functionality include ethers such as tetrahydrothiopyranyl, tetrahydrothiofuranyl, 2-(phenylselenyl)ethyl ether, o-nitrobenzyl ether, trimethylsilyl ether, isopropyldimethylsilyl ether, t-butyldimethylsilyl ether, t-butyldiphenylsilyl ether, tribenzylsilyl ether,

10 triisopropylsilyl ether; and esters, such as acetate ester, isobutyrate ester, pivaloate ester, adamantate ester, benzoate ester, 2,4,6-trimethylbenzoate (mesitoate) ester, methyl carbonate, p-nitrophenyl carbonate, p-nitrobenzyl carbonate, S-benzyl thiocarbonate and N-phenylcarbamate,

15 with acetoxy being preferred.

For those ω -halo hydroxyethylphenylketone of structure (4), wherein A' is hydrogen, hydroxy or a protected hydroxy and D is hydrogen, the Friedel-Crafts acylation may result

20 in acylation of the hydroxyethyl functionality and will require deprotection prior to the oxidation reaction described in optional step d. Suitable deprotecting agents and methods are described in optional step d, infra.

25 While also not necessary for utilization in the acylation reaction of step b, the phenol functionality of those phenethyl alcohols of structure (2), wherein A' is hydroxy may be protected with a suitable protecting group. For example, suitable protecting groups for the phenolic

30 hydroxy include methyl ether, 2-methoxyethoxymethyl ether (MEM), cyclohexyl ether, o-nitrobenzyl ether, 9-anthryl ether, t-butyldimethylsilyl ether, acetate, benzoate, methyl carbamate, benzyl carbamate, aryl pivaloate and aryl methanesulfonate.

In step c, the ω -halo functionality of the appropriate ω -halo hydroxyethylphenylketone of structure (4) is alkylated with the appropriate piperidine compound of structure (5) to give the corresponding piperidine hydroxyethylphenylketone derivative of formula (II) wherein R_3 is $-\text{CH}_2\text{OH}$.

For example, the alkylation reaction is carried out in a suitable solvent preferably in the presence of a base and optionally in the presence of a catalytic amount of an iodide source, such as potassium or sodium iodide, for about 4 to 120 hours and at temperatures of about 70°C to the reflux temperature of the solvent. Suitable solvent for the alkylation reaction include alcohol solvents such as, methanol, ethanol, isopropyl alcohol, or n-butanol; ketone solvents, such as, methyl isobutyl ketone; hydrocarbon solvents, such as, benzene, toluene or xylene; halogenated hydrocarbons, such as, chlorobenzene or methylene chloride or dimethylformamide. Suitable bases for the alkylation reaction include inorganic bases, for example, sodium bicarbonate, potassium carbonate, or potassium bicarbonate or organic bases, such as, a trialkylamine, for example, triethylamine or pyridine, or an excess of an appropriate piperidine compound of structure (5) may be used.

For those piperidine compounds of structure (5), wherein R_1 is hydroxy, it is preferred that R_1 be unprotected for utilization in the alkylation reaction of step c, but those hydroxy functionalities present in the piperidine compounds of structure (5), wherein R_1 is hydroxy may be protected with a suitable protecting group. The selection and utilization of suitable protecting groups for the piperidine compounds of structure (5), wherein R_1 is hydroxy is well known by one of ordinary skill in the art

and is described in "Protective Groups in Organic Syntheses", Theodora W. Greene, Wiley (1981). For example, suitable protecting groups for those hydroxy functionalities present include ethers such as
5 tetrahydrothiopyranyl, tetrahydrothiofuranyl, 2-(phenylselenyl)ethyl ether, o-nitrobenzyl ether, trimethylsilyl ether, isopropyldimethylsilyl ether, t-butylldimethylsilyl ether, t-butylldiphenylsilyl ether, tribenzylsilyl ether, triisopropylsilyl ether; and esters,
10 such as acetate ester, isobutyrate ester, pivaloate ester, adamantate ester, benzoate ester, 2,4,6-trimethylbenzoate (mesitoate) ester, methyl carbonate, p-nitrophenyl carbonate, p-nitrobenzyl carbonate, S-benzyl thiocarbonate and N-phenylcarbamate.

15

The piperidine compounds of structure (5) wherein R_1 and R_2 are hydrogen and where R_1 is hydroxy and R_2 is hydrogen are readily available to one of ordinary skill in the art. The piperidine compounds of structure (5) wherein
20 R_1 and R_2 form a second bond between the carbon atoms bearing R_1 and R_2 may be prepared by dehydration of the corresponding compound wherein R_1 is hydroxy by procedures generally known in the art.

25 In optional step d, the hydroxyethyl functionality of the appropriate piperidine hydroxyethylphenylketone derivative of formula (II) wherein R_3 is $-CH_2OH$ is oxidized to give the corresponding piperidine carboxyphenylketone derivative of formula (II) wherein R_3 is $COOH$.

30

For example, oxidation of the appropriate piperidine hydroxyethylphenylketone derivative of formula (II) wherein R_3 is $-CH_2OH$ may be achieved using a variety of oxidizing agents and methods.

35

One such method involves a two-step procedure in which the hydroxyethyl functionality of the appropriate piperidine hydroxyethylphenylketone derivative of formula (II) wherein R_3 is $-CH_2OH$ is first oxidized to the
5 corresponding aldehyde functionality using, for example, Swern Oxidation conditions (dimethyl sulfoxide, oxalyl chloride and triethylamine), as is known in the art. The Swern Oxidation is carried out in suitable aprotic organic solvents such as methylene chloride at temperatures ranging
10 from about $-78^\circ C$ to room temperature, and the reaction time varies from about 1/2 hour to 8 hours. Other suitable reagents for the oxidation of the hydroxyethyl functionality of the appropriate piperidine hydroxyethylphenylketone derivative of formula (II) wherein
15 R_3 is $-CH_2OH$ to the corresponding aldehyde functionality are Dess-Martin reagent, chromium (IV) oxide, nickel peroxide, sodium dichromate, potassium dichromate, t-butyl chromate, silver oxide, argentic picolinate manganese dioxide lead tetraacetate, dicyclohexylcarbodiimide, 2,3-dichloro-5,6-
20 dicyanoquinone, tetrachloro-1,2-benzoquinone, 2,2,6,6-tetramethylpiperidiny-1-oxyl (TEMPO) or quinolinium chlorochromate.

The intermediate aldehyde compound is then oxidized
25 further to give the corresponding piperidine carboxyphenylketone derivative of formula (II) wherein R_3 is $-COOH$ using, for example, potassium permanganate. The potassium permanganate oxidation is carried out in a suitable acidic medium such as hydrochloric acid/acetone at
30 a temperature ranging from about $0^\circ C$ to room temperature and the reaction time varies from about 1/2 hour to 8 hours. Other suitable reagents for the oxidation of the intermediate aldehyde to the corresponding piperidine carboxyphenylketone derivative of formula (II) wherein R_3 is
35 $-COOH$ are chromium (IV) oxide, silver (I) oxide, silver

2117892

oxide, argentic picolinate, peroxide, nitric acid, m-chloroperbenzoic acid and peracetic acid.

Another method involves a one-step procedure in which
5 the hydroxyethyl functionality of the appropriate
piperidine hydroxyethylphenylketone derivative of formula
(II) wherein R_3 is $-CH_2OH$ is oxidized directly to the
carboxy functionality to give the corresponding piperidine
carboxyphenylketone derivative of formula (II) wherein R_3 is
10 $-COOH$. Oxidizing reagents suitable for direct, one-step
oxidation of the hydroxyethyl functionality to the carboxy
functionality include, for example, chromaium (IV) oxide,
potassium permanganate, nitric acid, nitrogen dioxide,
ruthenium (VIII) oxide, nickel peroxide, silver oxide, t-
15 butyl chromate and xenic acid.

Oxidation using Swern Oxidation conditions, nickel
peroxide, chromium (IV) oxide, silver oxide, sodium
dichromate, potassium dichromate, manganese dioxide, 2,3-
20 dichloro-5,6-dicyanoquinone and tetrachloro-1,2-
benzoquinone is preferred for those piperidine
hydroxyethylphenylketone derivatives of formula (II)
wherein R_3 is $-CH_2OH$ wherein R_1 and R_2 taken together form
a second bond between the carbon atoms bearing R_1 and R_2 .

25

As one skilled in the art would appreciate, those
piperidine hydroxyethylphenylketone derivatives of formula
(II) wherein R_3 is $-CH_2OH$ wherein the hydroxyethyl
functionality is protected must be reacted with an
30 appropriate deprotecting reagent prior to the oxidation
reaction described in step d. The selection and
utilization of appropriate deprotecting reagents is well
known by one of ordinary skill in the art and is described
in "Protective Groups in Organic Syntheses", Theodora W.
35 Greene, Wiley (1981). Examples of appropriate deprotecting

reagents are mineral acids, strong organic acids, Lewis acids, aqueous mineral bases, catalytic hydrogenation and the like. For example, cleavage of an acetate ester protecting group on the hydroxyethyl functionality of the piperidine hydroxyethylphenylketone derivatives of formula (II) wherein R_3 is $-CH_2OH$ can be achieved by using a base, such as sodium methoxide in methanol as is known in the art. Other methods known in the art for acetate ester cleavage include potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol.

In optional step e, the ketone functionality of the appropriate piperidine carboxyphenylketone derivatives of formula (II) wherein R_3 is $-CH_2OD$ or $-COOH$ is reduced to give the corresponding piperidine carboxyphenylalcohol derivatives of formula (I) wherein R_3 is $-CH_2OD$ or $-COOH$.

For example, reduction of the appropriate piperidine carboxyphenylketone derivatives of formula (II) wherein R_3 is $-CH_2OD$ or $-COOH$, using, for example, sodium borohydride, potassium borohydride, sodium cyanoborohydride, or tetramethylammonium borohydride is carried out in lower alcohol solvents, such as, methanol, ethanol, isopropyl alcohol or n-butanol at temperatures ranging from about $0^\circ C$ to the reflux temperature of the solvent, and the reaction time varies from about 1/2 hour to 8 hours. Other suitable reducing agents are, for example, lithium tri-tert-butylaluminumhydride and diisobutylaluminum hydride. These reduction reactions are carried out in suitable solvents diethyl ether, tetrahydrofuran or dioxane at temperatures ranging from about $0^\circ C$ to the reflux temperature of the solvent, and the reaction time varies from about 1/2 hour to 8 hours.

-22-

Catalytic reduction may also be employed in the preparation of appropriate piperidine carboxyphenylalcohol derivatives of formula (I) wherein R_3 is $-\text{CH}_2\text{OD}$ or $-\text{COOH}$ from an appropriate piperidine carboxyphenylketone derivatives of formula (II) wherein R_3 is $-\text{CH}_2\text{OD}$ or $-\text{COOH}$,
5 using, for example, RaneyTM nickel, palladium, platinum or rhodium catalysts in lower alcohol solvents, such as, methanol, ethanol, isopropyl alcohol or n-butanol or acetic acid or their aqueous mixtures, or by the use of aluminum
10 isopropoxide in isopropyl alcohol.

Reduction using sodium borohydride or potassium borohydride is preferred over catalytic reduction for those piperidine carboxyphenylketone derivatives of formula (II)
15 wherein R_3 is $-\text{CH}_2\text{OD}$ or $-\text{COOH}$ wherein R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 .

In addition, a chiral reduction of the appropriate
20 piperidine carboxyphenylketone derivatives of formula (II) wherein R_3 is $-\text{CH}_2\text{OD}$ or $-\text{COOH}$, using, for example, (+)-B-chlorodiisopinocampheylborane gives the corresponding (R)-piperidine carboxyphenylalcohol derivatives of formula (I) wherein R_3 is $-\text{CH}_2\text{OD}$ or $-\text{COOH}$ and (-)-B-chlorodiisopinocampheylborane gives the corresponding (S)-
25 piperidine carboxyphenylalcohol derivatives of formula (I) wherein R_3 is $-\text{CH}_2\text{OD}$ or $-\text{COOH}$. Other suitable chiral reducing agents are, (R) and (S)-oxazaborolidine/ BH_3 , potassium 9-O-(1,2:5,6-di-O-isopropylidene- α -D-glucopyranosyl)-9-boratabicyclo[3.3.1]nonane, (R) and (S)-
30 B-3-pinanyl-9-borabicyclo[3.3.1]nonane, NB-Enantride, Lithium (R)-(+)- and (S)-(-)-2,2'-dihydroxy-1,1'-binaphthyl alkoxyl aluminum hydride, (R)-(+)- and (S)-(-)-2,2'-dihydroxy-6,6'-dimethylbiphenyl borane-amine complex,
35 tris[[(1S,2S,5R)-2-isopropyl-5-methyl-cyclohex-1-

yl)methyl]aluminum, [[[1R,3R)-2,2-
dimethylbicyclo[2.2.1]hept-3-yl)methyl]beryllium chloride,
(R)-BINAP-ruthenium complex/H₂ and 6,6'-
bis(diphenylphosphino)-3,3'-dimethoxy-2,2',4,4'-
5 tetramethyl-1,1'-biphenyl.

As one skilled in the art would appreciate, the carboxy
functionalities of the piperidine carboxyphenylketone
derivatives of formula (II) wherein R₃ is -COOH and
10 piperidine carboxyphenylalcohol derivatives of formula (I)
wherein R₃ is -COOH may be esterified by techniques and
procedures well known and appreciated by one of ordinary
skill in the art to give the corresponding piperidine
carboxyphenylketone ester derivatives of formula (II)
15 wherein R₃ is -COOalkyl and piperidine carboxyphenylalcohol
ester derivatives of formula (I) wherein R₃ is -COOalkyl.

For example, one such method involves reacting an
appropriate piperidine carboxyphenylketone derivative of
20 formula (II) wherein R₃ is -COOH with an excess of an
appropriate HOalkyl wherein the alkyl moiety has from 1 to
6 carbon atoms and is straight or branched in the presence
of a small amount of mineral acid, e.g. sulfuric acid at
reflux. Another suitable method involves reacting an
25 appropriate piperidine carboxyphenylketone derivative of
formula (II) wherein R₃ is -COOH or piperidine
carboxyphenylalcohol derivative of formula (I) wherein R₃ is
-COOH with an excess of diazomethane in a suitable solvent
such as ether at room temperature to give the methyl ester.
30 In addition, the piperidine carboxyphenylketone ester
derivatives of formula (II) wherein R₃ is -COOalkyl or
piperidine carboxyphenylalcohol ester derivatives of
formula (I) wherein R₃ is -COOalkyl may also be prepared by
reacting an appropriate piperidine carboxyphenylketone
35 derivatives of formula (II) wherein R₃ is -COOH or

piperidine carboxyphenylalcohol derivatives of formula (I) wherein R_3 is $-\text{COOH}$ with an excess of 2,2-dimethoxypropane in a suitable solvent such as methanol at 0°C to room temperature to give the methyl ester. Another suitable
5 method involves first reacting an appropriate piperidine carboxyphenylketone derivatives of formula (II) wherein R_3 is $-\text{COOH}$ with thionyl chloride in a suitable solvent such as methylene chloride to give an intermediate acid chloride, followed by addition of a suitable alcohol of the
10 formula HOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched.

As one skilled in the art would appreciate, the reduction of the ketone functionality of the appropriate
15 piperidine carboxyphenylketone derivatives of formula (II) wherein R_3 is $-\text{COOH}$ described in optional step e can be conducted on the ω -halo hydroxyethylphenylketone of structure (4) or piperidine hydroxyethylphenylketone derivatives of formula (II) wherein R_3 is $-\text{CH}_2\text{OH}$.

20

For example, reduction of an appropriate ω -halo hydroxyethylphenylketone of structure (4) using the techniques and methods described previously in step e gives the corresponding ω -halo hydroxyethylphenylalcohol. The
25 resulting benzylic alcohol functionality may be optionally protected using the protecting groups described previously for hydroxyethyl in step b. The ω -halo hydroxyethylphenylalcohol so formed is then subjected to the alkylation reaction with an appropriate piperidine compound of
30 structure (5) described previously in step c to give the corresponding piperidine hydroxyethylphenylalcohol derivative of formula (I) wherein R_3 is protected or unprotected $-\text{CH}_2\text{OH}$. The appropriate piperidine hydroxyethylphenylalcohol derivative of formula (I) wherein
35 R_3 is $-\text{CH}_2\text{OH}$ is then subjected to the oxidation reaction

2117892

-25-

described previously in step d using a selective oxidizing agent such as 2,2,6,6-tetramethylpiperidiny1-1-oxy (TEMPO) or quinolinium chlorochromate to give the intermediate aldehyde followed by oxidation with silver oxide to give
5 the corresponding piperidine carboxyphenylalcohol derivative of formula (I) wherein R_3 is $-\text{COOH}$. Reduction of an appropriate piperidine hydroxyethylphenylketone derivative of formula (II) wherein R_3 is protected or unprotected $-\text{CH}_2\text{OH}$ using the techniques and methods
10 described previously in step e gives the corresponding piperidine hydroxyethylphenylalcohol derivative of formula (I) wherein R_3 is $-\text{CH}_2\text{OH}$ which is then subjected to the oxidation reaction described previously in step d using a selective oxidizing agent such as 2,2,6,6-
15 tetramethylpiperidiny1-1-oxy (TEMPO) or quinolinium chlorochromate to give the intermediate aldehyde followed by oxidation with silver oxide to give the corresponding piperidine carboxyphenylalcohol derivative of formula (I) wherein R_3 is $-\text{COOH}$.

20

As one skilled in the art would appreciate, the benzeneacetic acid compounds of structure (1), the phenethyl alcohols of structure (2), the ω -halo hydroxyethylphenylketones of structure (4), piperidine
25 compounds of structure (5), piperidine hydroxyethylphenylketone derivatives of formula (II) wherein R_3 is $-\text{CH}_2\text{OH}$, the piperidine carboxyphenylketone derivatives of formula (II) wherein R_3 is $-\text{COOH}$, the piperidine carboxyphenylketone ester derivatives of formula
30 (II) wherein R_3 is $-\text{COOalkyl}$, the piperidine hydroxyethylphenylalcohol derivatives of formula (I) wherein R_3 is $-\text{CH}_2\text{OH}$, the piperidine carboxyphenylalcohol derivatives of formula (I) wherein R_3 is COOH or the piperidine carboxyphenylalcohol ester derivatives of
35 formula (I) wherein R_3 is $-\text{COOalkyl}$ which bear hydroxy or

phenolic functionalities may be protected prior to use in the synthesis depicted in Scheme A using suitable protecting groups as described previously in step b.

5 As one skilled in the art would appreciate, the benzeneactic acids of structure (1), the phenethyl alcohols of structure (2), the ω -halo hydroxyethylphenylketones of structure (4), piperidine compounds of structure (5), piperidine hydroxyethylphenylketone derivatives of formula
10 (II) wherein R_3 is $-\text{CH}_2\text{OH}$, the piperidine carboxyphenylketone derivatives of formula (II) wherein R_3 is $-\text{COOH}$ or the piperidine carboxyphenylketone ester derivatives of formula (II) wherein R_3 is $-\text{COOalkyl}$, the piperidine hydroxyethylphenylalcohol derivatives of formula
15 (I) wherein R_3 is $-\text{CH}_2\text{OH}$, the piperidine carboxyphenylalcohol derivatives of formula (I) wherein R_3 is COOH or the piperidine carboxyphenylalcohol ester derivatives of formula (I) wherein R_3 is COOalkyl which bear protected hydroxy or phenolic functionalities may be
20 reacting with prior appropriate deprotecting reagents prior to use in the synthesis depicted in Scheme A. The selection and utilization of appropriate deprotecting reagents is well known by one of ordinary skill in the art and is described in "Protective Groups in Organic
25 Syntheses", Theodora W. Greene, Wiley (1981). Examples of appropriate deprotecting reagents are mineral acids, strong organic acids, Lewis acids, aqueous mineral bases, catalytic hydrogenation and the like.

30 For example, cleavage of an acetate ester protecting group on the hydroxyethyl functionality of any of the ω -halo hydroxyethylphenylketones of structure (4), piperidine compounds of structure (5), piperidine hydroxyethylphenylketone derivatives of formula (II)
35 wherein R_3 is $-\text{CH}_2\text{OH}$ or piperidine hydroxyethylphenylalcohol

derivatives of formula (I) wherein R₃ is -CH₂OH can be achieved by using a base, such as sodium methoxide in methanol as is known in the art. Other methods known in the art for acetate ester cleavage include potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol.

Cleavage of β-methoxyethoxymethyl (MEM) protecting groups on any of those ω-halo hydroxyethylphenylketones of structure (4), piperidine compounds of structure (5), piperidine hydroxyethylphenylketone derivative of formula (II) wherein R₃ is -CH₂OH, piperidine carboxyphenylketone derivative of formula (II) wherein R₃ is -COOH, piperidine carboxyphenylketone ester derivatives of formula (II) wherein R₃ is -COOalkyl, piperidine carboxyphenylalcohol derivatives of formula (I) wherein R₃ is -COOH, piperidine carboxyphenylalcohol ester derivatives of formula (I) wherein R₃ is -COOalkyl or piperidine hydroxyethylphenylalcohol derivatives of formula (I) wherein R₃ is -CH₂OH wherein A is hydroxy, for example, can be achieved by using trifluoroacetic acid at room temperature or using 5 to 8 equivalents of powdered anhydrous zinc bromide in methylene chloride at about 25°C by the general procedure of E. J. Corey et al., *Tetrahedron Letters*, 11, 809-812 1976.

The following examples present typical syntheses as described in Scheme A. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. As used herein, the following terms have the indicated meanings: "g" refers to grams; "mmol" refers to millimoles; "mL" refers to milliliters; "bp" refers to boiling point; "mp" refers to melting point; "°C" refers to degrees Celsius; "mm Hg"

refers to millimeters of mercury; " μ L" refers to microliters; " μ g" refers to micrograms; and " μ M" refers to micromolar.

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Example 1

4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride

5 METHOD A

Step a: 2,2-Dimethyl-phenethyl acetate

Dissolve α,α -dimethylphenyl acetic acid (140.0g, 0.853mol) in anhydrous tetrahydrofuran (100mL) and place under a nitrogen atmosphere. Add, by dropwise addition, a solution
10 of lithium aluminum hydride (639mL of a 1.0M solution in tetrahydrofuran, 24.3g, 0.639mol) over a period of approximately 2 hours. Quench with deionized water (24mL), with 15% aqueous sodium hydroxide (24mL) and again with deionized water (72mL). Stir the milky white mixture for
15 20 minutes, filter through filter aid, dry (MgSO_4) and filter through filter aid once more. Evaporate the solvent *in vacuo* to give 2,2-dimethylphenethyl alcohol as a clear yellow oil.

20 Dissolve 2,2-dimethylphenethyl alcohol (118.0g, 0.786mol) in pyridine (700mL). Add, by dropwise addition, acetic anhydride (222mL, 240.7g, 2.358mol) and stir overnight at room temperature. Evaporate the solvent *in vacuo* and purify by distillation to give the title compound as a clear
25 colorless oil; bp 75°C @ 0.4mmHg.

METHOD B

Dissolve 2-methyl-2-propenyl acetate (1.28mmol) in benzene (80mL) and add to a stirred solution of AlCl_3 (172.3g, 1.29mol) in benzene (800mL) at -10°C over 45 minutes under
30 a stream of nitrogen. Stir at 5°C for 20 minutes, pour onto ice (800g) and stir for 10 minutes. Separate the organic phase, dry (MgSO_4) and evaporate the solvent *in vacuo* (30°C/60 torr). Purify by distillation to give the title
35 compound.

Step b: 4-(4-Chloro-1-oxobutyl)-2,2-dimethylphenethyl acetate

Charge a flask with aluminum chloride (223g, 1.68mol) and
5 methylene chloride (200mL). Place under a nitrogen
atmosphere, cool to 0°-5°C and add, by dropwise addition,
ω-chlorobutyryl chloride (188.6g, 1.34mol). After acid
chloride addition is complete, add, by dropwise addition,
2,2-dimethylphenethyl acetate (128.0g, 0.67mol), keeping
10 the temperature at approximately 0°C. Continue stirring at
0°C for 2 hours, quench by slowly pouring over
approximately 2L of crushed ice. Add methylene chloride
(500mL) and stir for 5 minutes. Separate the organic phase
and extract the aqueous phase with methylene chloride
15 (300mL). Combine the organic phases and wash with
saturated aqueous sodium hydrogen carbonate (3X200mL), with
deionized water (200mL) and brine (200mL). Dry (MgSO₄) and
stir for 30 minutes before filtering. Evaporate the
solvent *in vacuo* and purify by chromatography (ethyl
20 acetate/hexane) to give the title compound as an
orange/brown oil.

IR (neat) 3239, 2970, 1741, 1684, 1607, 1408, 1375, 1233,
1040, 998, 844, 823 cm⁻¹;

25 ¹H NMR (CDCl₃) δ 7.93 (d, 2H, J = 9.0Hz), 7.46 (d, 2H, J =
9.0 Hz), 4.14 (s, 2H), 3.68 (t, 2H, J = 7.5 Hz), 3.16 (t,
2H, J = 7.5 Hz), 2.2 (m, 2H), 2.00 (s, 3H), 1.38 (s, 6H);
¹³C NMR (CDCl₃) δ 198.5, 170.9, 151.9, 134.8, 127.9, 126.2,
72.4, 44.6, 38.6, 35.2, 26.7, 25.7, 20.8;
30 MS (CI, CH₄) m/z (rel. intensity) 297 (MH⁺, 56), 261 (59),
237 (100), 219 (52).

Step c: 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]-2,2-dimethylphenethyl alcohol

Mix 4-(4-chloro-1-oxobutyl)-2,2-dimethylphenethyl acetate (99.5g, 0.335mol), α,α -diphenyl-4-piperidinemethanol (101.8g, 0.335mol), potassium hydrogen carbonate (83.8g, 0.838mol), potassium iodide (1.00g, 0.006mol), toluene (600mL) and water (220mL). Stir at reflux for 72 hours, add toluene (200mL) and deionized water (100mL). Filter through filter aid while at 80°C and separate the organic phase. Dry (MgSO₄), filter and purify by chromatography (ethyl acetate) to give 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]-2,2-dimethylphenethyl acetate as an oily solid.

IR (KBr) 3690, 3608, 3012, 2950, 2810, 1734, 1681, 1607, 1470, 1448, 1376, 1253, 1040, 997, 704, 667 cm⁻¹;
15 ¹H NMR (CDCl₃) δ 7.90 (d, 2H, J = 8.2 Hz), 7.4 (m, 5H), 7.3 (m, 5H), 7.2 (m, 2H), 4.14 (s, 2H), 3.0 (m, 4H), 2.4 (m, 3H), 2.0 (m, 3H), 1.95 (s, 3H), 1.4 (m, 4H), 1.38 (s, 6H);
¹³C NMR (CDCl₃) δ 199.4, 170.9, 151.7, 145.8, 135.1, 128.1, 128.0, 126.5, 126.2, 125.7, 79.3, 72.5, 57.6, 53.7, 43.8,
20 38.6, 36.1, 25.7, 21.2, 20.8;
MS (CI, CH₄) m/z (rel. intensity) 528 (MH⁺, 100), 510 (63), 450 (12), 293 (14).

Dissolve 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]-2,2-dimethylphenethyl acetate (69.0g, 0.131mol) in methanol (2.5L) and add 10% aqueous sodium hydroxide (769mL, 1.92mol). Stir at reflux for 1.5 hours, cool to 68°C and evaporate the solvent *in vacuo* to a residue (700mL). Add chloroform (1L) and stir until solids are dissolved.
30 Separate the organic phase and extract the aqueous phase with chloroform (3X300mL). Combine the organic phases, dry (MgSO₄) and evaporate the solvent *in vacuo* and recrystallize (toluene) to give the title compound as a cream-colored powder; mp 135-137°C.

IR (KBr) 3609, 3011, 2950, 2809, 2772, 1680, 1606, 1492, 1470, 1448, 1366, 1282, 1238, 1044, 791, 704, 668 cm^{-1} ;
 ^1H NMR (CDCl_3) δ 7.93 (d, 2H, $J = 8.2$ Hz), 7.4 (m, 5H), 7.3 (m, 5H), 7.2 (m, 2H), 3.64 (s, 2H), 2.9 (m, 4H), 2.4 (m, 3H), 1.9 (m, 5H), 1.38 (s, 6H), 1.3 (m, 4H);
5 ^{13}C NMR (CDCl_3) δ 199.6, 152.1, 145.9, 135.2, 128.2, 126.4, 125.7, 79.5, 72.7, 57.8, 53.9, 44.0, 40.4, 36.2, 26.1, 25.2, 22.2;
MS (CI, CH_4) m/z (rel. intensity) 486 (MH^+ , 100), 468 (81),
10 408 (19), 293 (23).

METHOD A

Step d: 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -dimethylbenzeneacetic acid hydrochloride

- 15 Dissolve oxalyl chloride (1.57g, 12.4mmol) in methylene chloride (17mL), cool to -55°C and place under a nitrogen atmosphere. Add, by dropwise addition, a solution of dimethylsulfoxide (1.77g, 1.61mL) in methylene chloride (4.5mL). Stir for 15 minutes and add, by dropwise
20 addition, a solution of 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]-2,2-dimethylphenethyl alcohol (5.0g, 10.3mol) in methylene chloride (33mL). Stir for 30 minutes and add, by dropwise addition, triethylamine (7.2mL). Stir for 15 minutes and then allow to warm to
25 -10°C . Add a solution of oxone (12.66g) in deionized water (50mL). Stir for 15 minutes and add methylene chloride (25mL). Separate the organic phase, wash with brine, dry (MgSO_4) and evaporate the solvent in vacuo. Purify by chromatography (ethyl acetate) to give 4-[4-[4-
30 (hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -dimethylbenzeneacetaldehyde.

^1H NMR (CDCl_3) δ 9.52 (s, 1H), 7.95 (d, 2H, $J = 8.2$ Hz), 7.5 (m, 4H), 7.36 (d, 2H, $J = 8.2$ Hz), 7.3 (m, 4H), 7.2 (m,

2H), 2.9 (m, 4H), 2.4 (m, 4H), 2.0 (m, 4H), 1.50 (s, 6H),
1.4 (m, 4H);
13C NMR (CDCl₃) δ 202, 199.9, 146.2, 136.2, 128.7, 128.3,
127.1, 126.6, 125.9, 79.4, 57.7, 53.8, 50.6, 43.9, 42.5,
5 36.2, 25.9, 22.3, 21.5;
MS (CI, CH₄) m/z (rel. intensity) 484 (MH⁺, 76), 466 (100),
454 (19), 406 (16), 293 (16), 233 (19), 183 (49), 155 (54).

Dissolve 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-
10 oxobutyl]-α,α-dimethylbenzeneacetaldehyde (3.40g, 7.03mmol)
in acetone (30mL) and cool to 15°C. Add, by dropwise
addition, 1N hydrochloric acid (10.5mL). After addition of
the hydrochloric acid is complete, add, by dropwise
addition, a solution of potassium permanganate (1.82g,
15 11.51mmol) in acetone (80mL). Stir at room temperature for
6 hours, filter and wash the filter cake with acetone
(60mL). Evaporate the filtrate *in vacuo*, dilute with
methylene chloride (500mL), dry (MgSO₄) and filter.
Evaporate the solvent *in vacuo* and purify by chromatography
20 (ethyl acetate) to give the title compound as a pale yellow
solid.

IR (KBr) 3420, 3057, 2964, 1677, 1604, 1569, 1470, 1448,
1406, 1363, 1249, 1189, 1099, 750, 705 cm⁻¹;
25 1H NMR (CDCl₃) δ 7.75 (d, 2H, J = 8.2 Hz), 7.4 (m, 6H), 7.2
(m, 4H), 7.1 (m, 2H), 3.9 (br. s, 2H), 3.1 (m, 2H), 2.9 (m,
2H), 2.6 (m, 2H), 2.3 (m, 2H), 1.9 (m, 3H), 1.7 (m, 2H).
1.44 (s, 6H), 1.4 (m, 2H);
13C NMR (CDCl₃) δ 199.4, 147.2, 134.5, 127.7, 127.5, 126.2,
30 125.7, 78.4, 57.3, 53.5, 46.6, 43.5, 35.6, 26.8, 25.9,
21.3;
MS (CI, CH₄) m/z (rel. intensity) 500 (MH⁺, 79), 482 (62),
456 (100), 422 (30), 366 (42).

35 METHOD B

Mix 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]-2,2-dimethylphenethyl alcohol (9.7mmol), chloroform (20mL), acetonitrile (20mL), water (30mL) and H₅IO₆ (5.6g, 24.3mmol). Add RuCl₃•5H₂O (0.15g, 0.49mmol) and stir at room temperature for 2 hours. Dilute the reaction mixture with methylene chloride (200mL), wash with saturated NaHSO₃ (2X100mL) and dry (MgSO₄). Filter, evaporate the filtrate *in vacuo* (20°C/60 torr) and purify by silica gel chromatography to give the title compound.

10

METHOD C

Mix K₂S₂O₈ (2.8g, 10.2mmol), KOH (85%, 1.95g, 30mmol) and water (20mL). Add RuCl₃•5H₂O (30mg, 0.2mmol) and stir at room temperature for 5 minutes. Dissolve 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]-2,2-dimethylphenethyl alcohol (0.97mmol) in acetone (14mL) and acetonitrile (2mL) and add to the above solution. Stir at room temperature for 2.5 hours, filter and neutralize the filtrate with 1N HCl to pH 5. Extract with methylene chloride (2X50mL), dry (MgSO₄), evaporate the solvent *in vacuo* (20°C/60 torr) and purify by silica gel chromatography to give the title compound.

Step e: 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-α,α-dimethylbenzeneacetic acid hydrochloride
Add sodium borohydride (0.105g, 2.77mmol) to a solution of sodium hydroxide (0.053g, 1.33mmol) in deionized water (2mL) and add, by dropwise addition, to a solution of 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]-α,α-dimethylbenzeneacetic acid hydrochloride (0.70g, 1.31mmol) in ethanol (30mL). Stir at room temperature for 3.5 hours at pH 7-8. Evaporate the solvent *in vacuo* and stir the residue with methylene chloride (15mL) and deionized water (15mL). Dry (MgSO₄), acidify to pH 3 with gaseous hydrogen chloride and evaporate the solvent. Add ether with

2117892

stirring, filter the white solid and wash with additional ether. Dry to give the title compound.

IR (KBr) 3403, 3058, 2971, 1718, 1634, 1492, 1471, 1448,
5 1393, 1227, 1150, 1099, 1069, 839, 750, 706 cm^{-1} ;
 ^1H NMR (CDCl_3) δ 7.50 (d, 4H, $J = 8.2$ Hz), 7.3 (m, 8H), 7.2
(m, 2H), 4.66 (t, 1H, $J = 5.6$ Hz), 3.5 (m, 2H), 3.0 (m,
4H), 2.8 (m, 2H), 1.7 (m, 8H), 1.53 (s, 6H);
 ^{13}C NMR (CDCl_3) δ 181.1, 147.4, 146.1, 144.4, 129.5, 128.0,
10 127.4, 127.2, 79.9, 73.9, 57.0, 54.1, 42.7, 36.8, 27.1,
25.7, 21.7;
MS (CI, CH_4) m/z (rel. intensity) 502 (MH^+ , 50), 485 (33),
484 (100), 458 (25), 454 (33), 424 (17).

15

Example 2

(R)-4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-
hydroxybutyl]- α,α -dimethylbenzeneacetic, ethyl ester

Dissolve (+)-B-chlorodiisopinocampheylborane (2.5g,
7.8mmol) in anhydrous tetrahydrofuran (5mL). Add a
20 solution of 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-
1-oxobutyl]- α,α -dimethylbenzeneacetic, ethyl ester (2g,
3.54mmol) in anhydrous tetrahydrofuran (5mL). Stir at room
temperature for 3 days and cool to 0°C . Add water (1mL)
and 30% hydrogen peroxide (2mL) and stir for 20 minutes.
25 Add methylene chloride (30mL) and wash with brine (30mL),
then aqueous sodium hydrogen carbonate (30mL), then brine
(30mL). Dry (MgSO_4), evaporate the solvent *in vacuo* and
purify by chromatography (1:19 methanol:ethyl acetate) to
give the title compound as a solid; mp $87-90^\circ\text{C}$.

30

IR (KBr) 3436, 3058, 2932, 2813, 1725, 1632, 1599, 1470,
1448, 1255, 1147, 1097, 830, 749, 704 cm^{-1} ;
 ^1H NMR (CDCl_3) δ 7.5 (m, 4H), 7.3 (m, 8H), 7.2 (m, 2H), 4.6
(m, 1H), 4.08 (q, 2H, $J = 7.5$ Hz), 3.1 (m, 1H), 3.0 (m,

35

1H), 2.4 (m, 3H), 2.0 (m, 3H), 1.7 (m, 5H), 1.53 (s, 6H),
1.5 (m, 2H), 1.42 (s, 2H), 1.15 (t, 3H, J = 7.5 Hz);
[α]_D²⁰ +39.4° (c = 0.99, CHCl₃).

5

Example 3

(S)-4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-
hydroxybutyl]- α,α -dimethylbenzeneacetic acid, ethyl ester

Dissolve (-)-B-chlorodiisopinocampheylborane (2.5g,
10 7.8mmol) in anhydrous tetrahydrofuran (5mL). Add a
solution of 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-
1-oxobutyl]- α,α -dimethylbenzeneacetic acid, ethyl ester
(2g, 3.54mmol) in anhydrous tetrahydrofuran (5mL). Stir at
room temperature for 3 days and cool to 0°C. Add water
15 (1mL) and 30% hydrogen peroxide (2mL) and stir for 20
minutes. Add methylene chloride (30mL) and wash with brine
(30mL), then aqueous sodium hydrogen carbonate (30mL), then
brine (30mL). Dry (MgSO₄), evaporate the solvent *in vacuo*
and purify by chromatography to give the title compound.

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25

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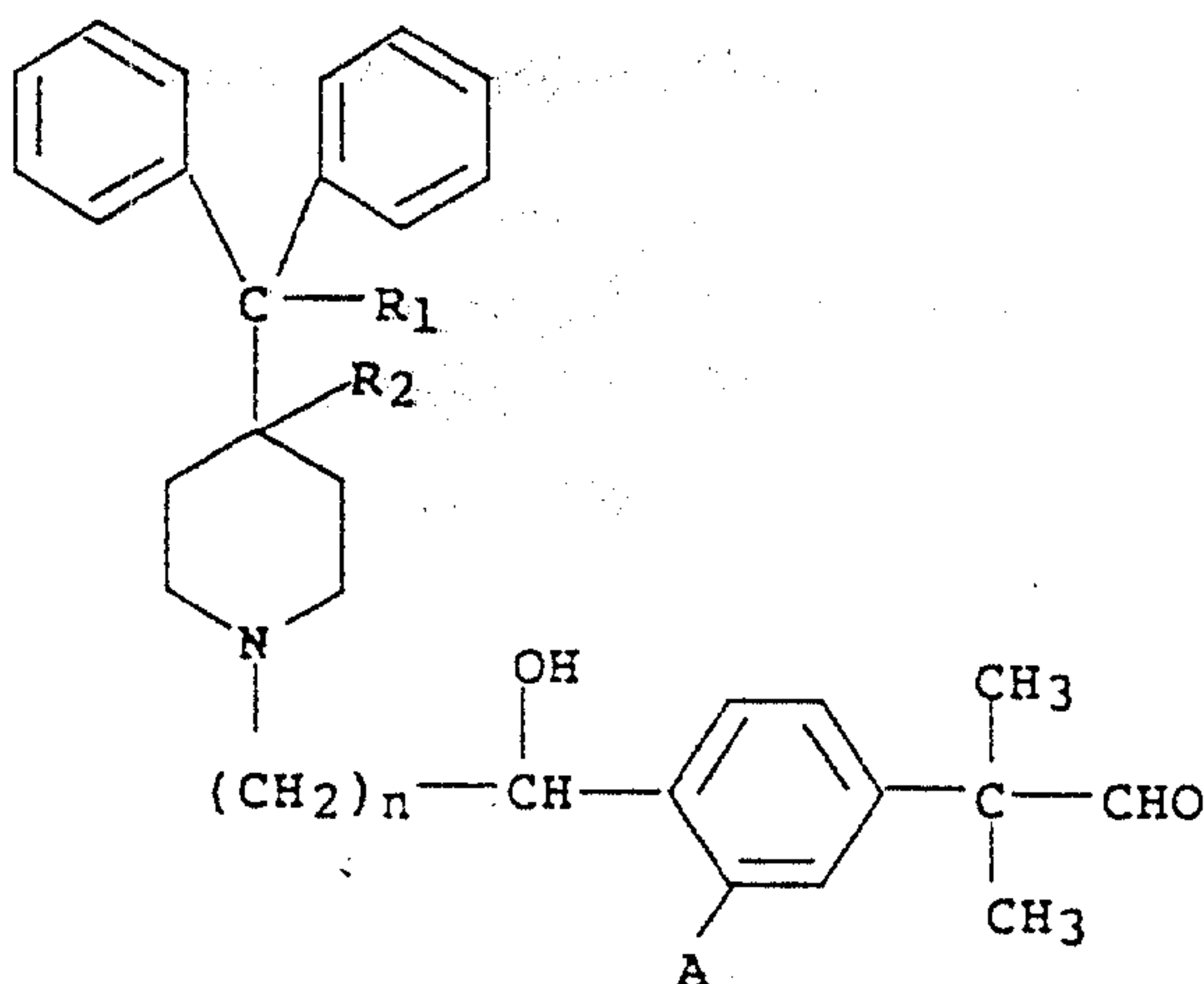
WHAT IS CLAIMED IS:

10

1. A piperidine formylphenylalcohol compound of the formula

15

20



25 wherein

R₁ represents hydrogen or hydroxy;

R₂ represents hydrogen; or

R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;

30

n is an integer of from 1 to 5; and

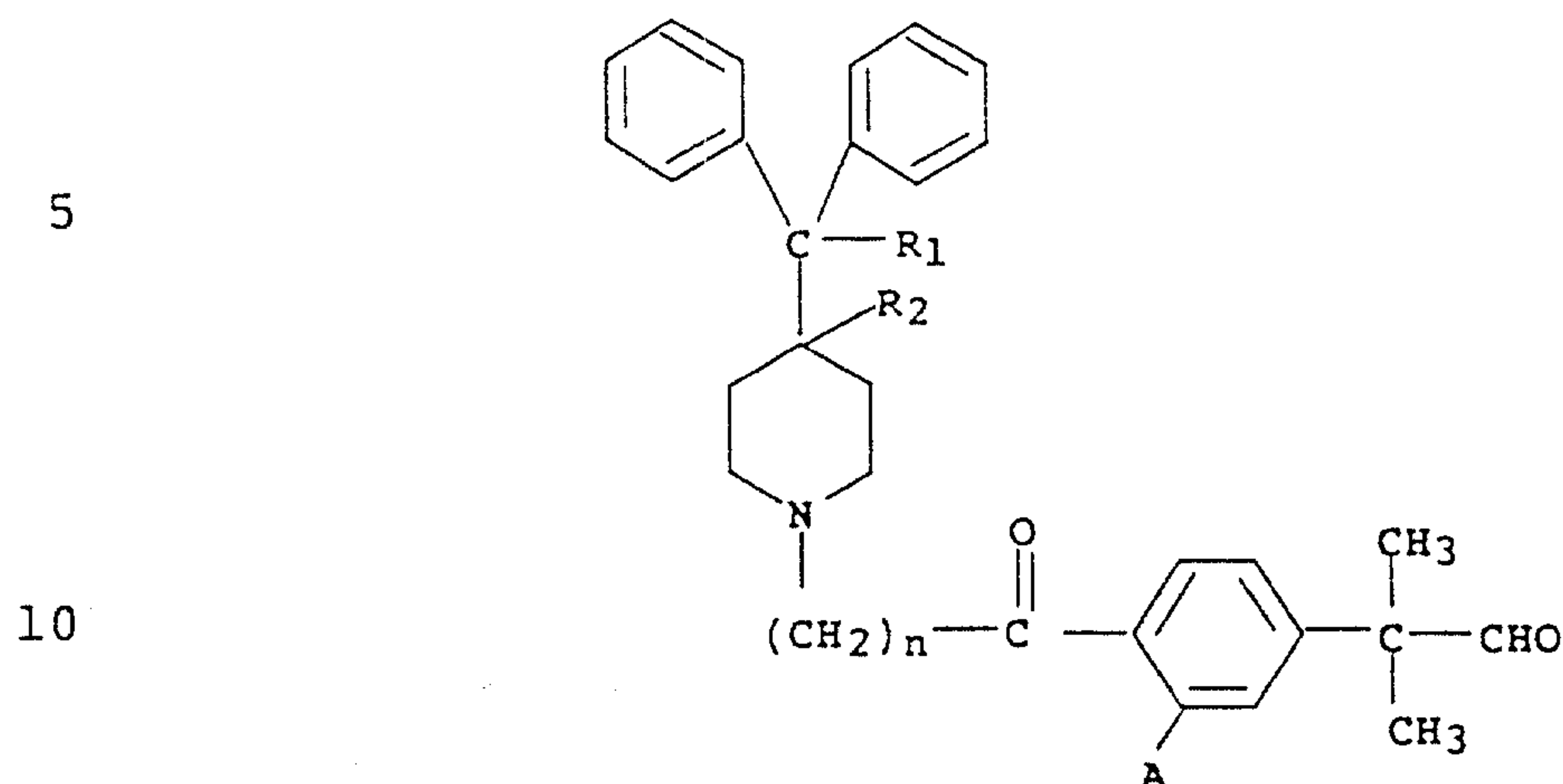
A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected.

35

2. A piperidine formylphenylketone compound of the formula

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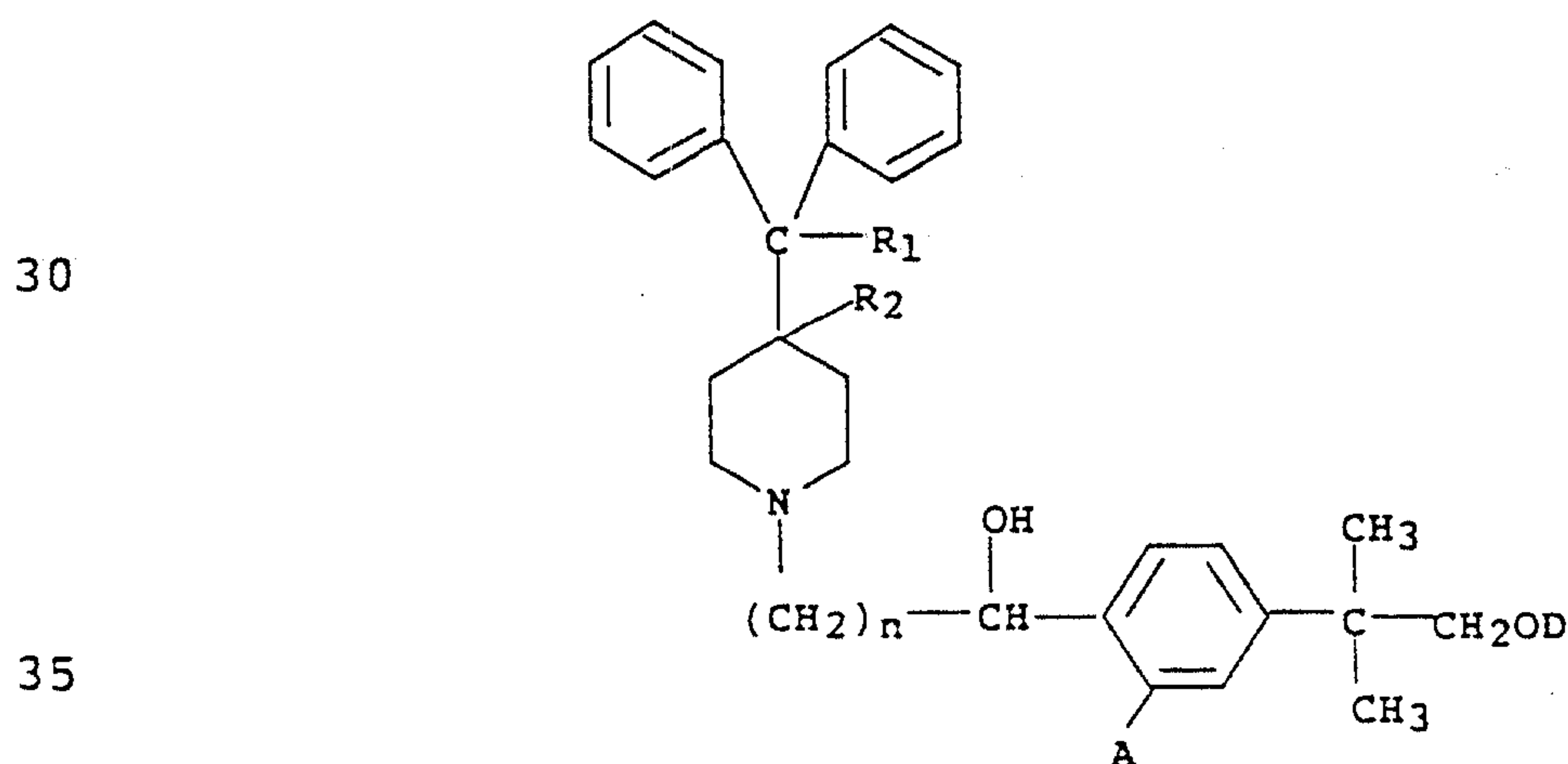
-38-



wherein

- 15 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the
carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5; and
20 A is hydrogen or hydroxy with the proviso that when A
is hydroxy, A may be optionally protected or
unprotected.

3. A piperidine protected hydroxyethylphenylalcohol
25 compound of the formula



wherein

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-39-

R_1 represents hydrogen or hydroxy;

R_2 represents hydrogen; or

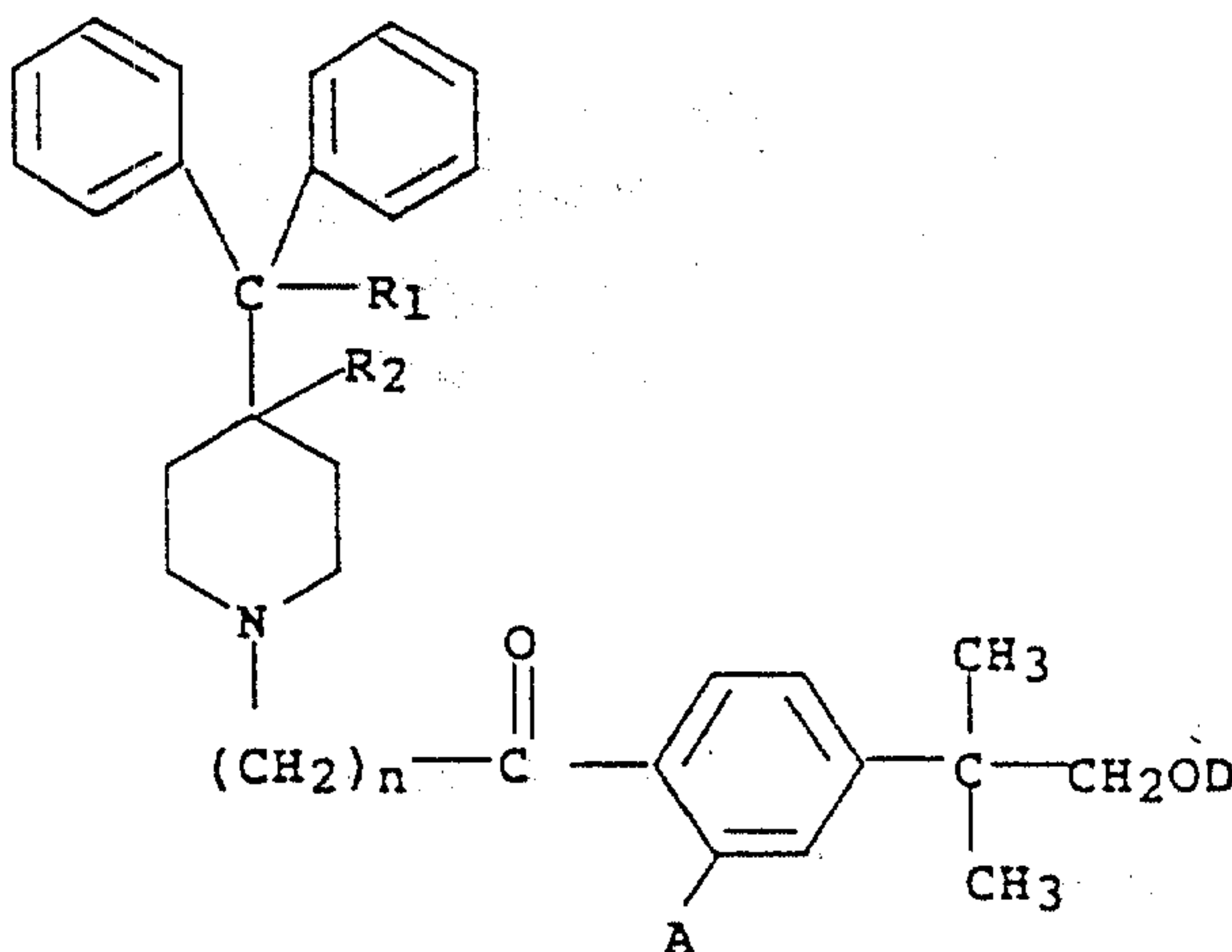
R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;

n is an integer of from 1 to 5;

A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected; and

D is $C(=O)CH_3$ or $C(=O)C_6H_5$.

4. A piperidine protected hydroxyethylphenylketone compound of the formula



wherein

R_1 represents hydrogen or hydroxy;

R_2 represents hydrogen; or

R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;

n is an integer of from 1 to 5;

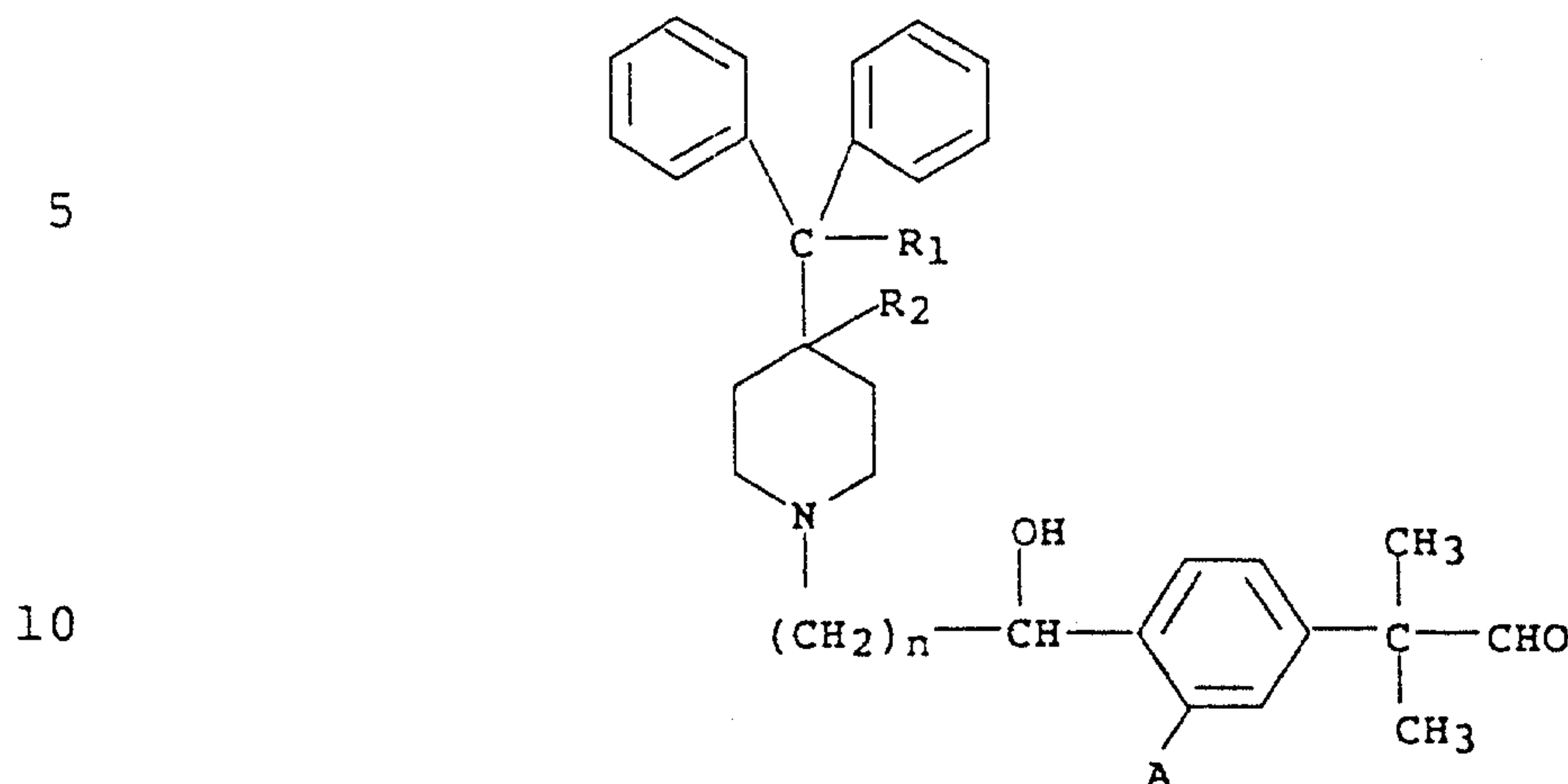
A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected; and

D is $C(=O)CH_3$ or $C(=O)C_6H_5$.

5. A process for preparing a piperidine formylphenylalcohol compound of the formula

AMENDED SHEET

-40-



wherein

- 15 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the
carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5; and
20 A is hydrogen or hydroxy with the proviso that when A
is hydroxy, A may be optionally protected or
unprotected,
comprising the steps of:

- 25 (a) reacting a benzeneacetic acid compound of the
formula

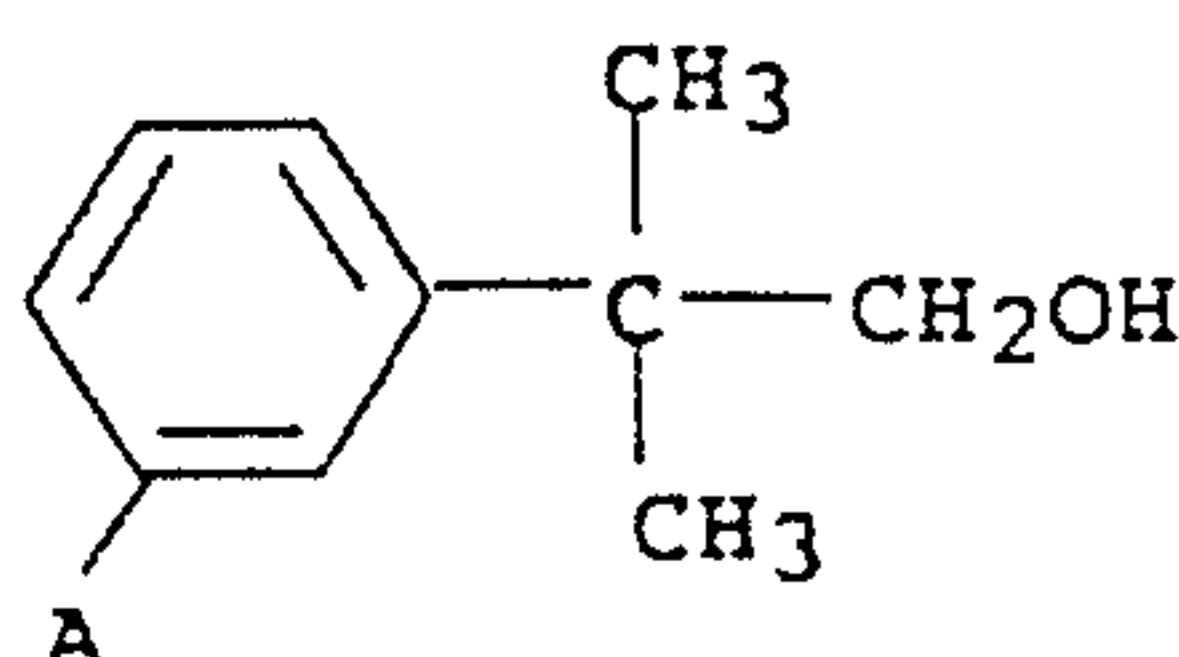


- 35 wherein A is hydrogen or hydroxy with the proviso that when
 A is hydroxy, A may be optionally protected or unprotected
and R is hydrogen or C_1 - C_6 alkyl with sodium bis(2-
methoxyethoxy)aluminum hydride, lithium aluminum hydride,
diborane, lithium borohydride, lithium triethylborohydride

-41-

and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

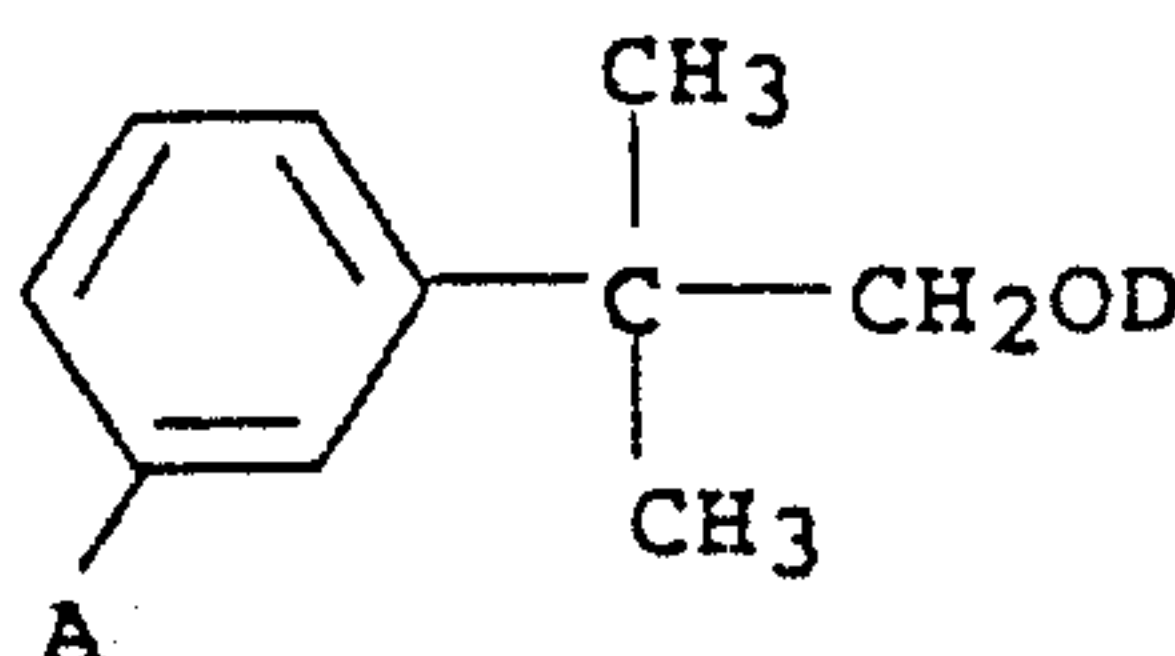
5



10. wherein A is hydrogen or hydroxy, with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

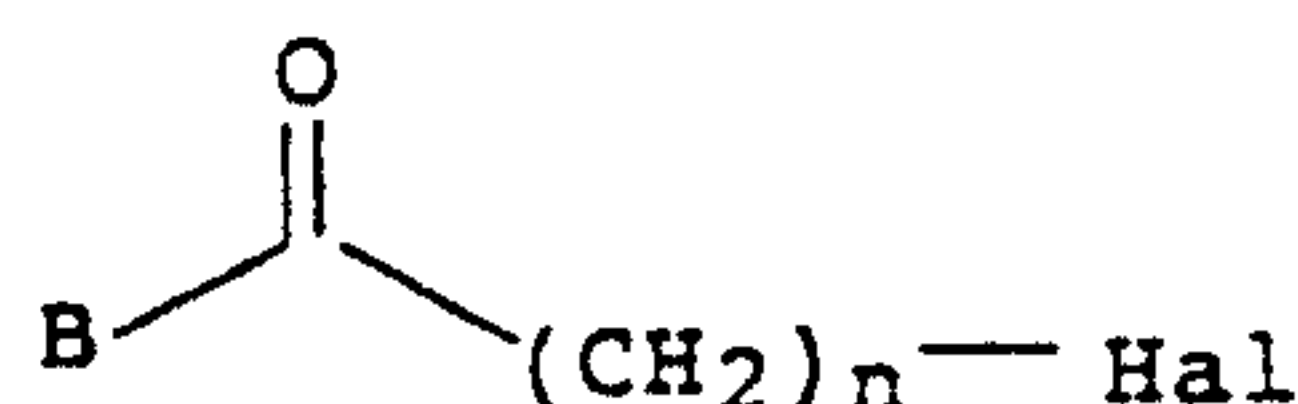
15. (b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

20



25. wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is C(=O)CH₃ or C(=O)C₆H₅;

30. (c) reacting the protected phenethyl alcohol with a ω-halo compound of the formula



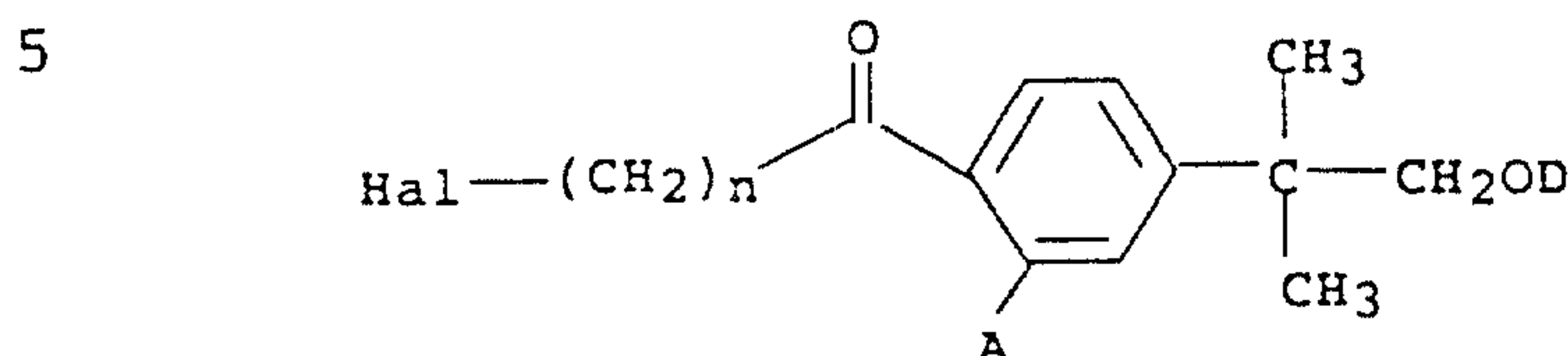
35

wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron

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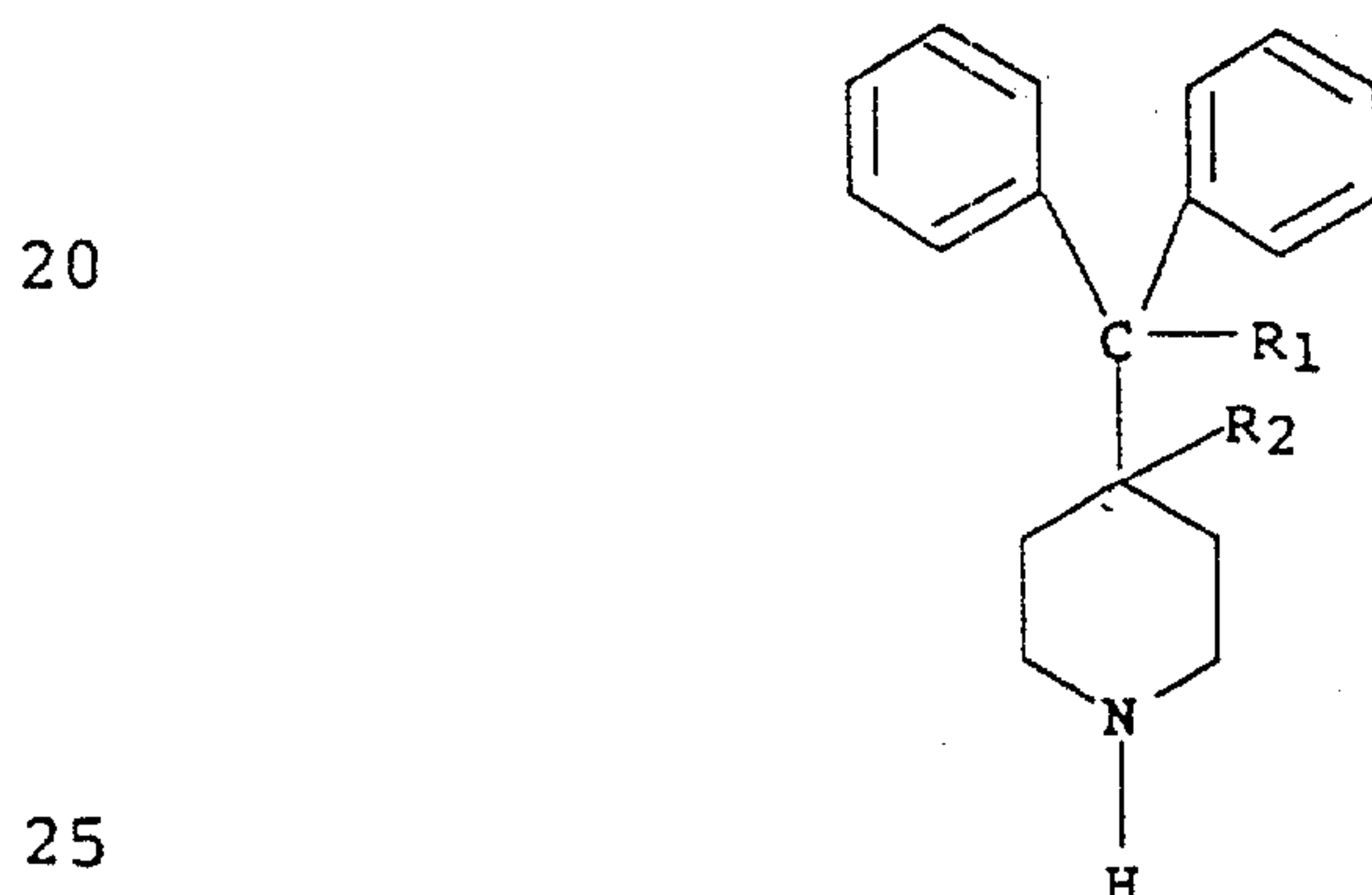
-42-

trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula



10 wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

15 (d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

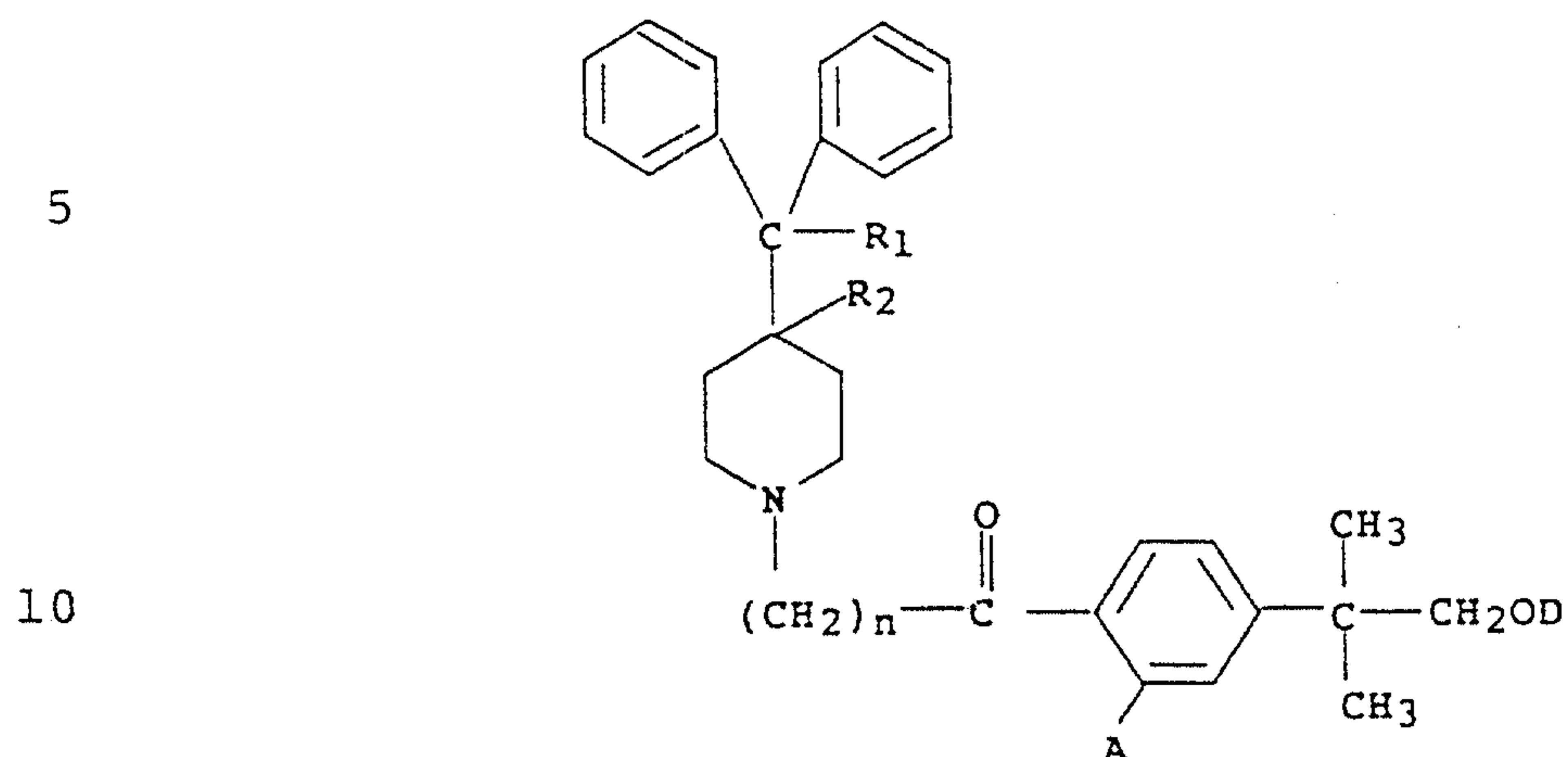


wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylketone of the formula

30

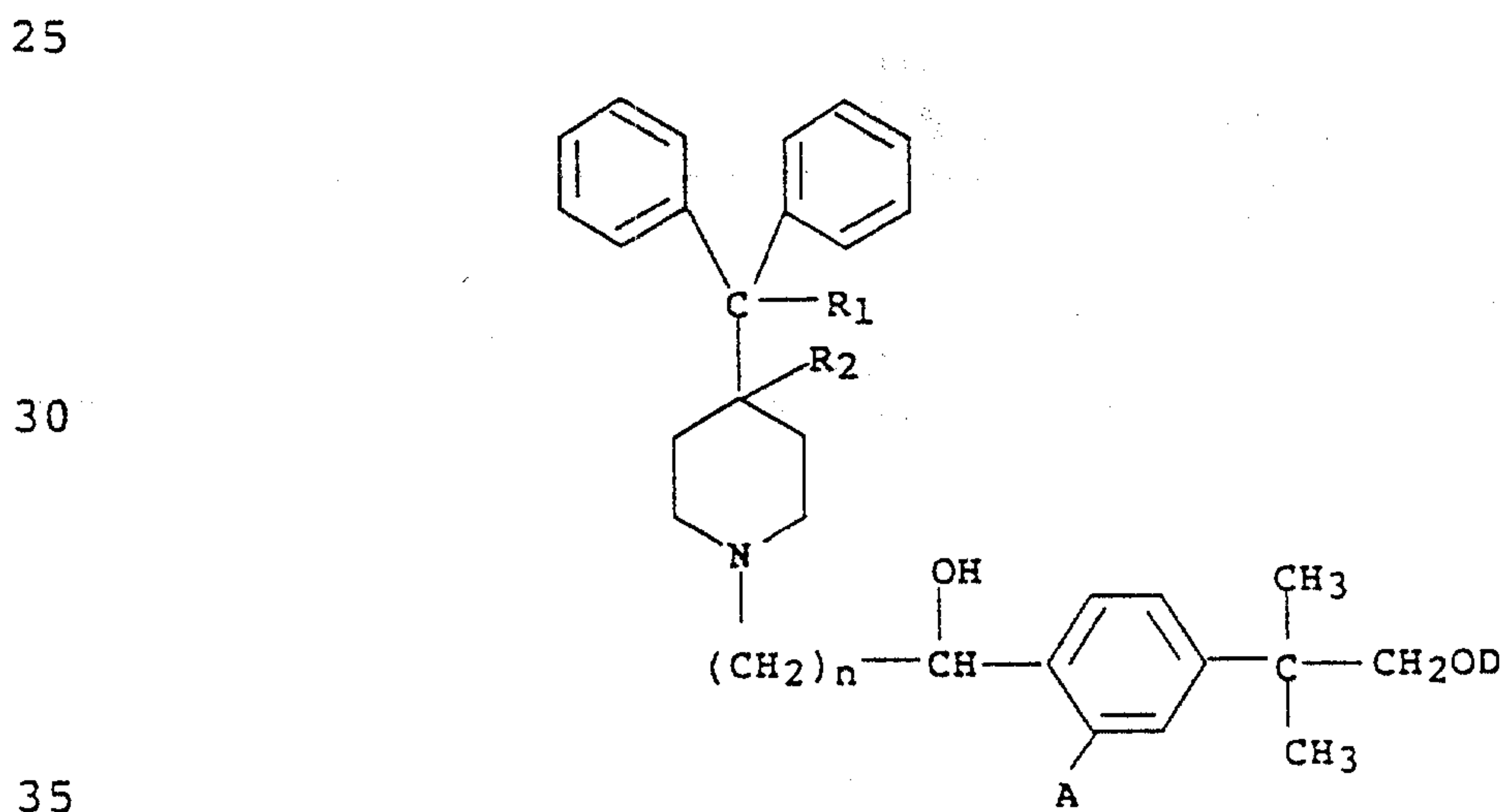
35

-43-



15 wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(e) reacting the piperidine protected hydroxyethylphenylketone with sodium borohydride, potassium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, lithium tri-tert-butylaluminumhydride, diisobutylaluminum hydride or catalytic hydrogenation to produce a piperidine protected hydroxyethylphenylalcohol of the formula

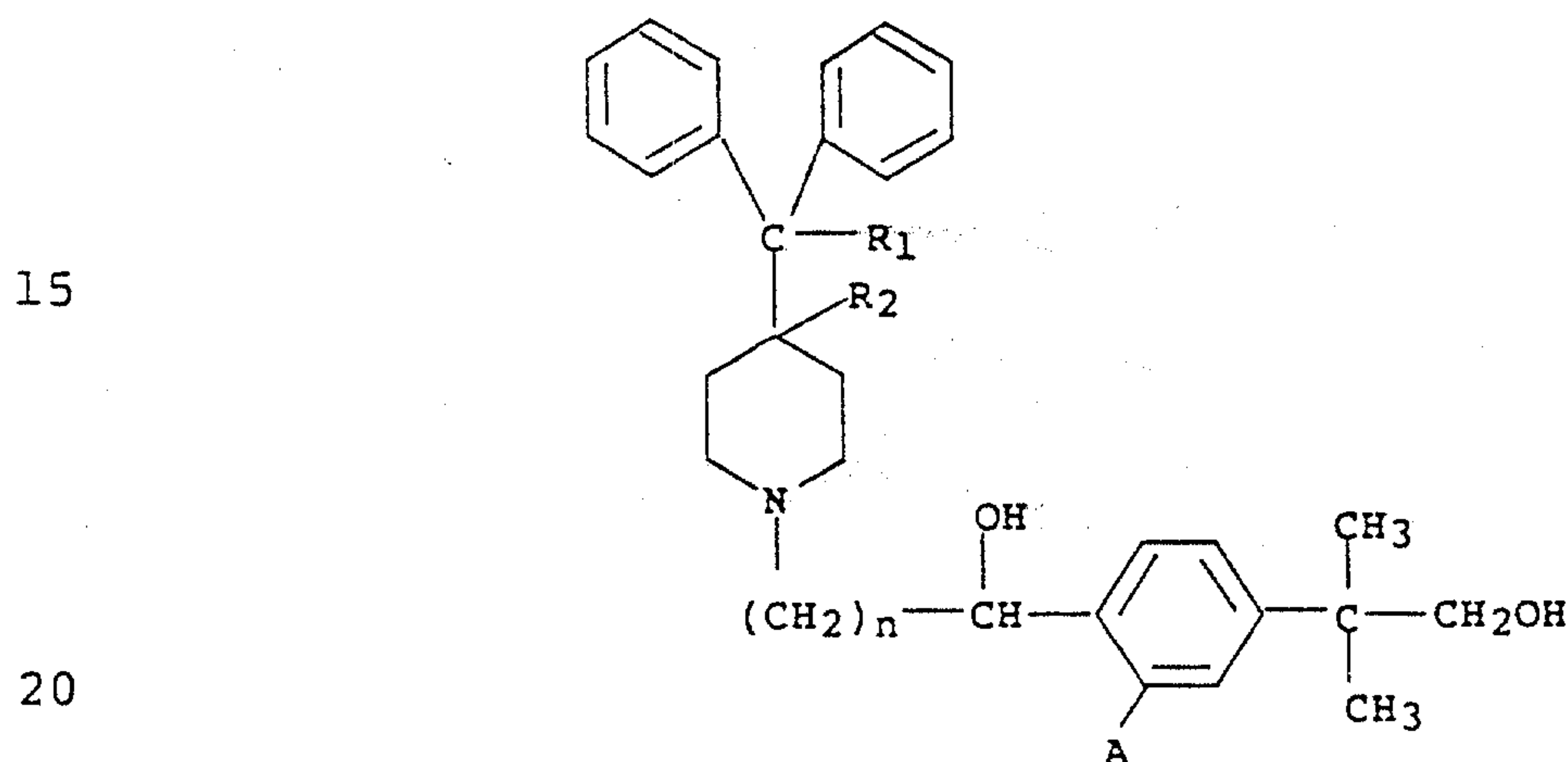


wherein R_1 , R_2 , D and n are defined above and A is hydrogen

-44-

or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

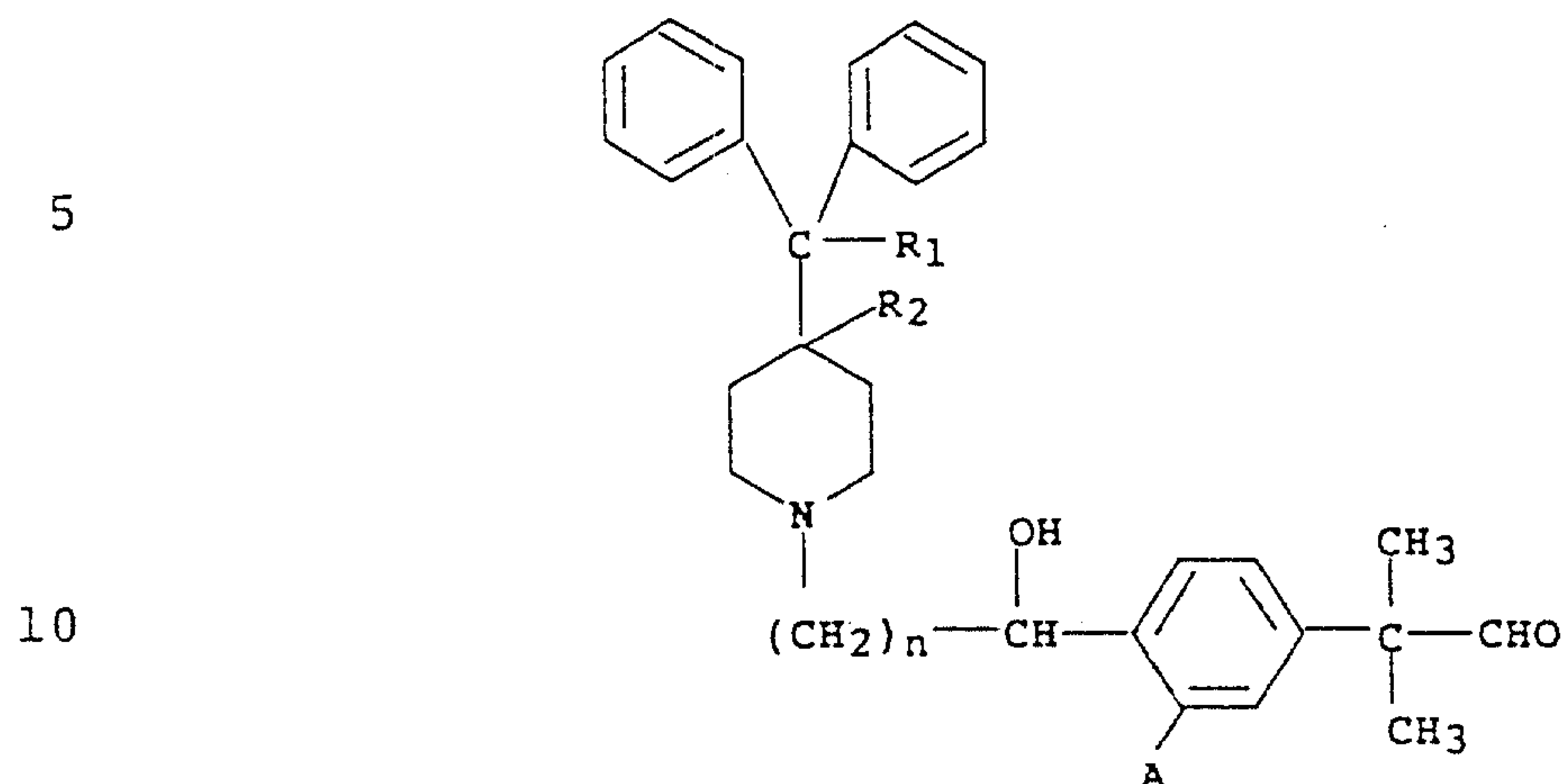
- 5 (f) reacting the piperidine protected hydroxyethylphenylalcohol with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine
10 hydroxyethylphenylalcohol of the formula



- wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be
25 optionally protected or unprotected;

- (g) reacting the piperidine hydroxyethylphenylalcohol with dimethyl sulfoxide, oxalyl chloride and triethylamine or with Dess-Martin reagent, chromium (IV) oxide, nickel
30 peroxide, sodium dichromate, potassium dichromate, t-butyl chromate, silver oxide, argentic picolinate manganese dioxide lead tetraacetate, dicyclohexylcarbodiimide, 2,3-dichloro-5,6-dicyanoquinone, tetrachloro-1,2-benzoquinone, 2,2,6,6-tetramethylpiperidiny-1-oxyl (TEMPO) or quinolinium
35 chlorochromate to produce a piperidine formylphenylalcohol of the formula

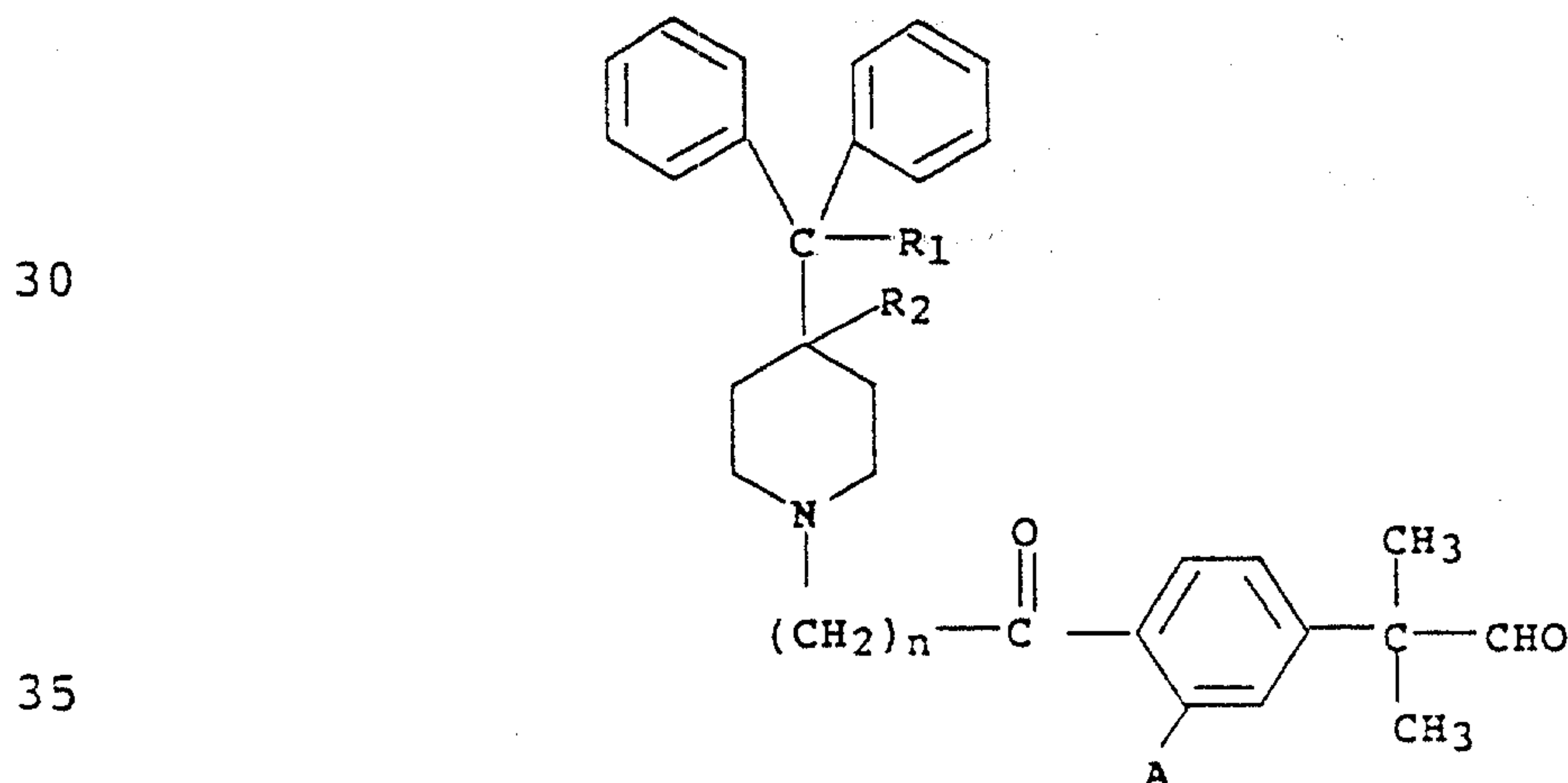
-45-



15 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(h) optionally reacting the piperidine formylphenylalcohol with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the piperidine formylphenylalcohol.

6. A process for preparing a piperidine formylphenyl ketone compound of the formula



wherein

R₁ represents hydrogen or hydroxy;

R₂ represents hydrogen; or

5 R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;

n is an integer of from 1 to 5;

A is hydrogen or hydroxy, with the proviso that when A is hydroxy, A may be optionally protected or unprotected,

10 comprising the steps of:

(a) reacting a benzeneacetic acid compound of the formula



20 wherein A is as defined above and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl

25 alcohol of the formula

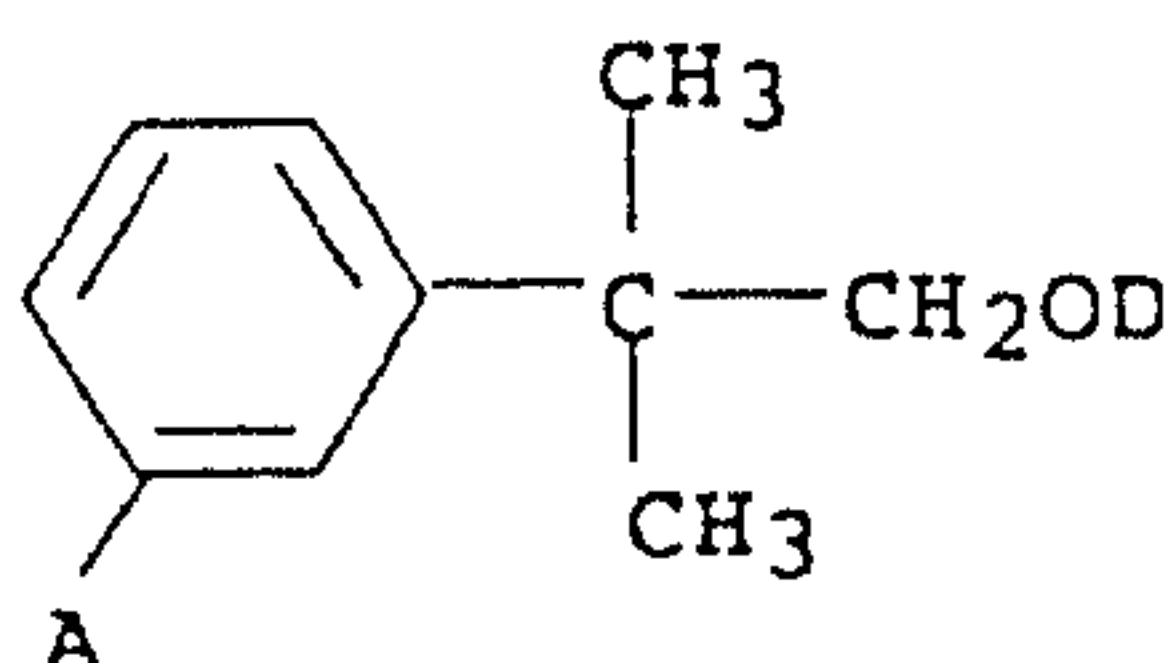


wherein A is defined above;

35 (b) reacting the phenethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

-47-

5

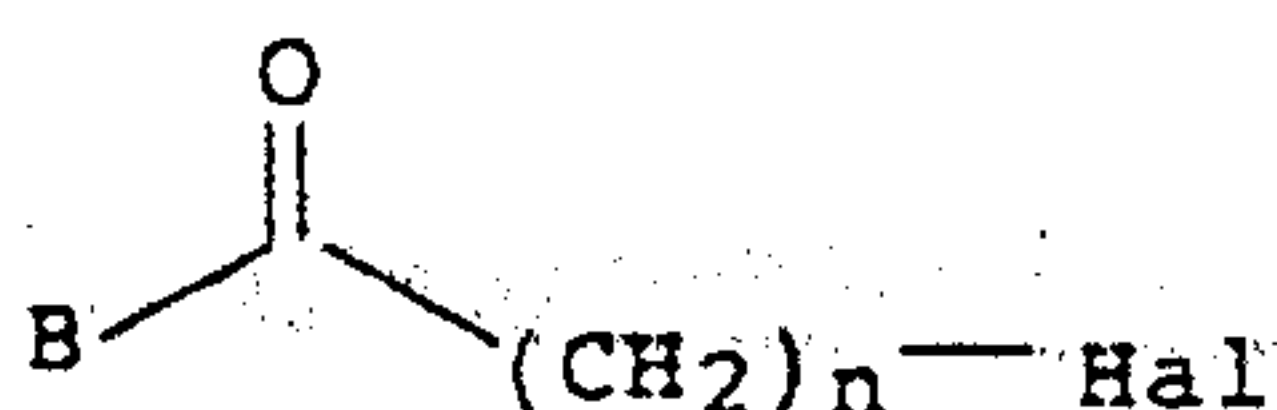


wherein A and D are defined above;

10

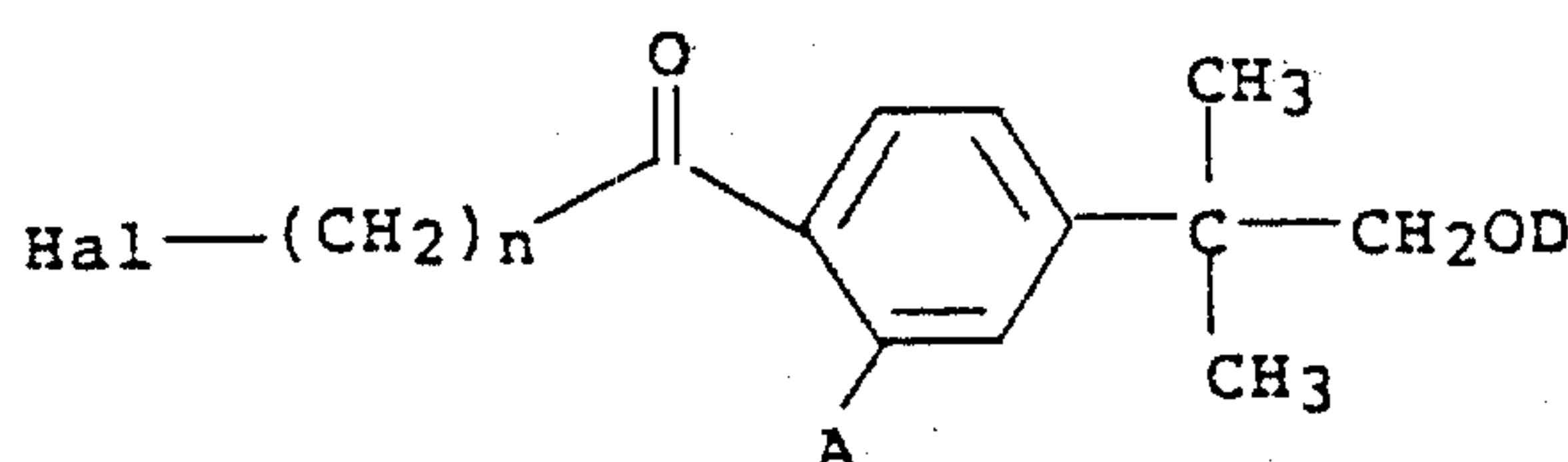
(c) reacting the protected phenethyl alcohol with a ω -halo compound of the formula

15



wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula

25



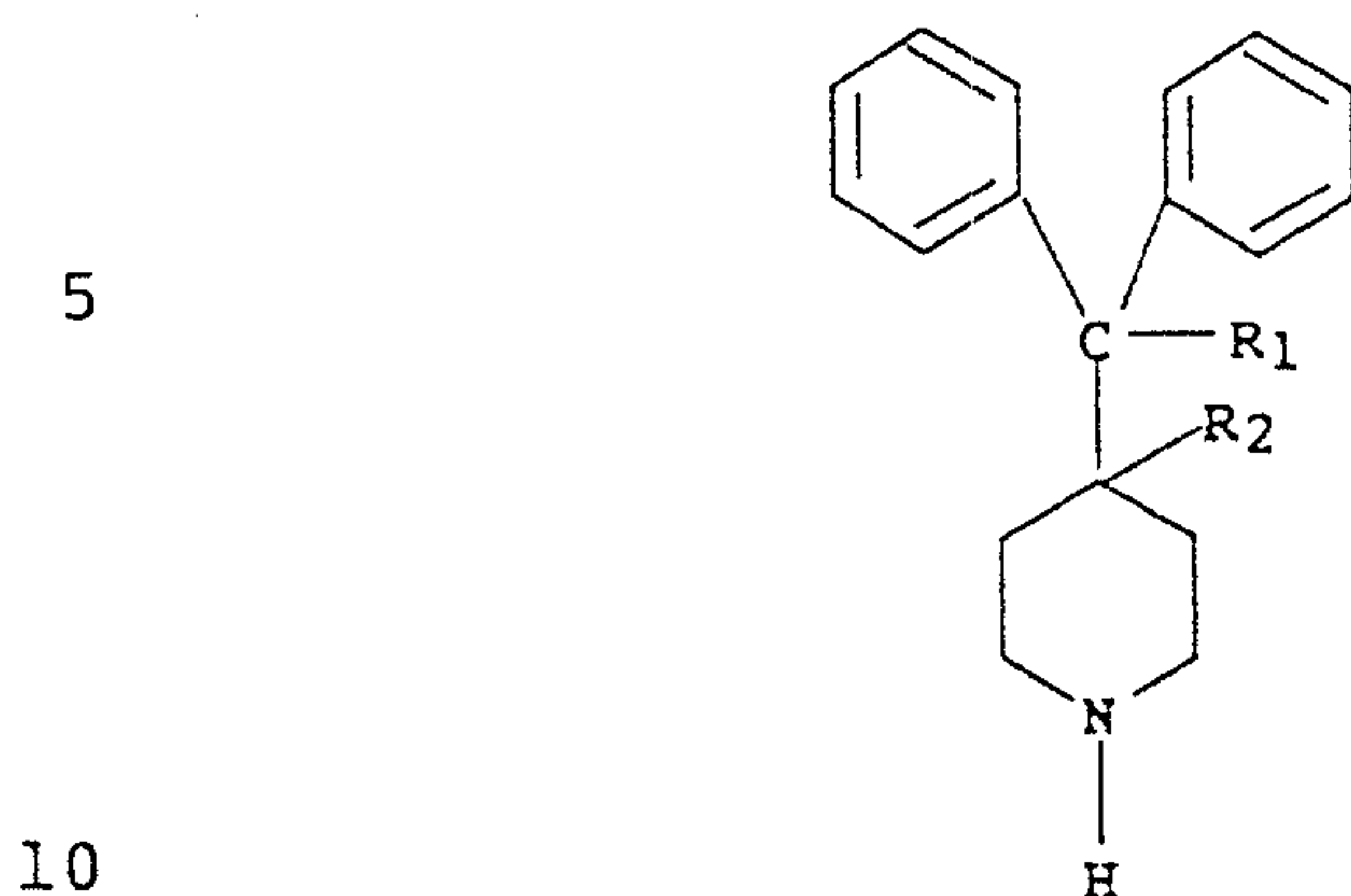
wherein Hal, n, A and D are defined above;

30

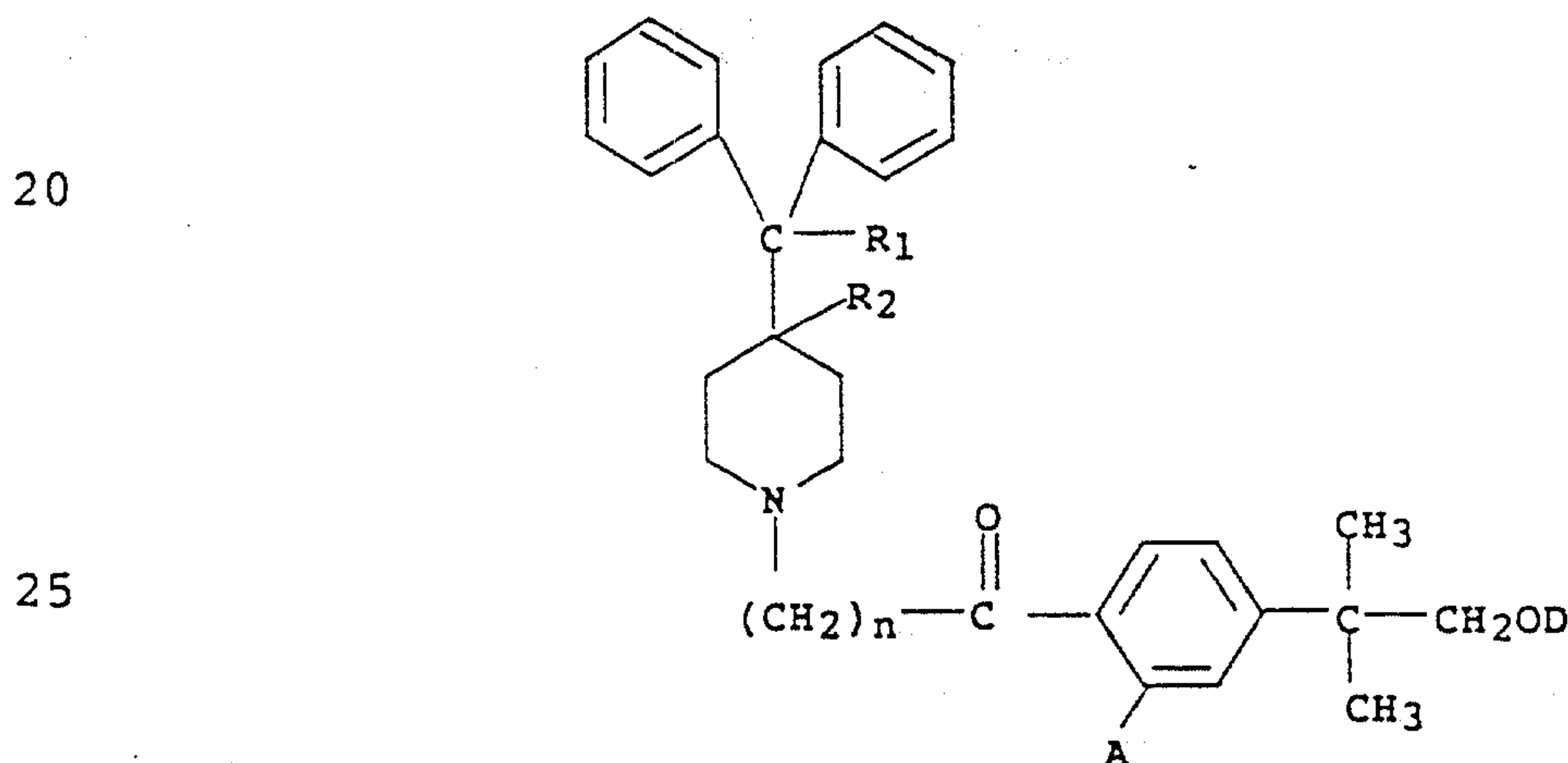
(d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

35

-48-



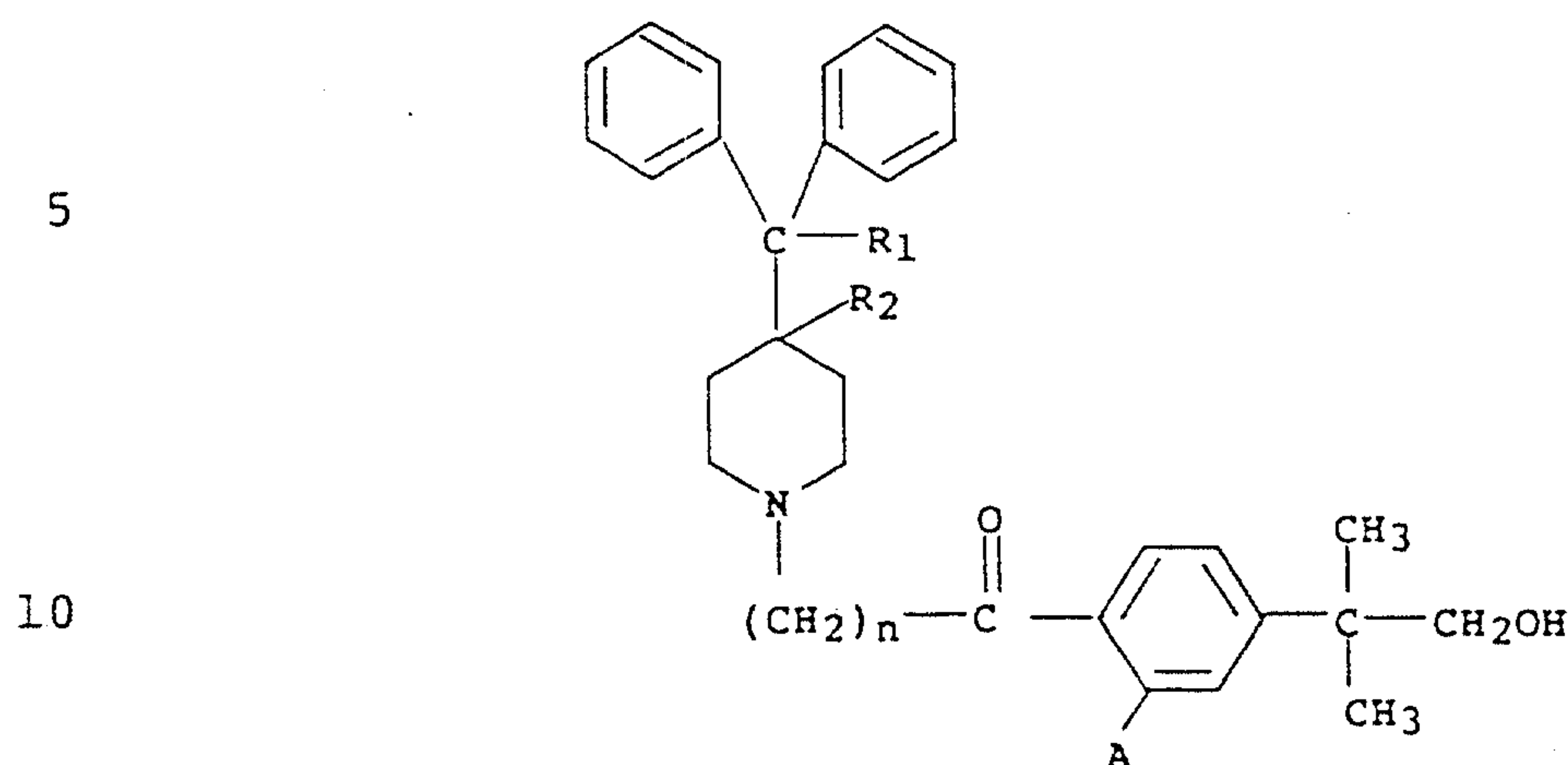
wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce the piperidine protected hydroxyethylphenylketone compound of the formula



wherein R_1 , R_2 , n and A are defined above and D is $-C(=O)CH_3$ or $-C(=O)C_6H_5$;

(e) reacting a piperidine protected hydroxyethylphenylketone with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroside/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylketone of the formula

-49-



wherein R₁, R₂, n and A are defined above; and

15

(f) reacting the piperidine hydroxyethylphenylketone compound with dimethyl sulfoxide, oxyallyl chloride and triethylamine or with Dess-Martin reagent, chromium (IV) oxide, nickel peroxide, sodium dichromate, potassium dichromate, t-butyl chromate, silver oxide, argentic picolinate manganese dioxide lead tetraacetate, dicyclohexylcarbodiimide, 2,3-dichloro-5,6-dicyanoquinone, tetrachloro-1,2-benzoquinone, 2,2,6,6-tetramethylpiperidiny-1-oxyl (TEMPO) or quinolinium chlorochromate to produce the piperidine formylphenyl ketone; and

20

25

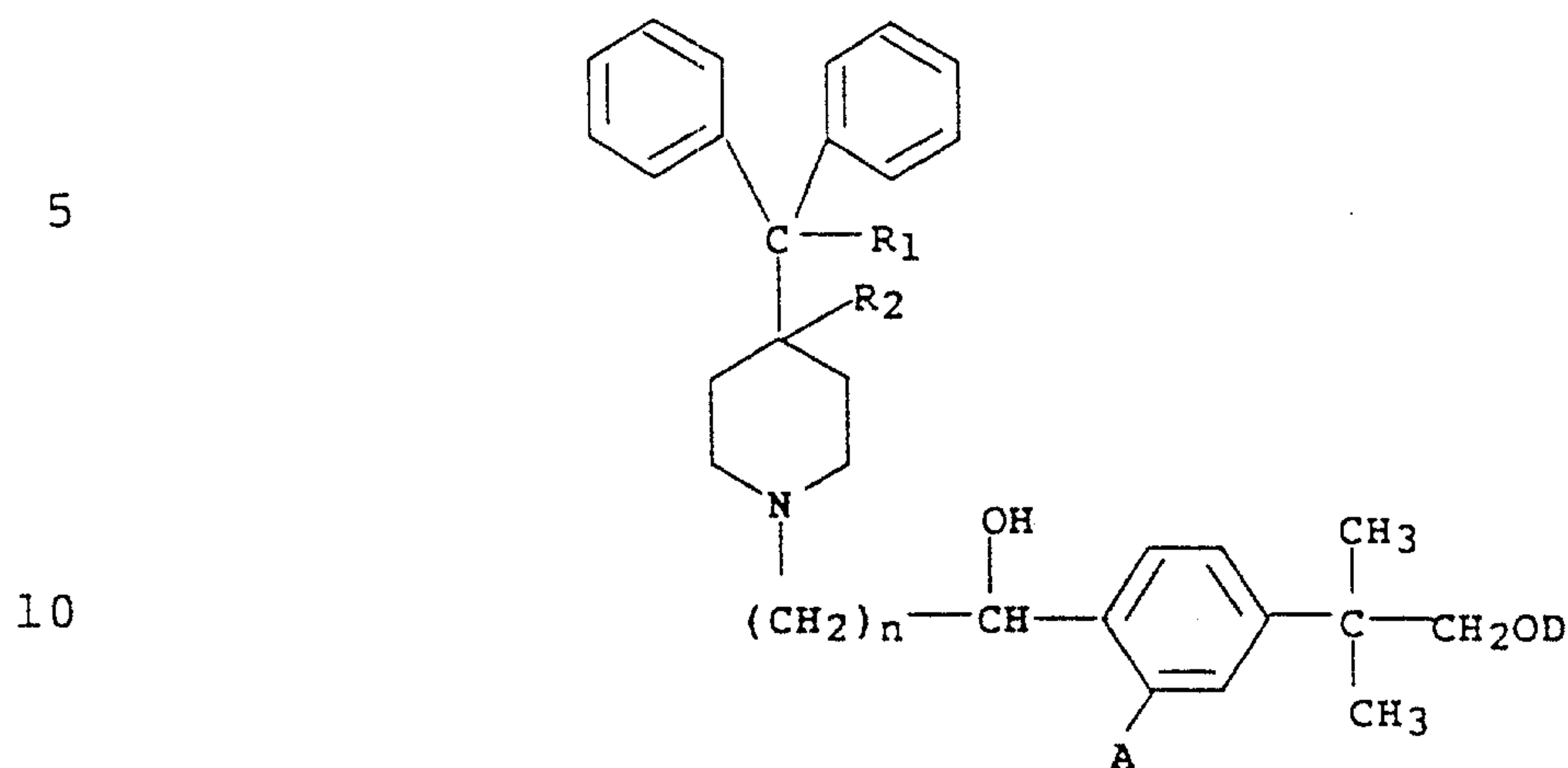
(g) optionally reacting the piperidine formylphenylketones which bear hydroxy protecting groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine formylphenylketones.

30

7. A process for preparing a piperidine protected hydroxyphenylalcohol compound of the formula

35

-50-



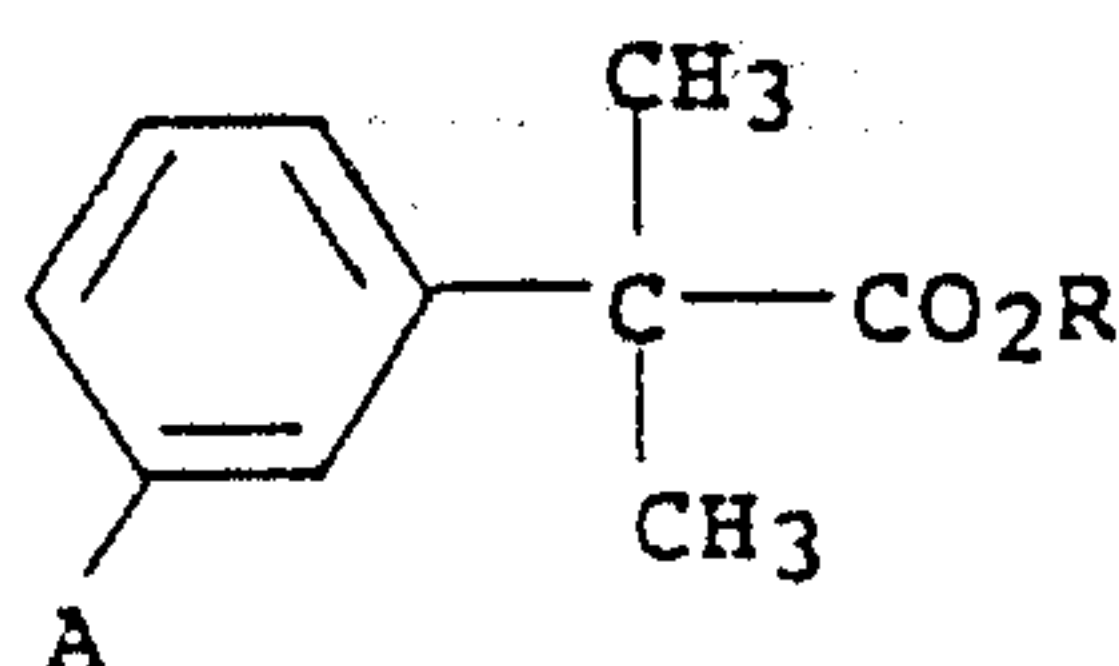
wherein

- 15 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the
carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;
20 A is hydrogen or hydroxy with the proviso that when A
is hydroxy, A may be optionally protected or
unprotected; and
 D is $-C(=O)CH_3$ or $-C(=O)C_6H_5$,
comprising the steps of:

25

- (a) reacting a benzeneacetic acid compound of the
formula

30



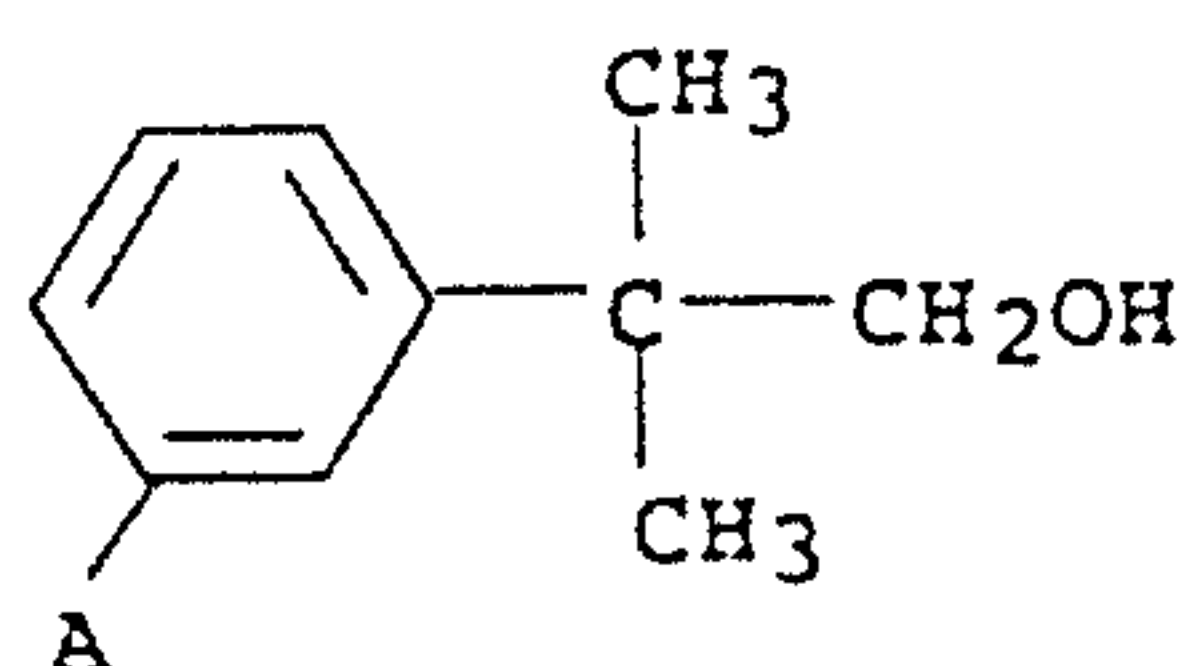
35

wherein A is hydrogen or hydroxy with the proviso that when
 A is hydroxy, A may be optionally protected or unprotected
and R is hydrogen or C_1 - C_6 alkyl with sodium bis(2-
methoxyethoxy)aluminum hydride, lithium aluminum hydride,
diborane, lithium borohydride, lithium triethylborohydride

-51-

and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

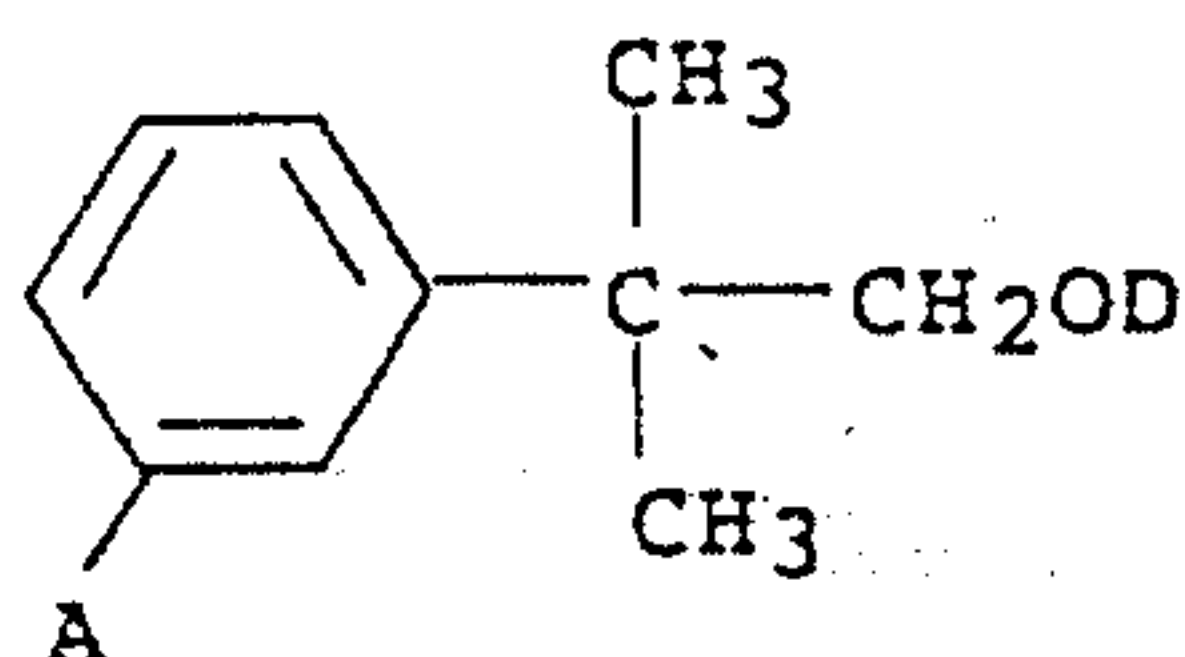
5



10 wherein A is hydrogen or hydroxy, with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

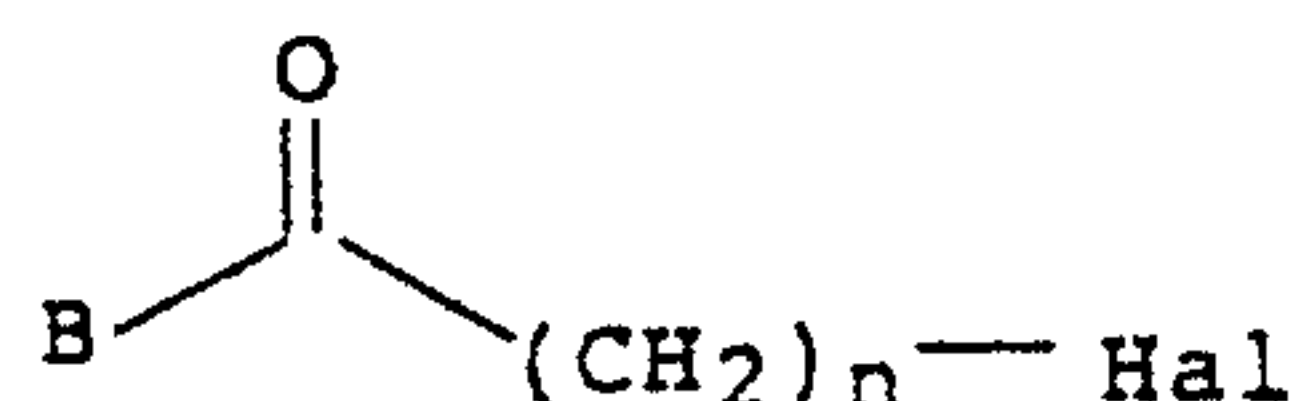
15 (b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

20



25 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected, and D is $\text{C}(=\text{O})\text{CH}_3$ or $\text{C}(=\text{O})\text{C}_6\text{H}_5$;

30 (c) reacting the protected phenethyl alcohol with a ω -halo compound of the formula

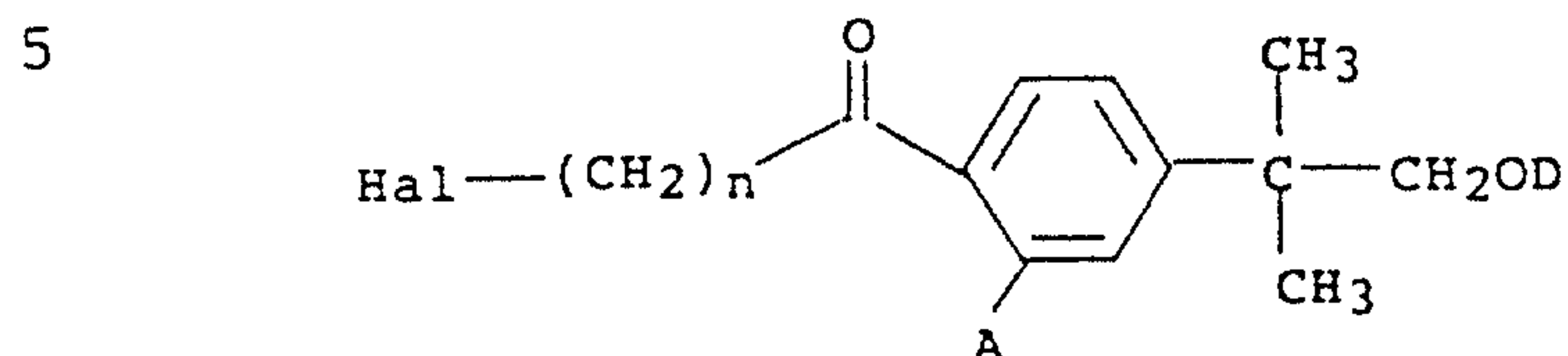


35

wherein B is halo or hydroxy, Hal represents Cl, Br or I, and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron

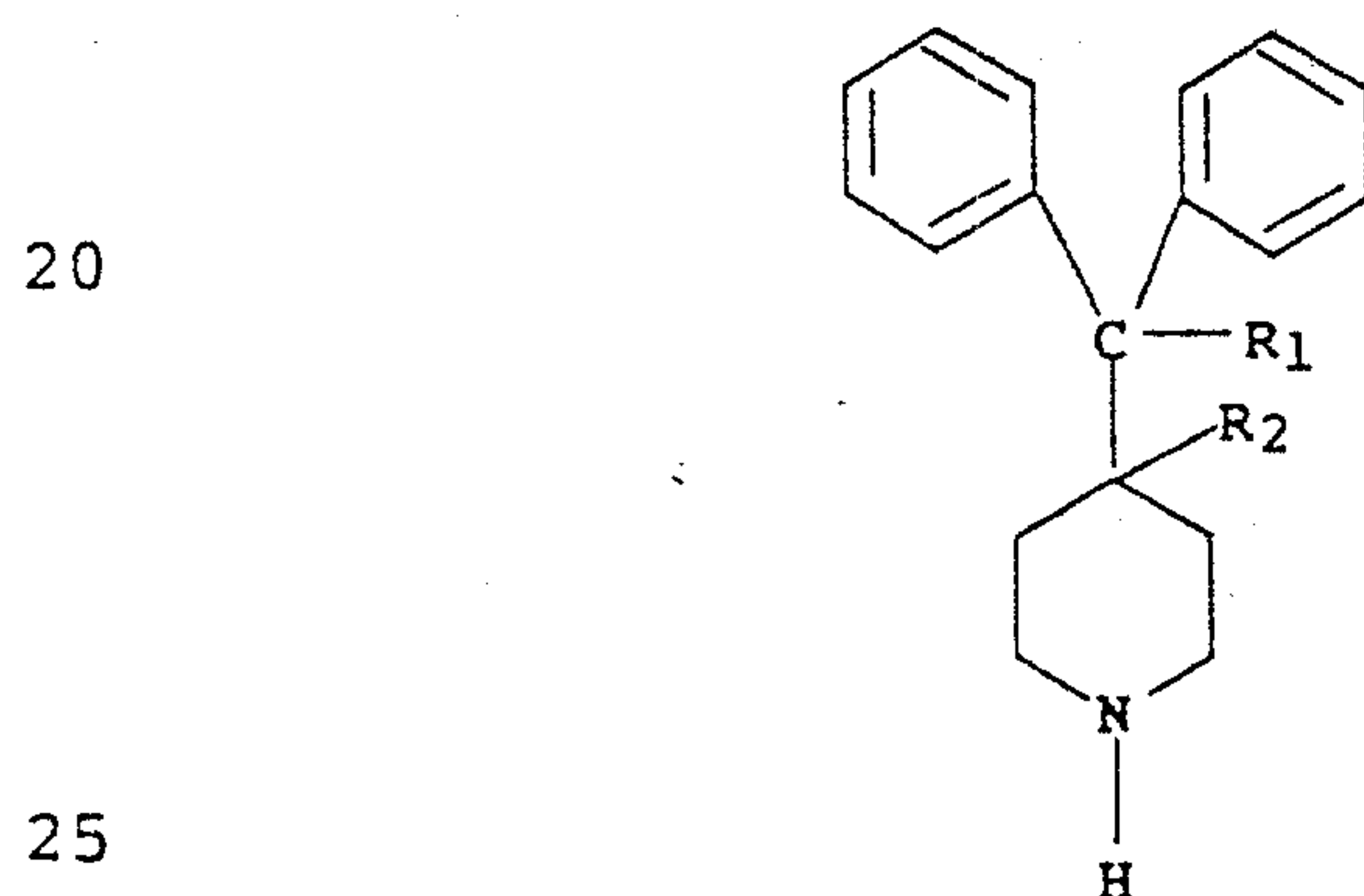
-52-

trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula



10 wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

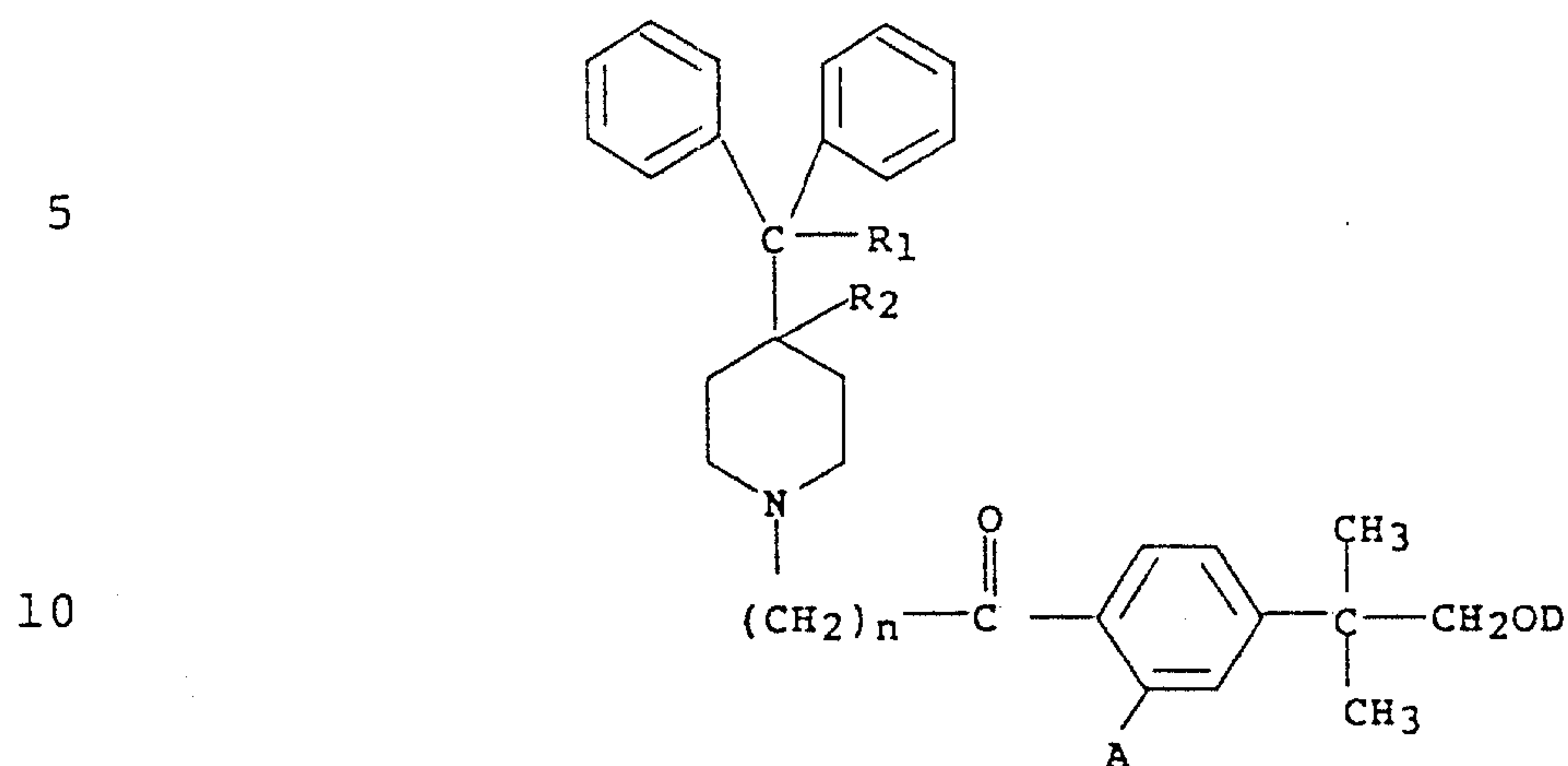
15 (d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula



wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the
 30 piperidine compound may be used to produce a piperidine protected hydroxyethylphenylketone of the formula

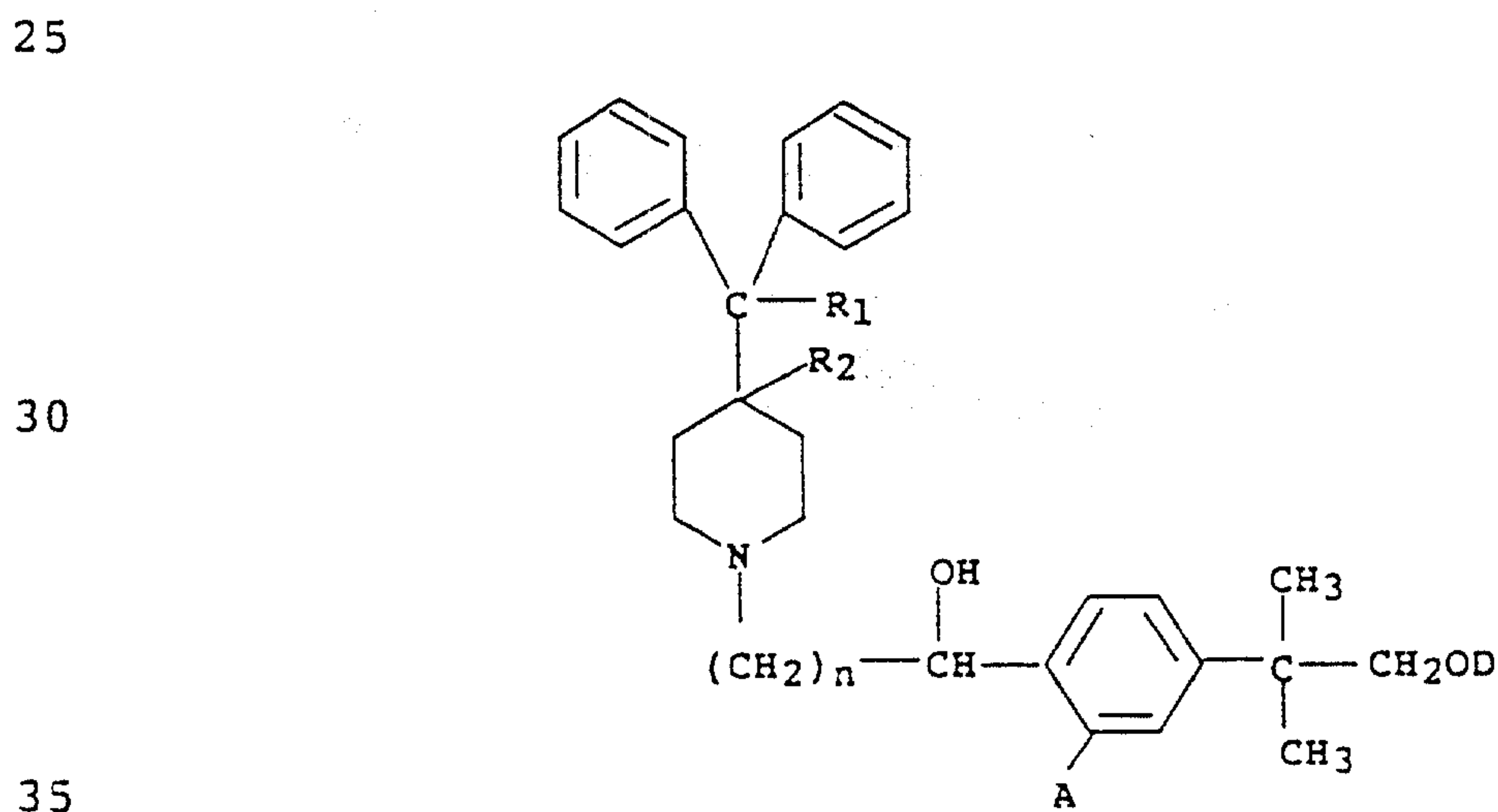
35

-53-



15 wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(e) reacting the piperidine protected hydroxyethylphenylketone with sodium borohydride, potassium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, lithium tri-tert-butylaluminumhydride, diisobutylaluminum hydride or catalytic hydrogenation to produce a piperidine protected hydroxyethylphenylalcohol of the formula



-54-

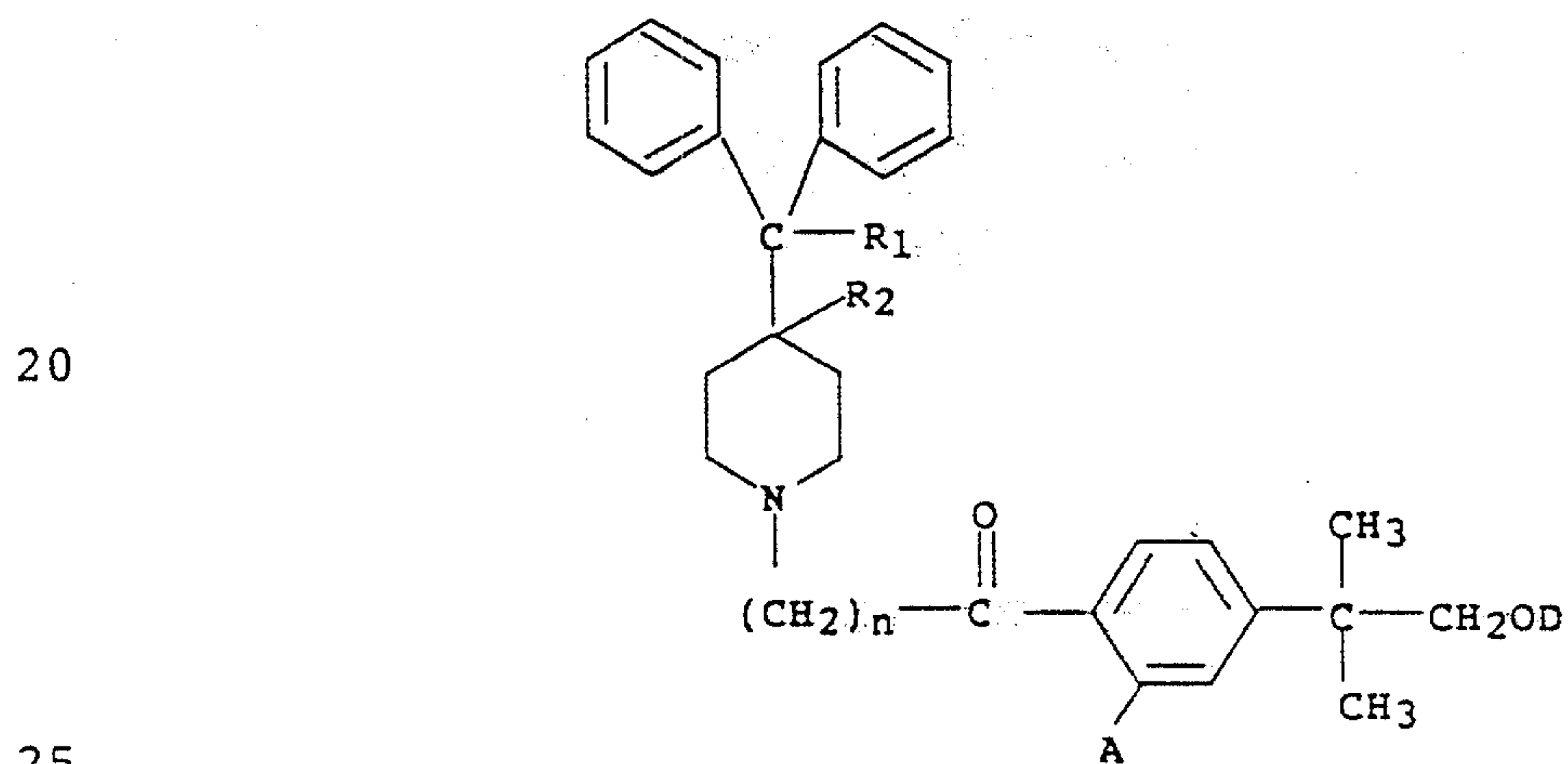
wherein R_1 , R_2 , D and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected; and

5

(f) optionally reacting the piperidine protected hydroxyethylphenylalcohols which bear hydroxy protecting groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to
10 produce the unprotected piperidine protected hydroxyethylphenylalcohols.

8. A process for preparing a piperidine protected hydroxyethylphenylketone compound of the formula

15



25

wherein

R_1 represents hydrogen or hydroxy;

R_2 represents hydrogen; or

30

R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;

n is an integer of from 1 to 5;

A is hydrogen or hydroxy, with the proviso that when A is hydroxy, A may be optionally protected or
35 unprotected; and

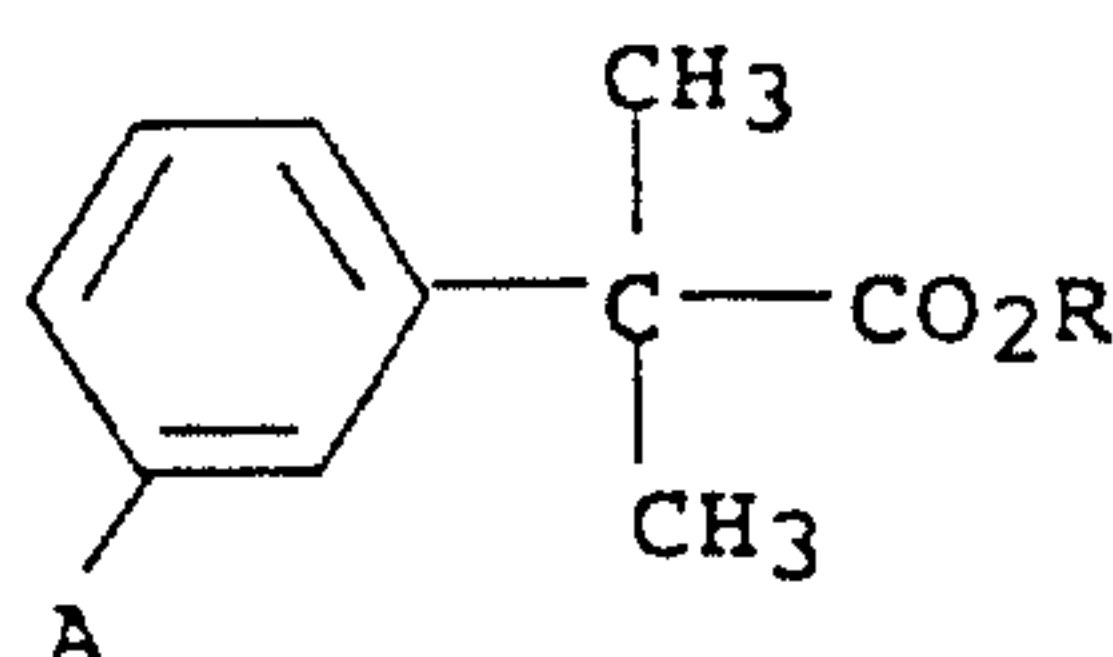
D is $-C(=O)CH_3$ or $-C(=O)C_6H_5$,

comprising the steps of:

-55-

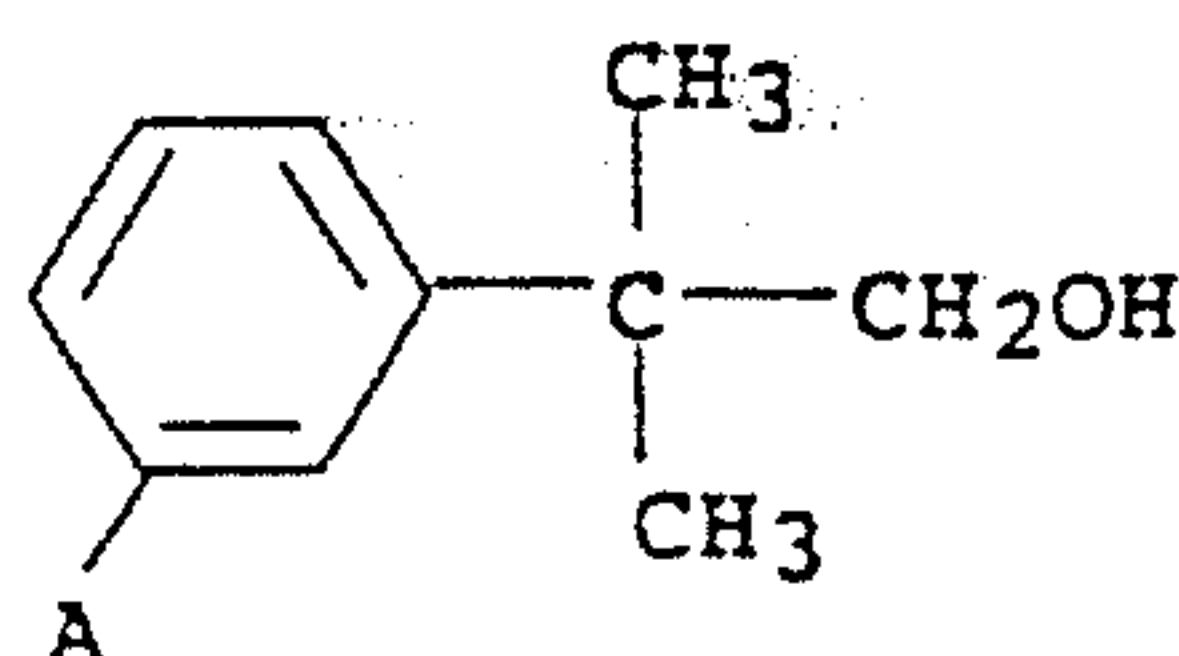
(a) reacting a benzeneacetic acid compound of the formula

5



10 wherein A is as defined above and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl
15 alcohol of the formula

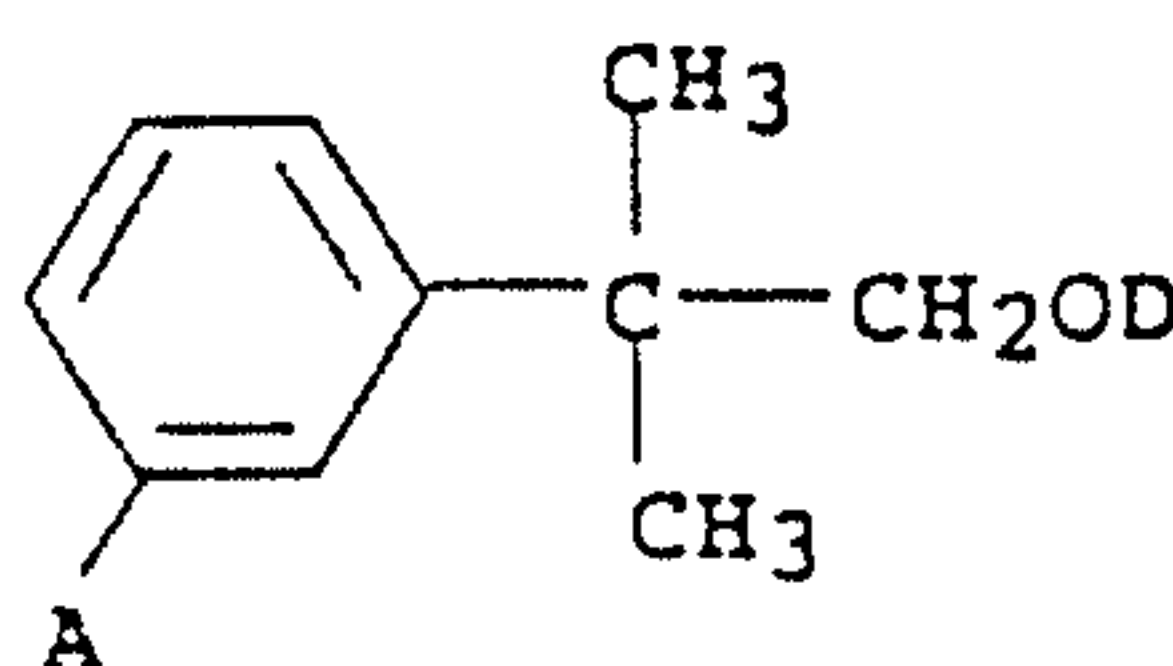
20



wherein A is defined above;

25 (b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

30



35

wherein A and D are defined above;

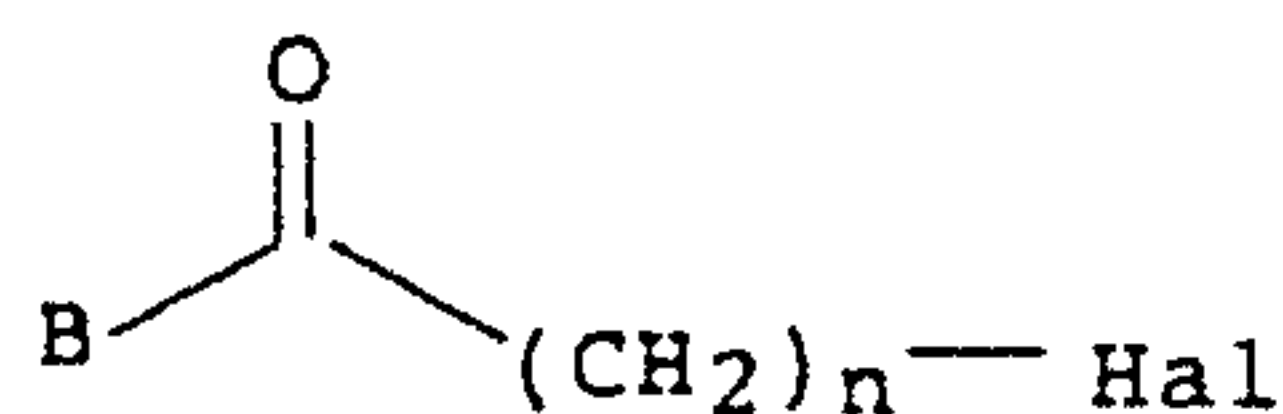
(c) reacting the protected phenethyl alcohol with a

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-56-

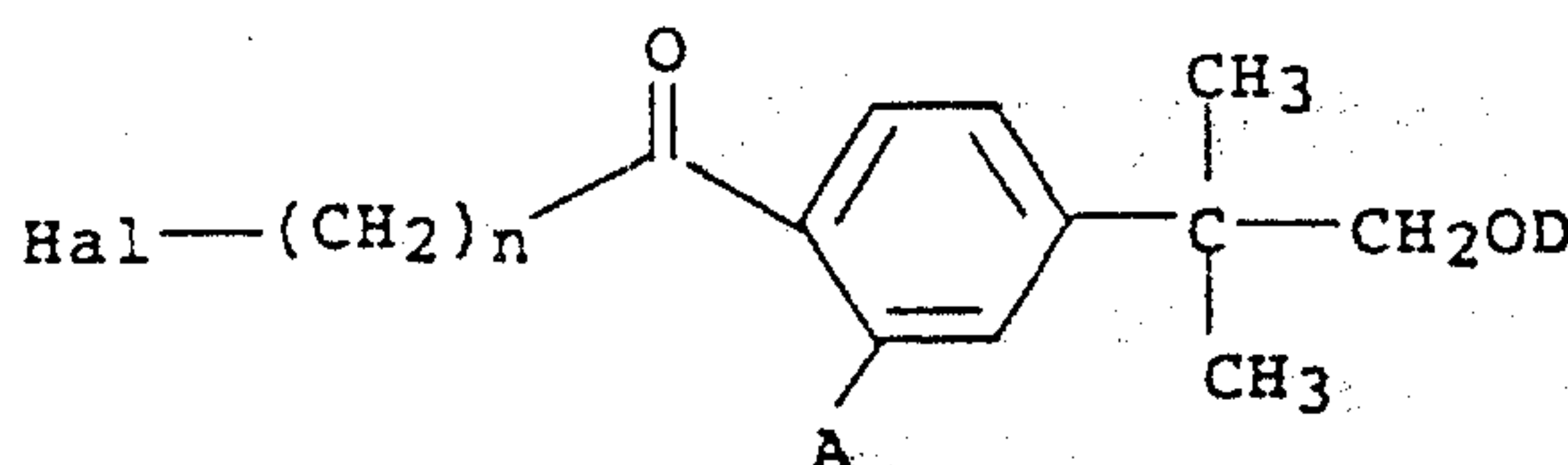
ω -halo compound of the formula

5



wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula

15

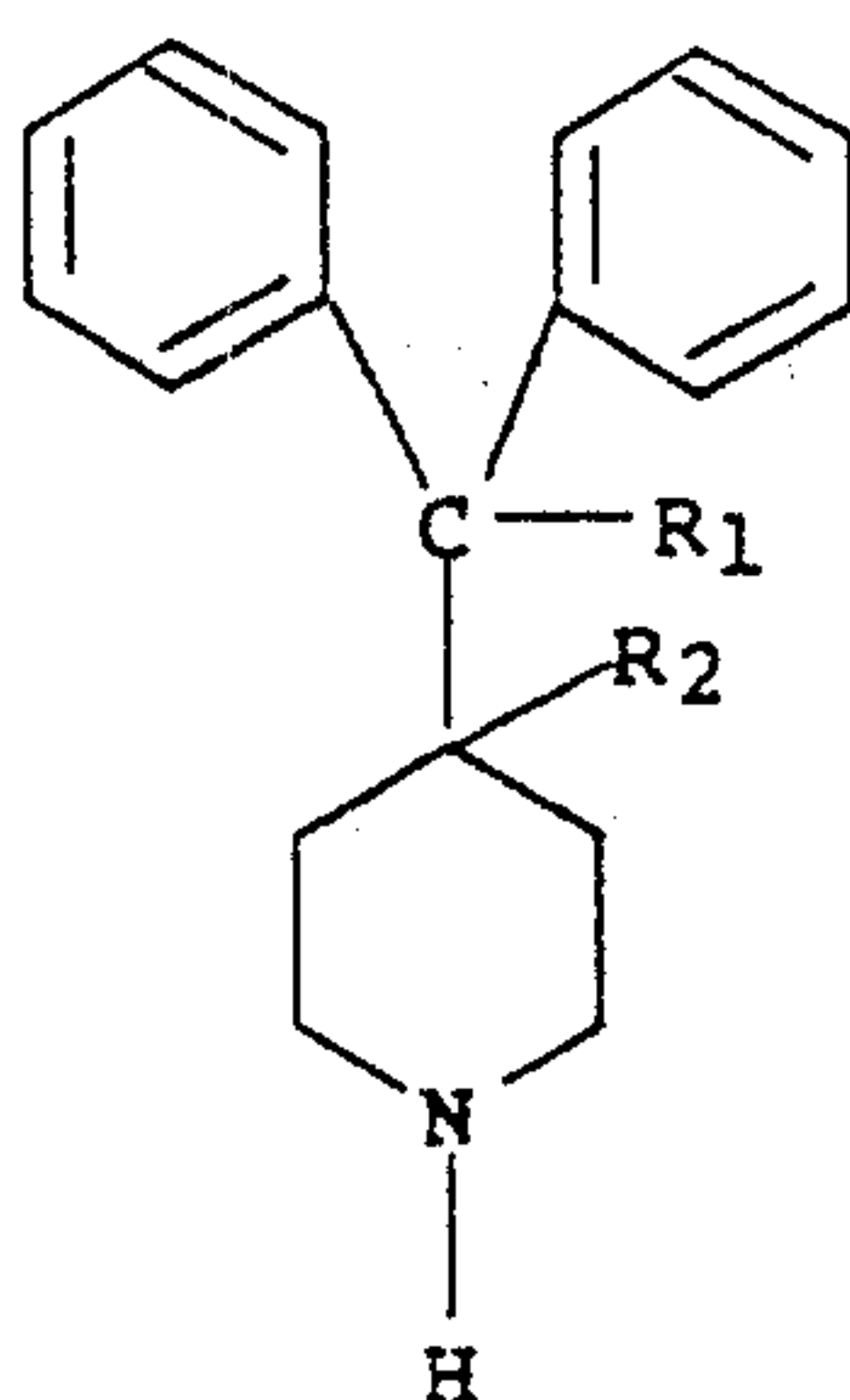


wherein Hal, n, A and D are defined above;

20

(d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

25

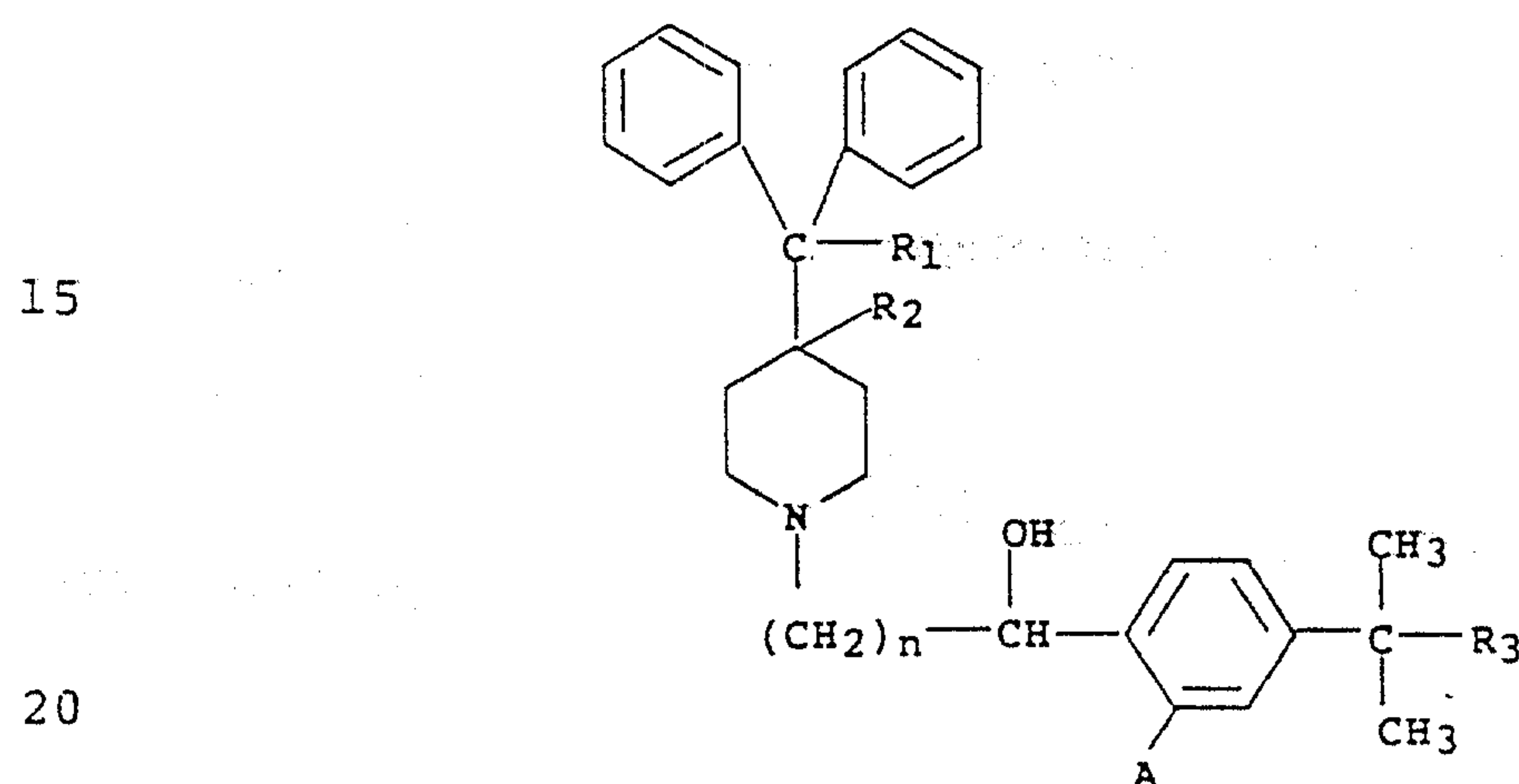


30

wherein R₁ and R₂ are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce the piperidine protected hydroxyethylphenylketone.

(e) optionally reacting the piperidine protected hydroxyethylphenylketones which bear hydroxy protecting groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine protected hydroxyethylphenylketones.

10 9. A process for preparing a compound of the formula



wherein

R_1 represents hydrogen or hydroxy;

25 R_2 represents hydrogen; or

R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;

n is an integer of from 1 to 5;

30 R_3 is $-\text{COOH}$ or $-\text{COOalkyl}$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

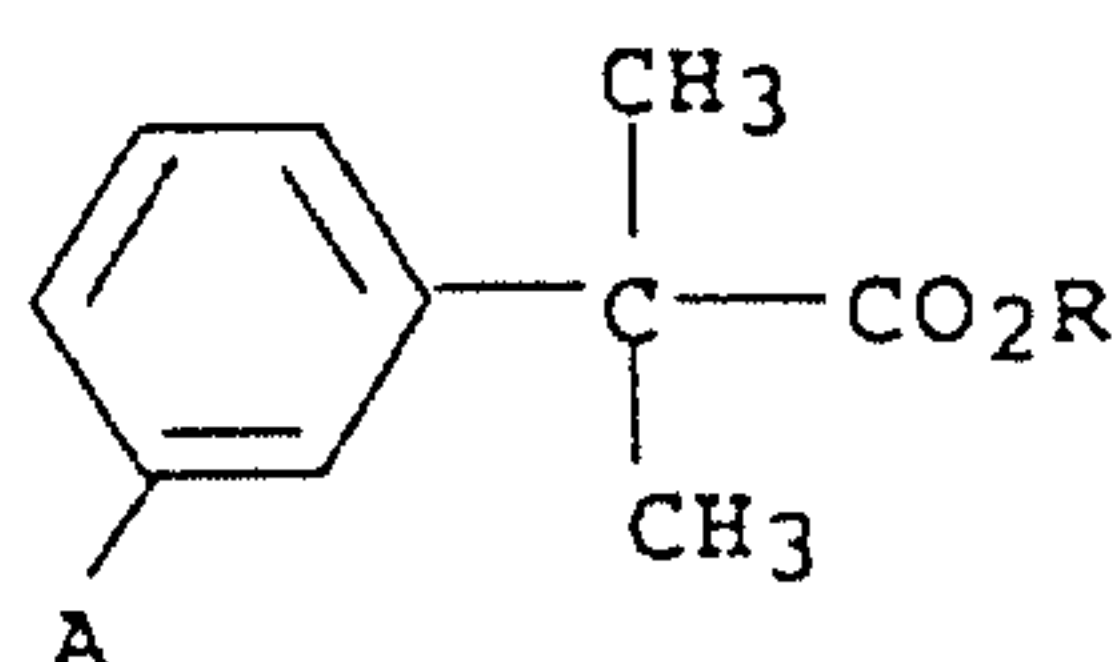
A is hydrogen or hydroxy; and

pharmaceutically acceptable salts thereof comprising the steps of:

35 (a) reacting a benzeneacetic acid compound of the formula

-58-

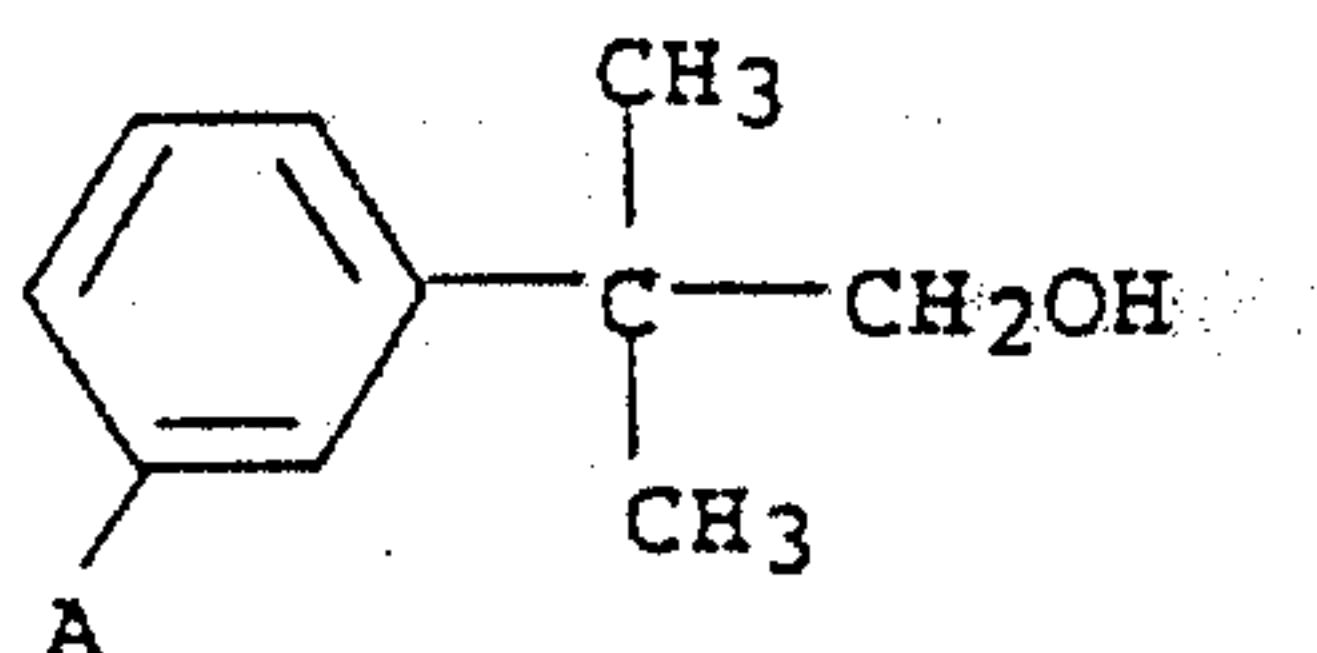
5



10

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

15



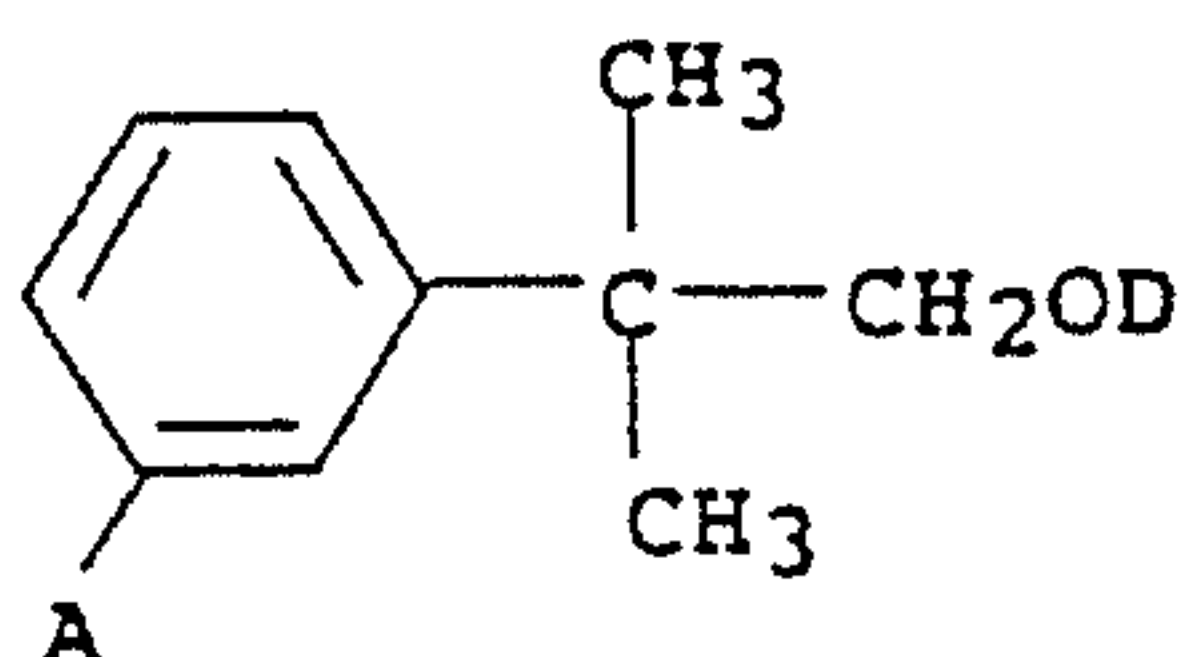
20

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

25

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

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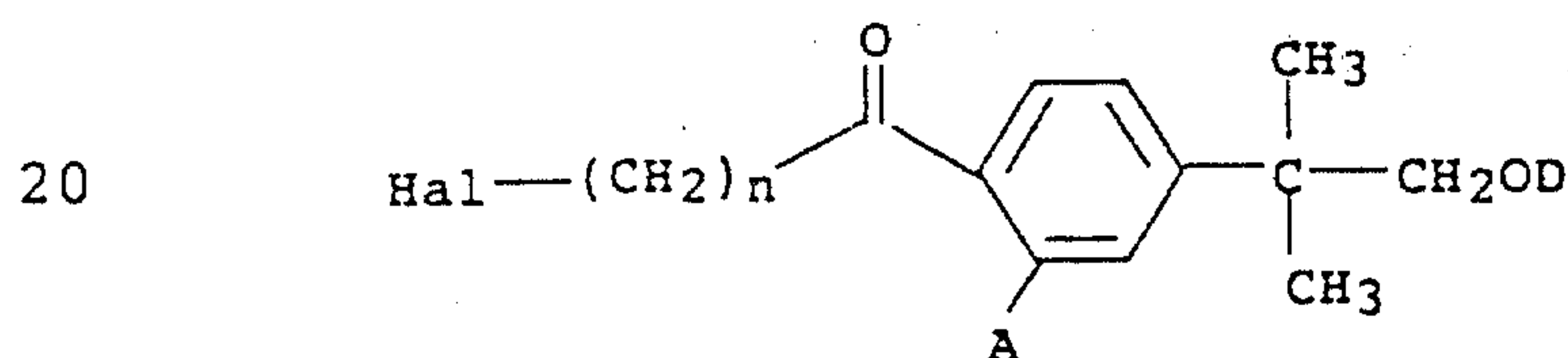
wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is C(=O)CH₃ or C(=O)C₆H₅;

5

(c) reacting the protected phenethyl alcohol with a ω -halo compound of the formula



wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula

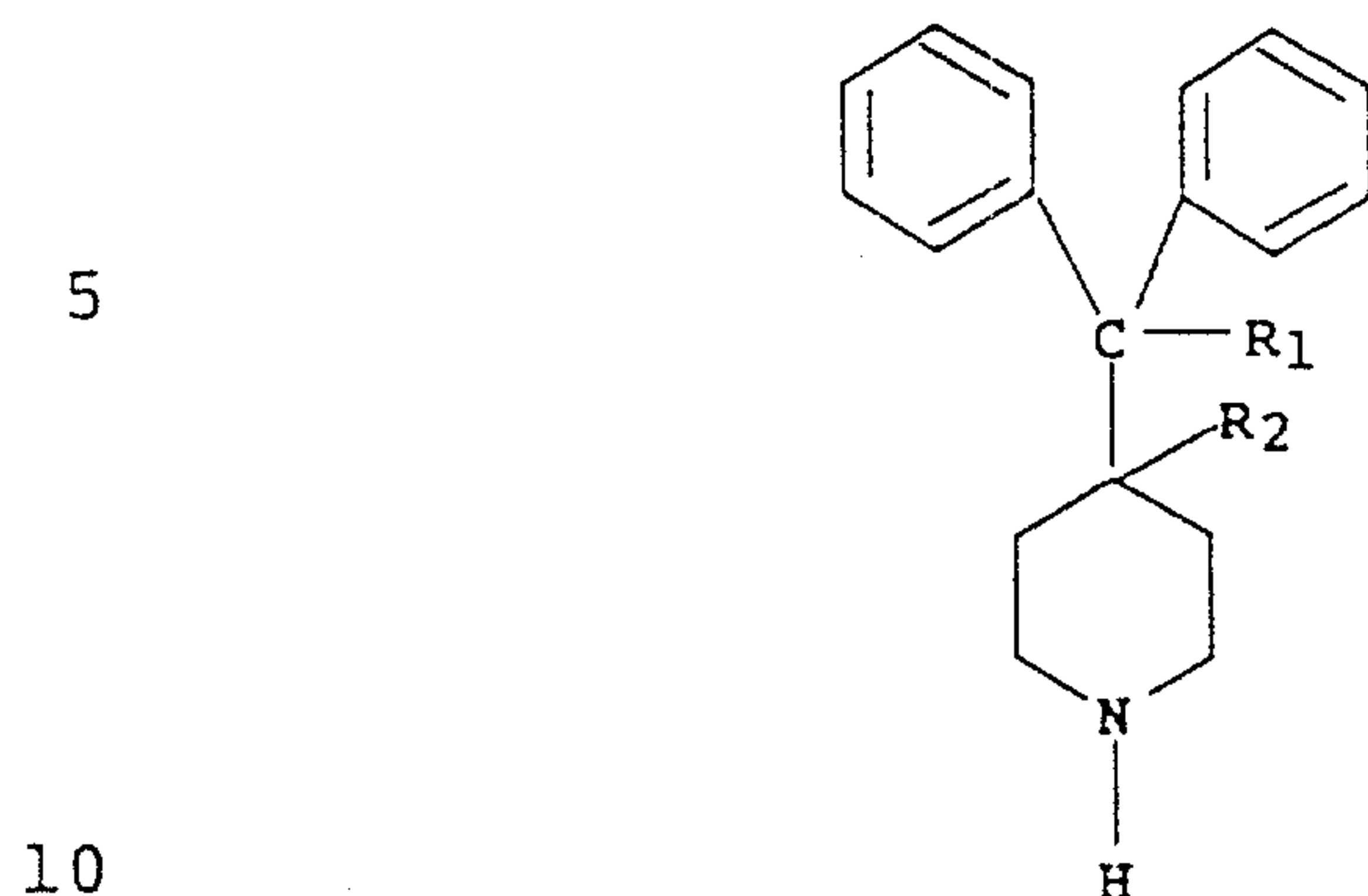


wherein Hal, n and D are defined above and A is hydrogen or
25 hydroxy with the proviso that when A is hydroxy, A may be
optionally protected or unprotected;

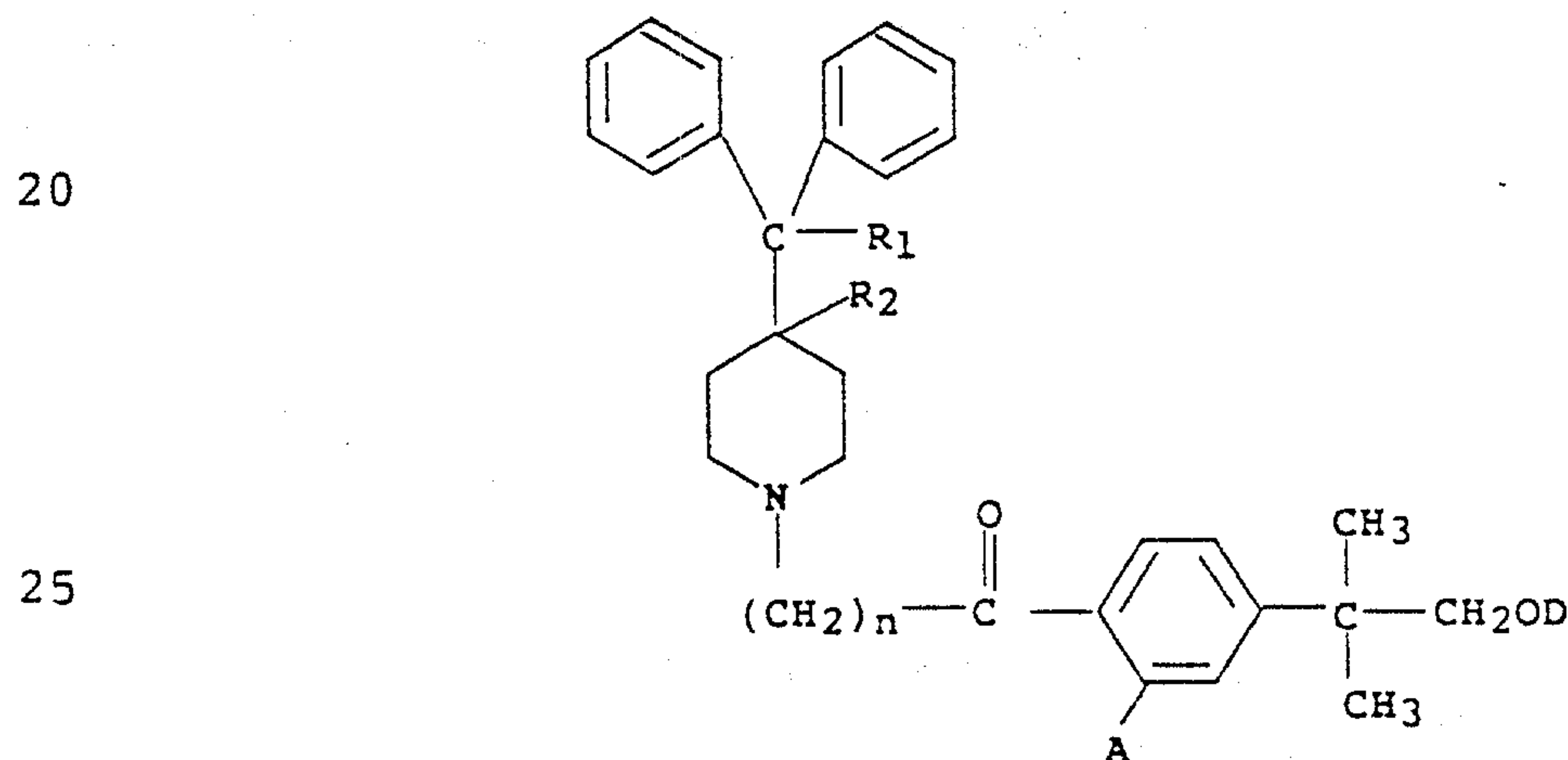
(d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

35

-60-



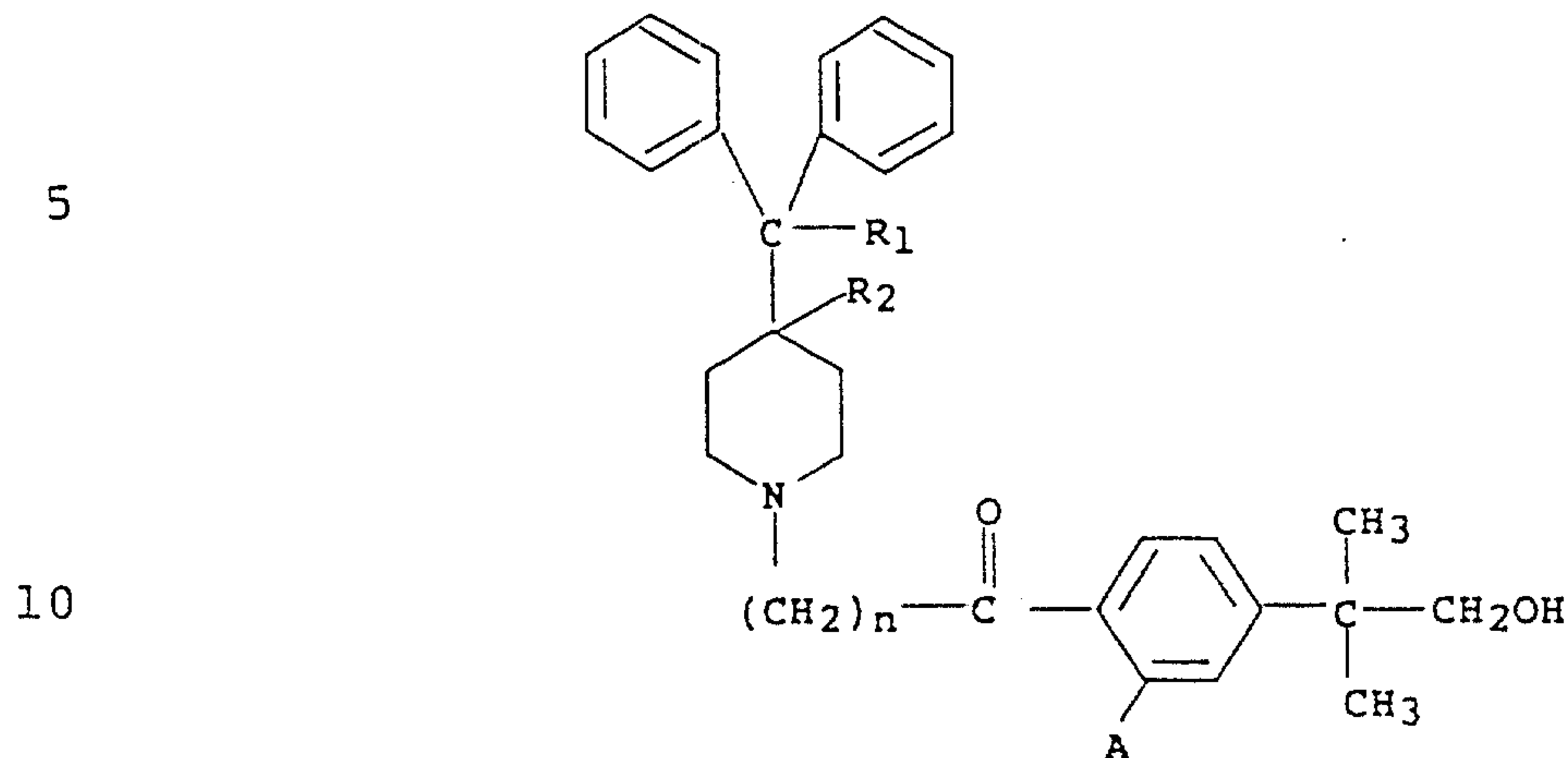
wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylketone of the formula



wherein R_1 , R_2 , and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(e) reacting the piperidine protected hydroxyethylphenylketone with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylketone of the formula

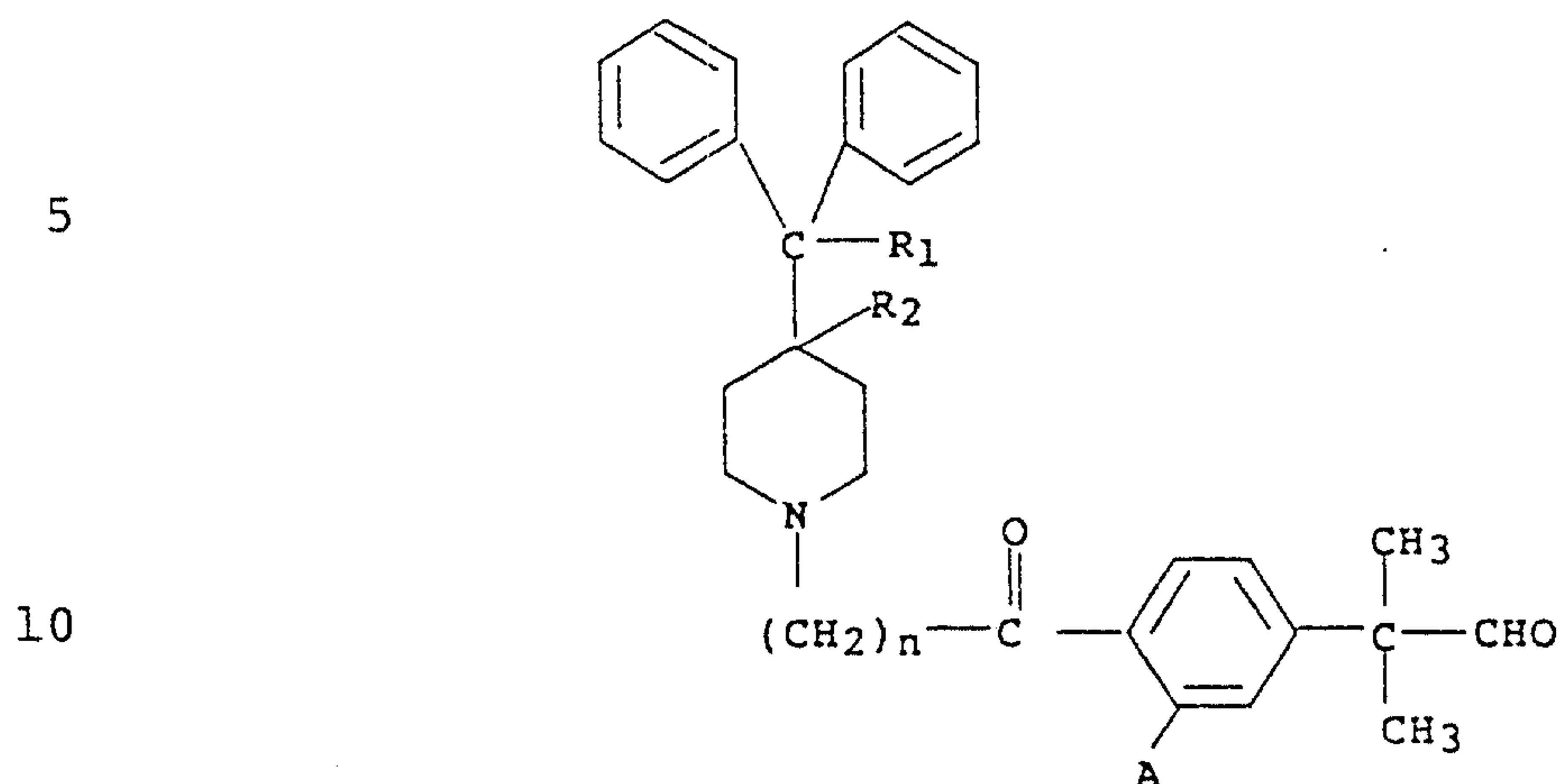
-61-



wherein R₁, R₂ and n are defined above and A is hydrogen or
 15 hydroxy with the proviso that when A is hydroxy, A may be
 optionally protected or unprotected;

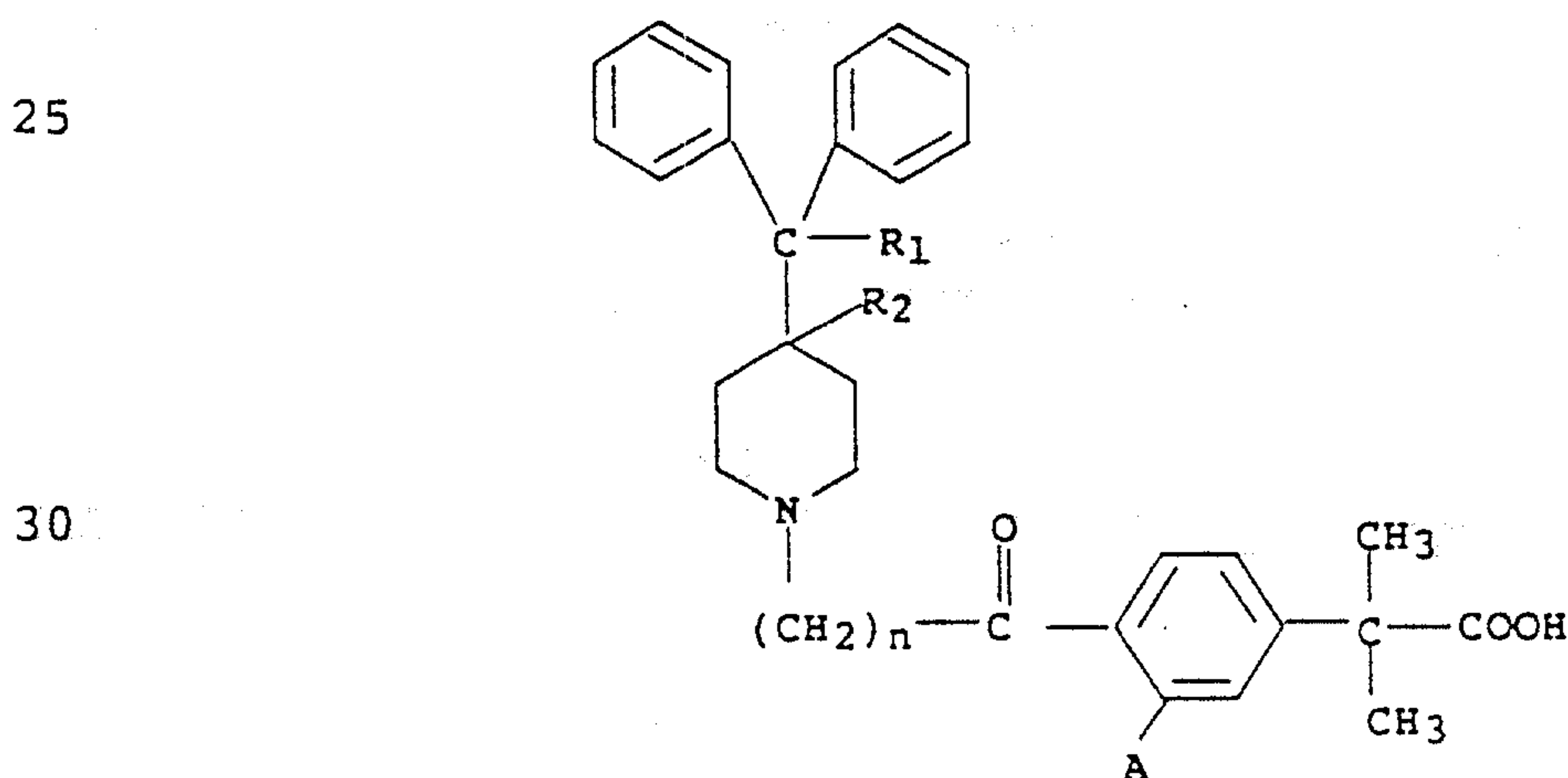
(f) reacting the piperidine hydroxyethylphenylketone
 with dimethyl sulfoxide, oxalyl chloride and triethylamine
 20 or with Dess-Martin reagent, chromium (IV) oxide, nickel
 peroxide, sodium dichromate, potassium dichromate, t-butyl
 chromate, silver oxide, argentic picolinate manganese
 dioxide, lead tetraacetate, dicyclohexylcarbodiimide, 2,3-
 25 dichloro-5,6-dicyanoquinone, tetrachloro-1,2-benzoquinone,
 2,2,6,6-tetramethylpiperidiny-1-oxy (TEMPO) or quinolinium
 chlorochromate to produce a piperidine formylphenylketone
 of the formula

-62-



wherein R₁, R₂ and n are defined above and A is hydrogen or
 15 hydroxy with the proviso that when A is hydroxy, A may be
 optionally protected or unprotected;

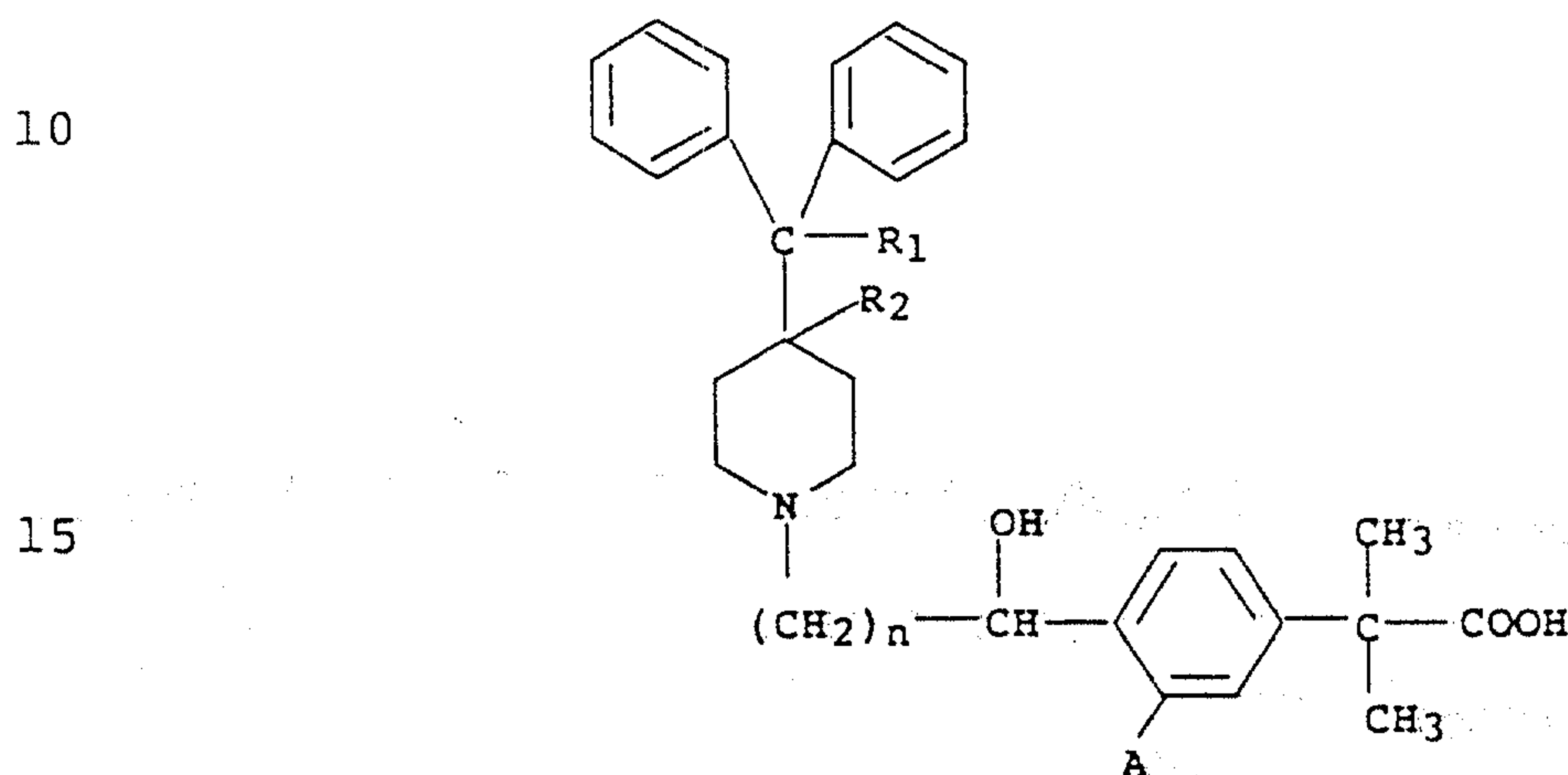
(g) reacting the piperidine formylphenylketone with
 potassium permanganate, chromium (IV) oxide, silver (I)
 20 oxide, silver oxide, argentic picolinate, peroxide, nitric
 acid, m-chloroperbenzoic acid and peracetic acid to produce
 a piperidine carboxyphenylketone of the formula



35 wherein R₁, R₂ and n are defined above and A is hydrogen or
 hydroxy with the proviso that when A is hydroxy, A may be
 optionally protected or unprotected;

-63-

- (h) reacting the piperidine carboxyphenylketone with sodium borohydride, potassium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, lithium tri-tert-butylaluminumhydride, diisobutylaluminum hydride or catalytic hydrogenation to produce a piperidine carboxyphenylalcohol of the formula

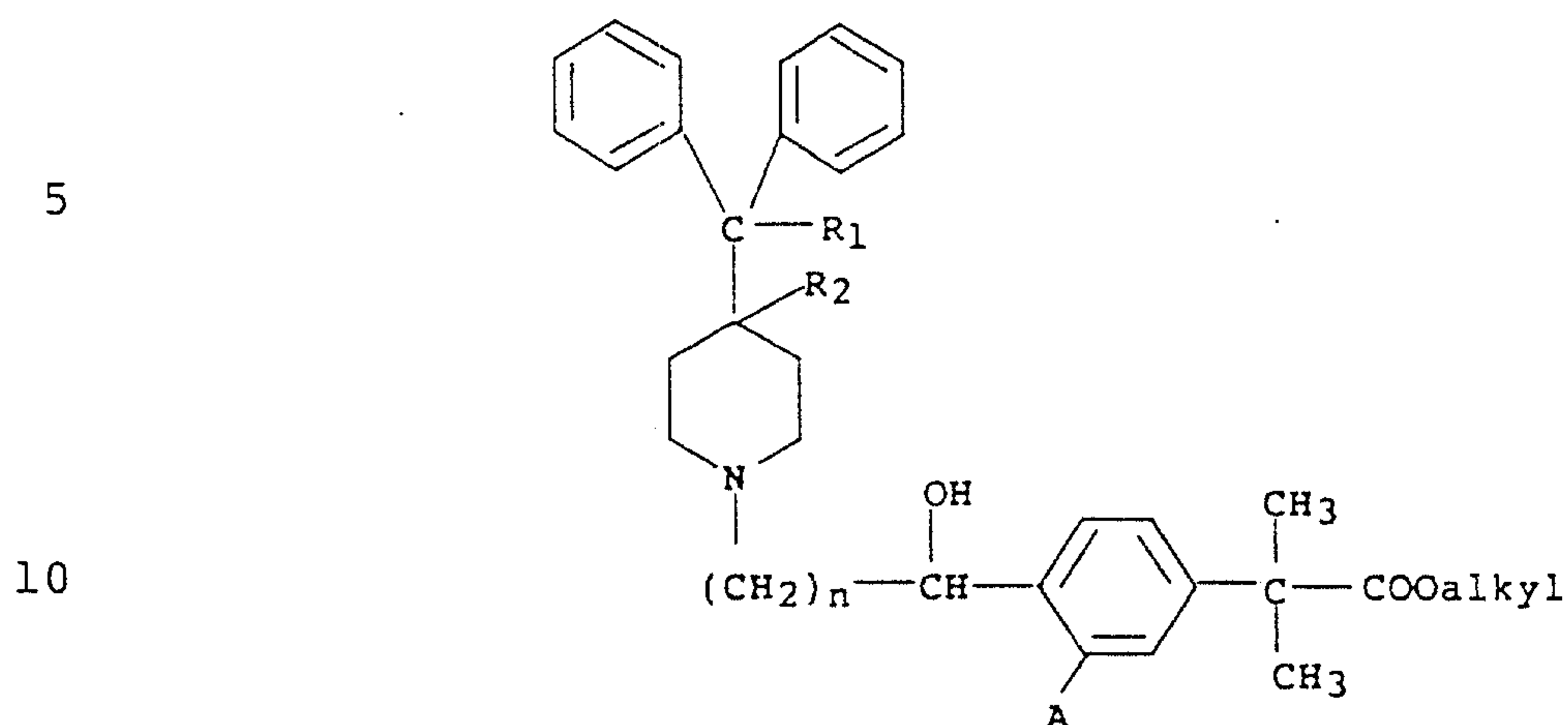


- 20 wherein R₁, R₂ and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

- (i) optionally reacting the piperidine carboxyphenylalcohol with diazomethane or 2,2-dimethoxypropane or with thionyl chloride followed by an alcohol of the formula HOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched to form a piperidine carboxyphenylalcohol ester of the formula
- 30

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-64-

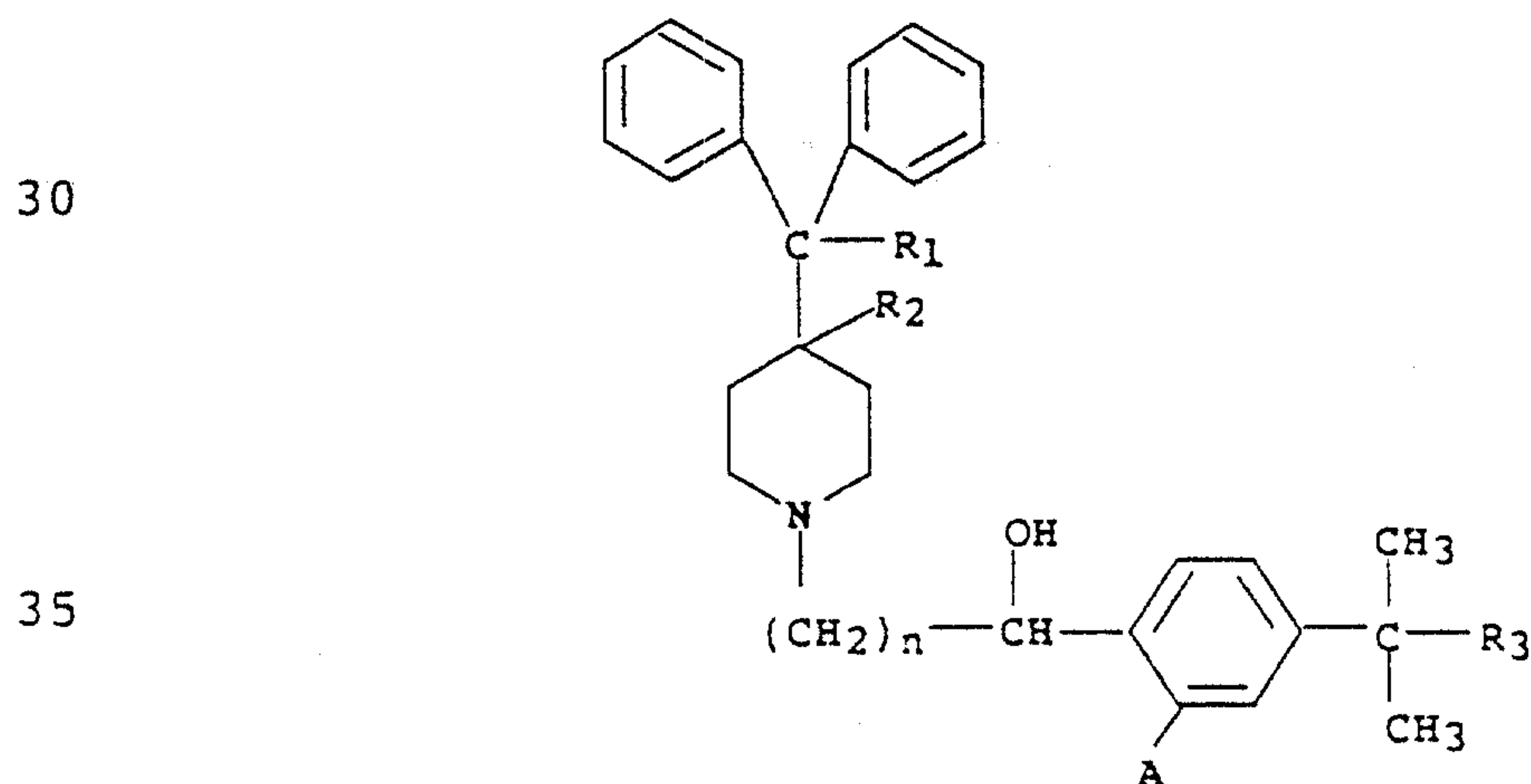


wherein R_1 , R_2 , n and alkyl are defined above and A is
 15 hydrogen or hydroxy with the proviso that when A is
 hydroxy, A may be optionally protected or unprotected; and

(j) optionally reacting the piperidine
 carboxyphenylalcohols or the piperidine
 20 carboxyphenylalcohol esters in which A is a protected
 hydroxy with mineral acids, strong organic acids, Lewis
 acids, aqueous mineral bases or catalytic hydrogenation to
 produce the unprotected piperidine carboxyphenylalcohols or
 the piperidine carboxyphenylalcohol esters.

25

10. A process for preparing a compound of the formula



-65-

wherein

R₁ represents hydrogen or hydroxy;

R₂ represents hydrogen; or

5 R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;

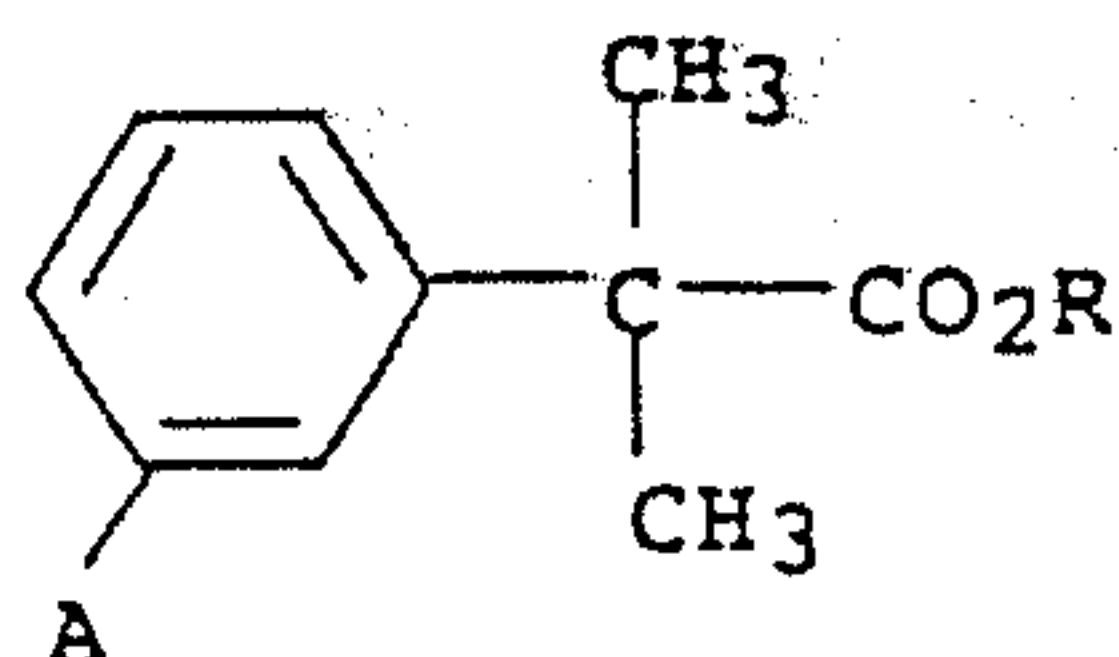
n is an integer of from 1 to 5;

R₃ is -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

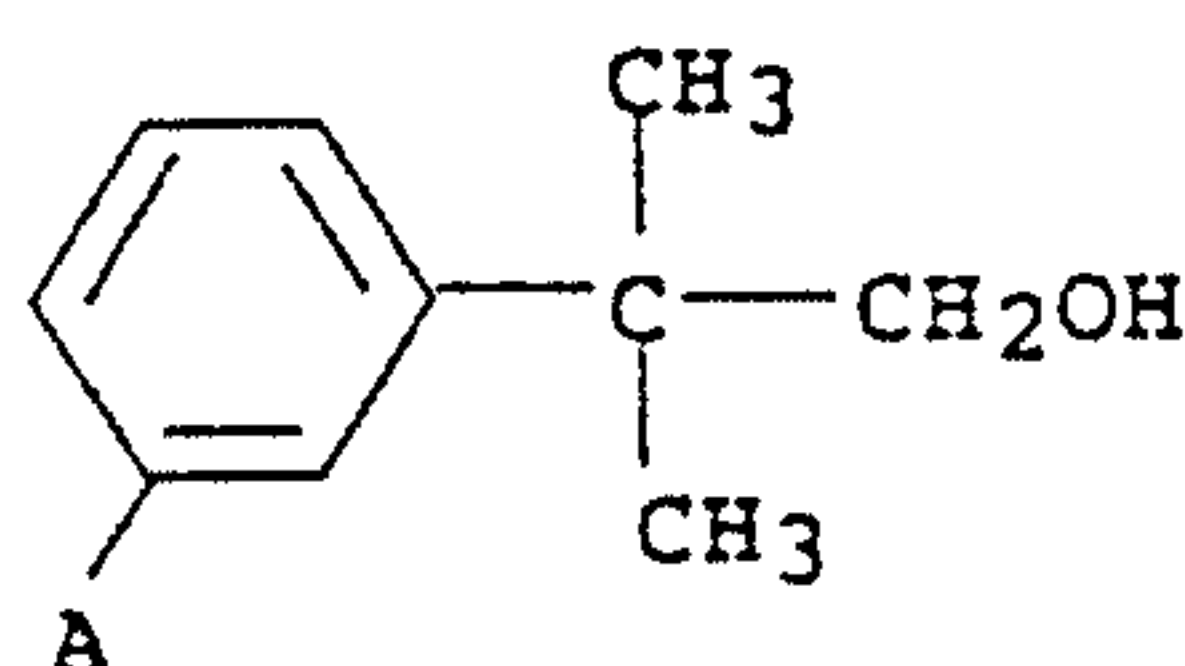
10 A is hydrogen or hydroxy; and

pharmaceutically acceptable salts thereof comprising the steps of:

(a) reacting a benzeneacetic acid compound of the
15 formula



20 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-
25 methoxyethoxy)aluminum hydride, lithium aluminum hydride, diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula



30
35 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

-66-

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

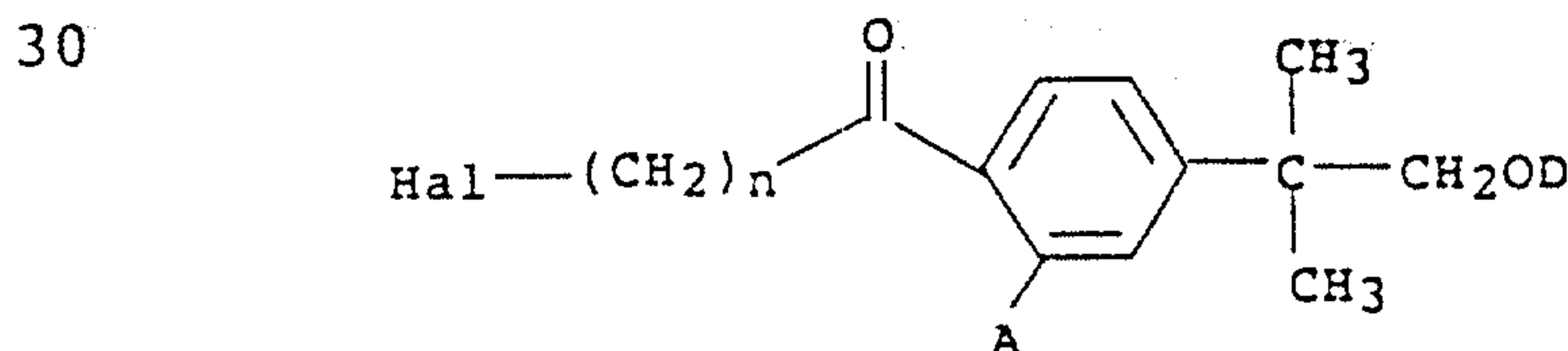


wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is $\text{C}(=\text{O})\text{CH}_3$ or $\text{C}(=\text{O})\text{C}_6\text{H}_5$;

(c) reacting the protected phenethyl alcohol with a ω -halo compound of the formula



wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula



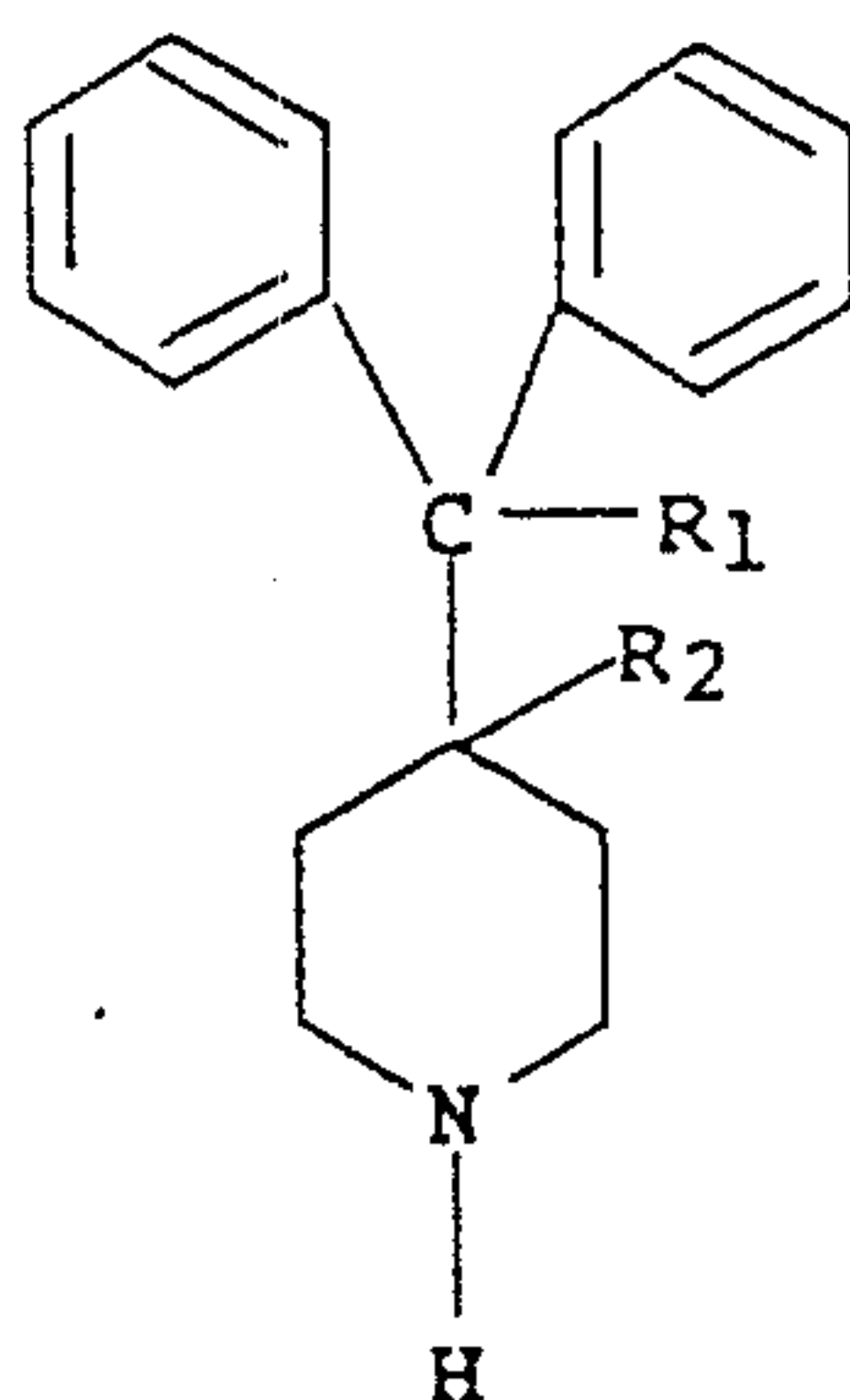
wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

-67-

(d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

5

10



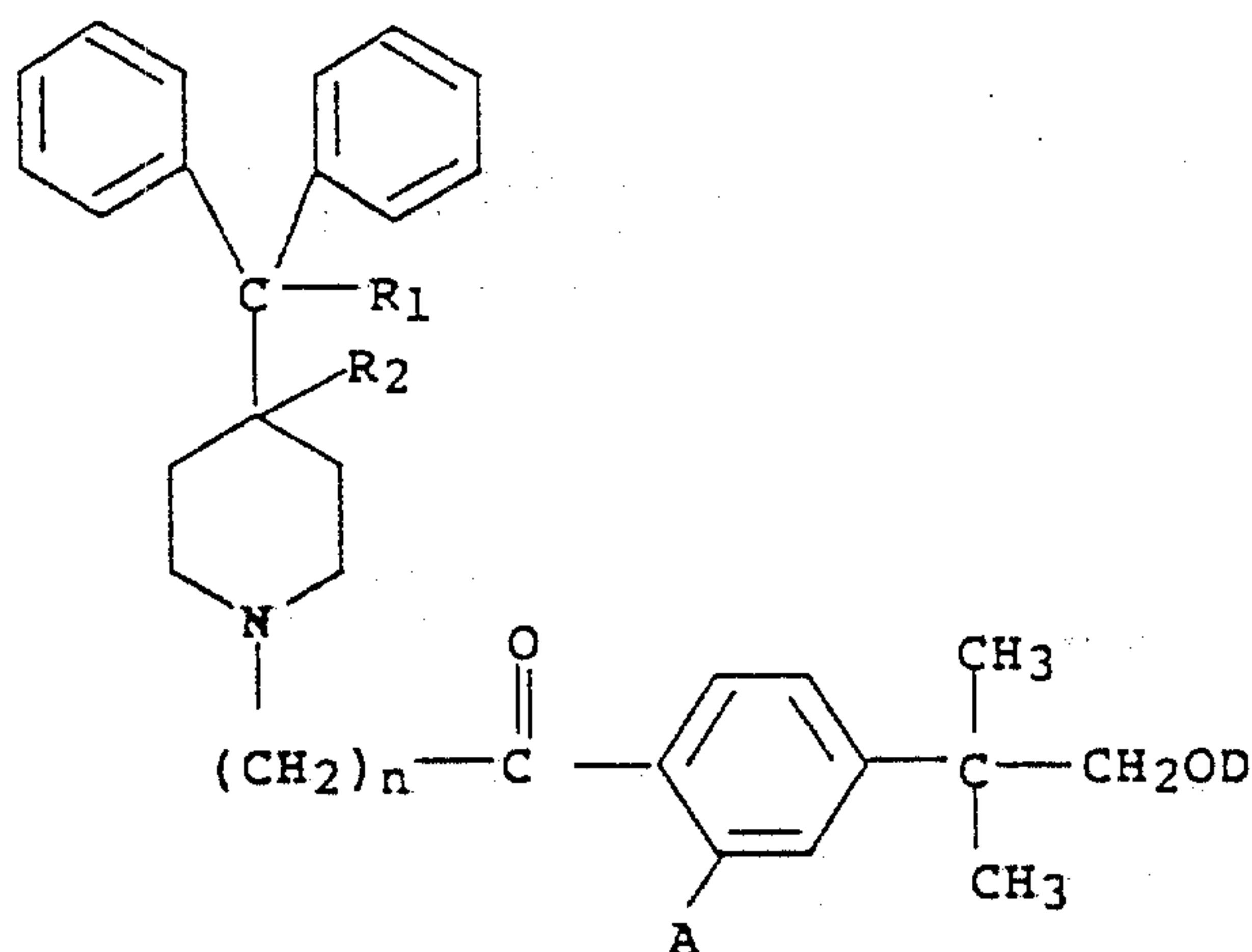
15

wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylketone of the formula

20

25

30



wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

35

(e) reacting the piperidine protected hydroxyethylphenylketone with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium

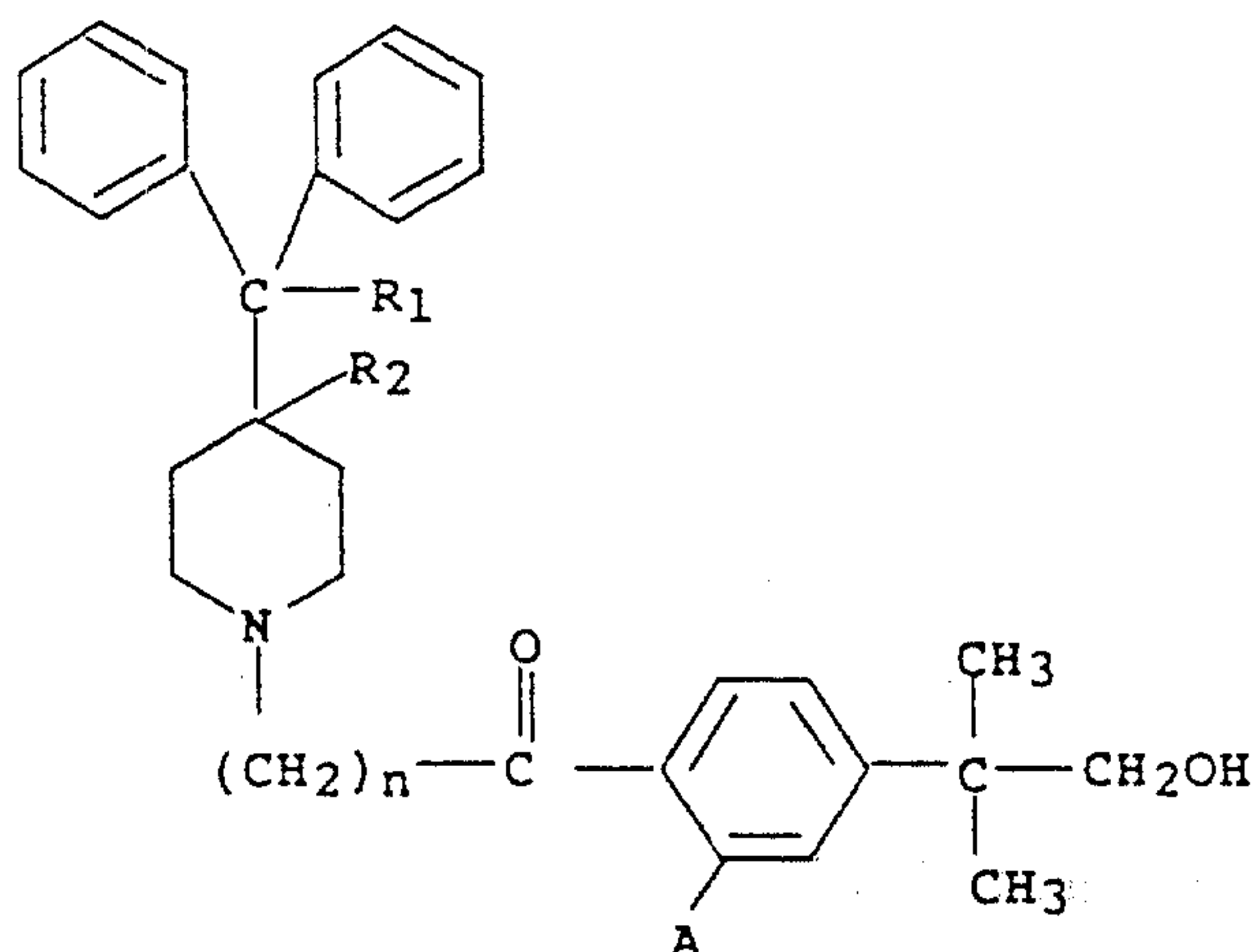
-68-

hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylketone of the formula

5

10

15



wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

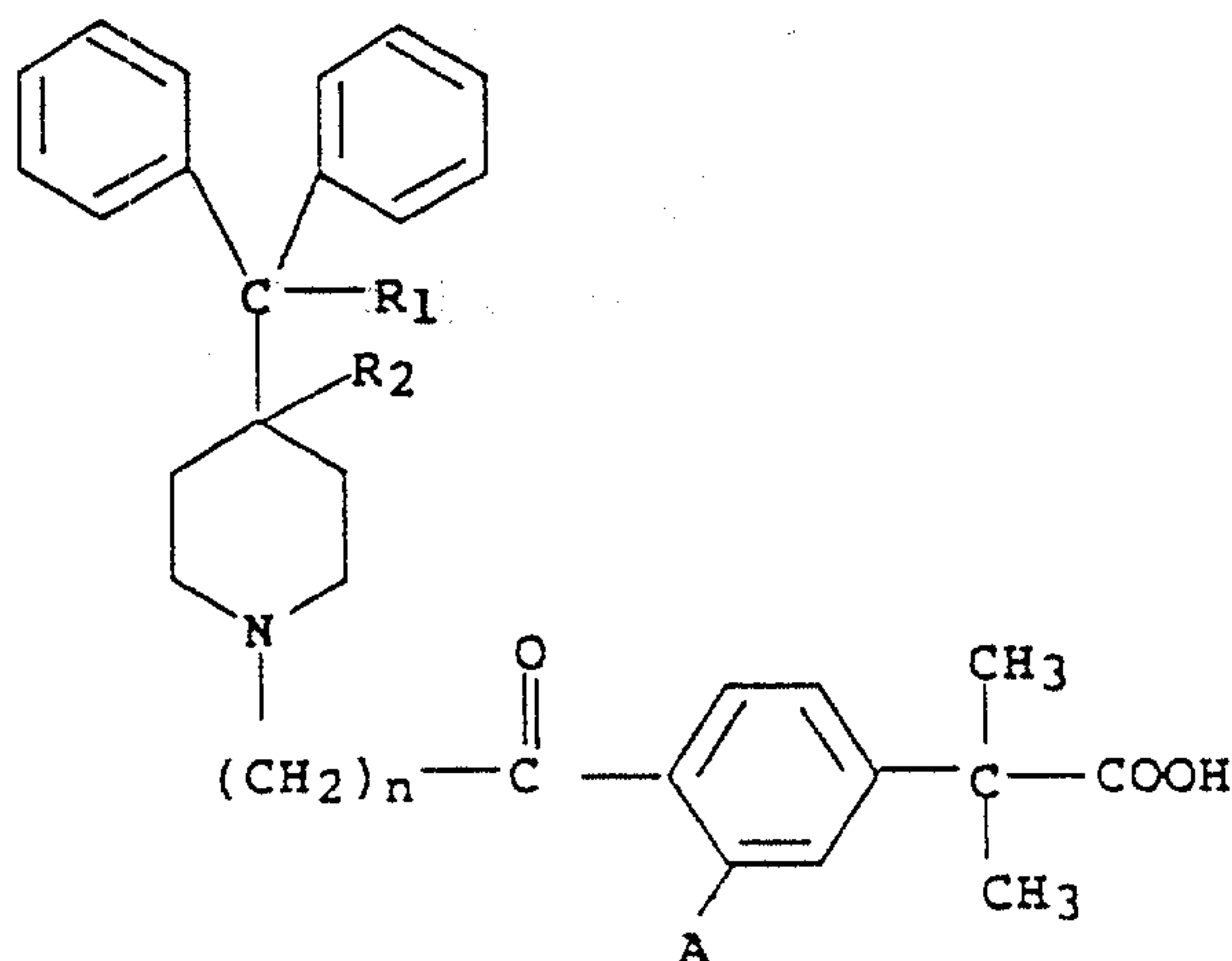
20

(f) reacting the piperidine hydroxyethylphenylketone with chromium (IV) oxide, potassium permanganate, nitric acid, nitrogen dioxide, ruthenium (VIII) oxide, nickel peroxide, silver oxide, t-butyl chromate or xenic acid to produce a piperidine carboxyphenylketone of the formula

25

30

35



-69-

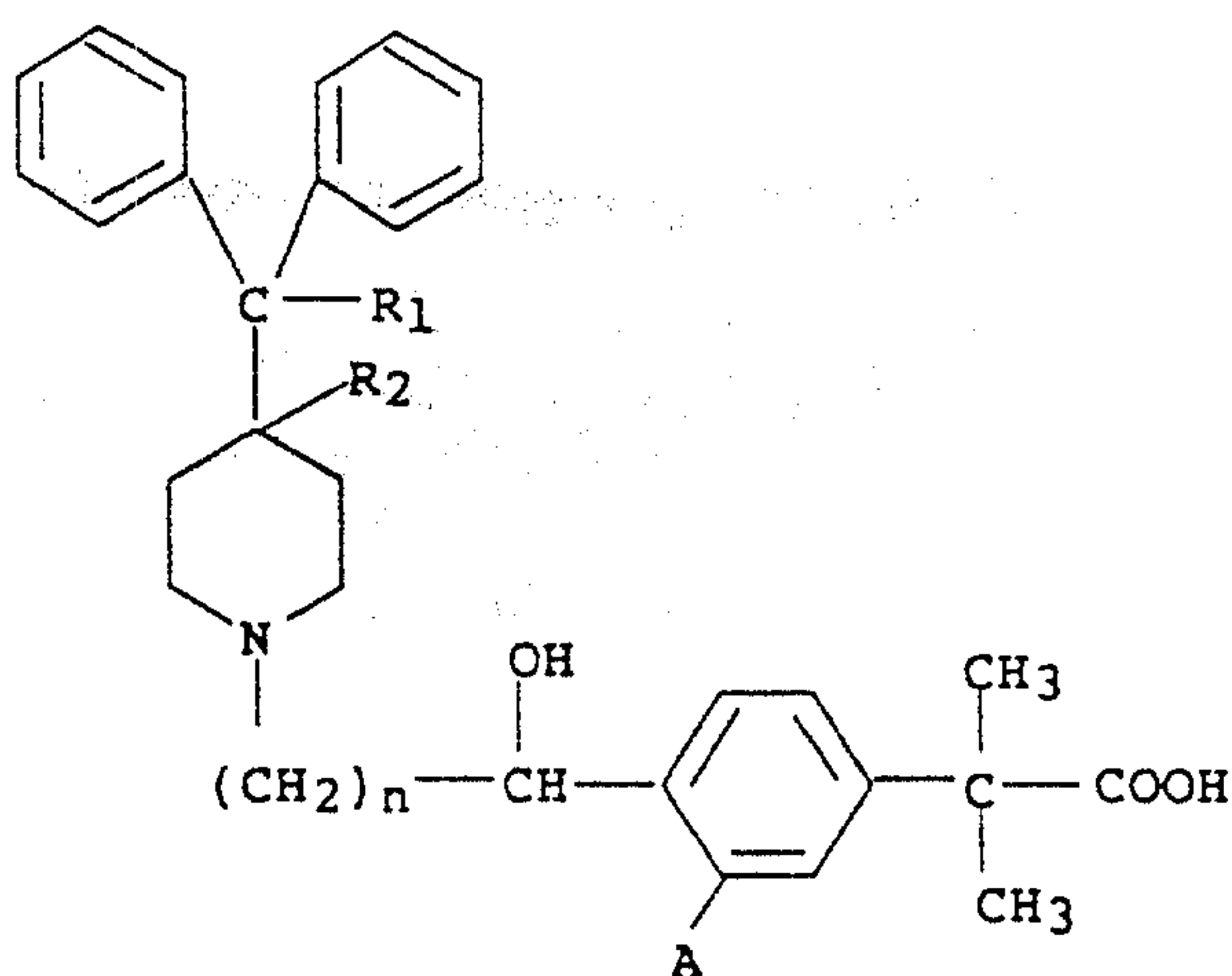
wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

5

(g) reacting the piperidine carboxyphenylketone with sodium borohydride, potassium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, lithium tri-tert-butylaluminumhydride, diisobutylaluminum hydride or
10 catalytic hydrogenation to produce a piperidine carboxyphenylalcohol of the formula

15

20

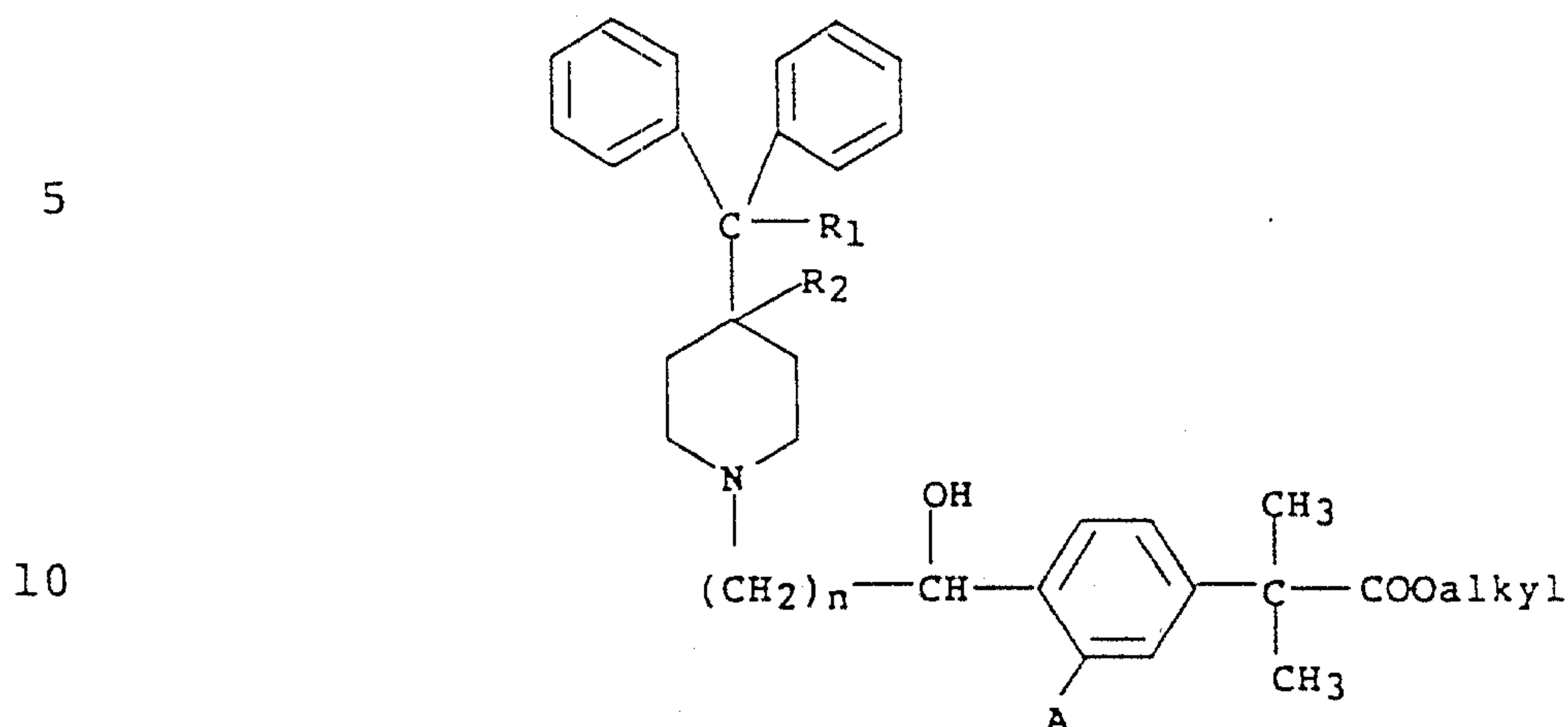


wherein R_1 , R_2 and n are defined above and A is hydrogen or
25 hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(h) optionally reacting the piperidine carboxyphenylalcohol with diazomethane or 2,2-
30 dimethoxypropane or with thionyl chloride followed by an alcohol of the formula $HOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched to form a piperidine carboxyphenylalcohol ester of the formula

35

-70-



wherein R₁, R₂, n and alkyl are defined above and A is
 15 hydrogen or hydroxy with the proviso that when A is
 hydroxy, A may be optionally protected or unprotected; and

(i) optionally reacting the piperidine
 carboxyphenylalcohols or the piperidine
 20 carboxyphenylalcohol esters in which A is a protected
 hydroxy with mineral acids, strong organic acids, Lewis
 acids, aqueous mineral bases or catalytic hydrogenation to
 produce the unprotected piperidine carboxyphenylalcohols or
 the piperidine carboxyphenylalcohol esters.

25

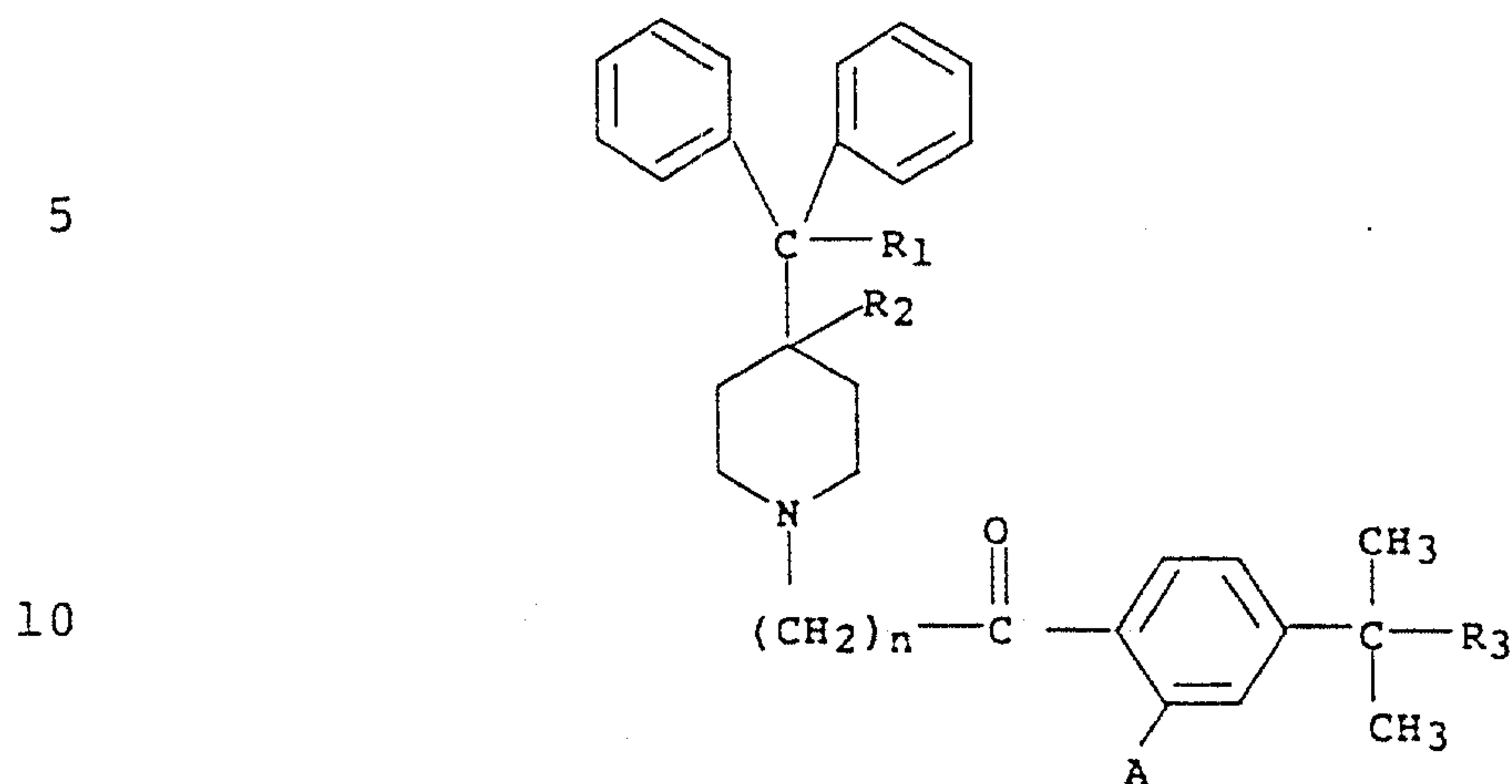
11. A process according to Claim 10 wherein the
 piperidine hydroxyethylphenylketone produced in step e is
 reacted with ruthenium(VIII) oxide to produce the
 piperidine carboxyphenylketone of step f.

30

12. A process for preparing a compound of the formula

35

-71-



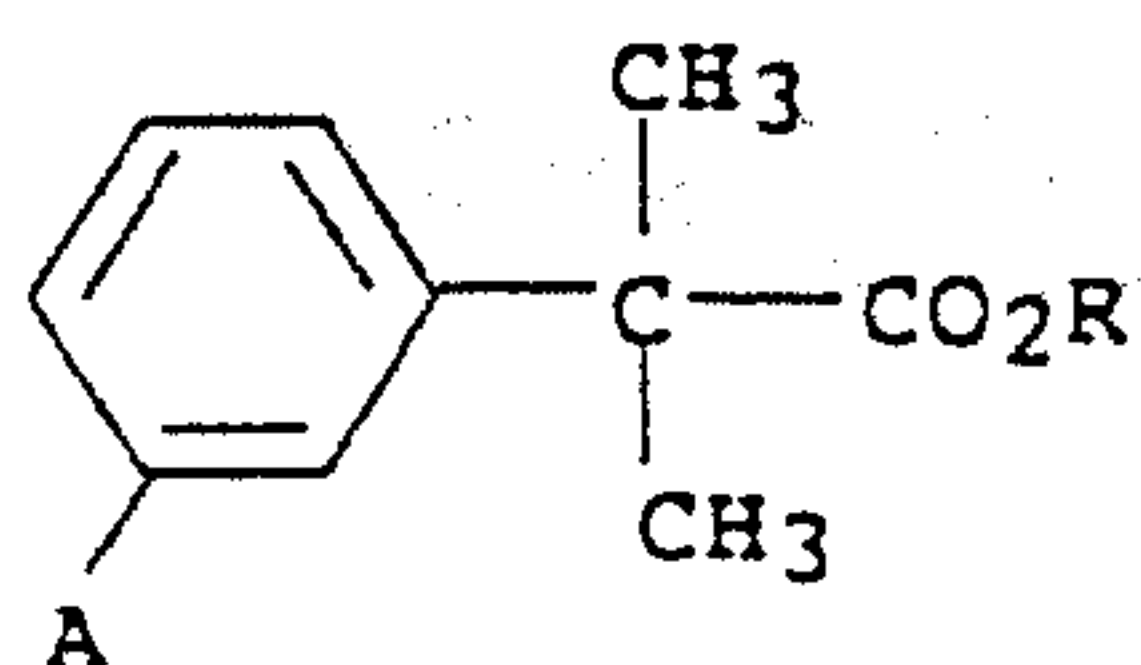
wherein

- 15 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the
carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;
20 R_3 is $-\text{COOH}$ or $-\text{COOalkyl}$ wherein the alkyl moiety has
from 1 to 6 carbon atoms and is straight or branched;
 A is hydrogen or hydroxy; and
pharmaceutically acceptable salts thereof comprising
the steps of:

25

- (a) reacting a benzeneacetic acid compound of the
formula

30



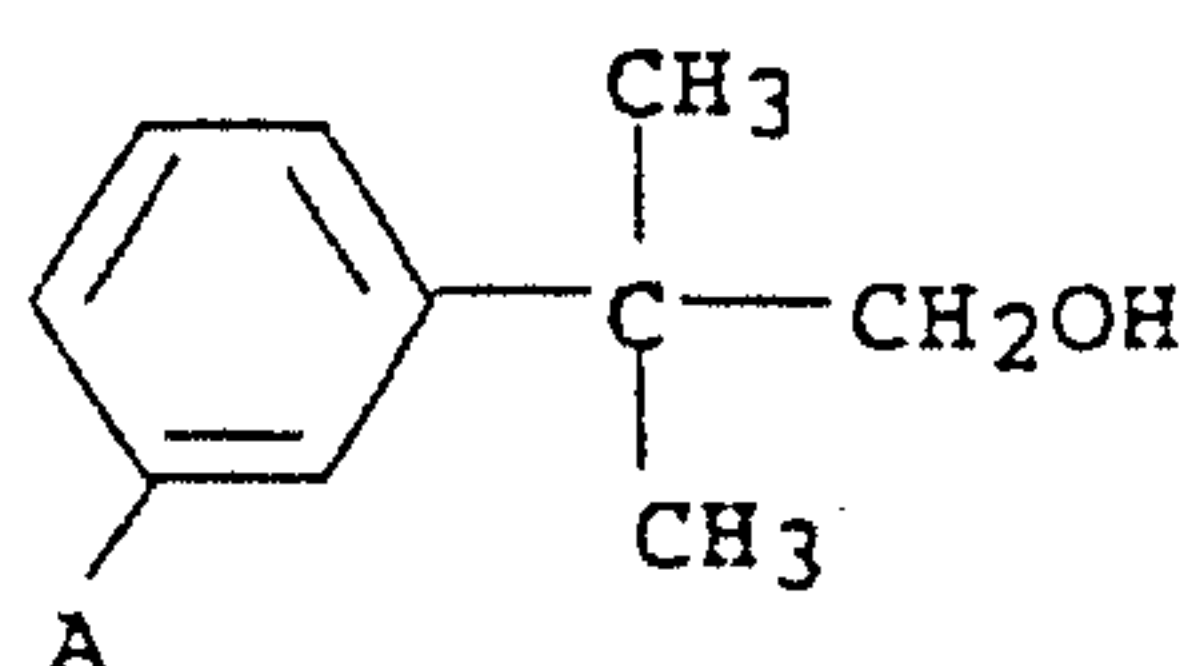
35

AMENDED SHEET

-72-

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

10

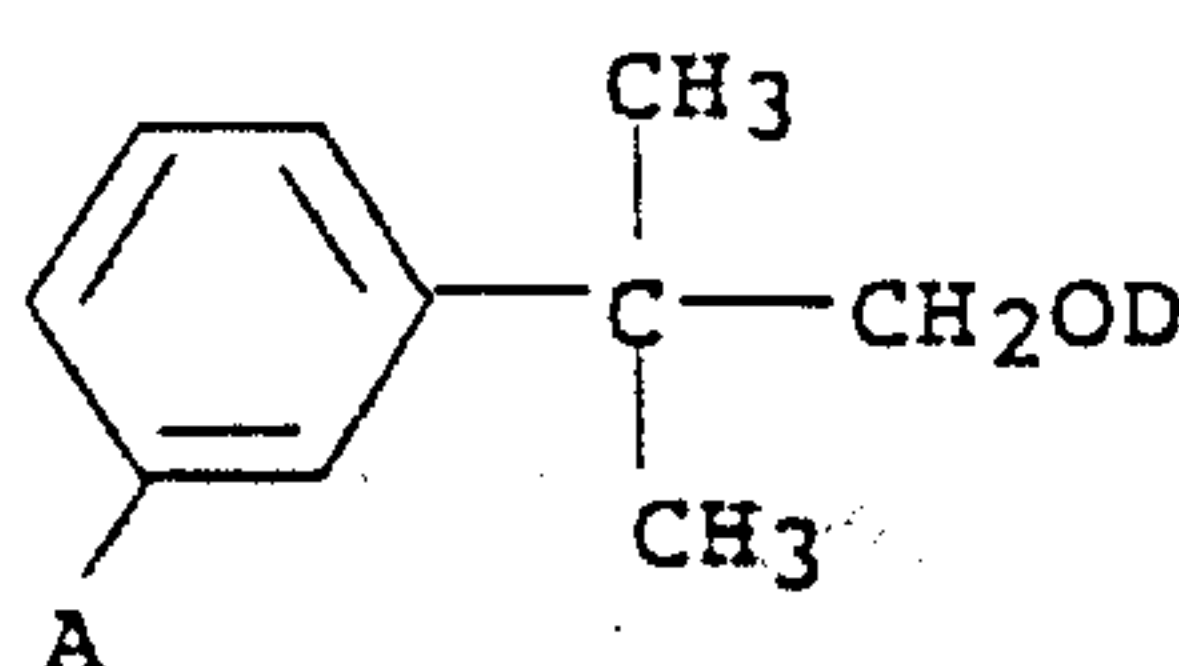


15

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

25



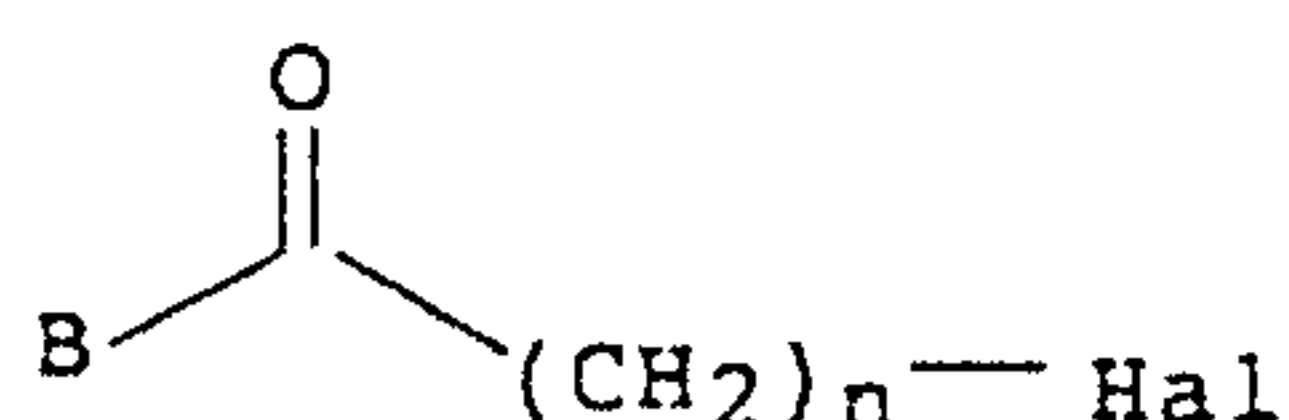
30

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is C(=O)CH₃ or C(=O)C₆H₅;

(c) reacting the protected phenethyl alcohol with a ω-halo compound of the formula

35

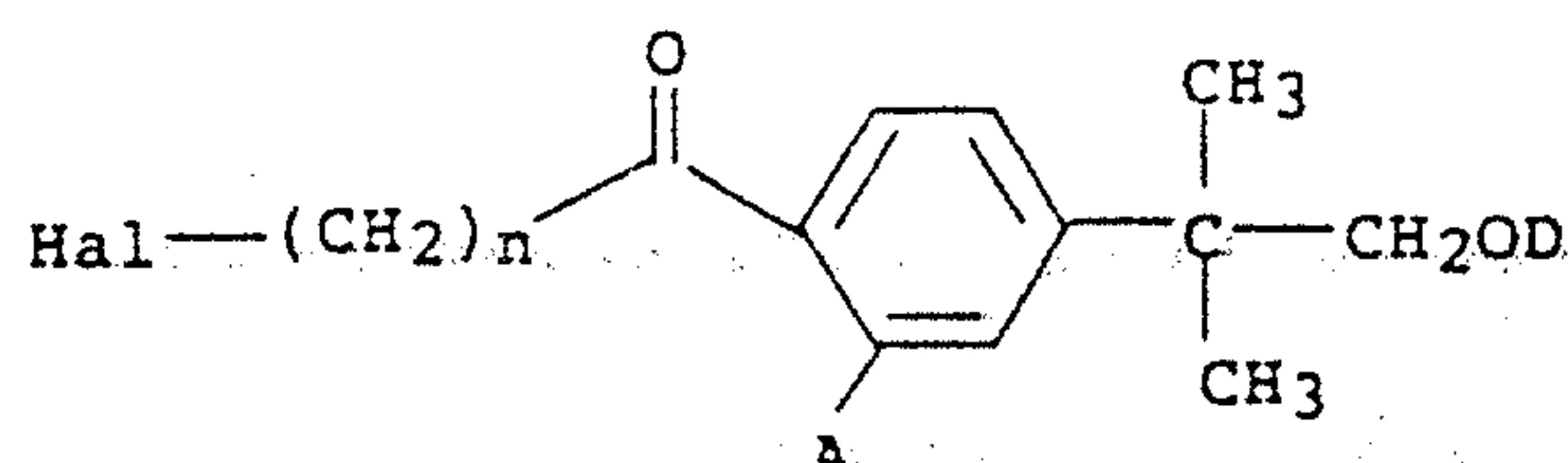
-73-



5

wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula

10



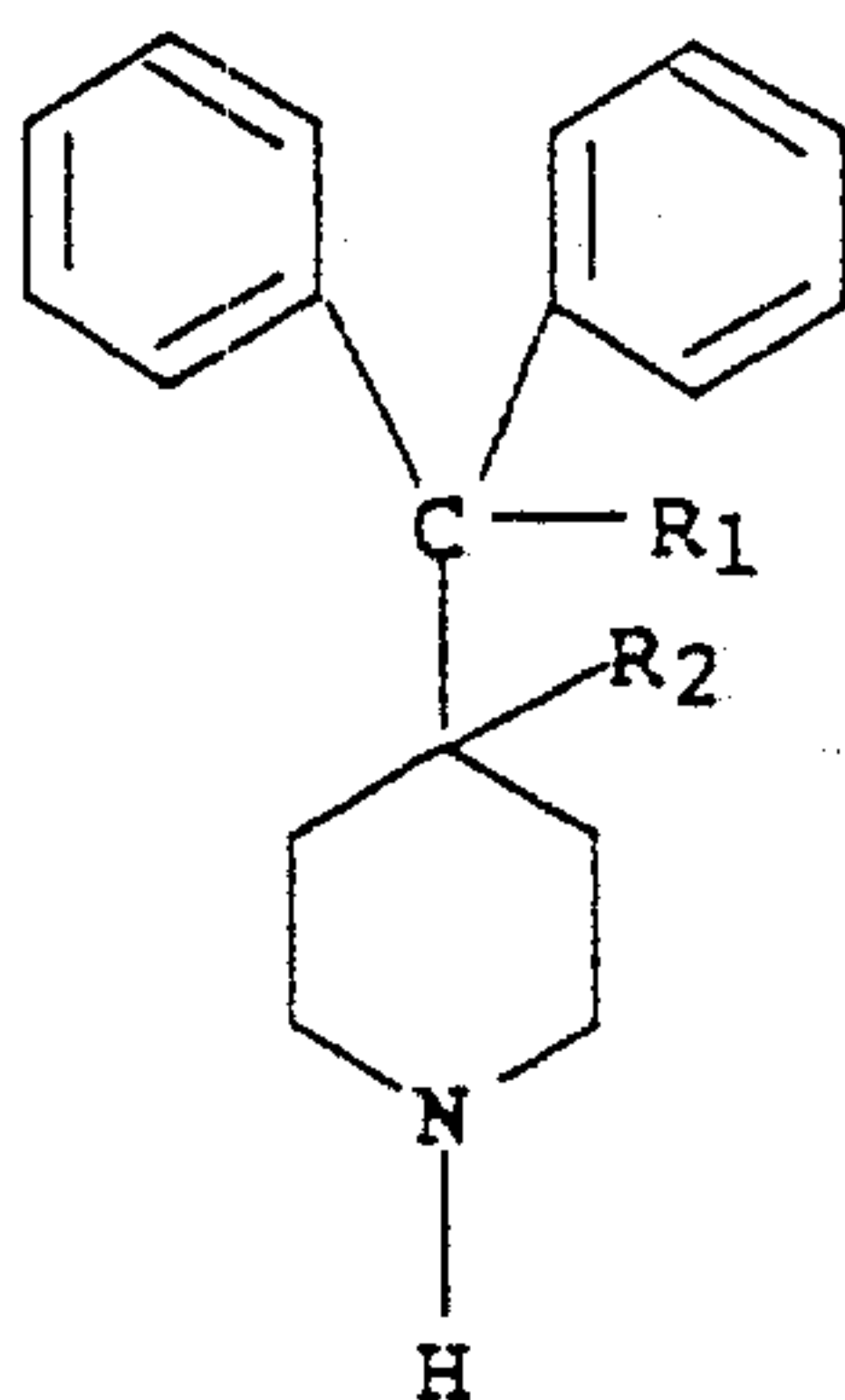
15

wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

20

(d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

25

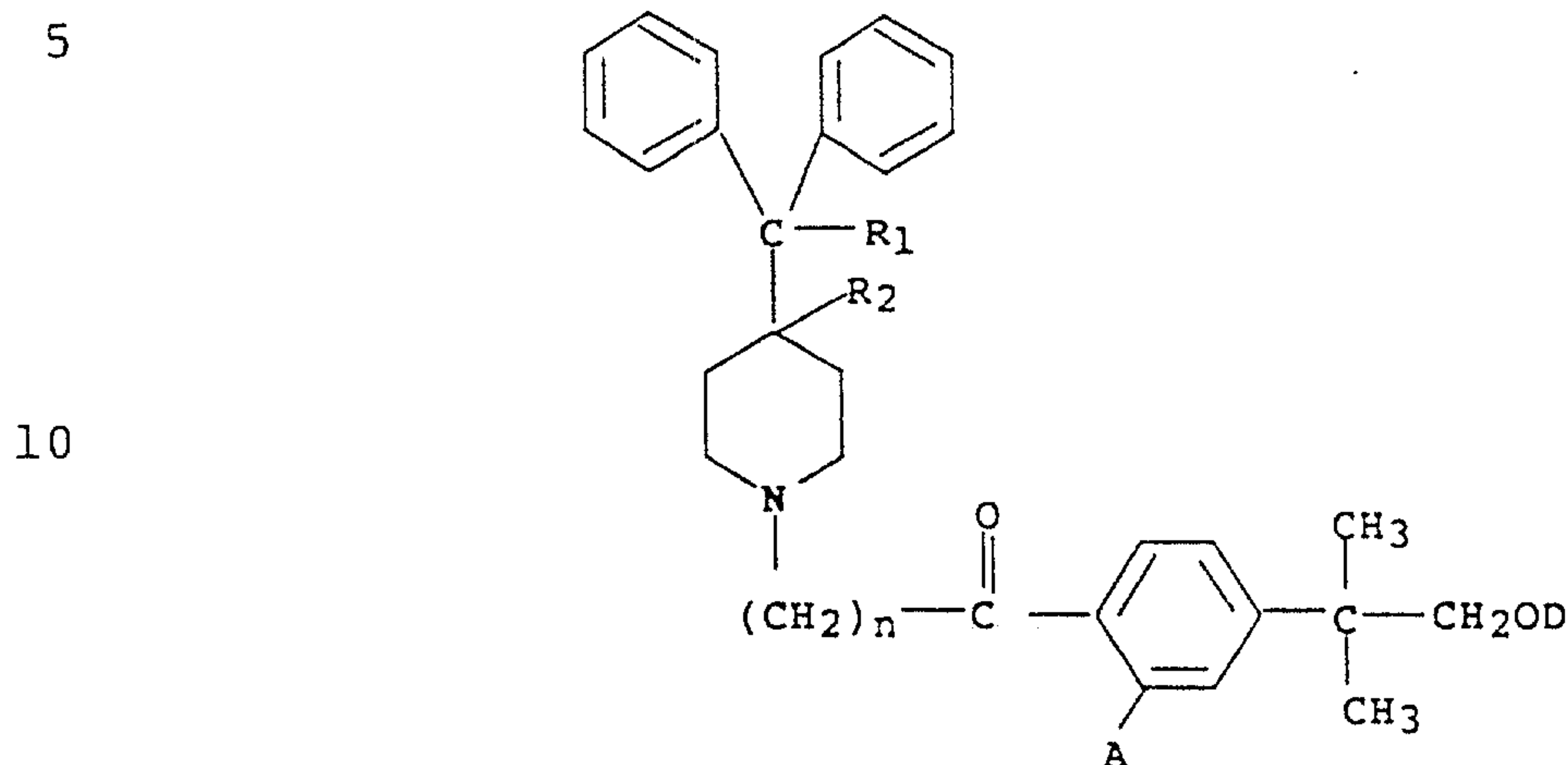


30

wherein R₁ and R₂ are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the

35

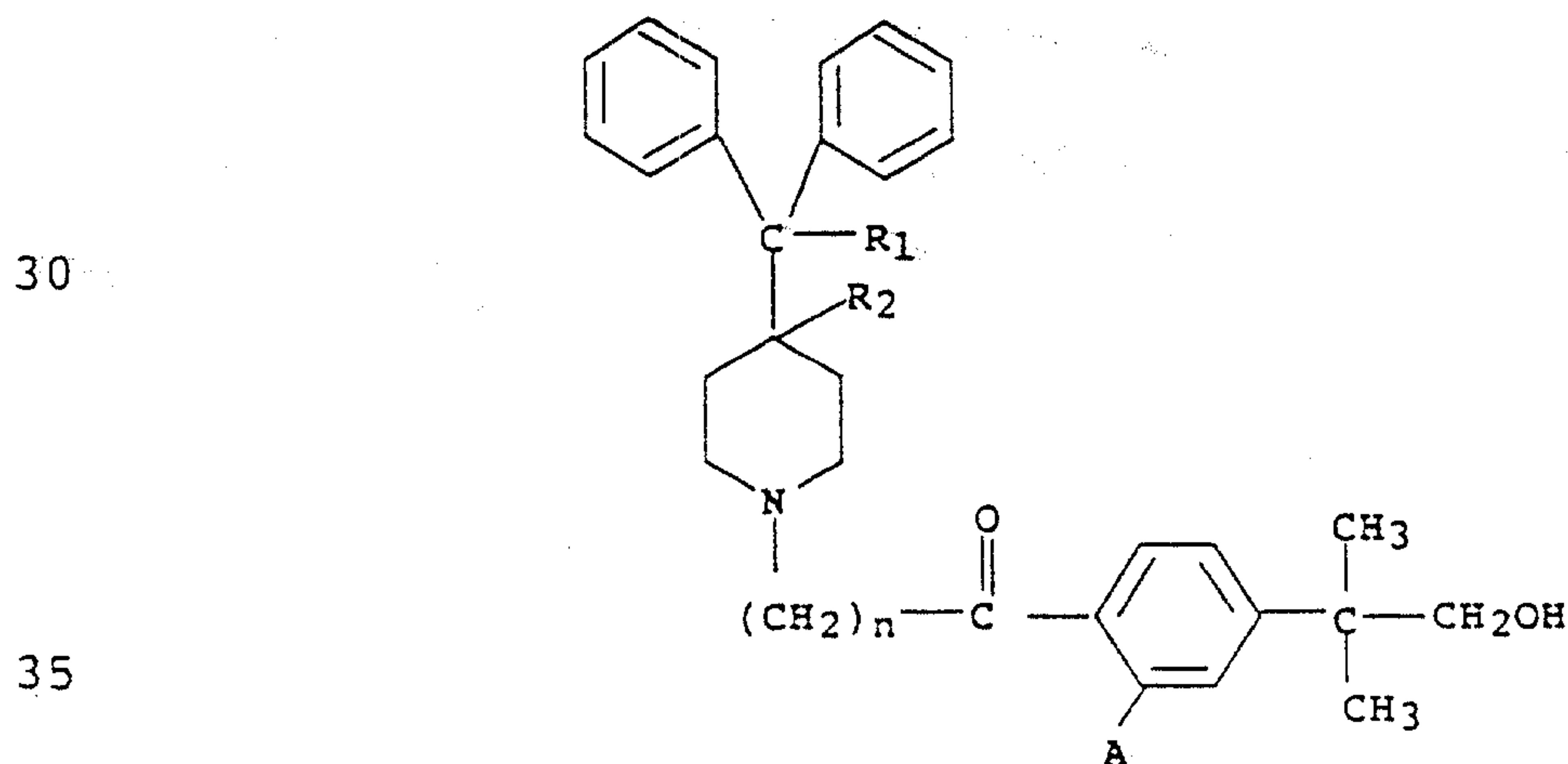
piperidine compound may be used to produce a piperidine protected hydroxyethylphenylketone of the formula



wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

20 (e) reacting the piperidine protected hydroxyethylphenylketone with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylketone of

25 the formula

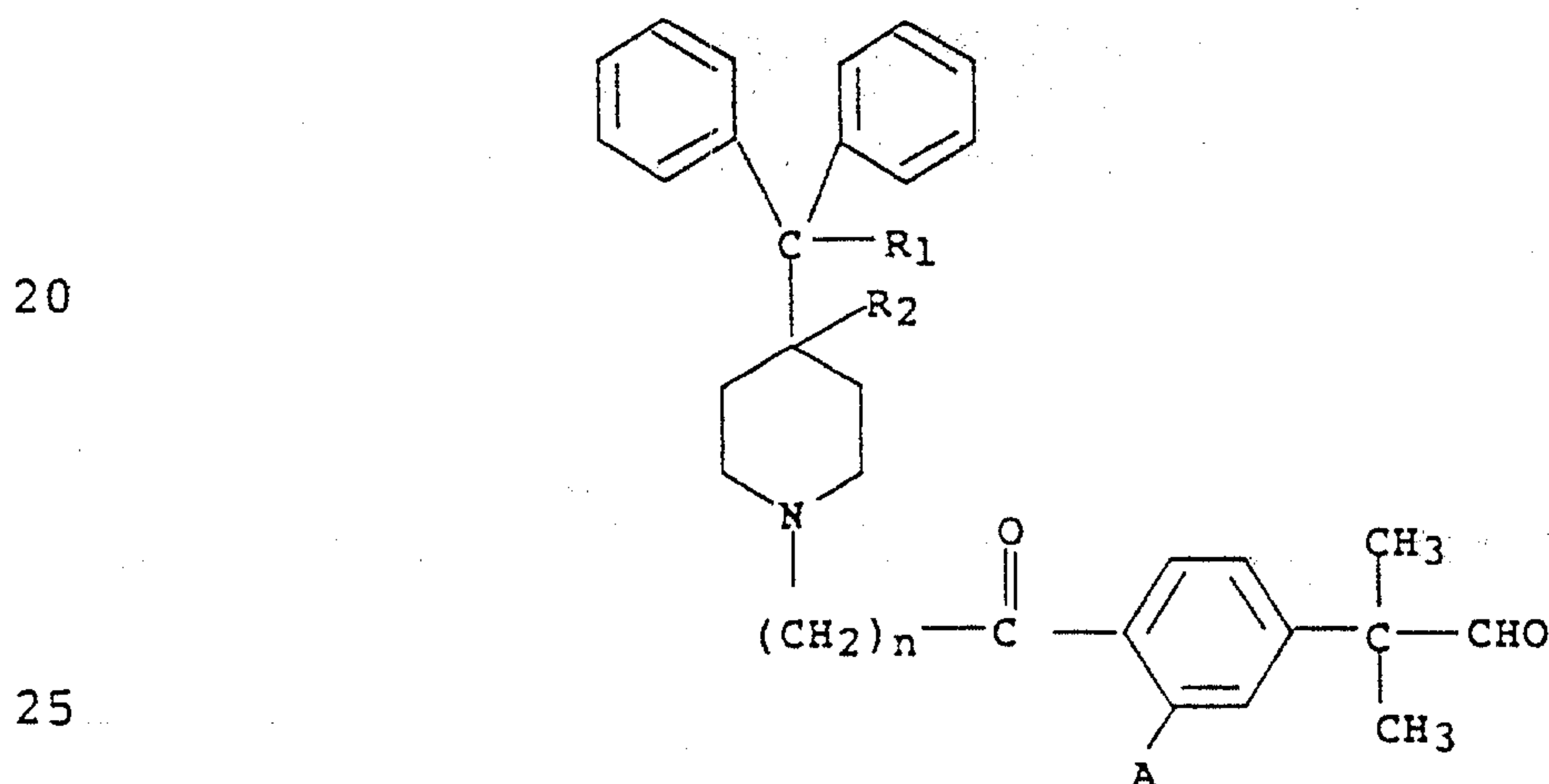


-75-

wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

5

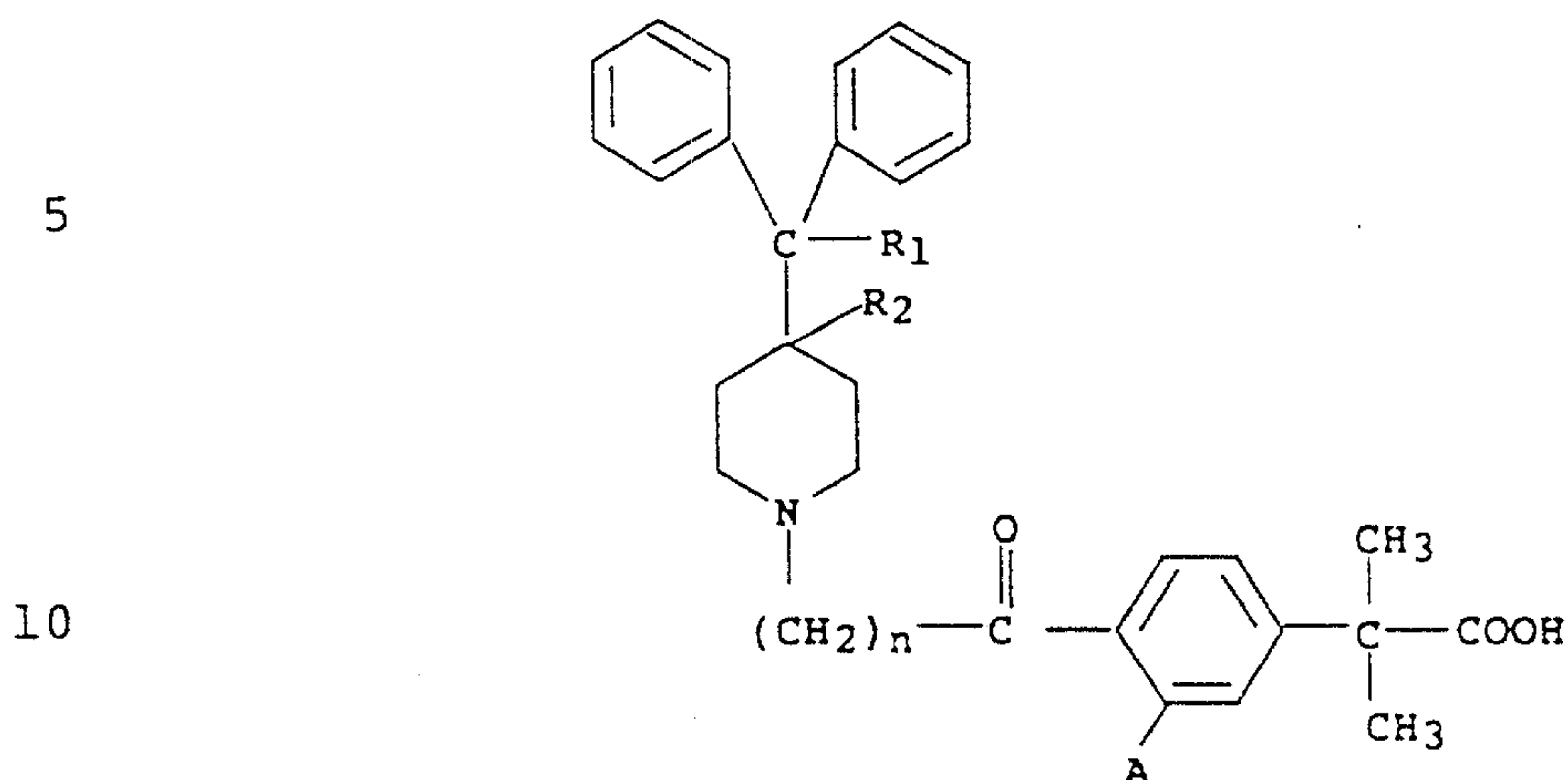
(f) reacting the piperidine hydroxyethylphenylketone with dimethyl sulfoxide, oxalyl chloride and triethylamine or with Dess-Martin reagent, chromium (IV) oxide, nickel peroxide, sodium dichromate, potassium dichromate, t-butyl chromate, silver oxide, argentic picolinate manganese dioxide lead tetraacetate, dicyclohexylcarbodiimide, 2,3-dichloro-5,6-dicyanoquinone, tetrachloro-1,2-benzoquinone, 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) or quinolinium chlorochromate to produce a piperidine formylphenylketone
15 of the formula



wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be
30 optionally protected or unprotected;

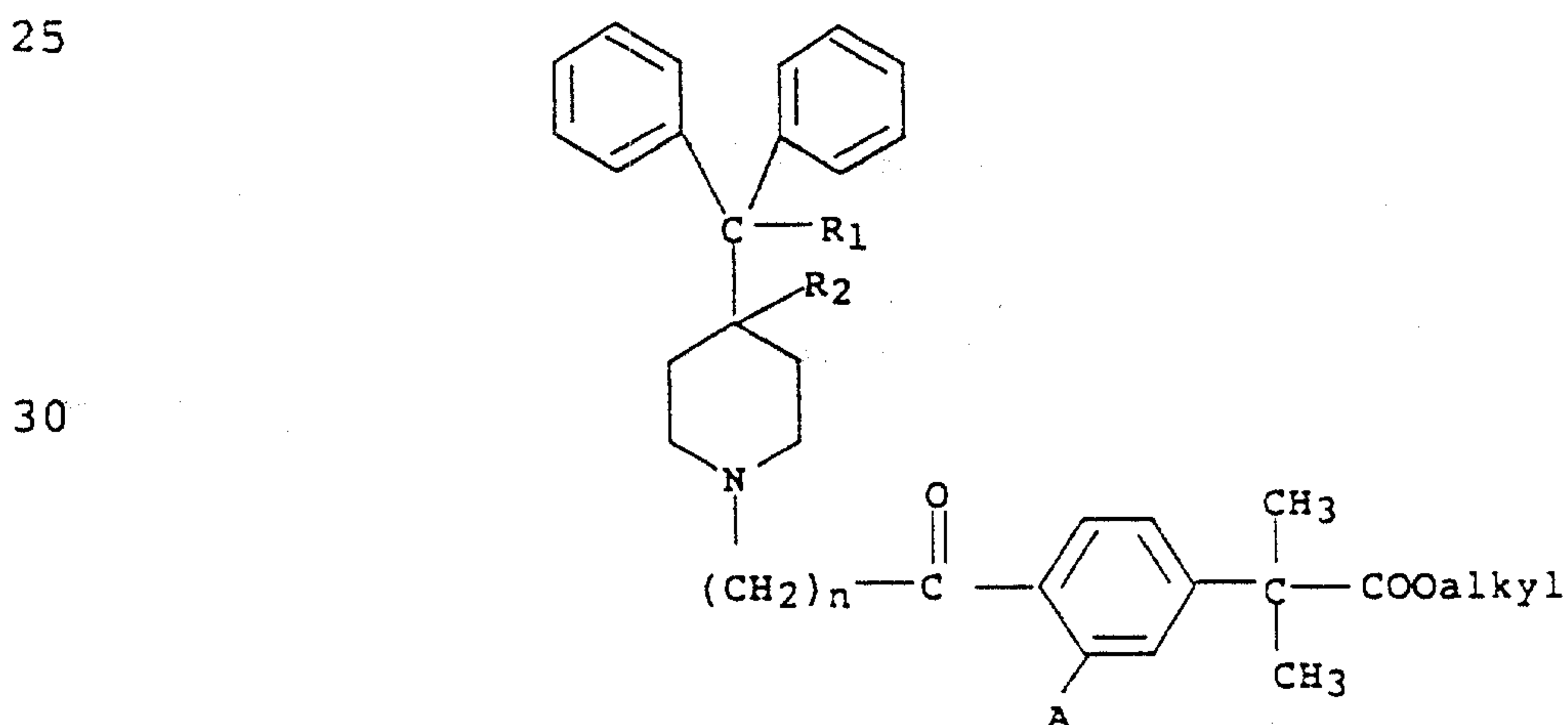
(g) reacting the piperidine formylphenylketone with potassium permanganate, chromium (IV) oxide, silver (I) oxide, silver oxide, argentic picolinate, peroxide, nitric
35 acid, m-chloroperbenzoic acid and peracetic acid to produce a piperidine carboxyphenylketone of the formula

-76-



wherein R_1 , R_2 and n are defined above and A is hydrogen or
 15 hydroxy with the proviso that when A is hydroxy, A may be
 optionally protected or unprotected;

(h) optionally reacting the piperidine
 carboxyphenylketone with diazomethane or 2,2-
 20 dimethoxypropane or with thionyl chloride followed by an
 alcohol of the formula $HOalkyl$ wherein the alkyl moiety has
 from 1 to 6 carbon atoms and is straight or branched to
 form a piperidine carboxyphenylketone ester of the formula



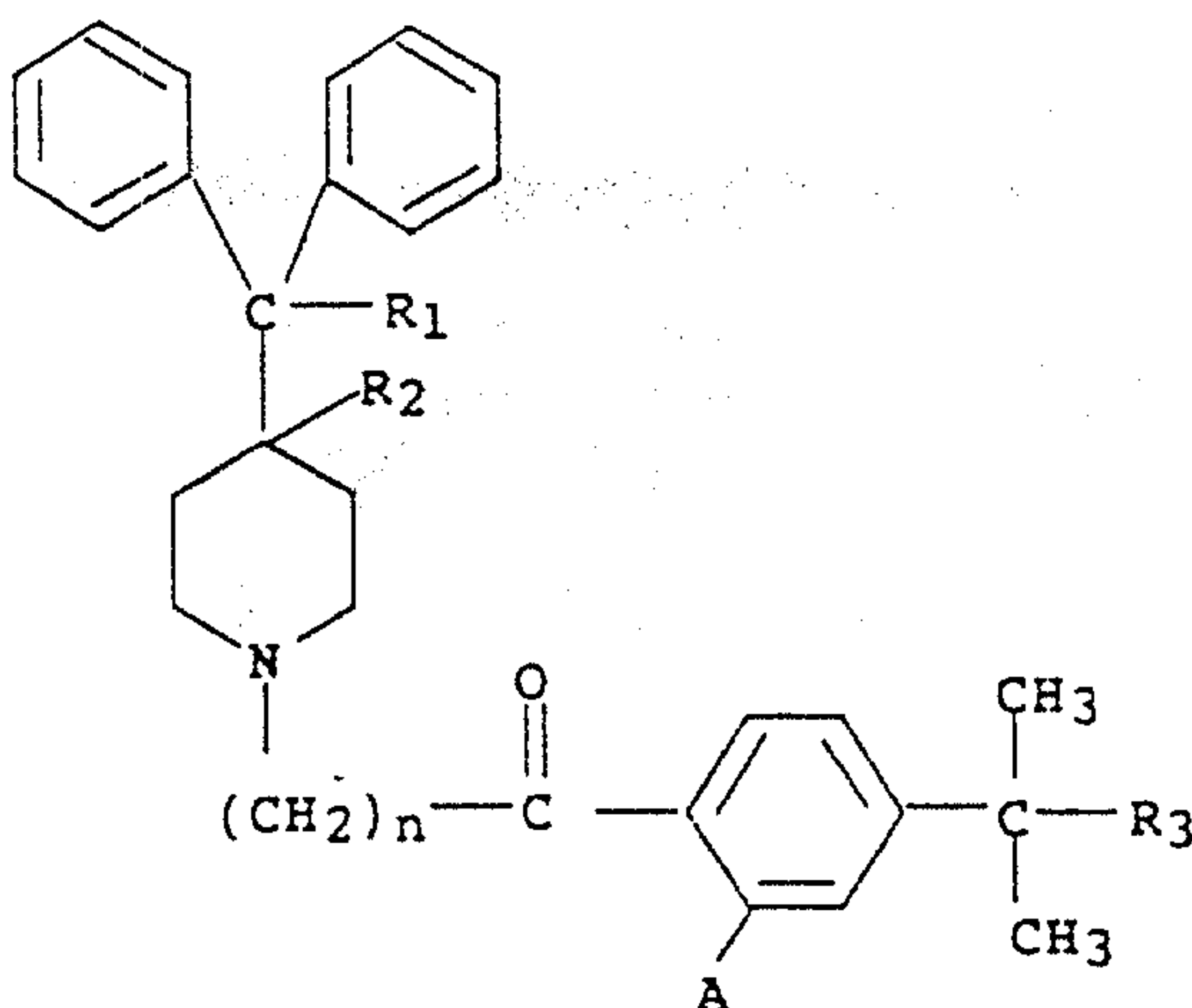
35 wherein R_1 , R_2 , n and $alkyl$ are defined above and A is
 hydrogen or hydroxy with the proviso that when A is
 hydroxy, A may be optionally protected or unprotected; and

AMENDED SHEET

-77-

(i) optionally reacting the piperidine
 carboxyphenylketones or piperidine carboxyphenylketones
 5 ester which bear hydroxy protecting groups with mineral
 acids, strong organic acids, Lewis acids, aqueous mineral
 bases or catalytic hydrogenation to produce the unprotected
 piperidine carboxyphenylketones or piperidine
 carboxyphenylketone esters.

10 13. A process for preparing a compound of the formula



wherein

25 R_1 represents hydrogen or hydroxy;

R_2 represents hydrogen; or

R_1 and R_2 taken together form a second bond between the
 carbon atoms bearing R_1 and R_2 ;

n is an integer of from 1 to 5;

30 R_3 is $-COOH$ or $-COOalkyl$ wherein the alkyl moiety has
 from 1 to 6 carbon atoms and is straight or branched;

A is hydrogen or hydroxy; and

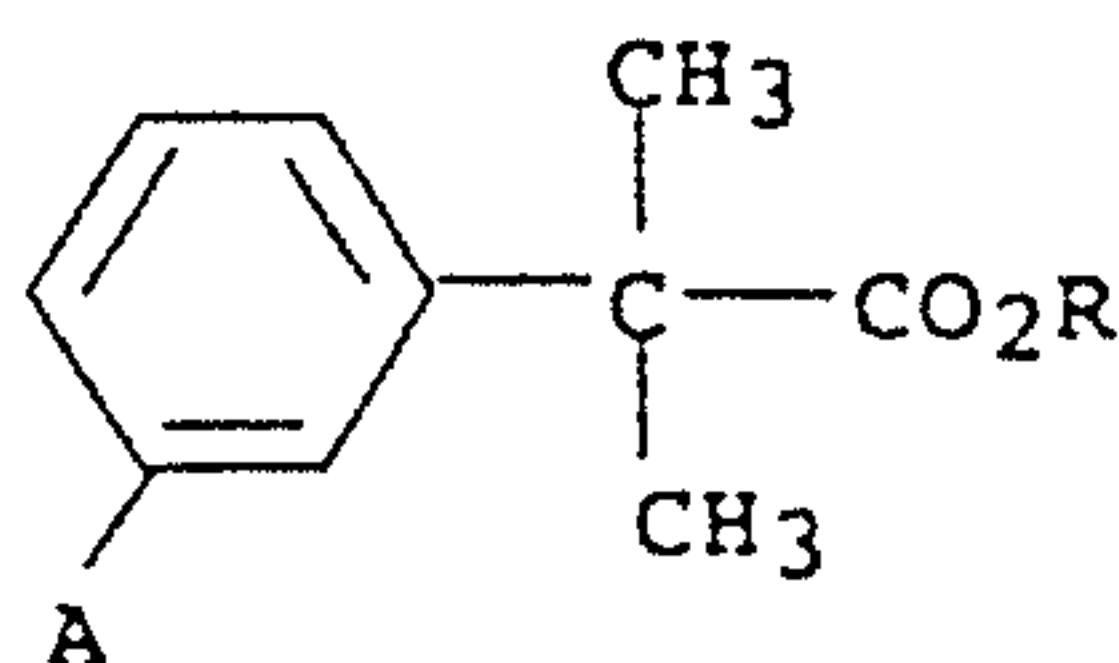
pharmaceutically acceptable salts thereof comprising
 the steps of:

35 (a) reacting a benzeneacetic acid compound of the
 formula

AMENDED SHEET

-78-

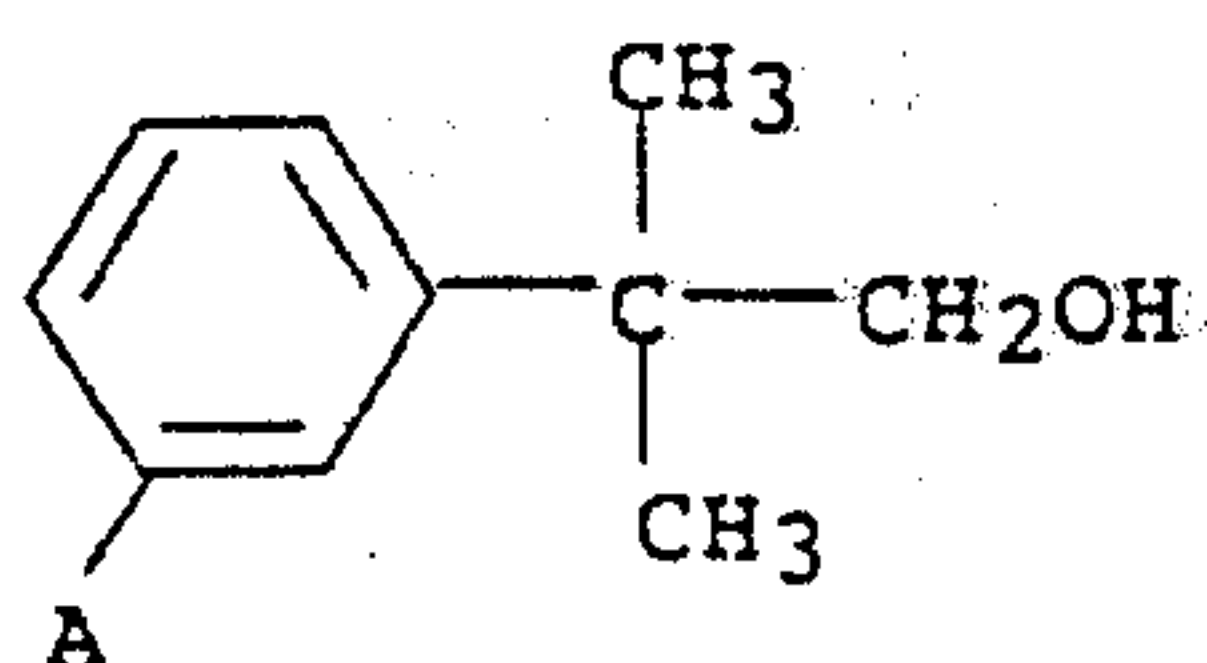
5



10

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

15



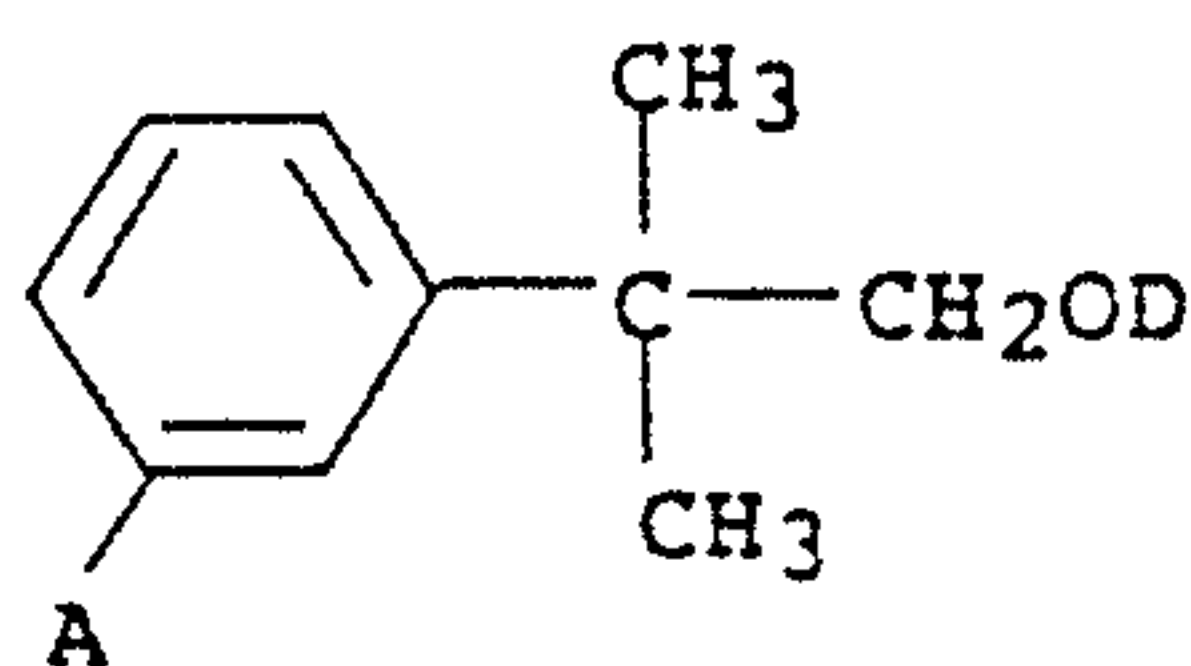
20

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

25

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

30

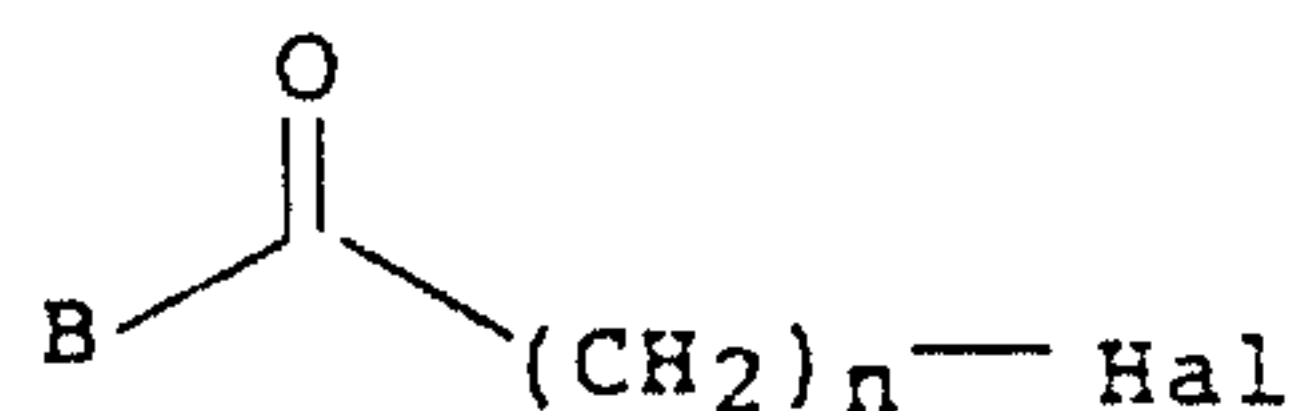


35

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is C(=O)CH₃ or C(=O)C₆H₅;

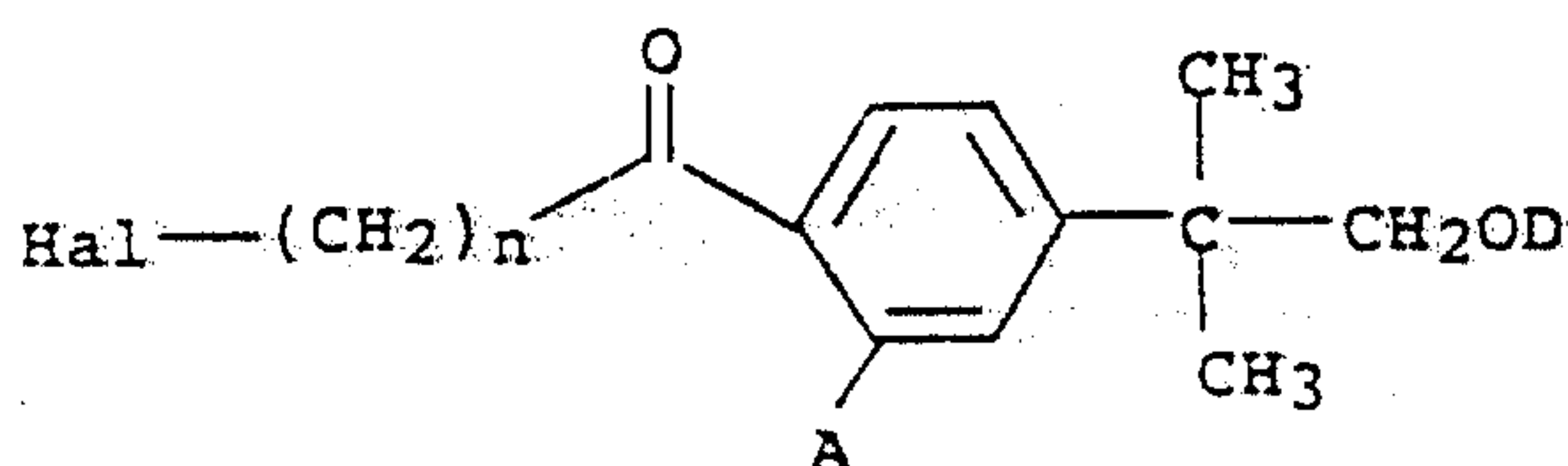
(c) reacting the protected phenethyl alcohol with a ω -halo compound of the formula

5



10 wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula

15

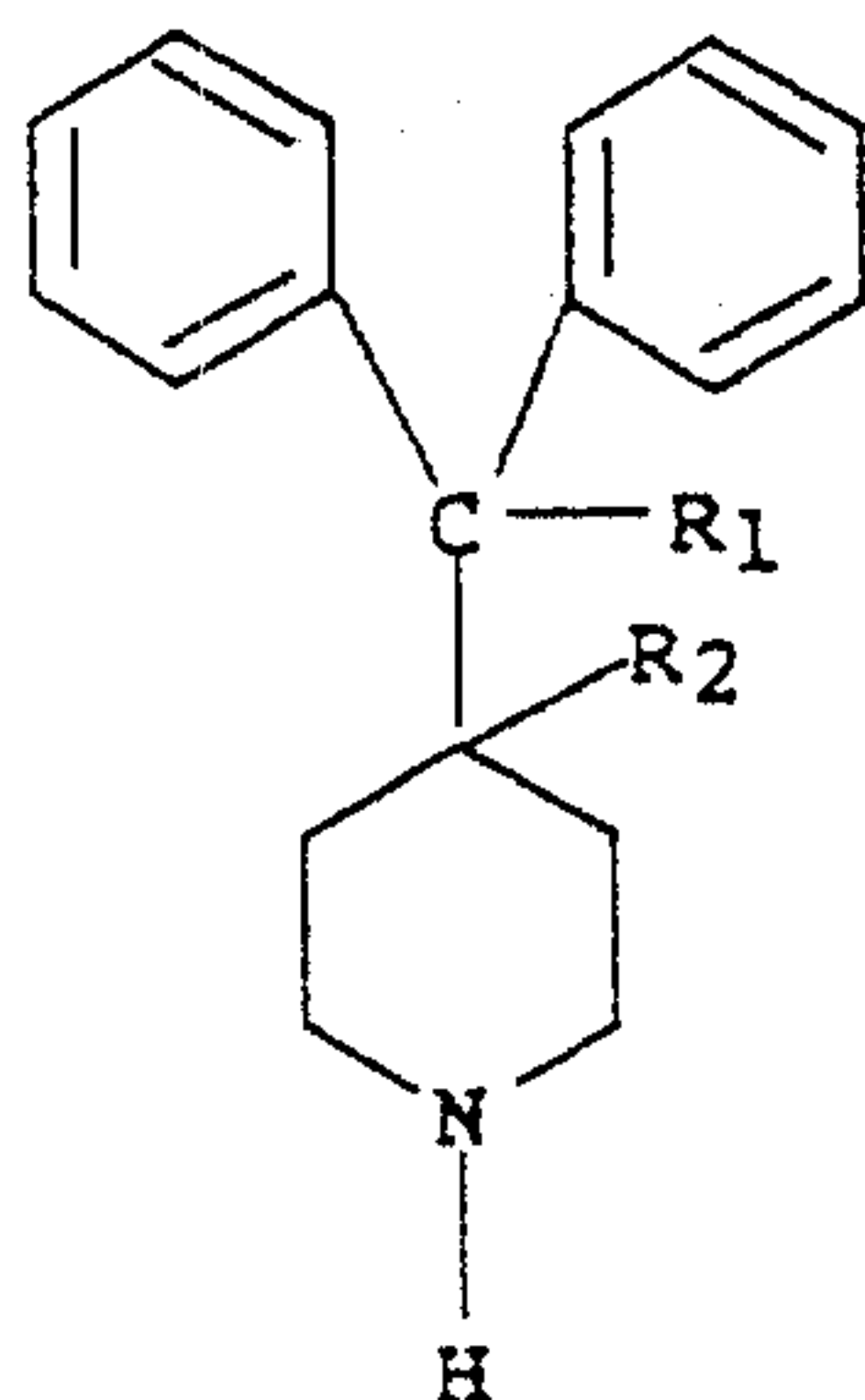


20

wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

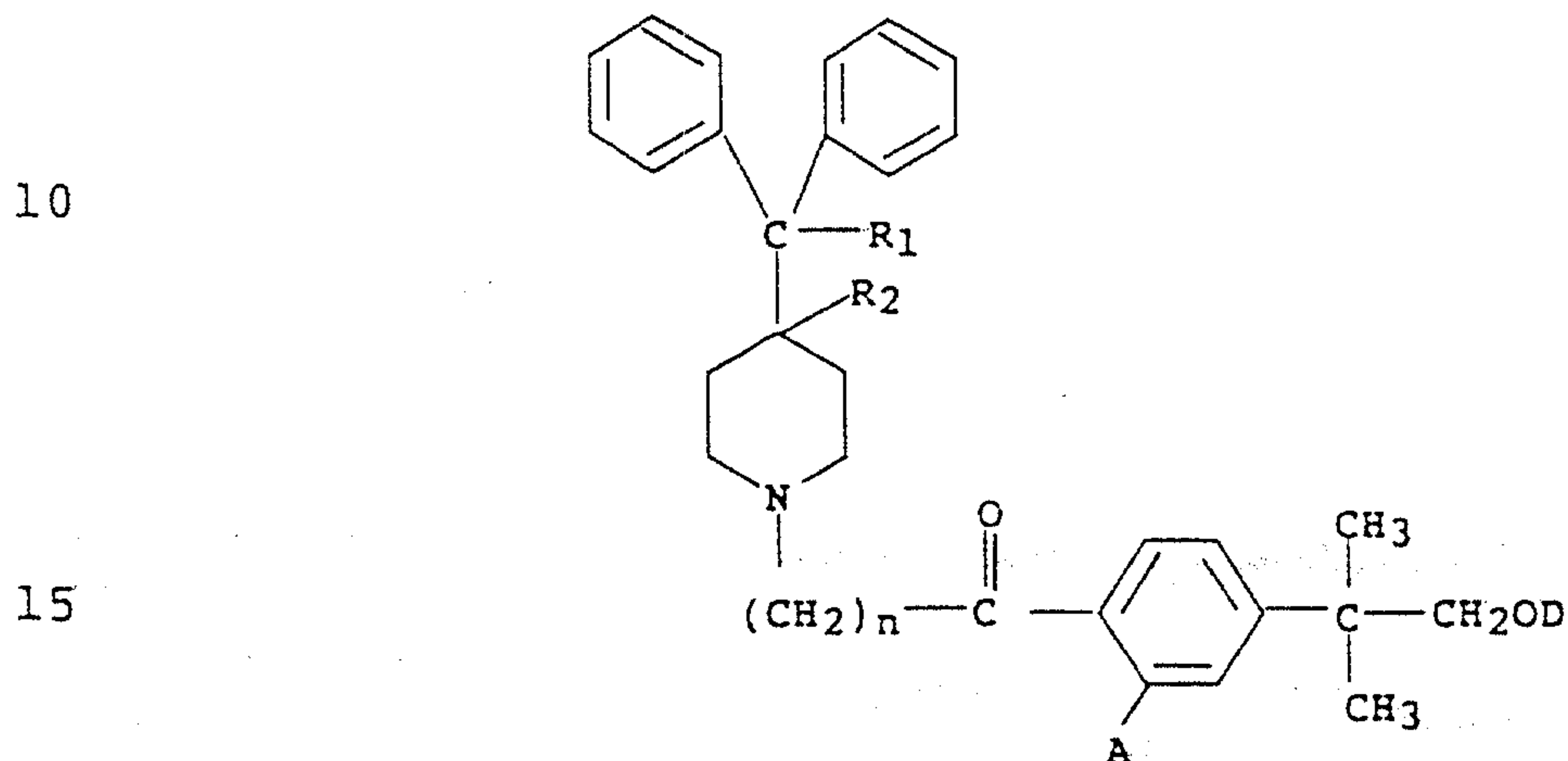
25 (d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

30



35

wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the
 5 piperidine compound may be used to produce a piperidine protected hydroxyethylphenylketone of the formula



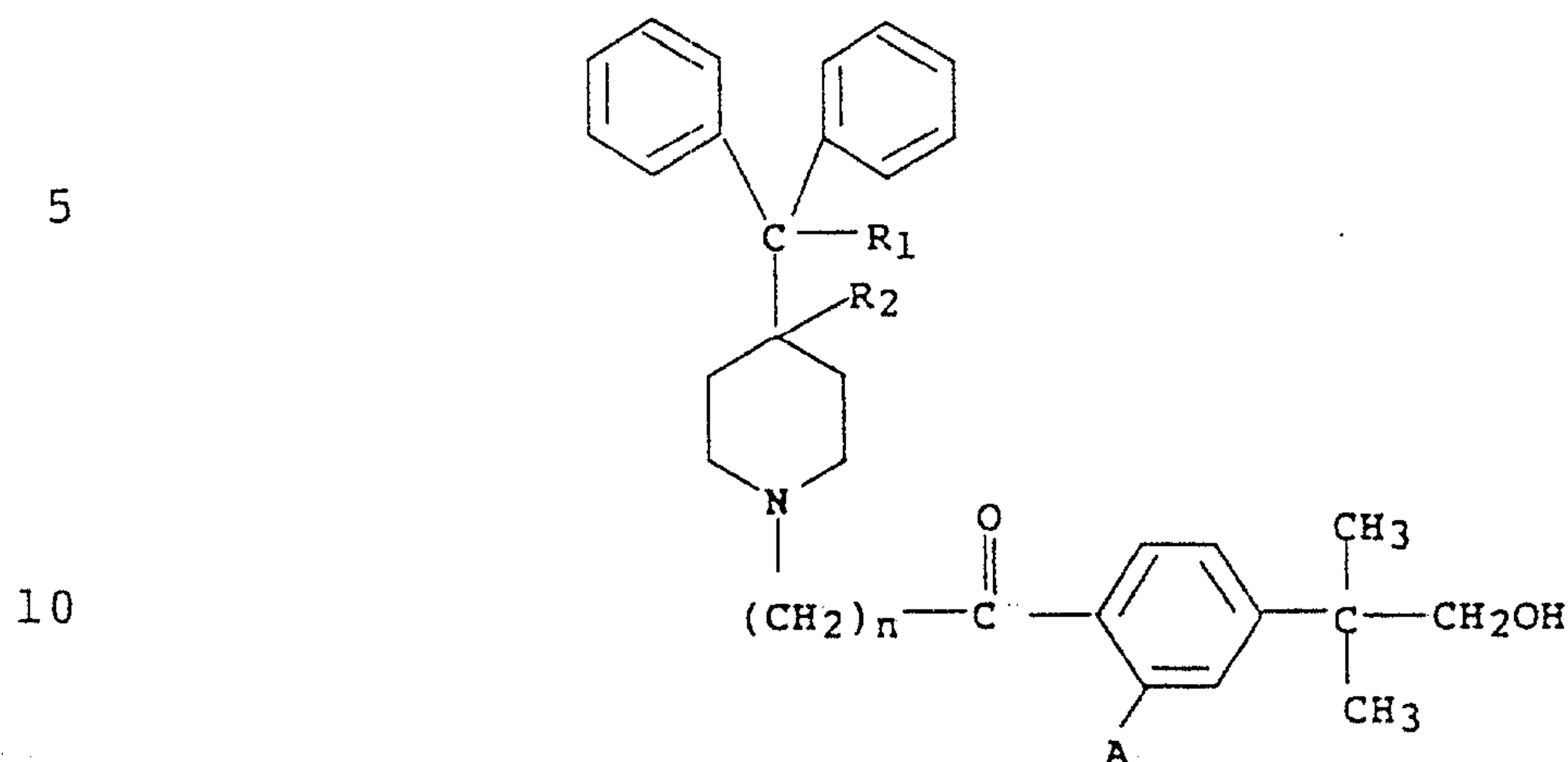
wherein R_1 , R_2 , n and D are defined above and A is hydrogen
 20 or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(e) reacting the piperidine protected
 hydroxyethylphenylketone with sodium methoxide in methanol,
 25 potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylketone of the formula

30

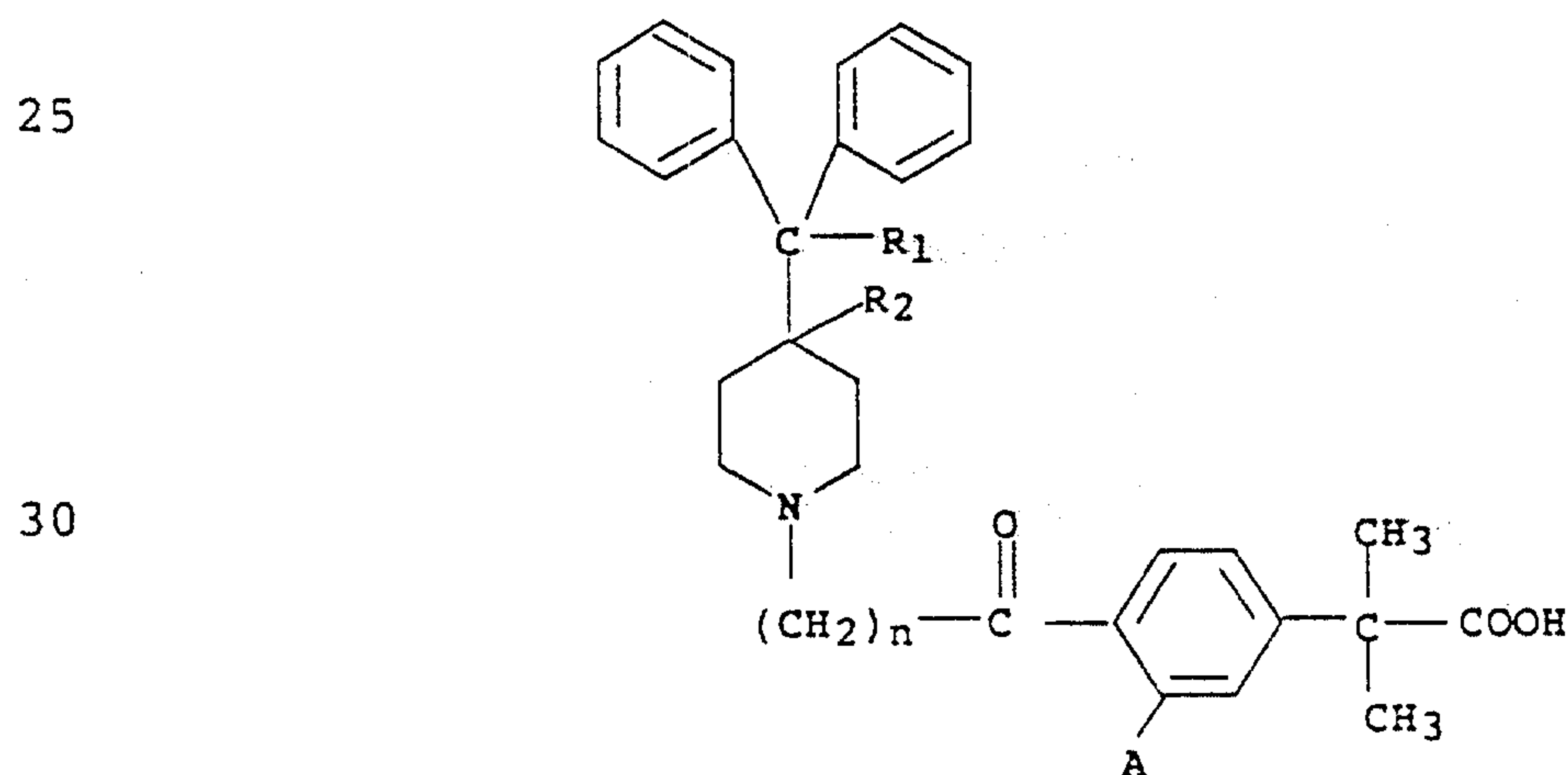
35

-81-



15 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(f) reacting the piperidine hydroxyethylphenylketone with chromium (IV) oxide, potassium permanganate, nitric
20 acid, nitrogen dioxide, ruthenium (VIII) oxide, nickel peroxide, silver oxide, t-butyl chromate or xenic acid to produce the piperidine carboxyphenylketone of formula

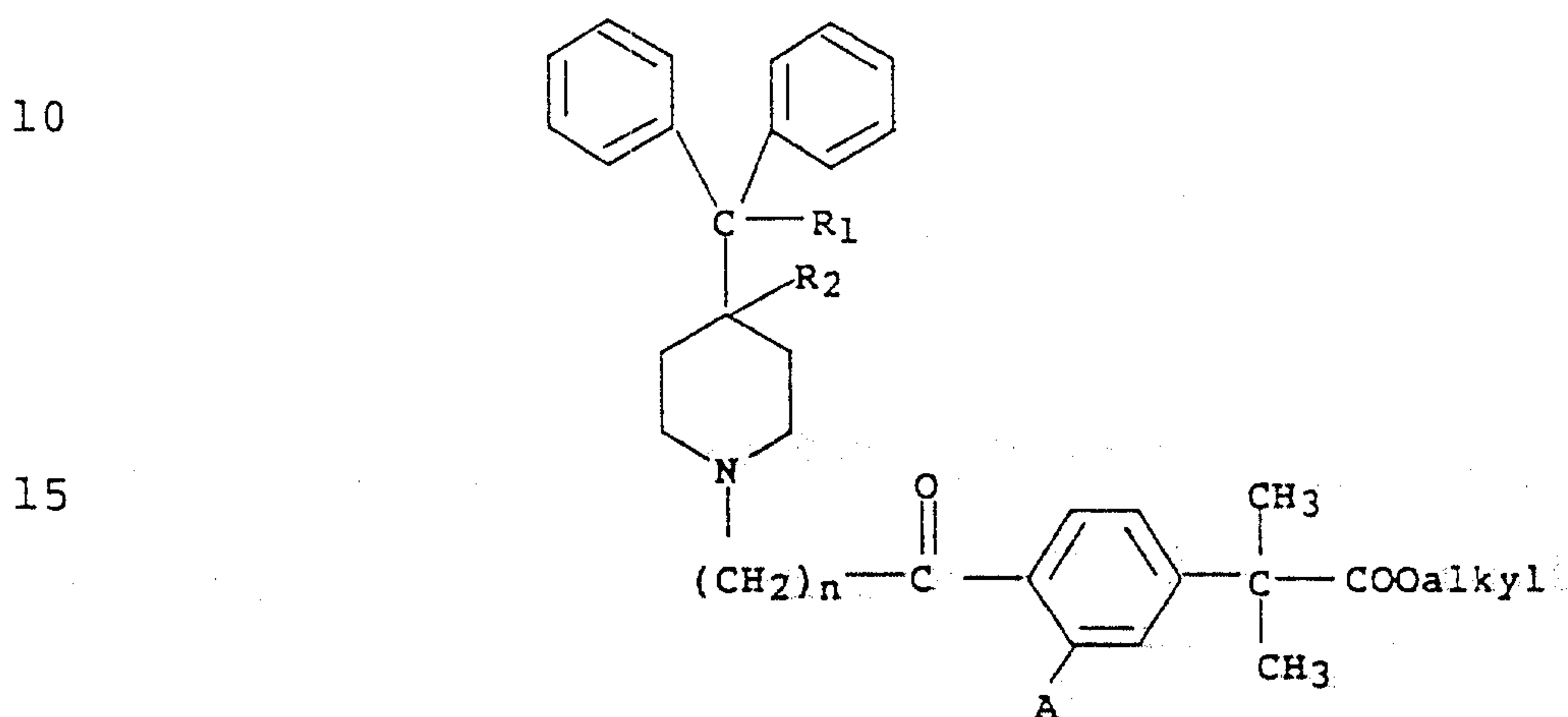


35 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

AMENDED SHEET

-82-

- (g) optionally reacting the piperidine carboxyphenylketone with diazomethane or 2,2-dimethoxypropane or with thionyl chloride followed by an alcohol of the formula HOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched to form a piperidine carboxyphenylketone ester of the formula



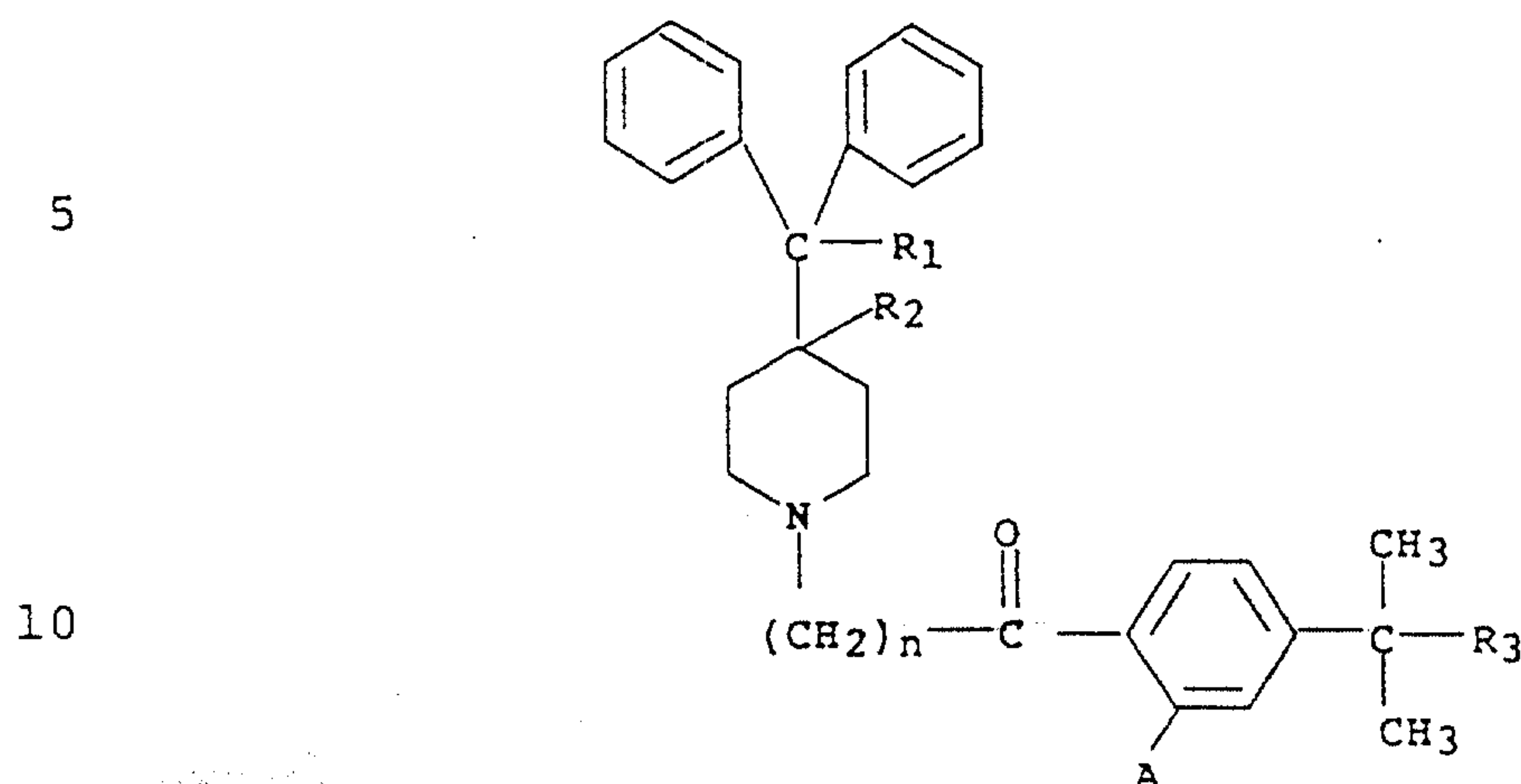
- 20 wherein R₁, R₂, n and alkyl are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected; and

- (h) optionally reacting the piperidine carboxyphenylketones or piperidine carboxyphenylketone esters which bear hydroxy protecting groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine carboxyphenylketones or piperidine carboxyphenylketone esters.

14. A process according to Claim 13 wherein the piperidine hydroxyethylphenylketone produced in step e is reacted with ruthenium(VIII) oxide to produce the piperidine carboxyphenylketone of step f.

15. A process for preparing a piperidine hydroxyethylphenylketone compound of the formula

-83-



wherein

- 15 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the
carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;
20 R_3 is $-\text{CH}_2\text{OH}$;
 A is hydrogen or hydroxy; and
pharmaceutically acceptable salts thereof comprising
the steps of:

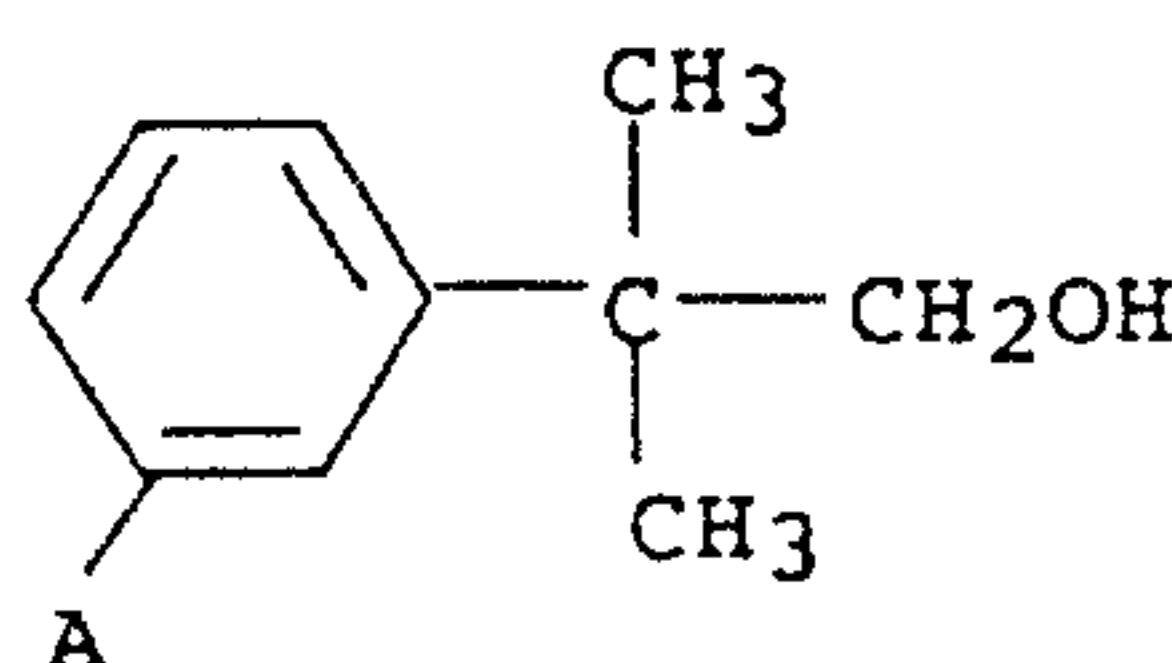
- 25 (a) reacting a benzeneacetic acid compound of the formula



- wherein A is hydrogen or hydroxy with the proviso that when
 A is hydroxy, A may be optionally protected or unprotected
and R is hydrogen or $\text{C}_1\text{-C}_6$ alkyl with sodium bis(2-
35 methoxyethoxy)aluminum hydride, lithium aluminum hydride,
diborane, lithium borohydride, lithium triethylborohydride
and lithium tri-sec-butylborohydride or aluminum hydride to
give a phenethyl alcohol of the formula

-84-

5

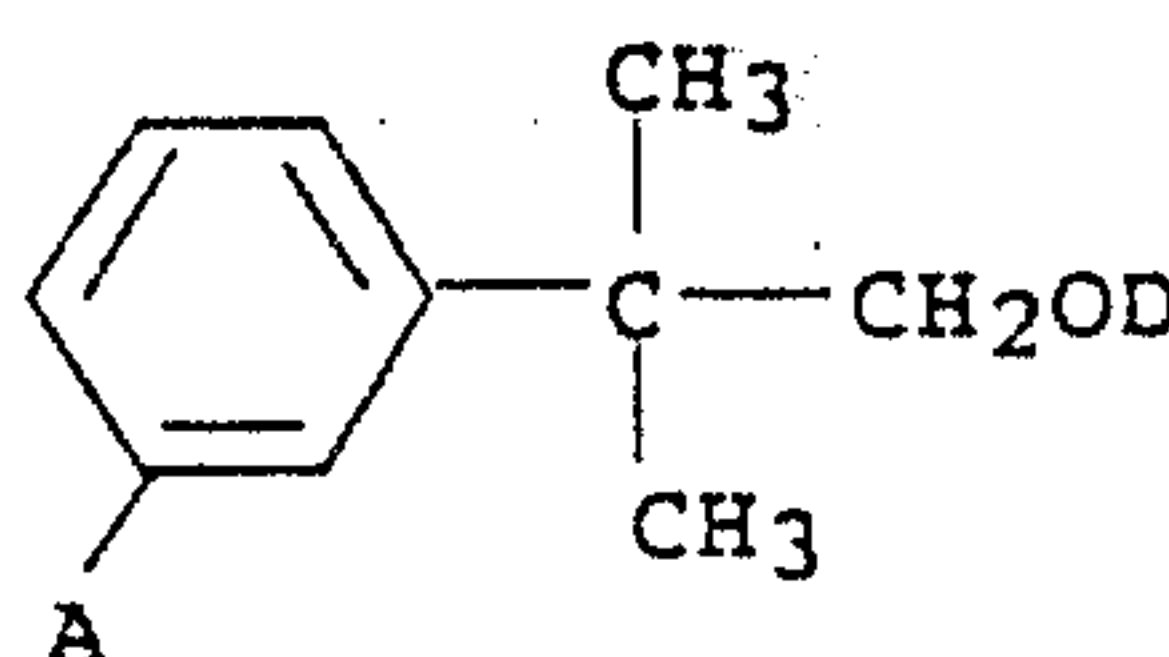


wherein A is hydrogen or hydroxy, with the proviso that
 when A is hydroxy, A is optionally protected or
 unprotected;

15

(b) reacting the phenylethyl alcohol with acetyl
 chloride, acetic anhydride, benzoyl chloride or benzoic
 anhydride in the presence of sodium bicarbonate, potassium
 carbonate, potassium bicarbonate, triethylamine or pyridine
 to give a protected phenethyl alcohol of the formula

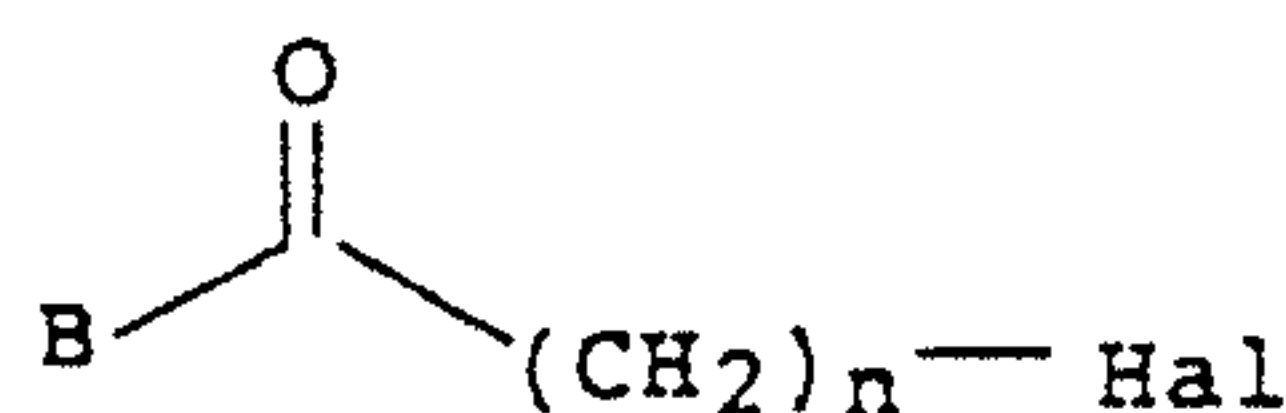
20



wherein A is hydrogen or hydroxy, with the proviso that
 when A is hydroxy, A is optionally protected or unprotected
 and D is C(=O)CH₃ or C(=O)C₆H₅;

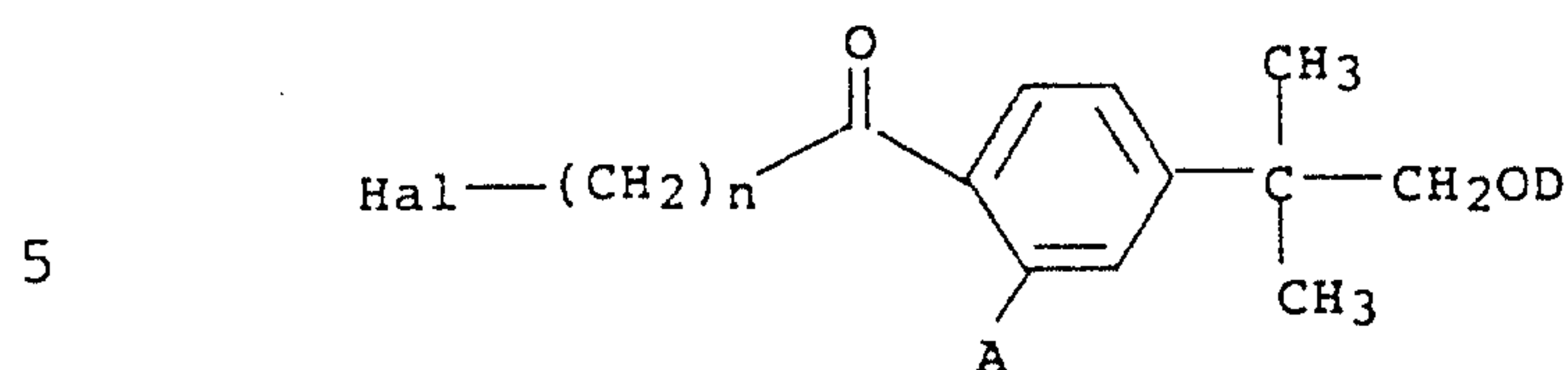
(c) reacting the protected phenethyl alcohol with a
 ω-halo compound of the formula

30



wherein B is halo or hydroxy, Hal represents Cl, Br or I
 and n is as defined above, in the presence of trichloride,
 aluminum chloride, titanium tetrachloride, boron
 trifluoride, tin tetrachloride and zinc chloride to produce
 a ω-halo protected hydroxyethylphenylketone of the formula

-85-

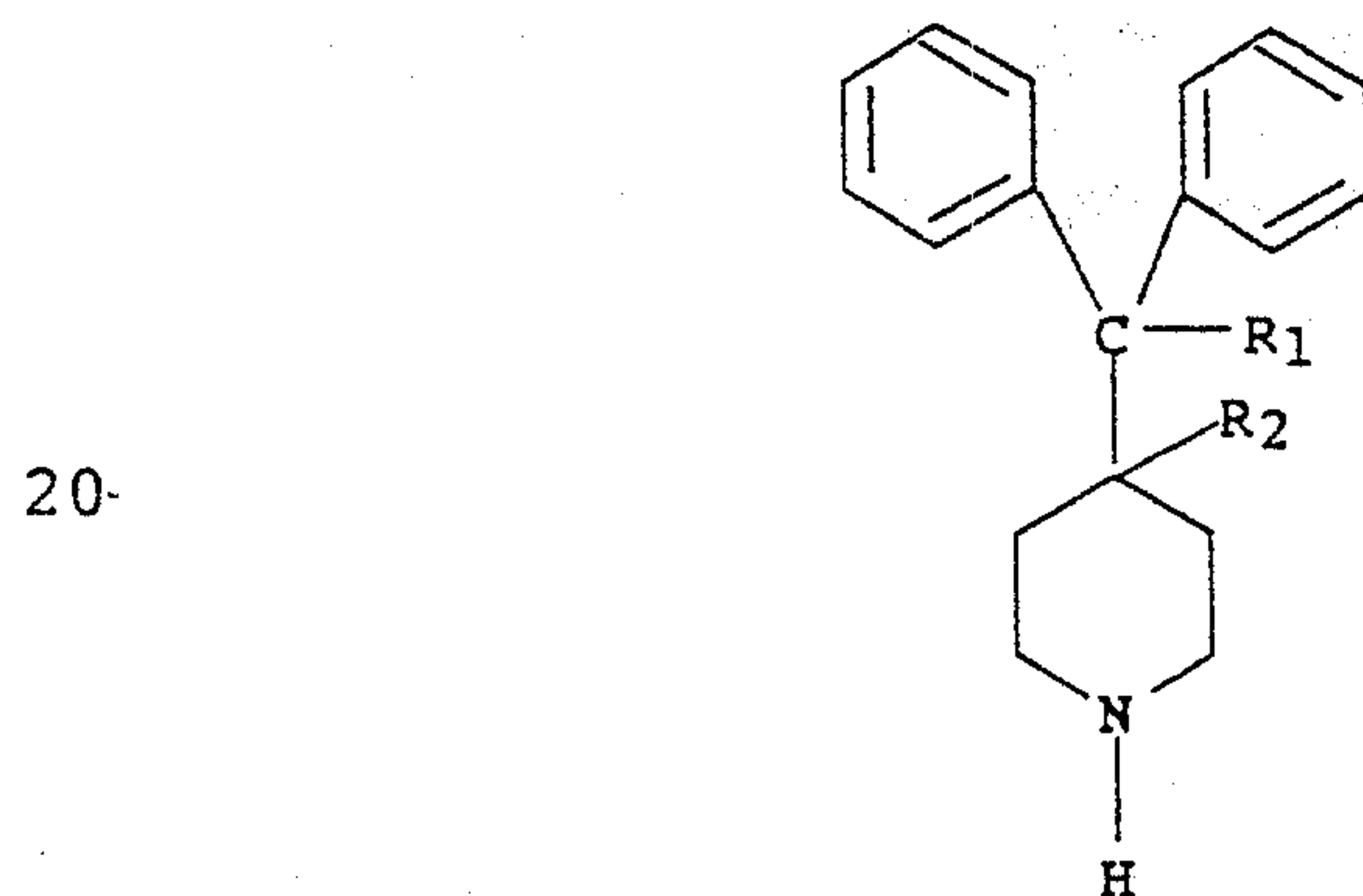


wherein Hal, n and D are defined above and A is hydrogen or hydroxy, with the proviso that when A is hydroxy, A is optionally protected or unprotected;

10

(d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

15

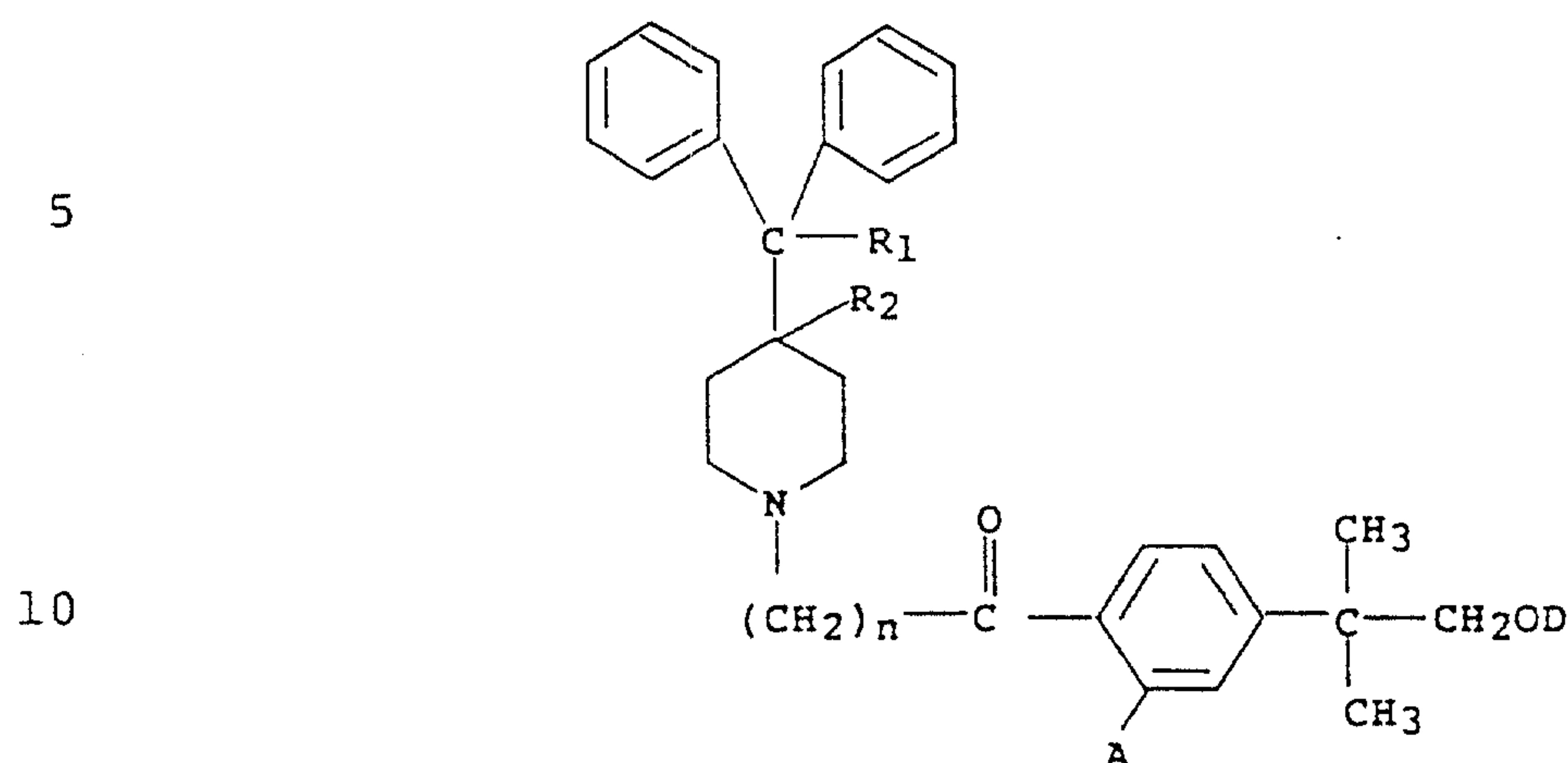


wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylketone of the formula

25

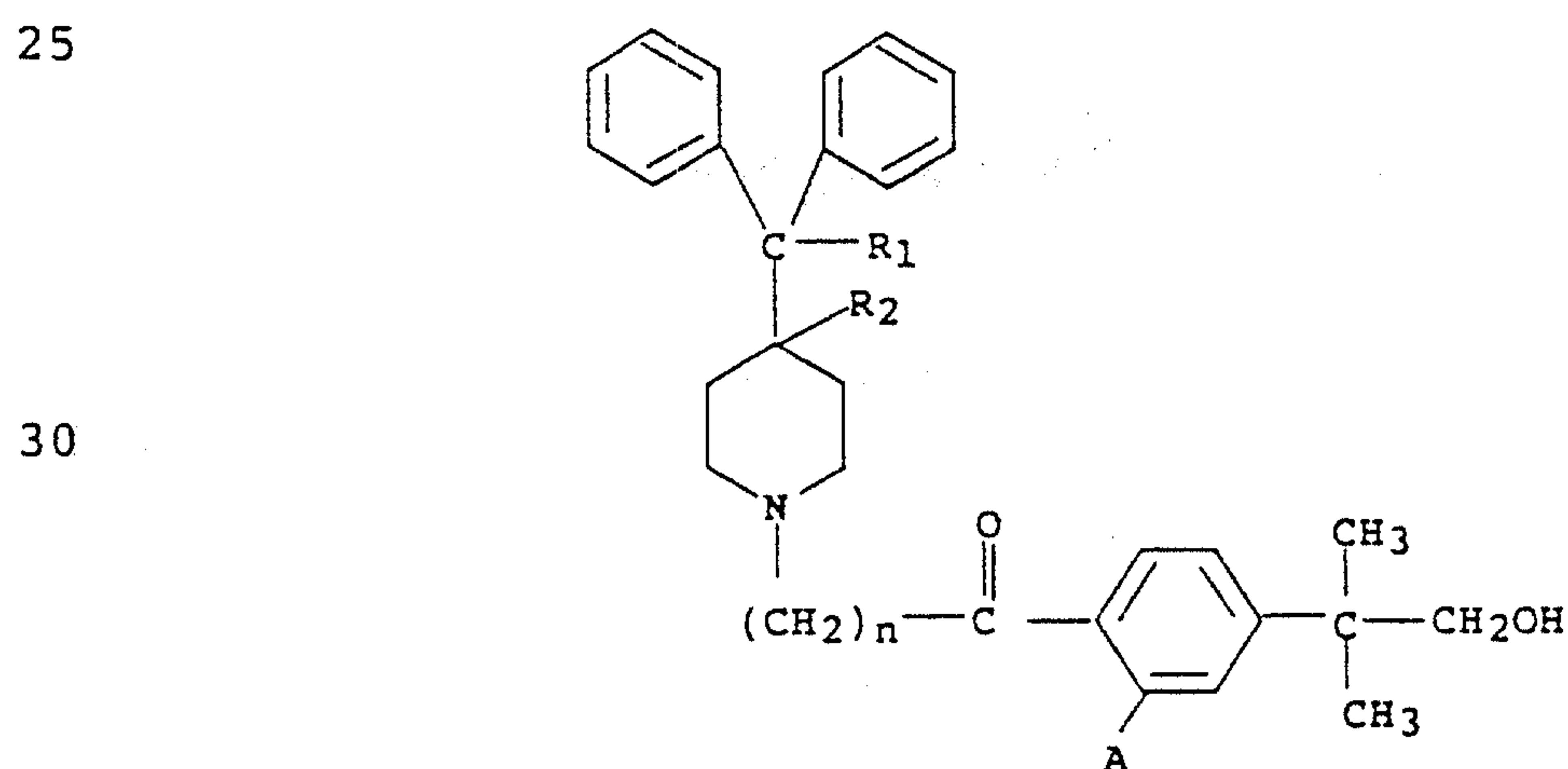
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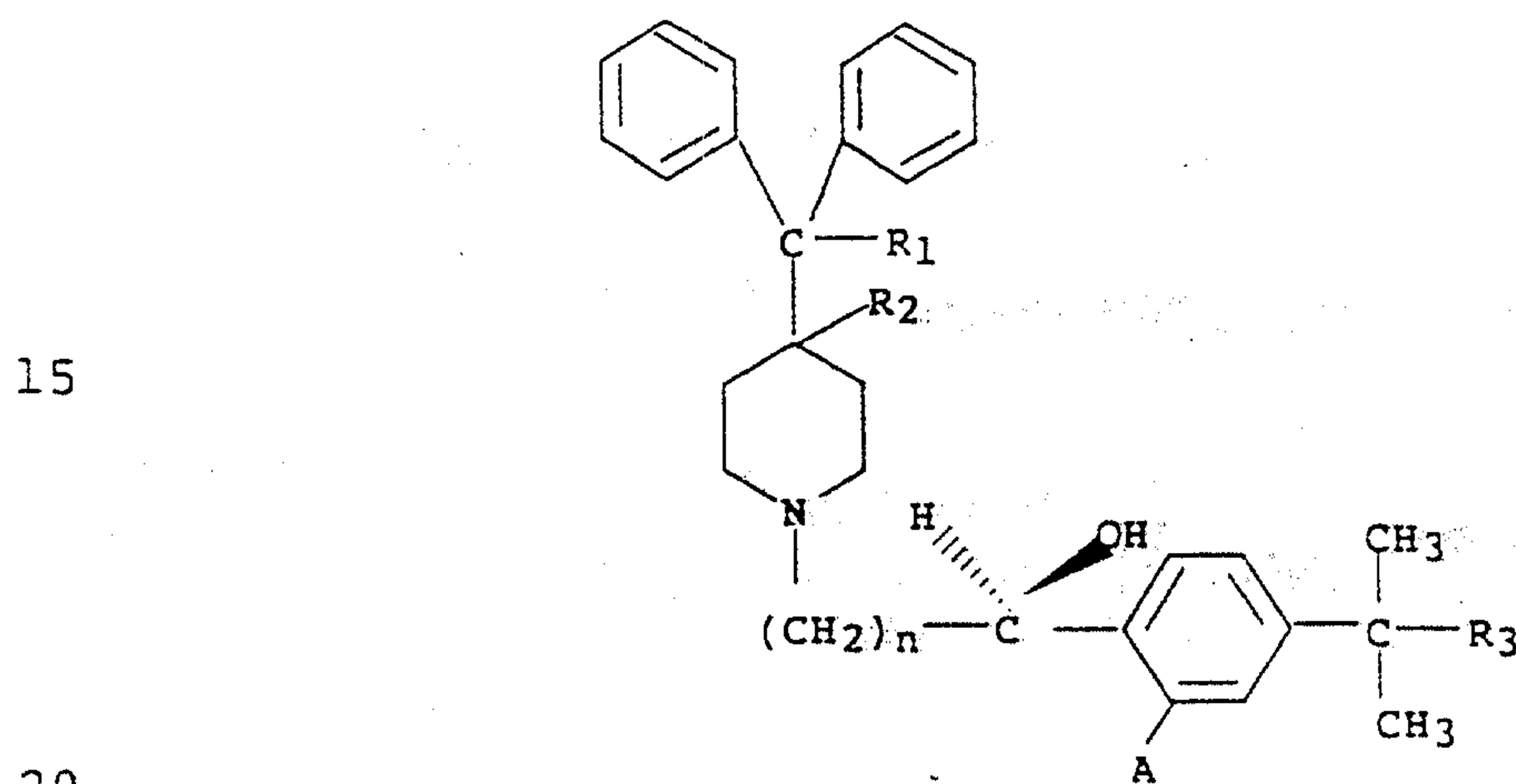
15 wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy, with the proviso that when A is hydroxy, A is optionally protected or unprotected;

(e) reacting the piperidine protected hydroxyethylphenylketone with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce the piperidine hydroxyethylphenylketone of the formula



wherein R_1 , R_2 and n are defined above A is hydrogen or hydroxy, with the proviso that when A is hydroxy, A is optionally protected or unprotected;

10



R₁ represents hydrogen or hydroxy;

R_2 represents hydrogen; or

25 R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;

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n is an integer of from 1 to 5;
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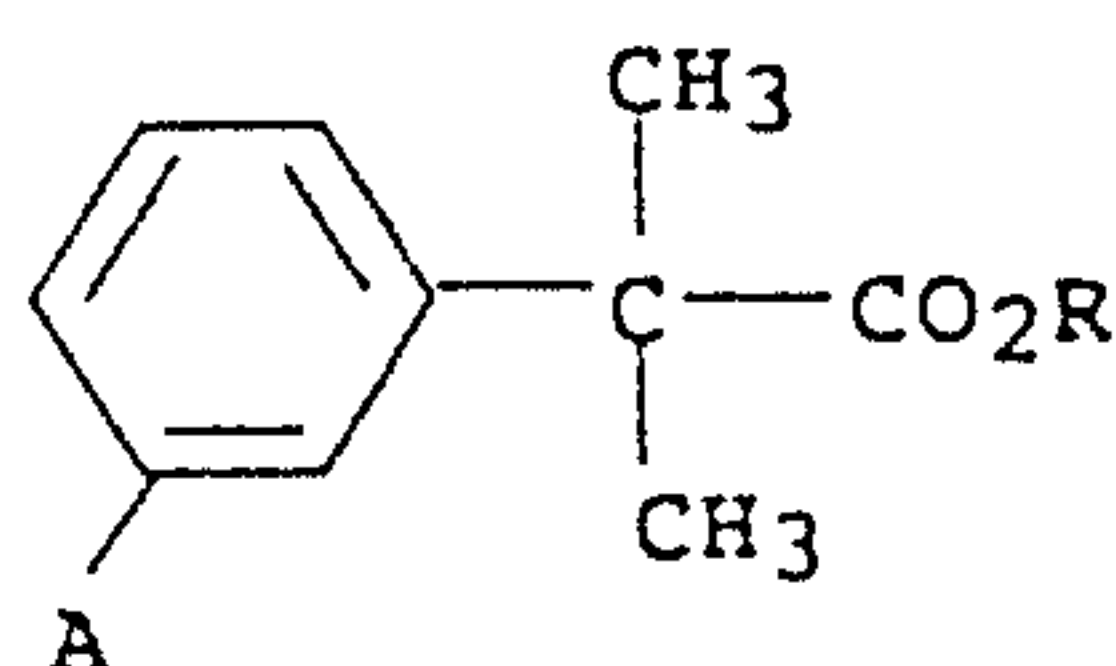
R₃ is -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

30 A is hydrogen or hydroxy; and

pharmaceutically acceptable salts thereof comprising
the steps of:

(a) reacting a benzeneacetic acid compound of the
35 formula

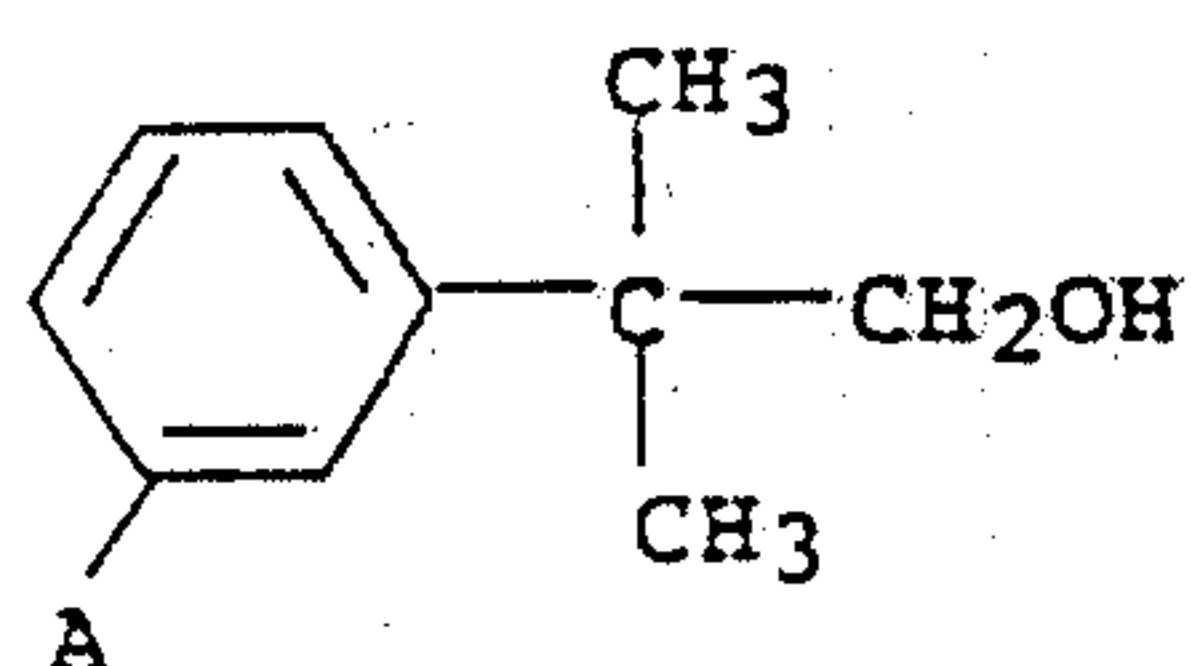
5



10

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

15



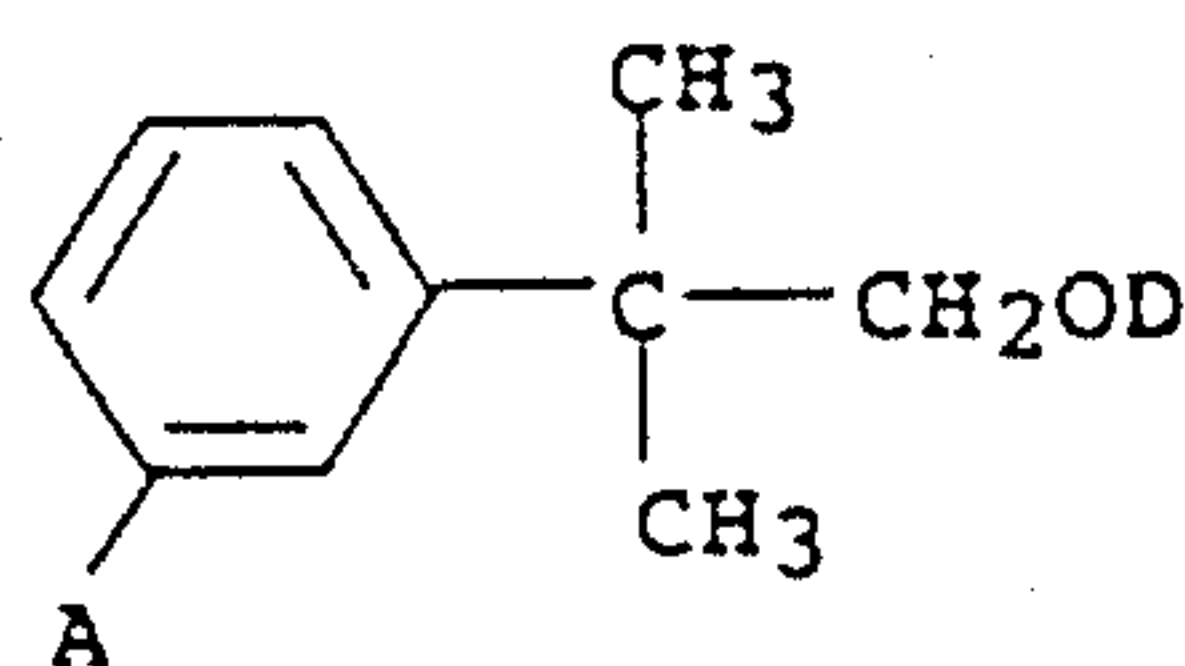
20

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

25

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

30



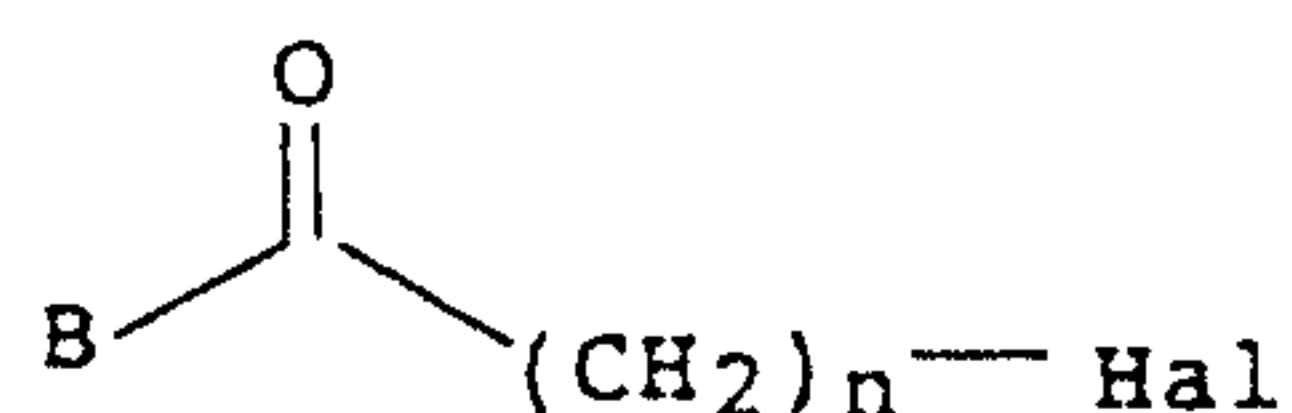
35

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is C(=O)CH₃ or C(=O)C₆H₅;

-89-

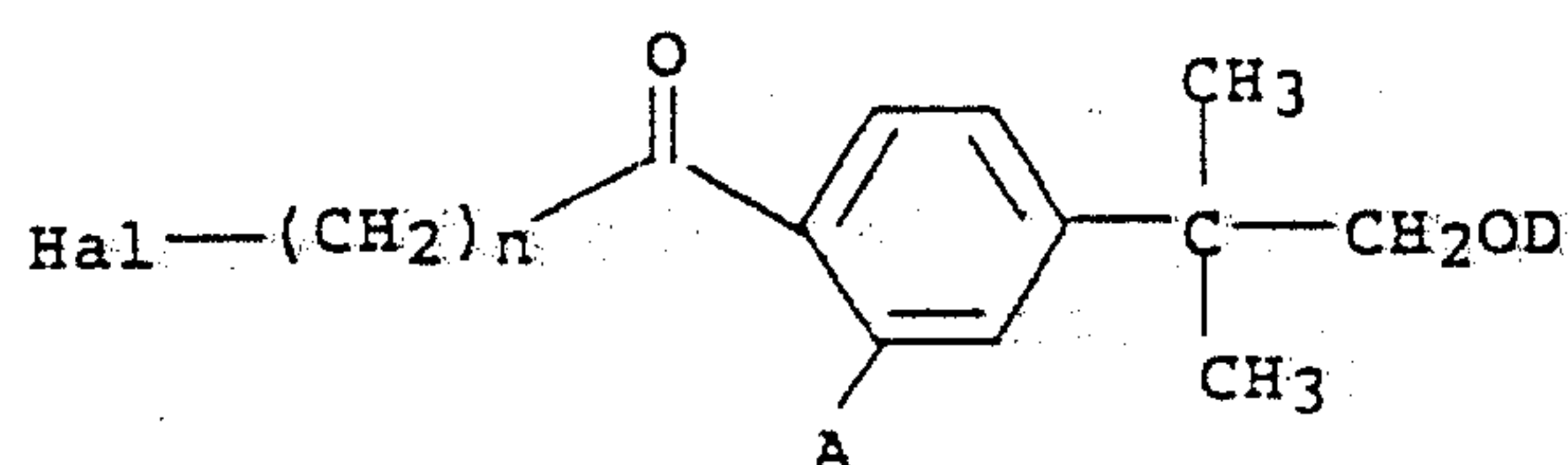
(c) reacting the protected phenethyl alcohol with a ω -halo compound of the formula

5



10 wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula

15



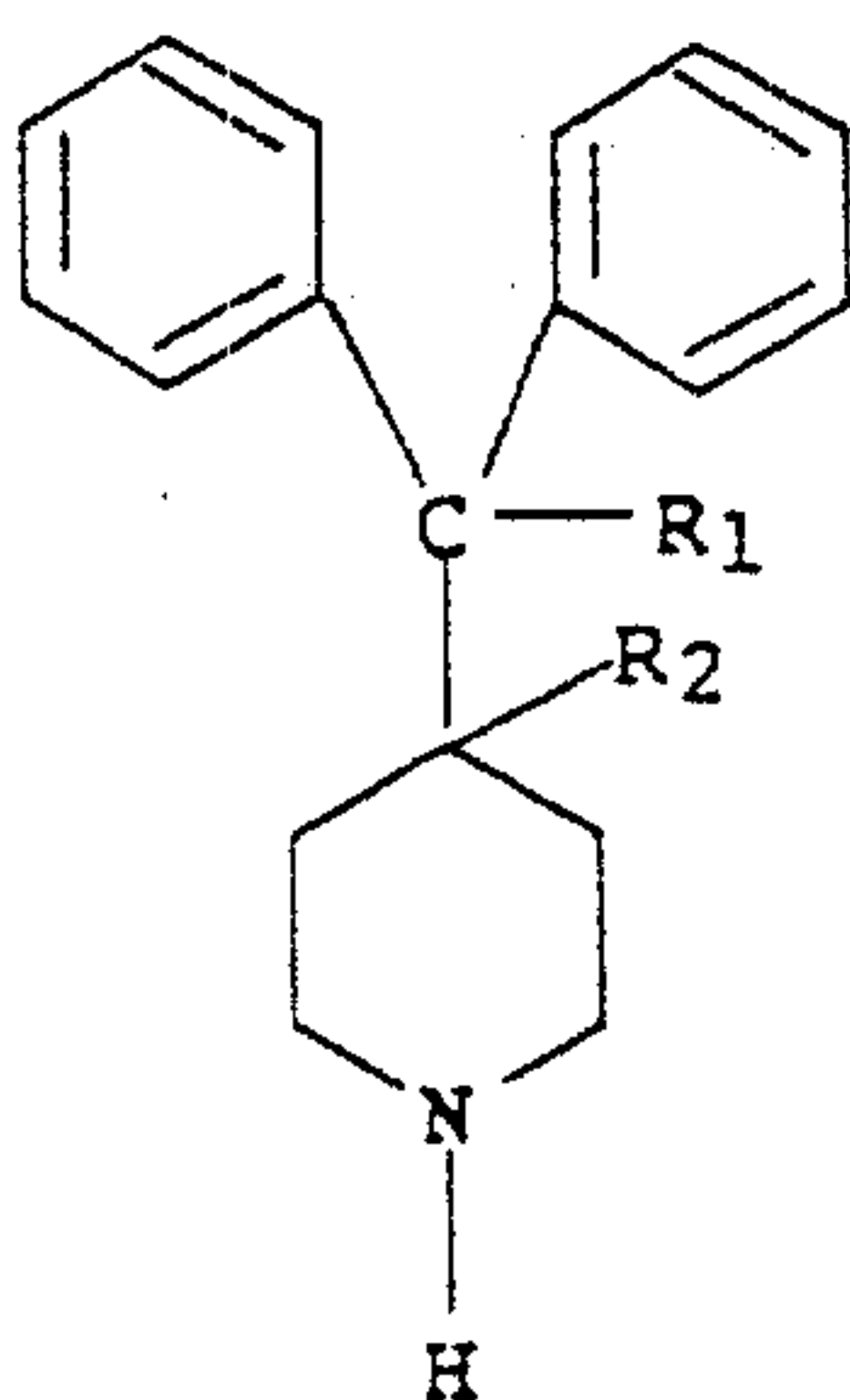
20

wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

25

(d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

30

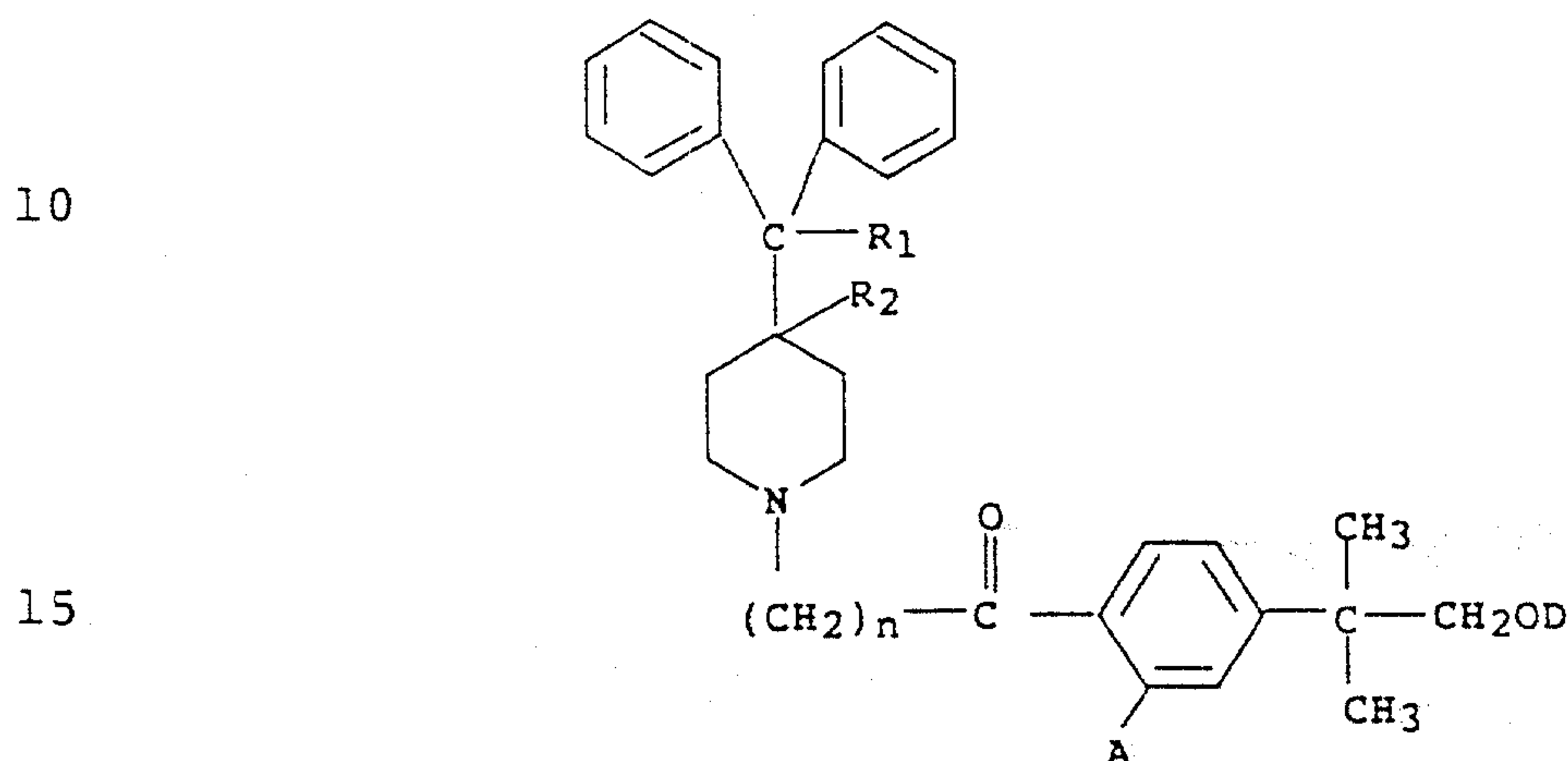


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AMENDED SHEET

-90-

wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the
5 piperidine compound may be used to produce a piperidine protected hydroxyethylphenylketone of the formula



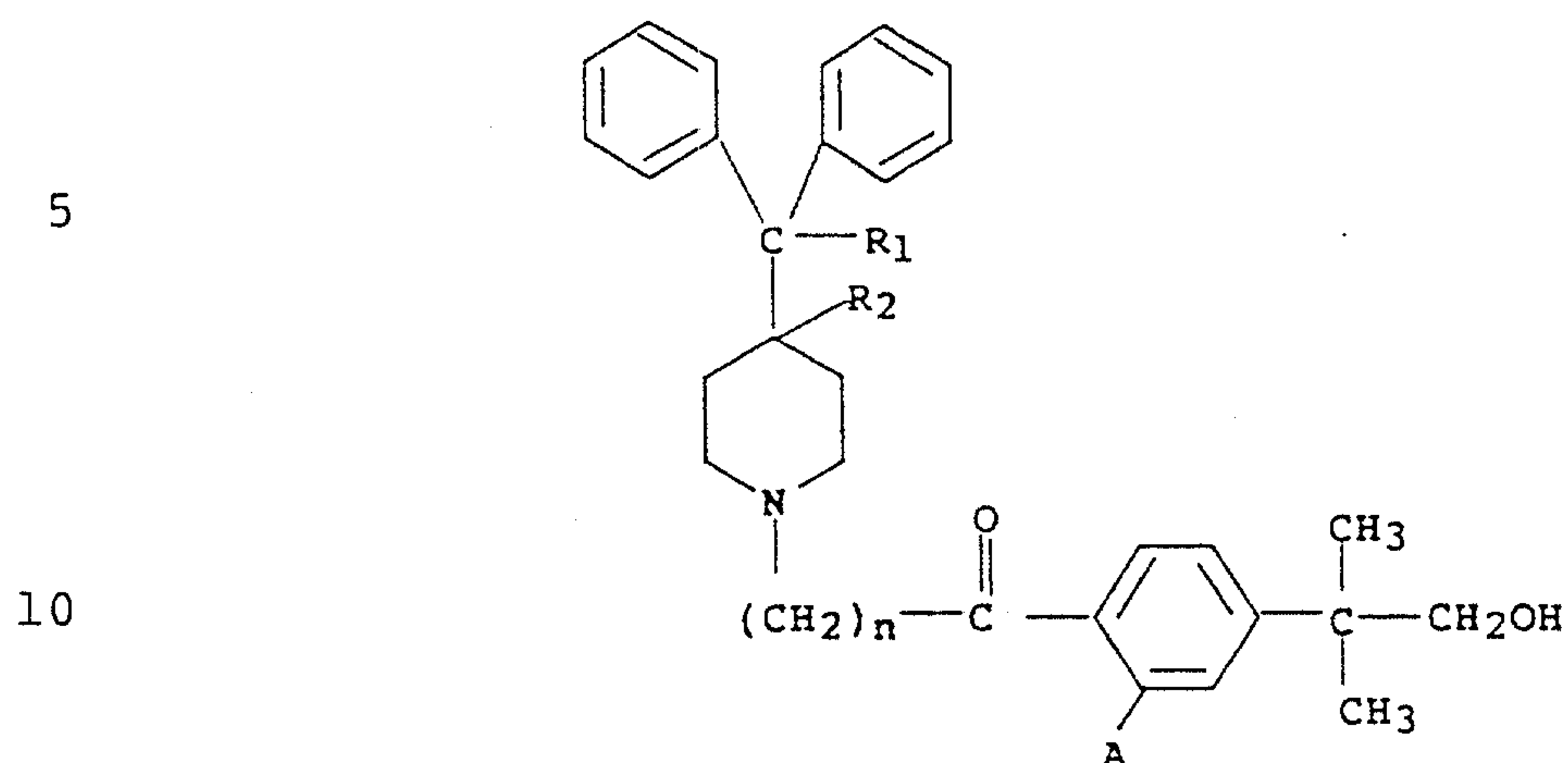
wherein R_1 , R_2 , n and D are defined above and A is hydrogen
20 or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(e) reacting the piperidine protected
hydroxyethylphenylketone with sodium methoxide in methanol,
25 potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylketone of the formula

30

35

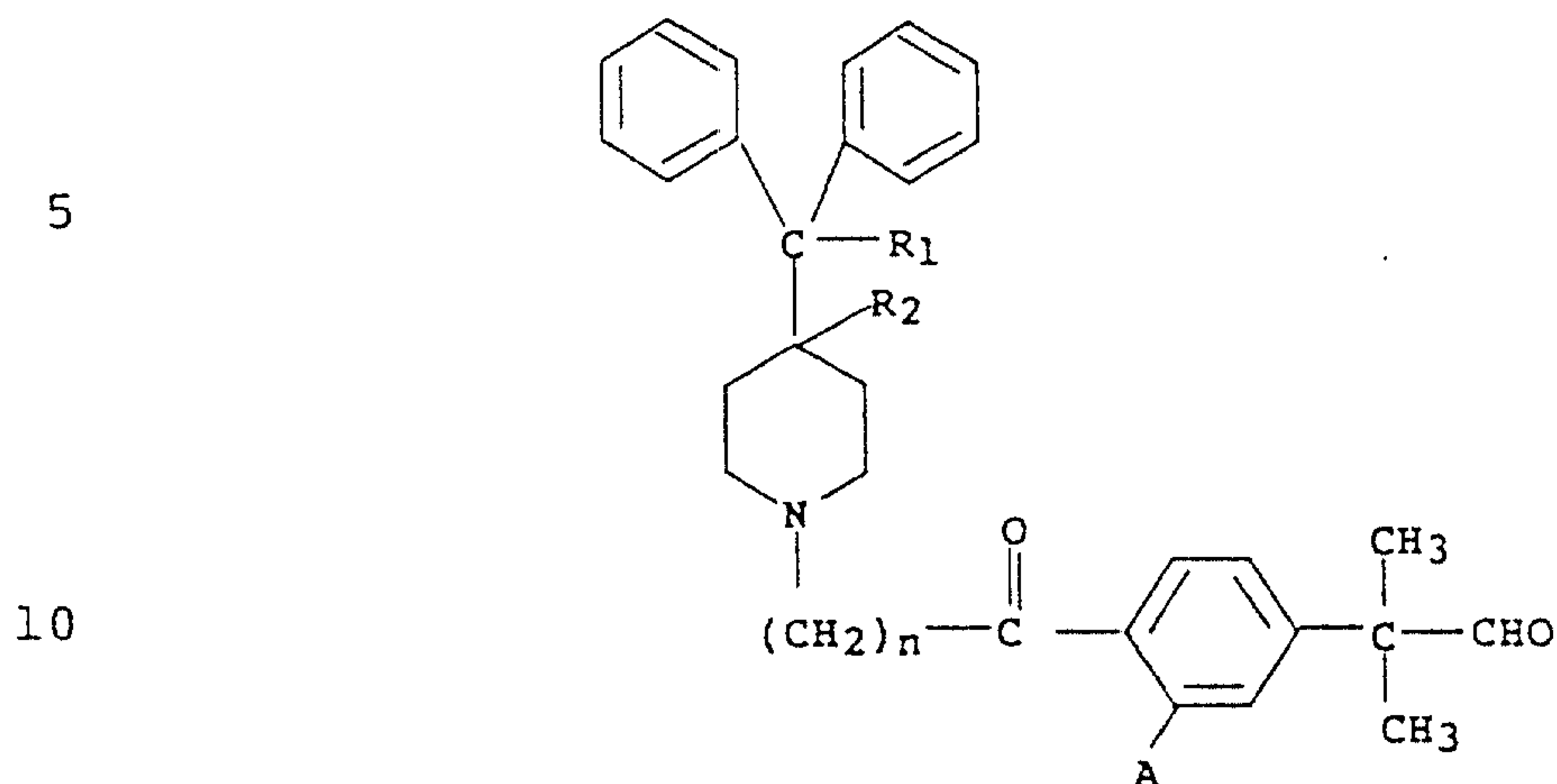
-91-



wherein R₁, R₂ and n are defined above and A is hydrogen or
 15 hydroxy with the proviso that when A is hydroxy, A may be
 optionally protected or unprotected;

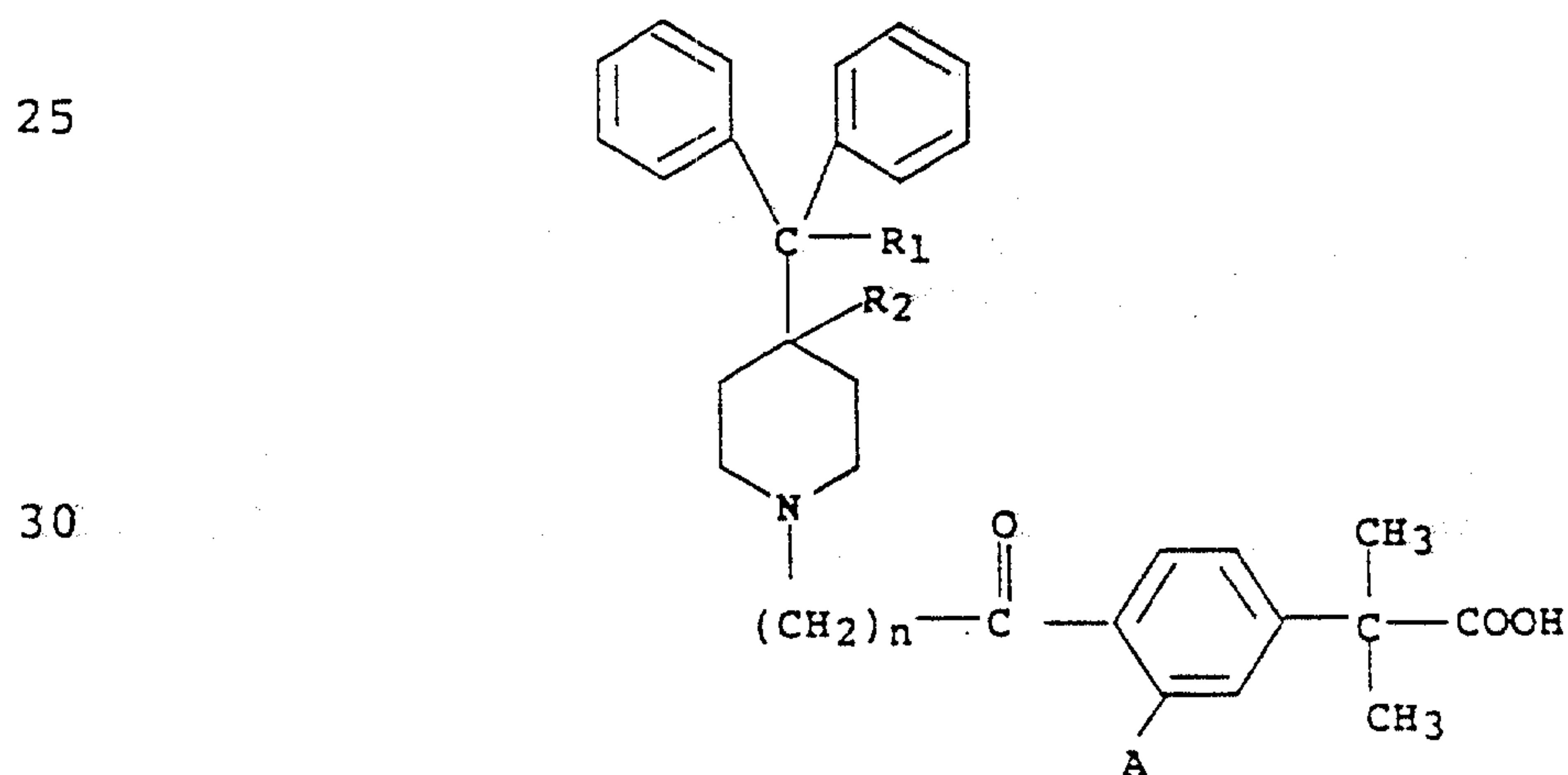
(f) reacting the piperidine hydroxyethylphenylketone
 with dimethyl sulfoxide, oxyalyl chloride and triethylamine
 20 or with Dess-Martin reagent, chromium (IV) oxide, nickel
 peroxide, sodium dichromate, potassium dichromate, t-butyl
 chromate, silver oxide, argentic picolinate manganese
 dioxide lead tetraacetate, dicyclohexylcarbodiimide, 2,3-
 dichloro-5,6-dicyanoquinone, tetrachloro-1,2-benzoquinone,
 25 2,2,6,6-tetramethylpiperidiny-1-oxy (TEMPO) or quinolinium
 chlorochromate to produce a piperidine formylphenylketone
 of the formula

AMENDED SHEET



wherein R_1 , R_2 and n are defined above and A is hydrogen or
 15 hydroxy with the proviso that when A is hydroxy, A may be
 optionally protected or unprotected;

(g) reacting the piperidine formylphenylketone with
 potassium permanganate, chromium (IV) oxide, silver (I)
 20 oxide, silver oxide, argentic picolinate, peroxide, nitric
 acid, m-chloroperbenzoic acid and peracetic acid to produce
 a piperidine carboxyphenylketone of the formula



35

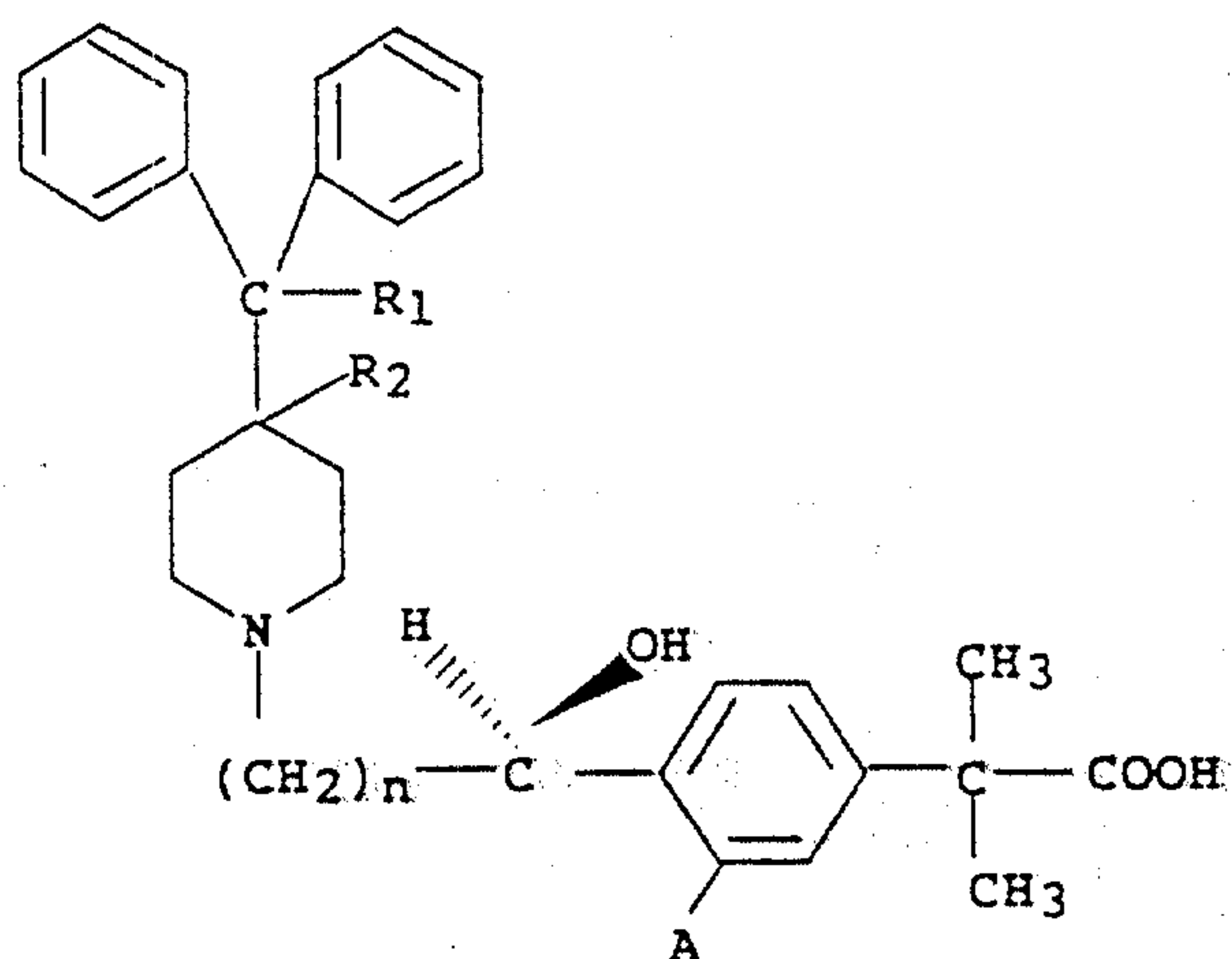
wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

5

(h) reacting the piperidine carboxyphenylketone with (+)-B-chlorodiisopinocampheylborane to produce a piperidine carboxyphenylalcohol of the formula

10

15



20

wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

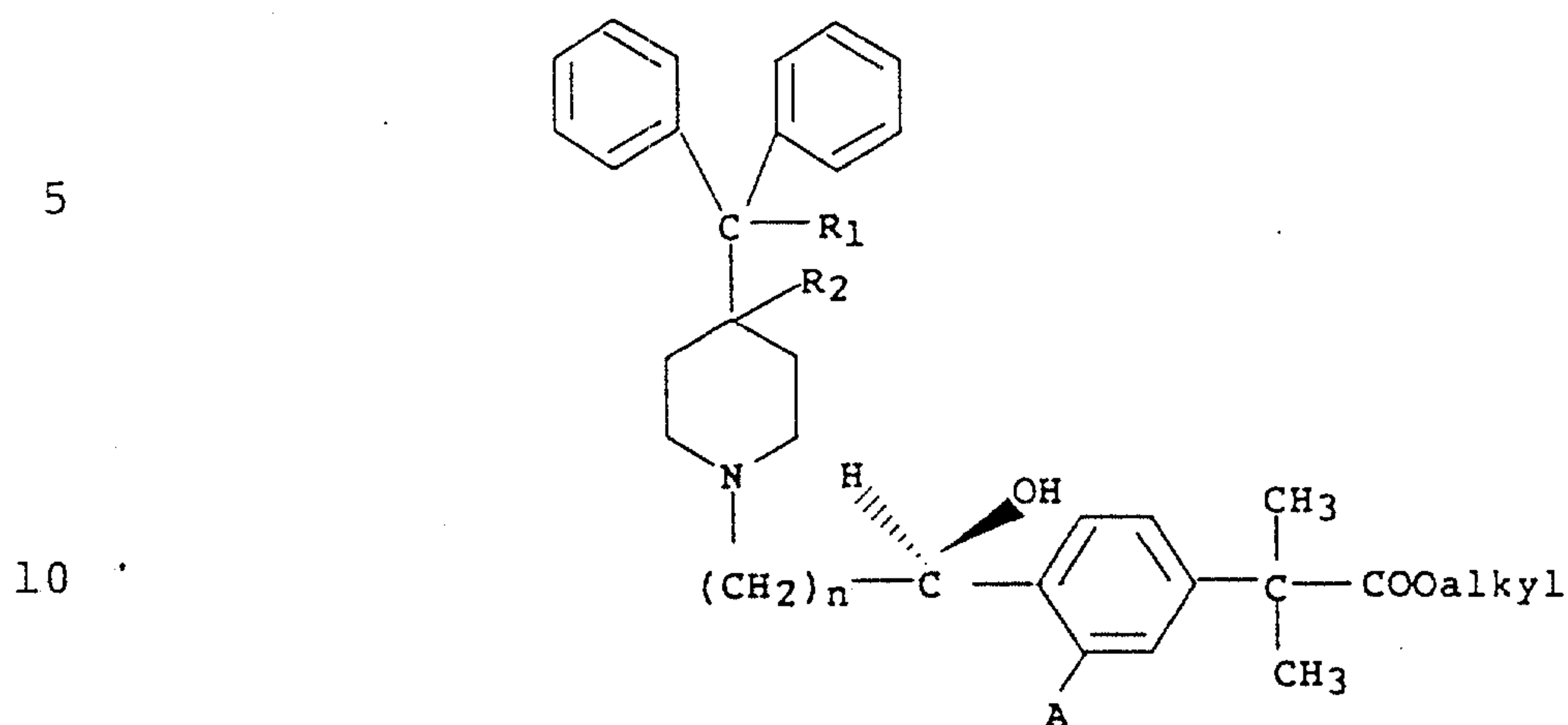
25

(i) optionally reacting the piperidine carboxyphenylalcohol with diazomethane or 2,2-dimethoxypropane or with thionyl chloride followed by an alcohol of the formula HOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched to

30

form a piperidine carboxyphenylalcohol ester of the formula

35

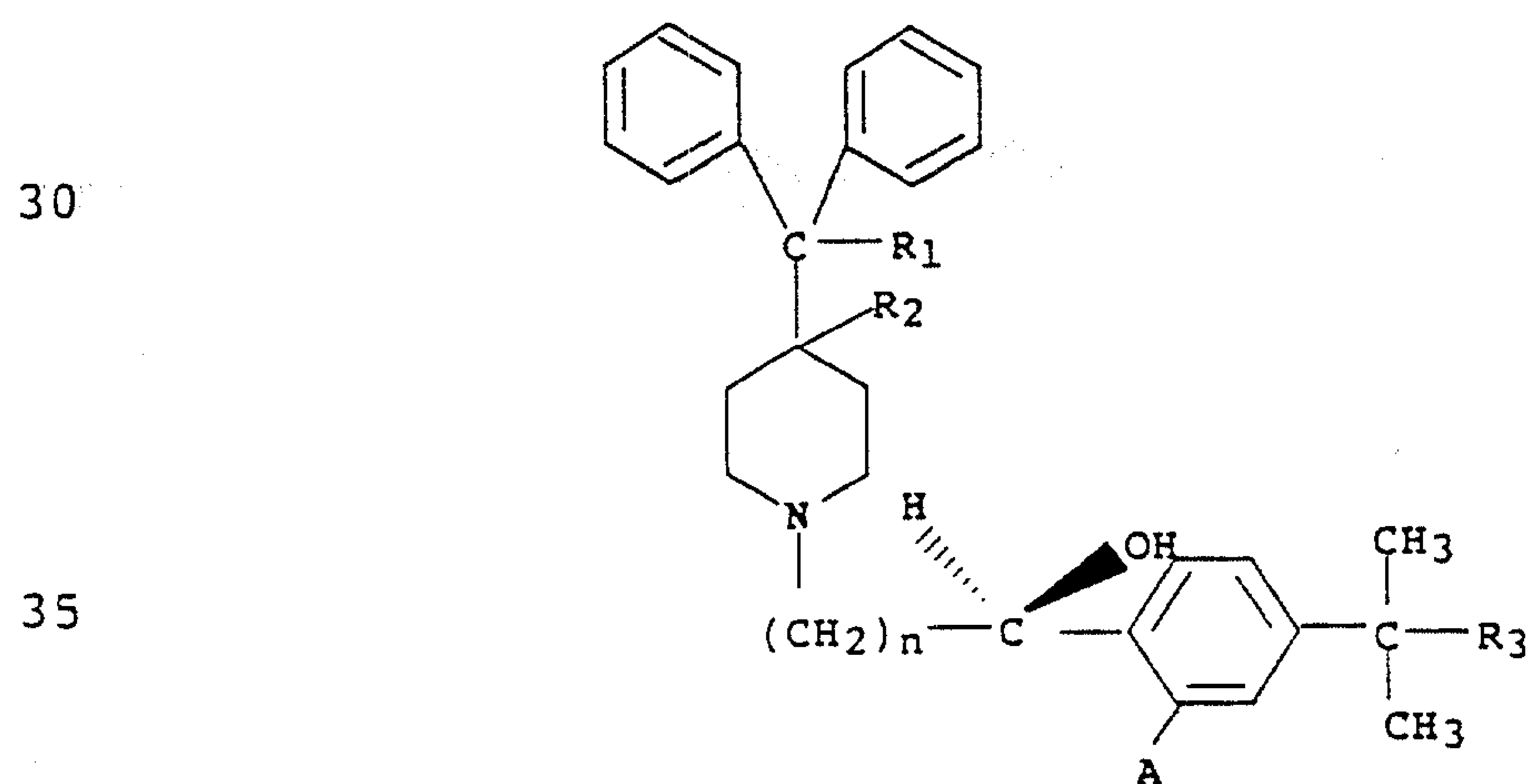


wherein R_1 , R_2 , n and alkyl are defined above and A is
 15 hydrogen or hydroxy with the proviso that when A is
 hydroxy, A may be optionally protected or unprotected; and

(j) optionally reacting the piperidine
 carboxyphenylalcohols or the piperidine
 20 carboxyphenylalcohol esters in which A is a protected
 hydroxy with mineral acids, strong organic acids, Lewis
 acids, aqueous mineral bases or catalytic hydrogenation to
 produce the unprotected piperidine carboxyphenylalcohols or
 the piperidine carboxyphenylalcohol esters.

25

17. A process for preparing a compound of the formula



AMENDED SHEET

-95-

wherein

R₁ represents hydrogen or hydroxy;

R₂ represents hydrogen; or

5 R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;

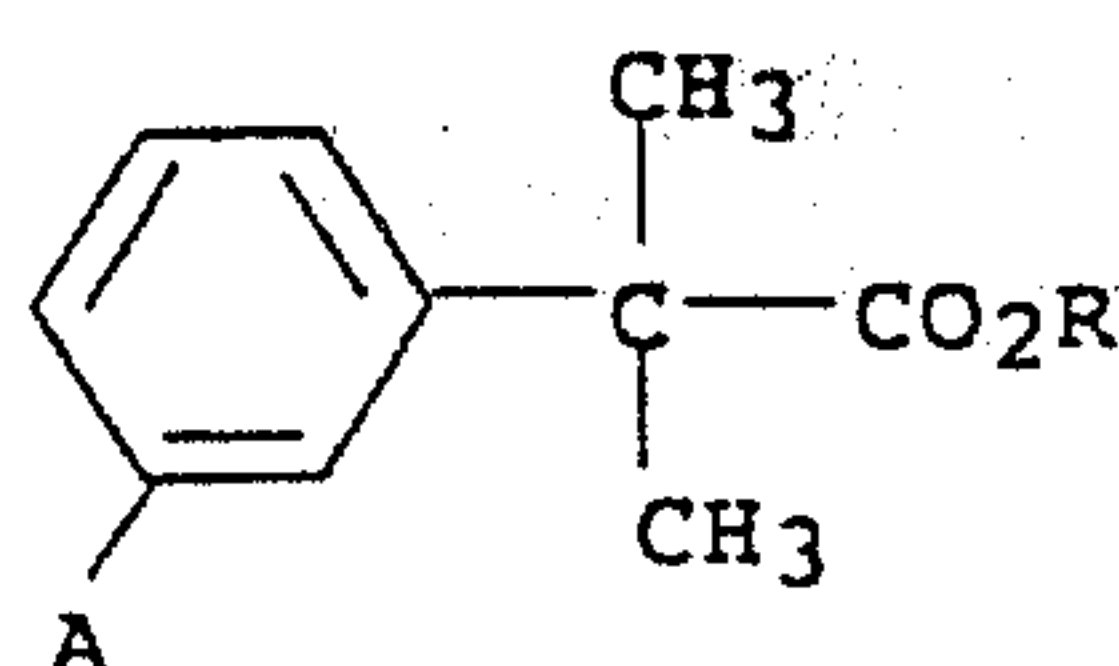
n is an integer of from 1 to 5;

R₃ is -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

10 A is hydrogen or hydroxy; and

pharmaceutically acceptable salts thereof comprising the steps of:

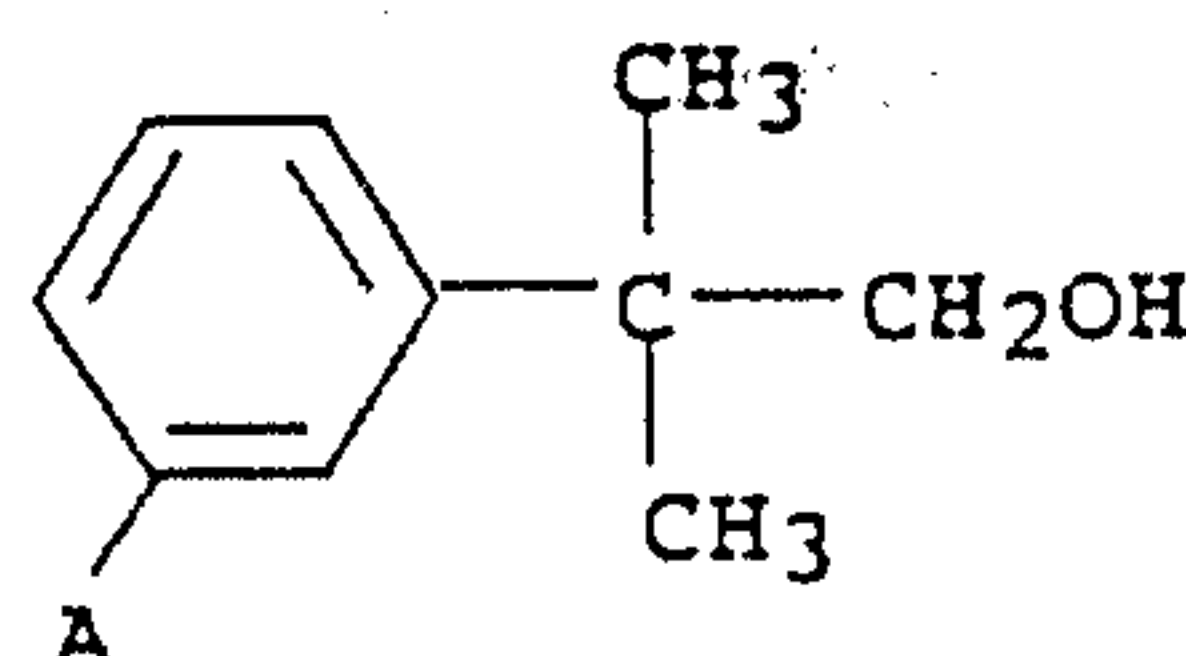
(a) reacting a benzeneacetic acid compound of the
15 formula



20

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-
25 methoxyethoxy)aluminum hydride, lithium aluminum hydride, diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

30



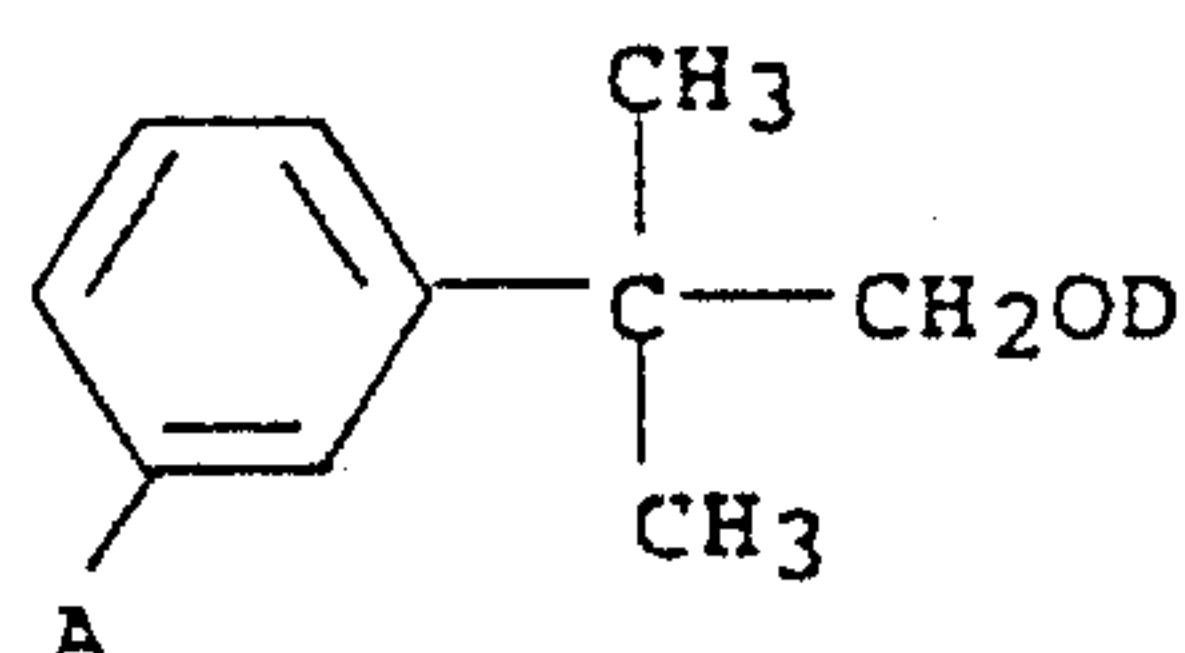
35

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

-96-

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

10

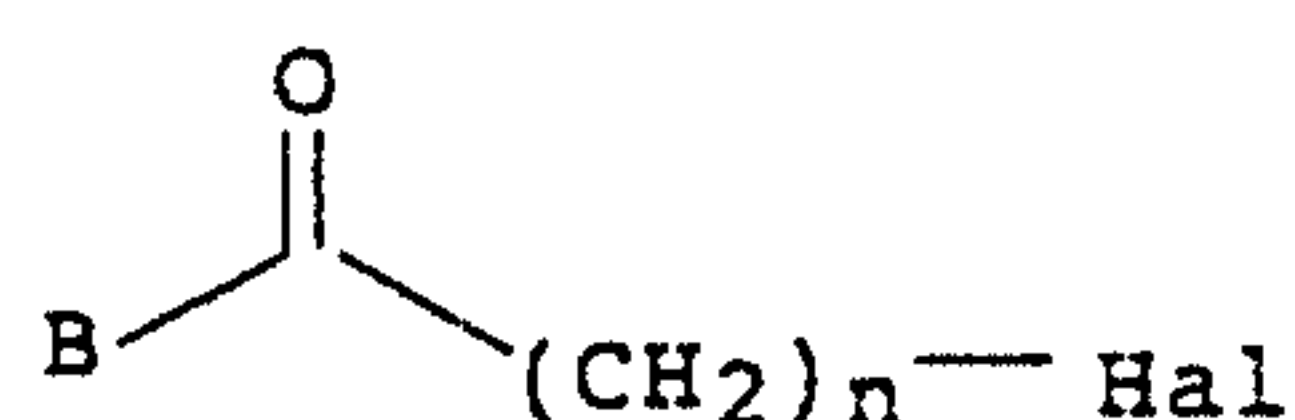


wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is $\text{C}(=\text{O})\text{CH}_3$ or $\text{C}(=\text{O})\text{C}_6\text{H}_5$;

15

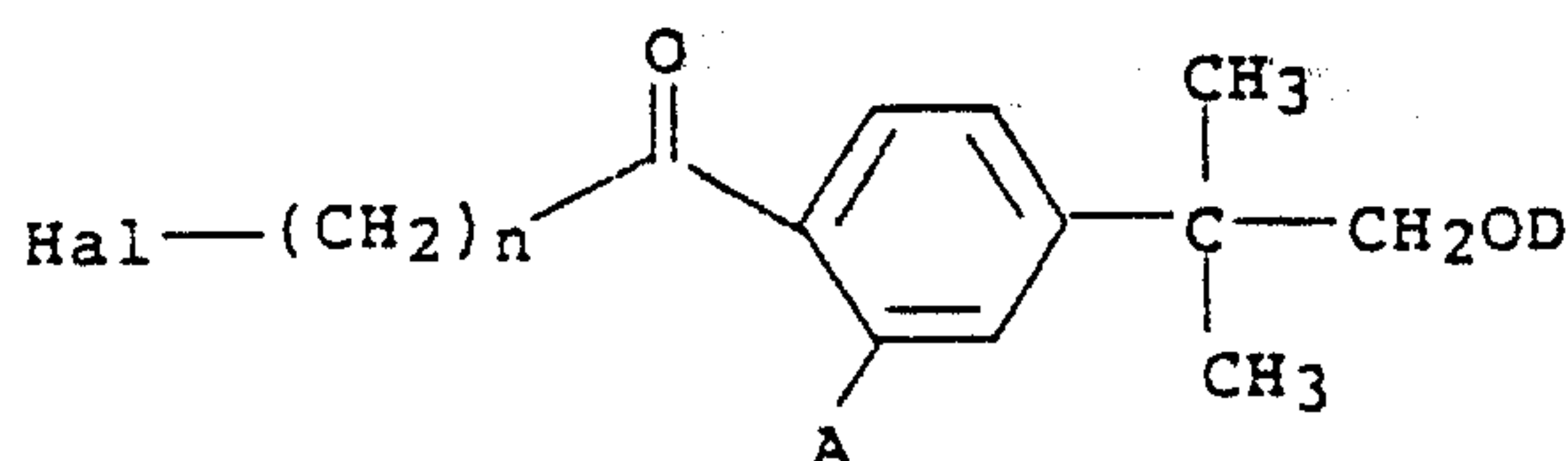
(c) reacting the protected phenethyl alcohol with a ω -halo compound of the formula

20



wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula

30



wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

35

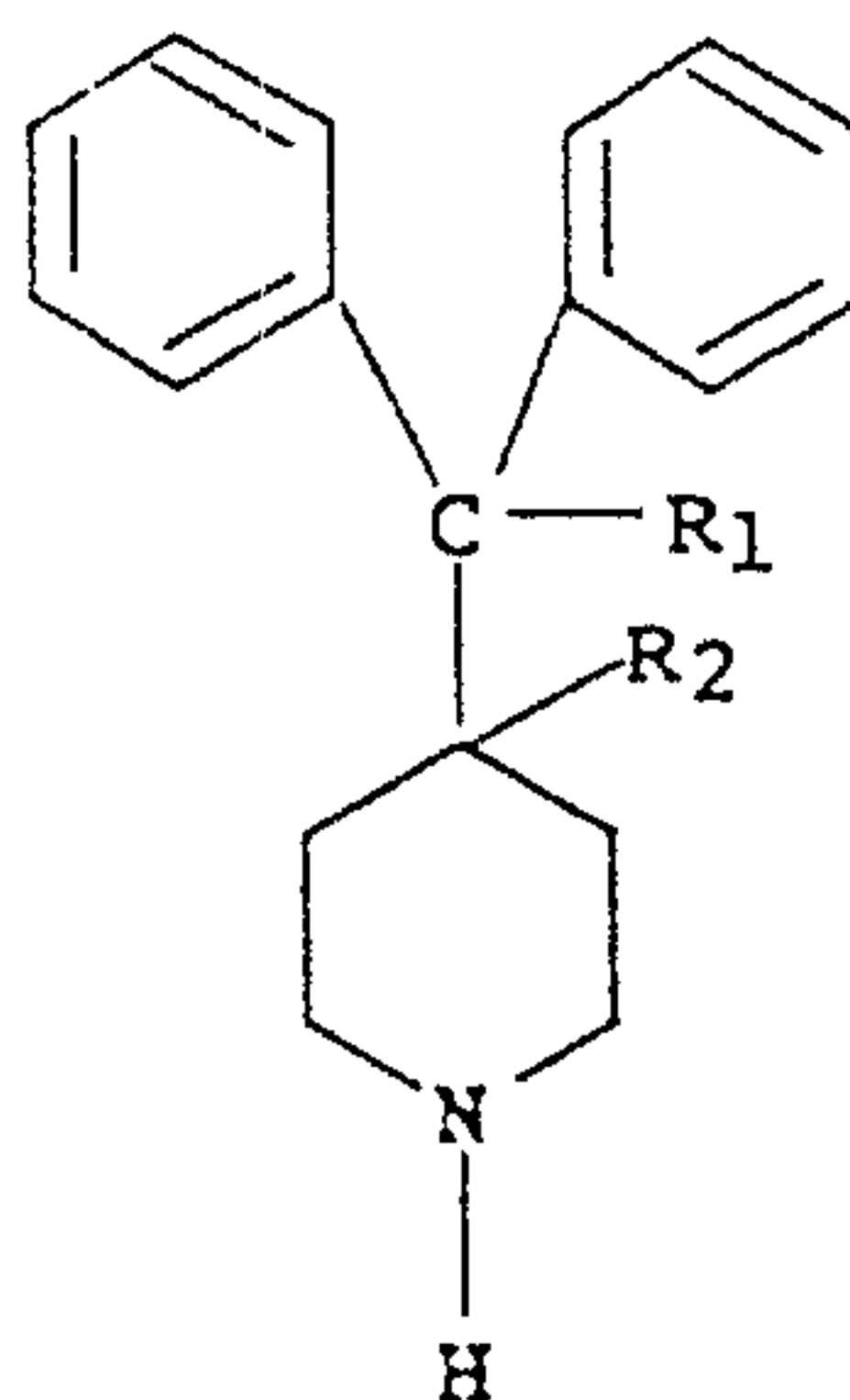
AMENDED SHEET

-97-

(d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

5

10

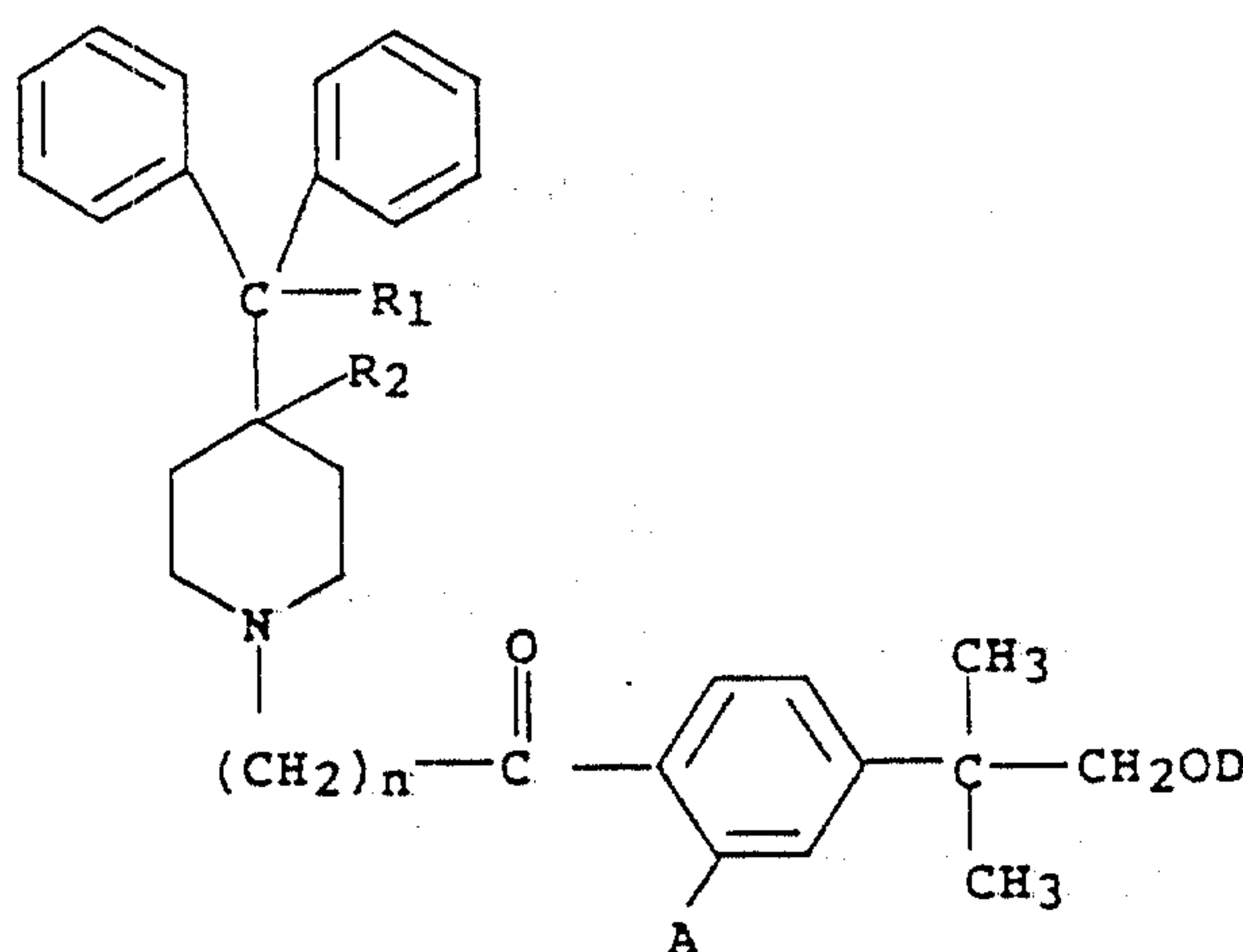


15 wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylketone of the formula

20

25

30



wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

35

(e) reacting the piperidine protected hydroxyethylphenylketone with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium

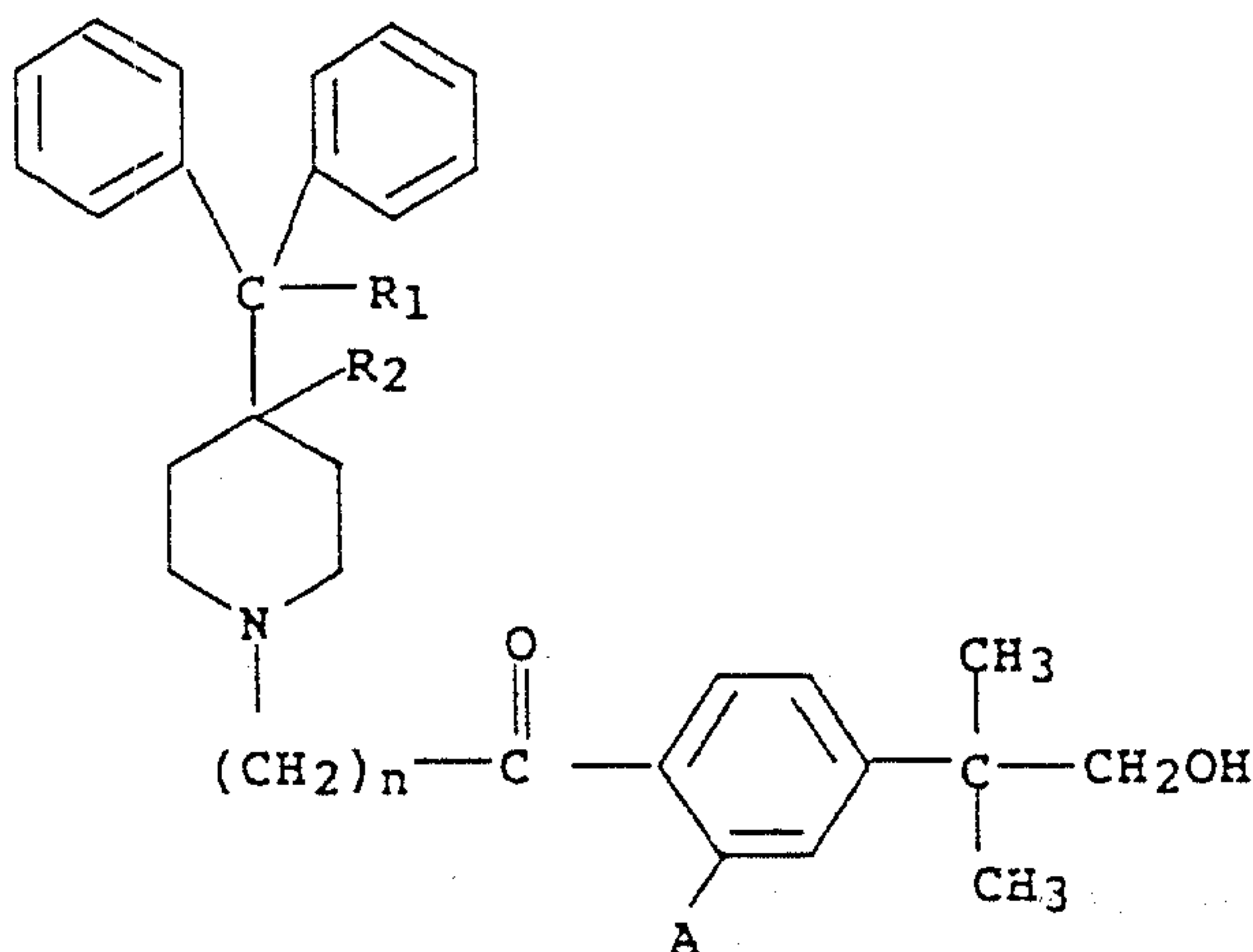
AMENDED SHEET

hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylketone of the formula

5

10

15



wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

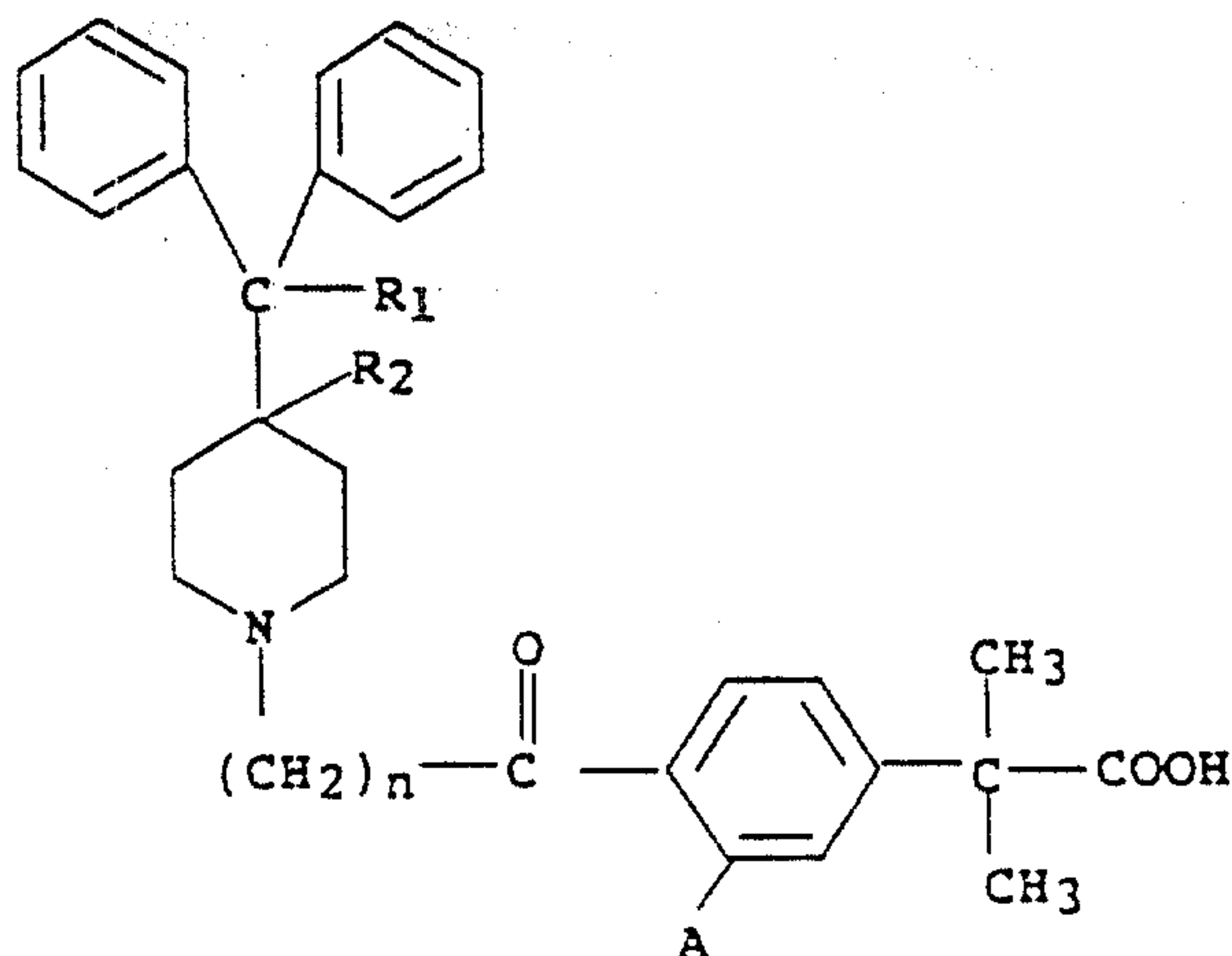
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(f) reacting the piperidine hydroxyethylphenylketone with chromium (IV) oxide, potassium permanganate, nitric acid, nitrogen dioxide, ruthenium (VIII) oxide, nickel peroxide, silver oxide, t-butyl chromate or xenic acid to produce a piperidine carboxyphenylketone of the formula

25

30

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-99-

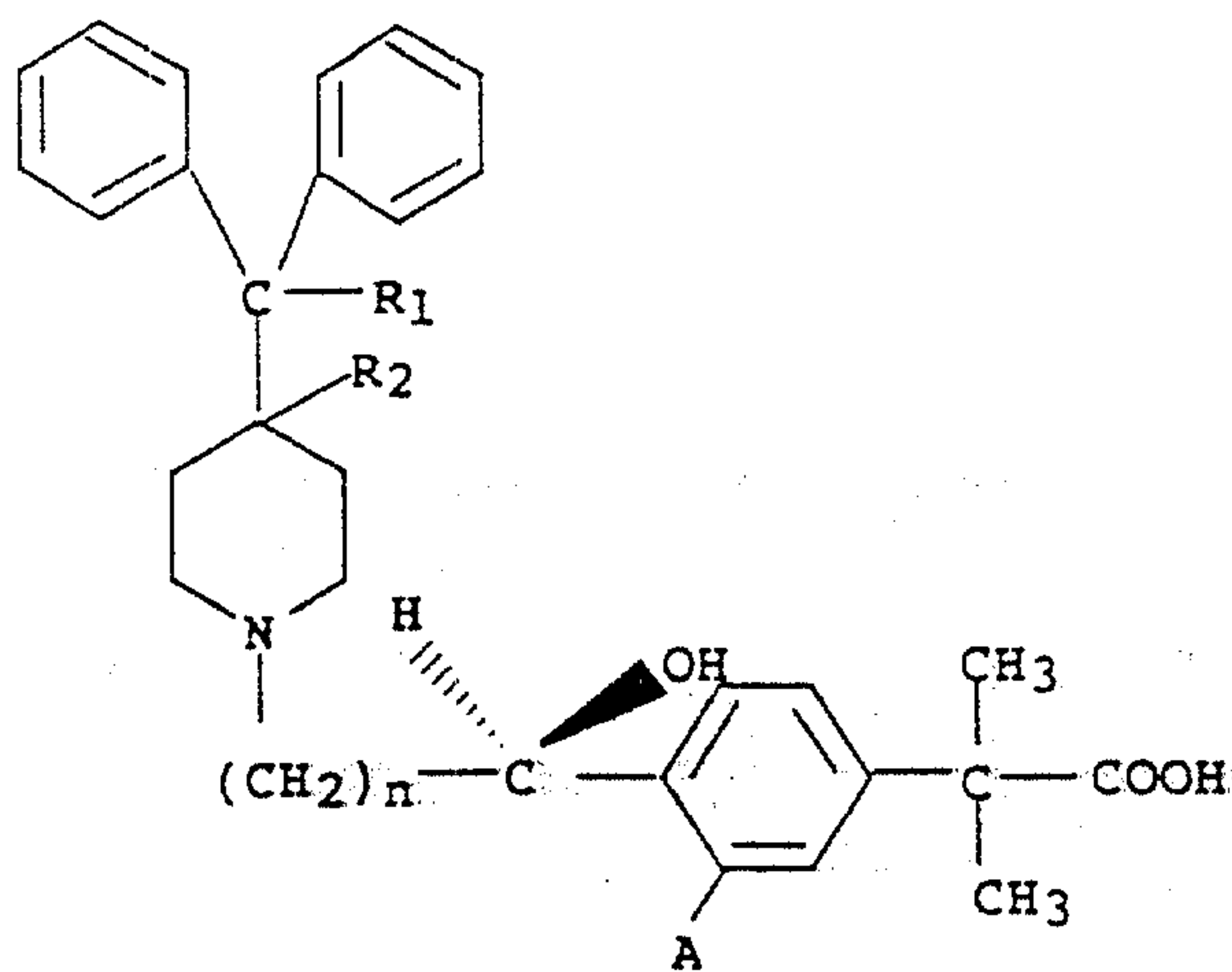
wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

5

(g) reacting the piperidine carboxyphenylketone with (+)-B-chlorodiisopinocampheylborane to produce a piperidine carboxyphenylalcohol of the formula

10

15



20

wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

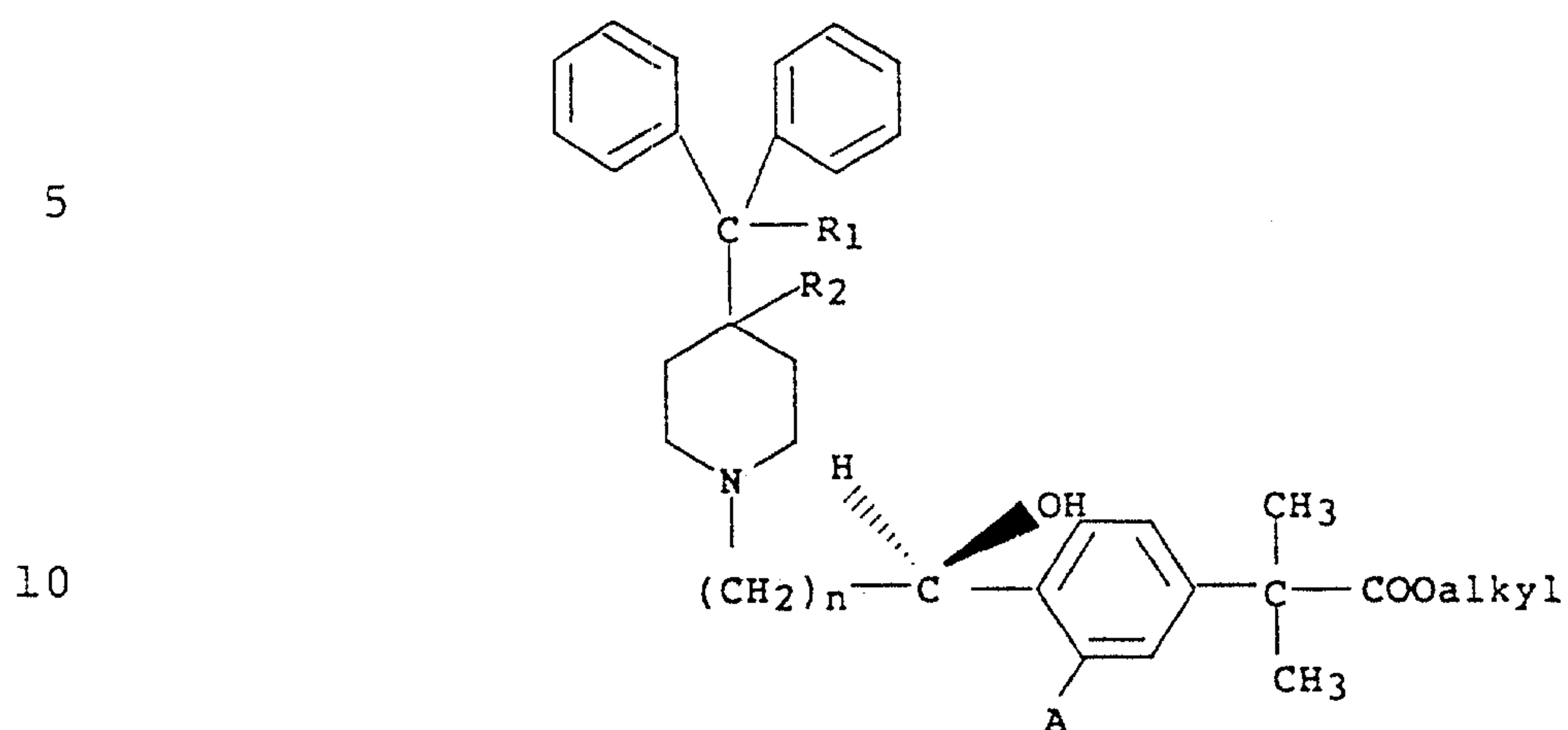
25

(h) optionally reacting the piperidine carboxyphenylalcohol with diazomethane or 2,2-dimethoxypropane or with thionyl chloride followed by an alcohol of the formula $HOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched to form a piperidine carboxyphenylalcohol ester of the formula

30

35

-100-

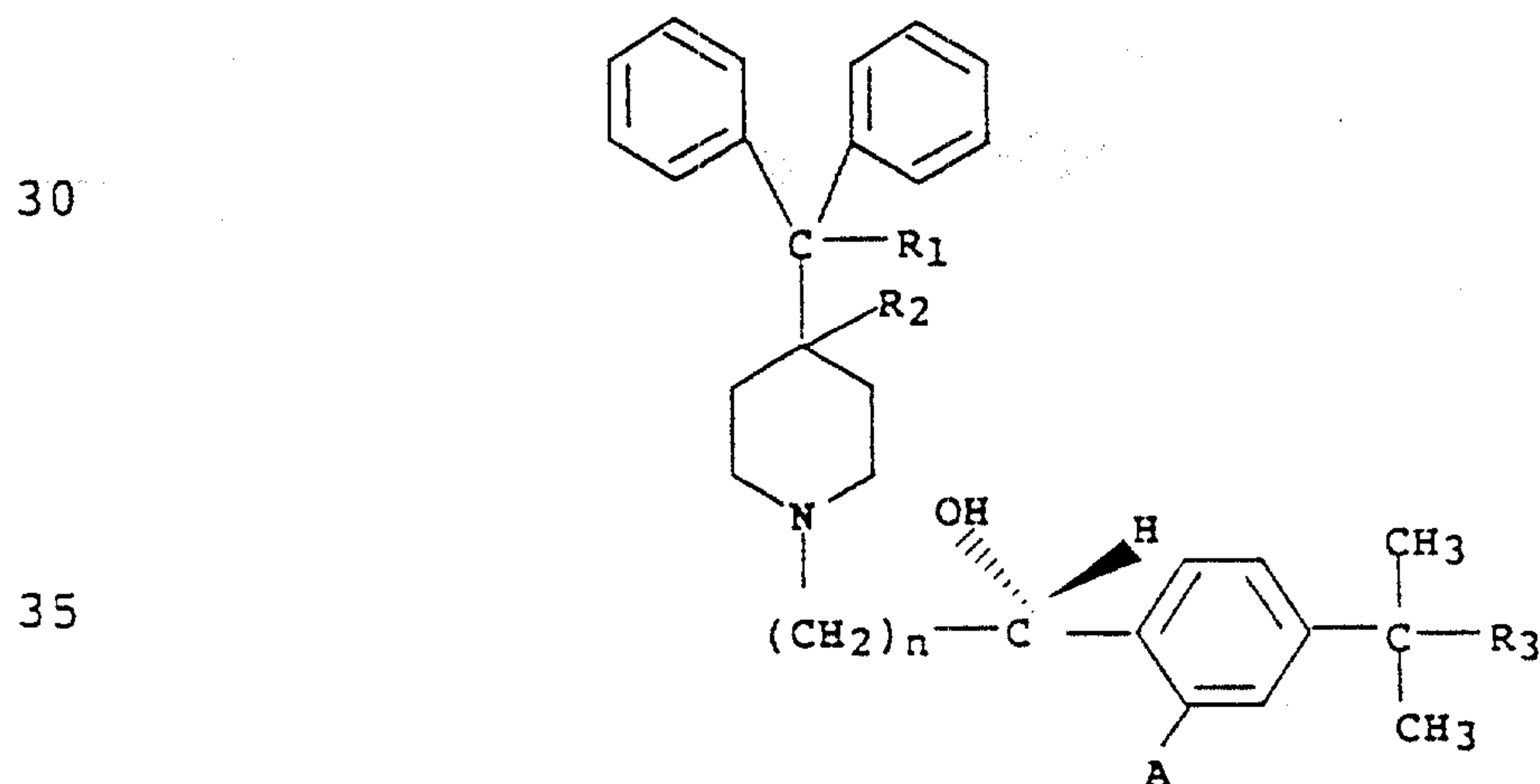


wherein R_1 , R_2 , n and alkyl are defined above and A is
 15 hydrogen or hydroxy with the proviso that when A is
 hydroxy, A may be optionally protected or unprotected; and

(i) optionally reacting the piperidine
 carboxyphenylalcohols or the piperidine
 20 carboxyphenylalcohol esters in which A is a protected
 hydroxy with mineral acids, strong organic acids, Lewis
 acids, aqueous mineral bases or catalytic hydrogenation to
 produce the unprotected piperidine carboxyphenylalcohols or
 the piperidine carboxyphenylalcohol esters.

25

18. A process for preparing a compound of the formula



-101-

wherein

R₁ represents hydrogen or hydroxy;

R₂ represents hydrogen; or

5 R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;

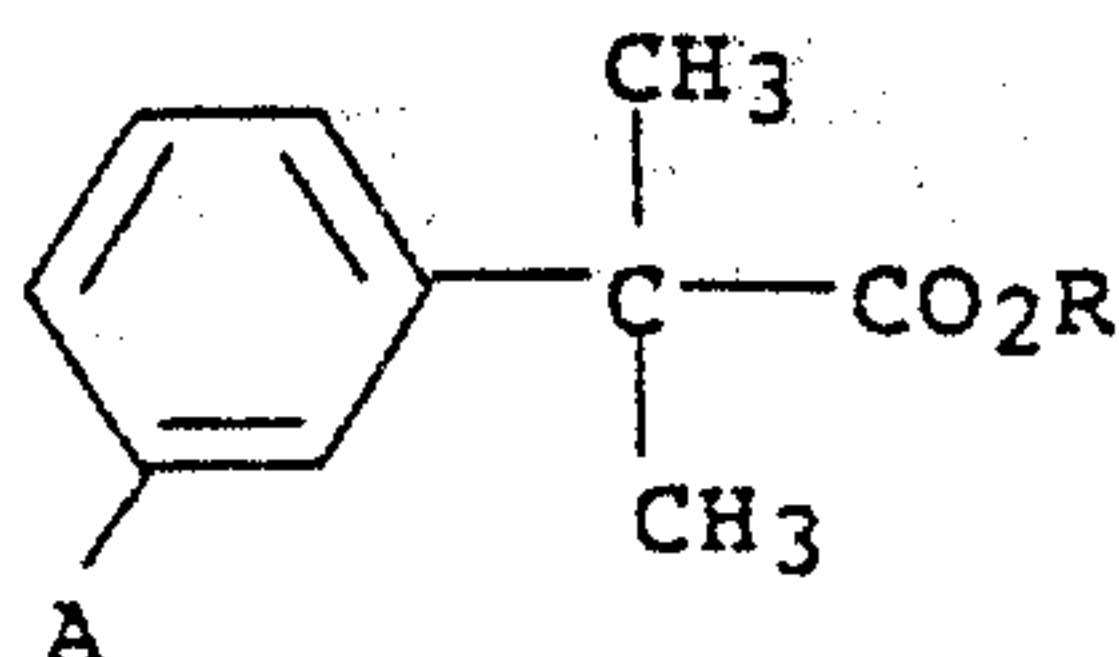
n is an integer of from 1 to 5;

R₃ is -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

10 A is hydrogen or hydroxy; and

pharmaceutically acceptable salts thereof comprising the steps of:

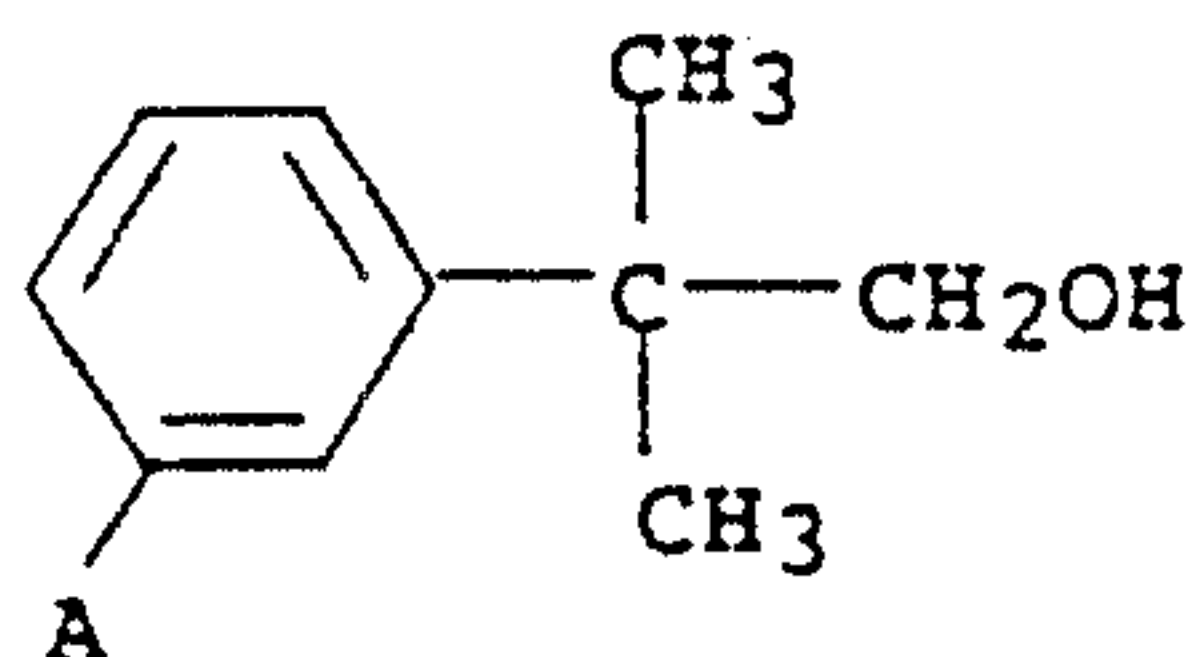
(a) reacting a benzeneacetic acid compound of the
15 formula



20

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-
25 methoxyethoxy)aluminum hydride, lithium aluminum hydride, diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

30



35

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

AMENDED SHEET

-102-

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

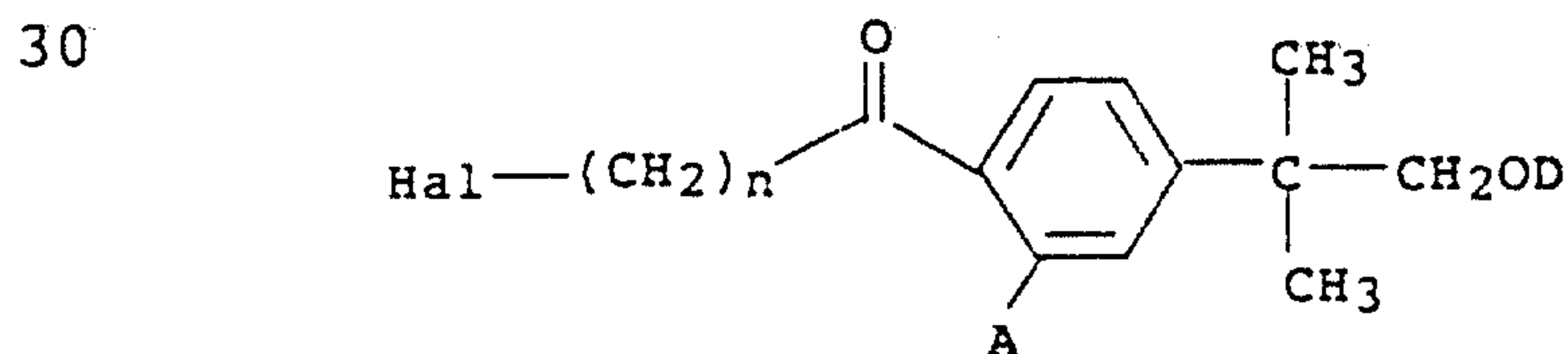


wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is C(=O)CH₃ or C(=O)C₆H₅;

(c) reacting the protected phenethyl alcohol with a ω-halo compound of the formula



wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω-halo protected hydroxyethylphenylketone of the formula

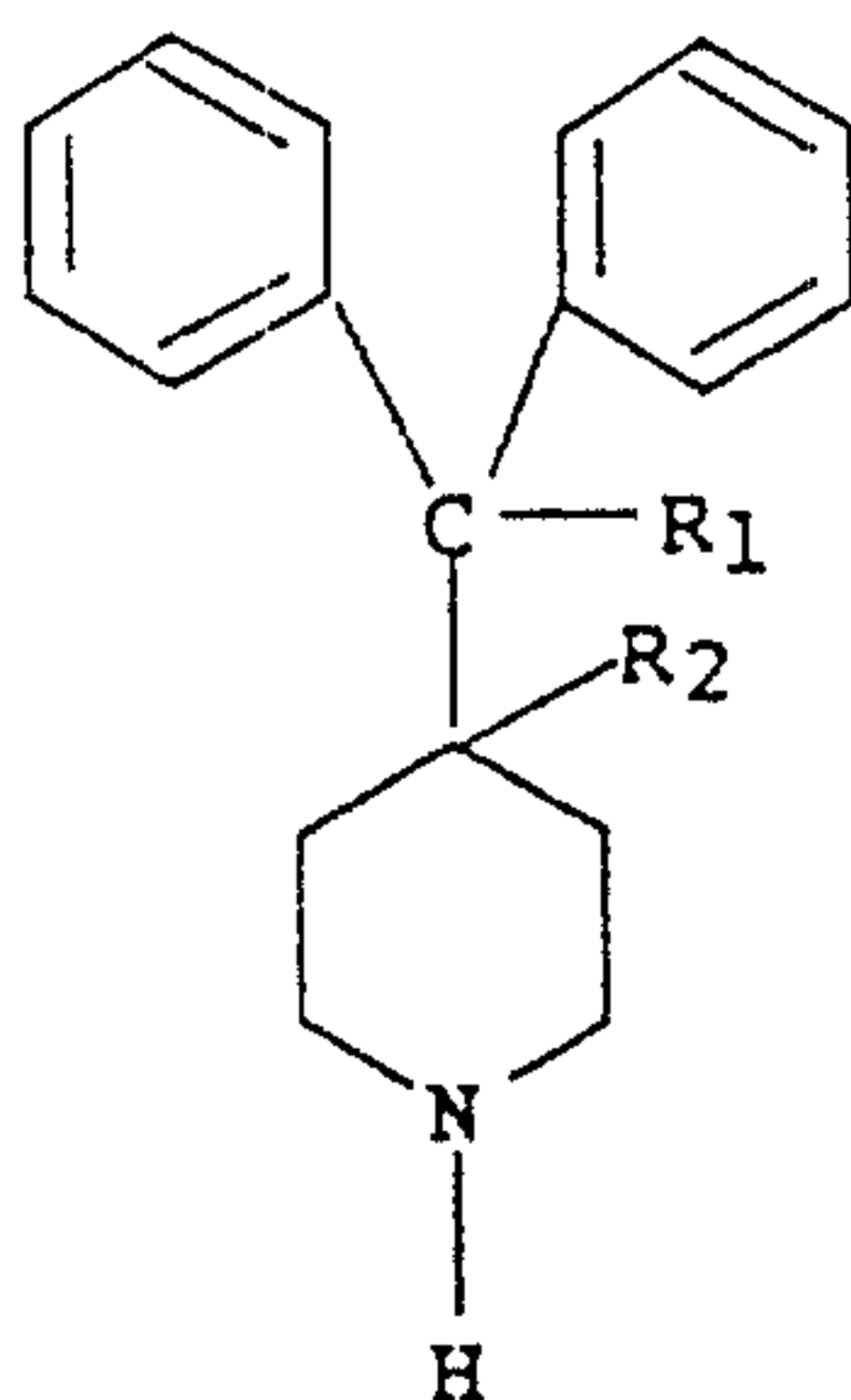


wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

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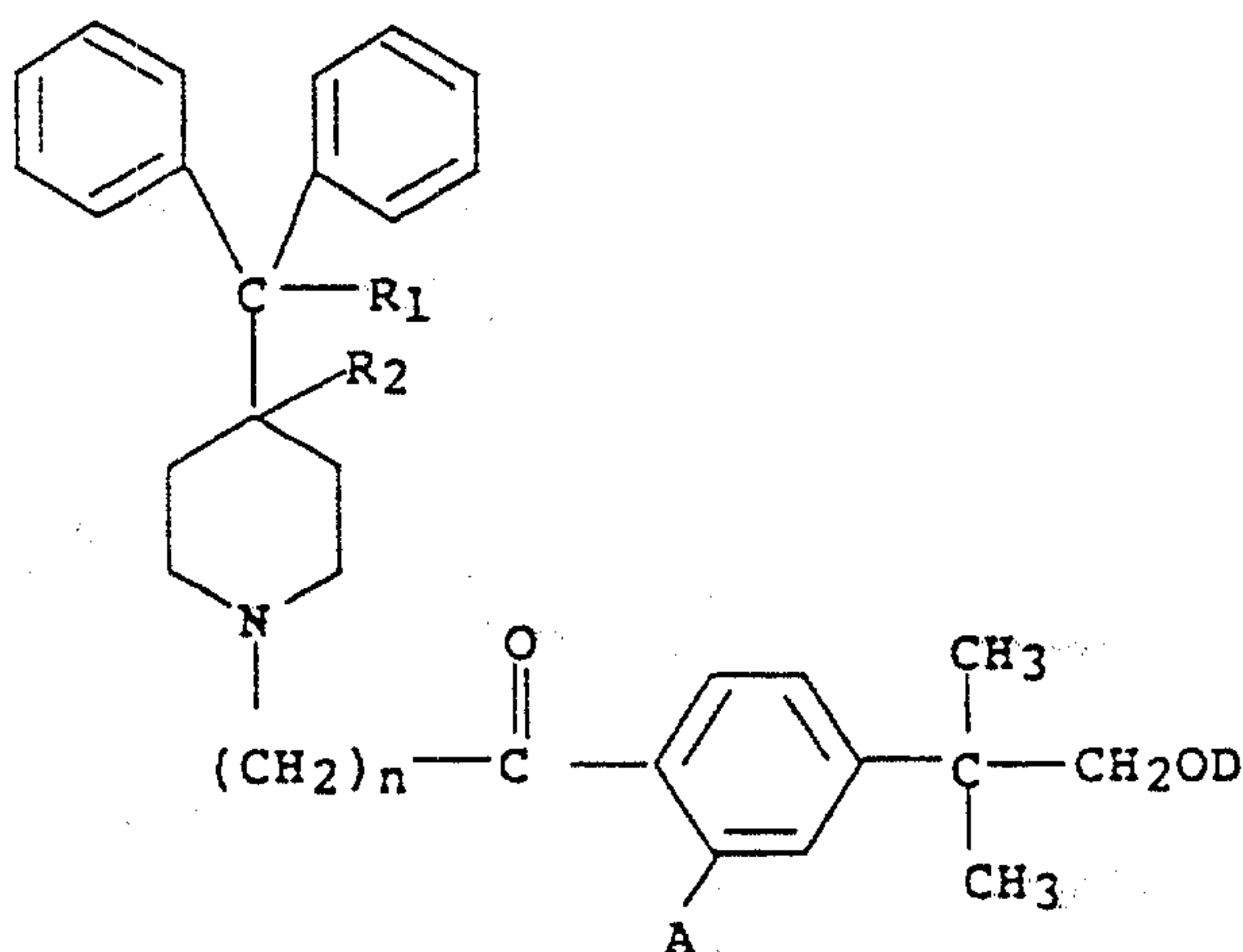


15 wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylketone of the formula

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25

30



wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

35

(e) reacting the piperidine protected hydroxyethylphenylketone with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium

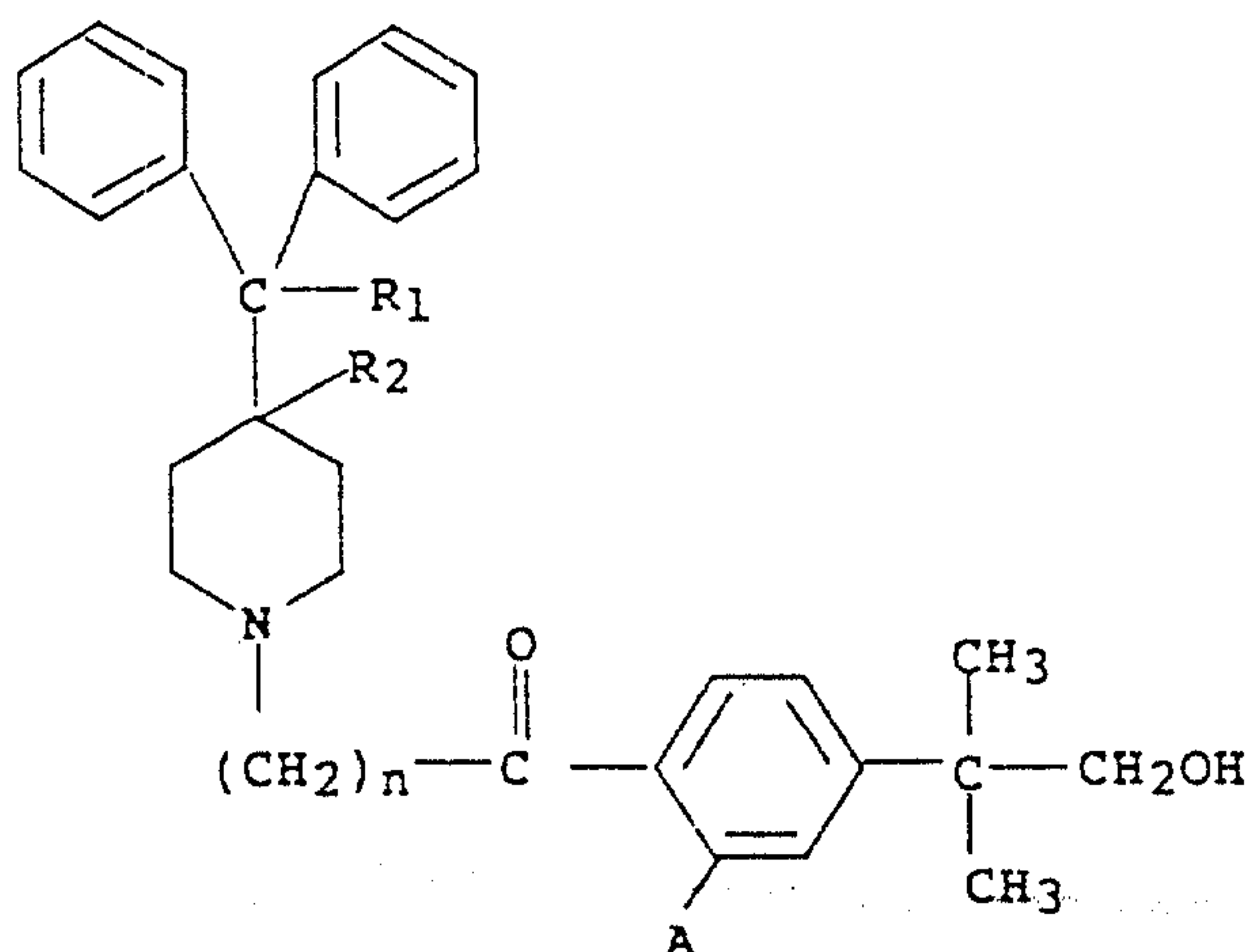
-104-

hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylketone of the formula

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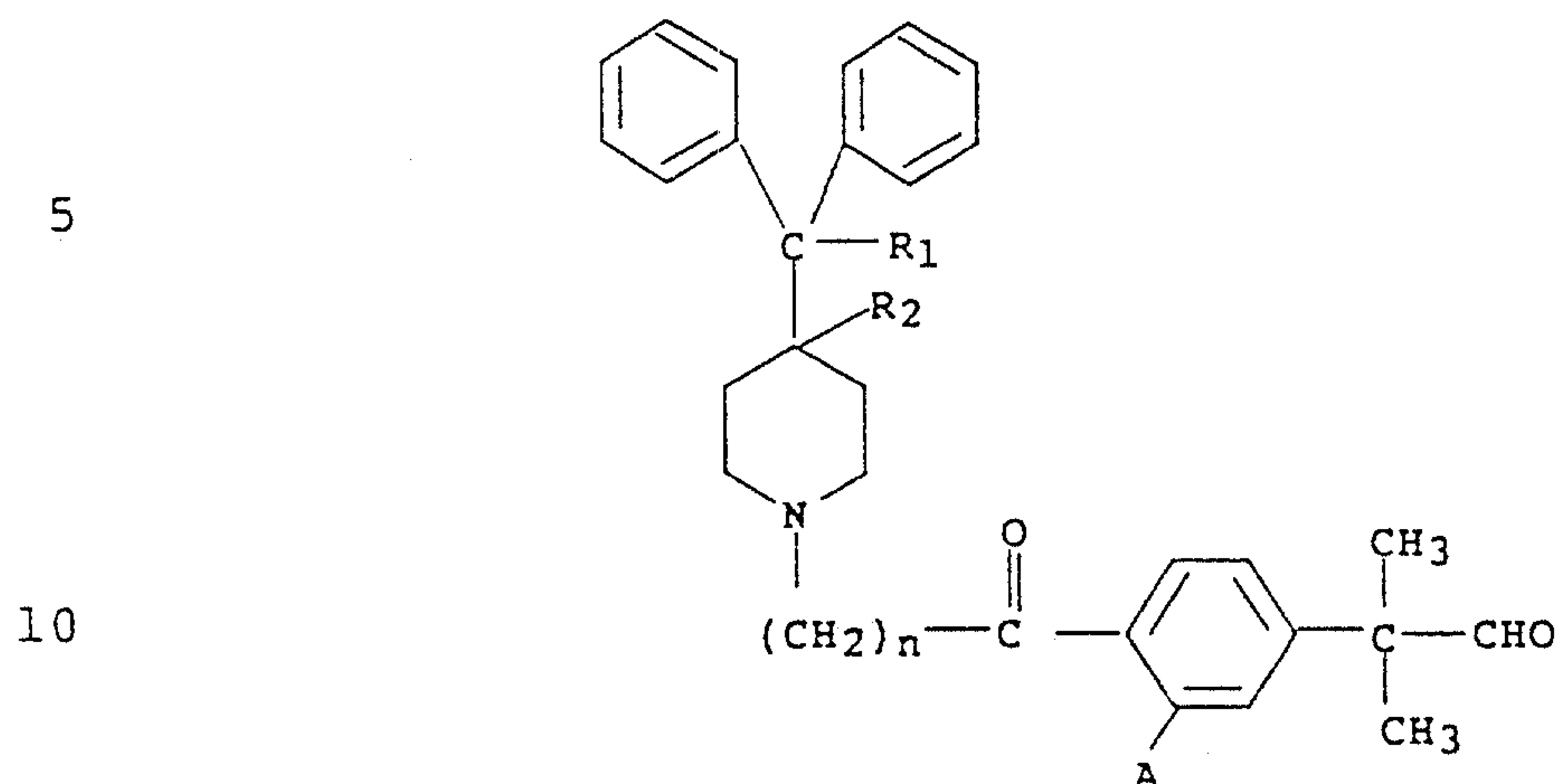
wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

20

(f) reacting the piperidine hydroxyethylphenylketone with dimethyl sulfoxide, oxalyl chloride and triethylamine or with Dess-Martin reagent, chromium (IV) oxide, nickel peroxide, sodium dichromate, potassium dichromate, t-butyl chromate, silver oxide, argentic picolinate manganese dioxide lead tetraacetate, dicyclohexylcarbodiimide, 2,3-dichloro-5,6-dicyanoquinone, tetrachloro-1,2-benzoquinone, 2,2,6,6-tetramethylpiperidiny-1-oxy (TEMPO) or quinolinium chlorochromate to produce a piperidine formylphenylketone of the formula

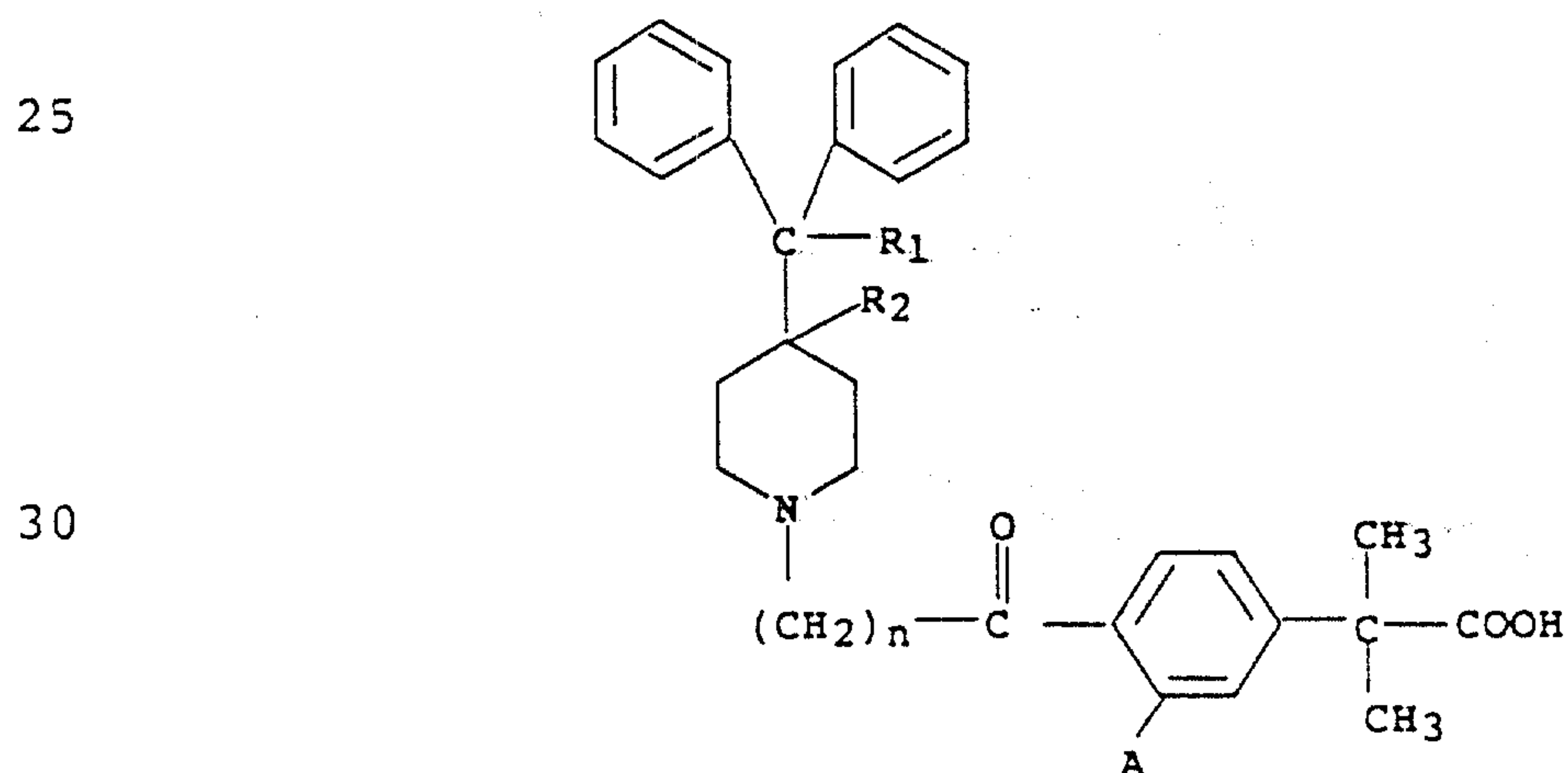
30

35



15 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(g) reacting the piperidine formylphenylketone with
 20 potassium permanganate, chromium (IV) aoxide, silver (I) oxide, silver oxide, argentic picolinate, peroxide, nitric acid, m-chloroperbenzoic acid and peracetic acid to produce a piperidine carboxyphenylketone of the formula



35 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

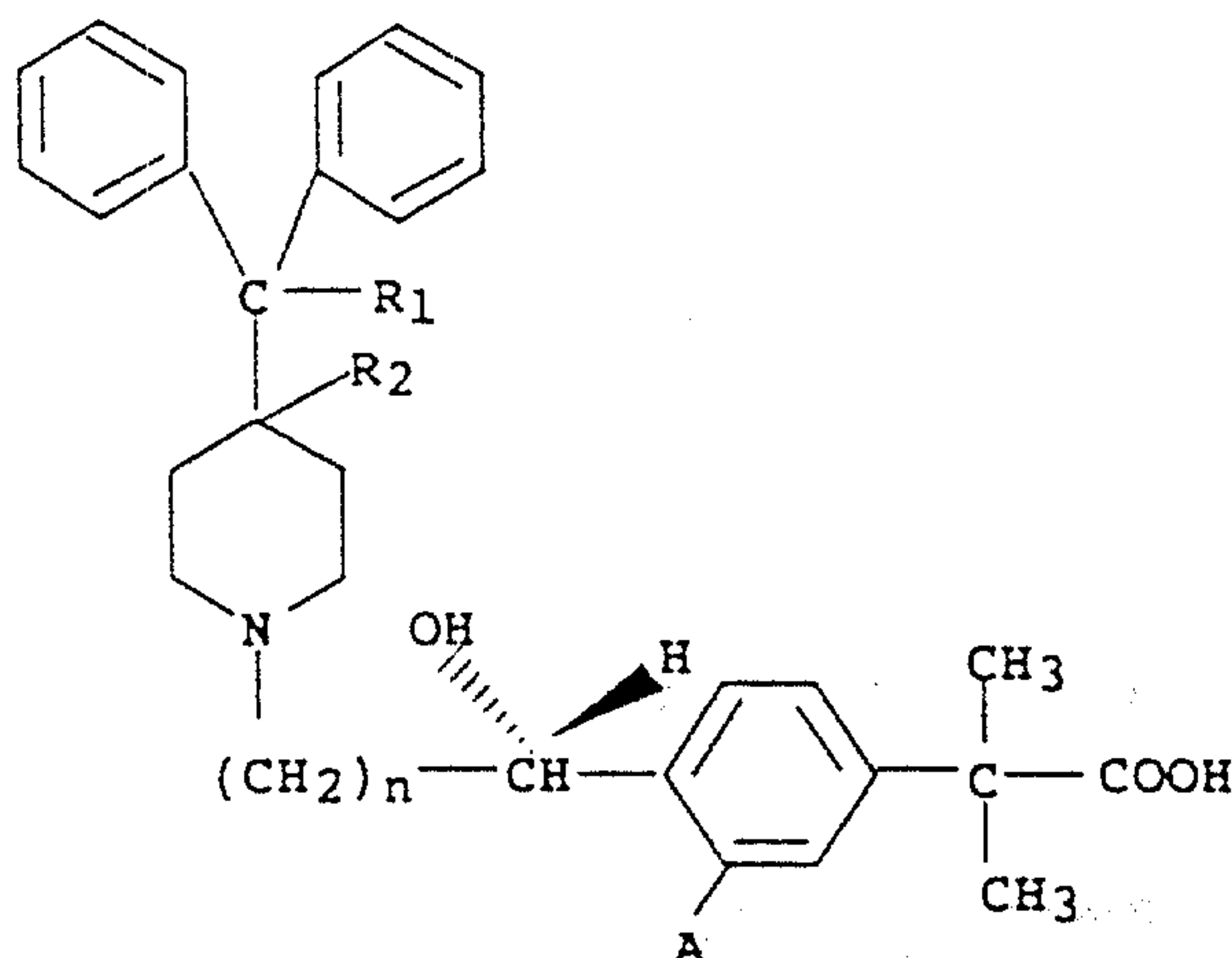
-106-

(h) reacting the piperidine carboxyphenylketone with (-)-B-chlorodiisopinocampheylborane to produce a piperidine carboxyphenylalcohol of the formula

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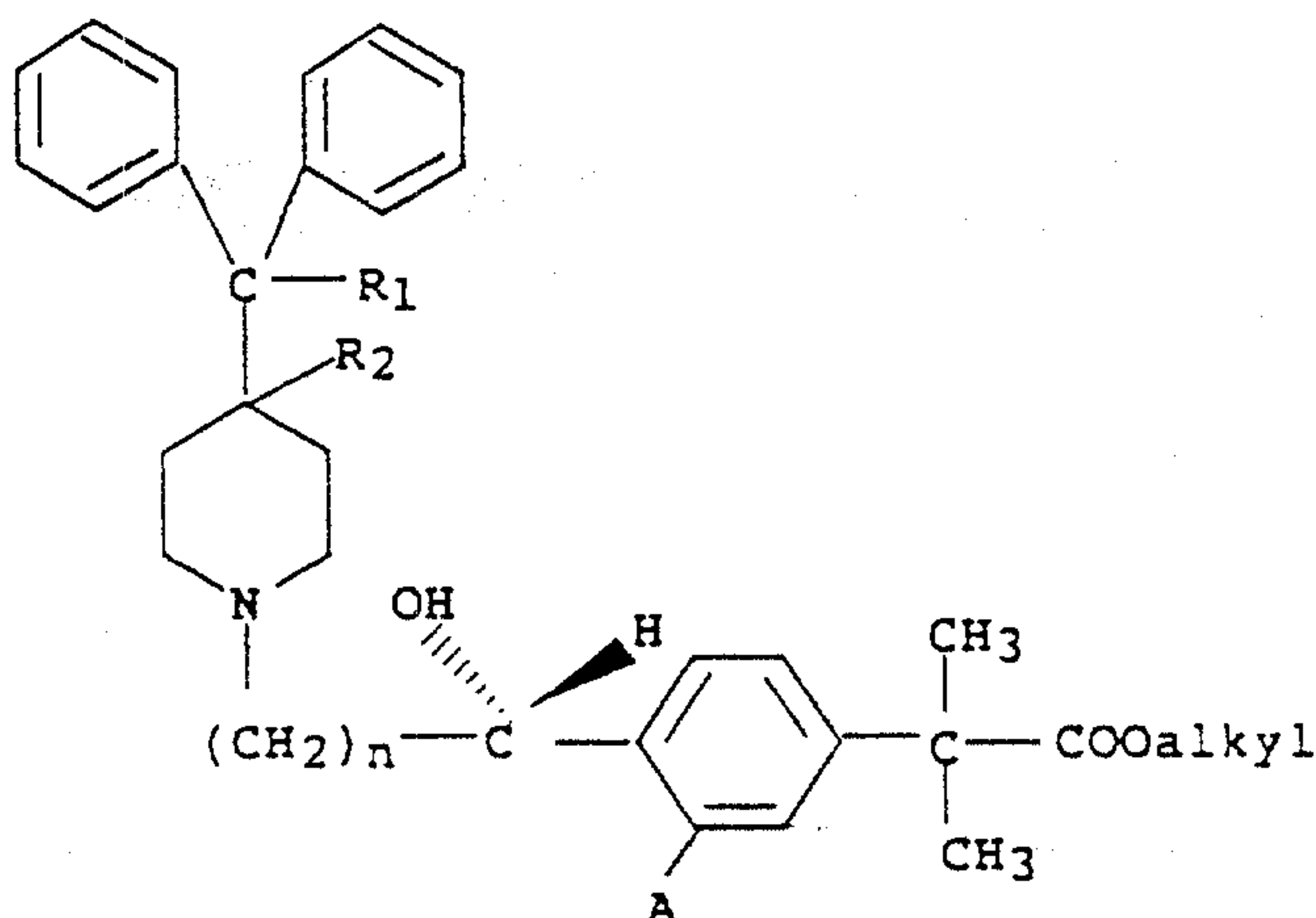
wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

20

(i) optionally reacting the piperidine carboxyphenylalcohol with diazomethane or 2,2-dimethoxypropane or with thionyl chloride followed by an alcohol of the formula $HOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched to form a piperidine carboxyphenylalcohol ester of the formula

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AMENDED SHEET

-107-

wherein R_1 , R_2 , n and alkyl are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected; and

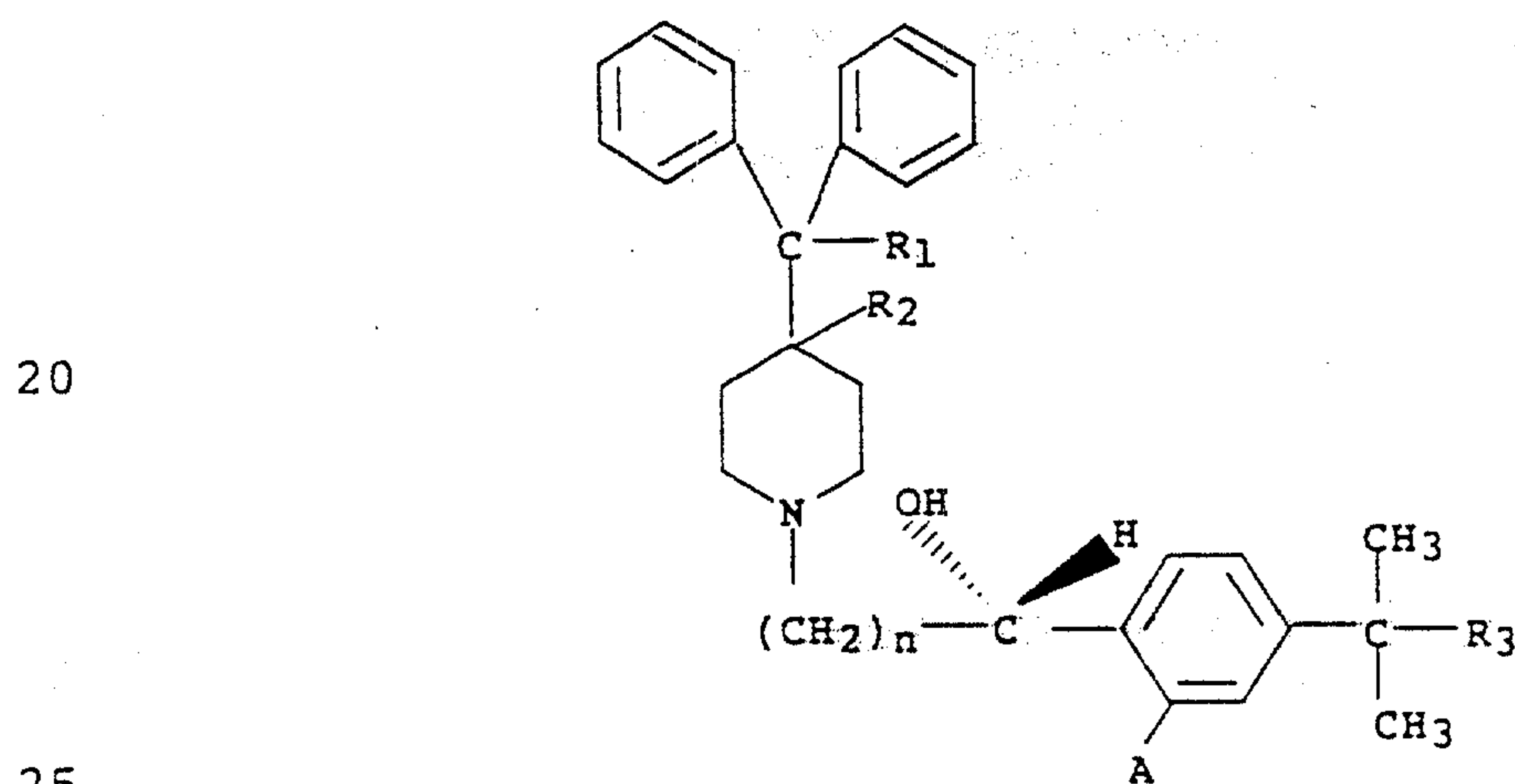
5

(j) optionally reacting the piperidine carboxyphenylalcohols or the piperidine carboxyphenylalcohol esters in which A is a protected hydroxy with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine carboxyphenylalcohols or the piperidine carboxyphenylalcohol esters.

10

19. A process for preparing a compound of the formula

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20

25

wherein

R_1 represents hydrogen or hydroxy;

R_2 represents hydrogen; or

30 R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;

n is an integer of from 1 to 5;

R_3 is $-COOH$ or $-COOalkyl$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

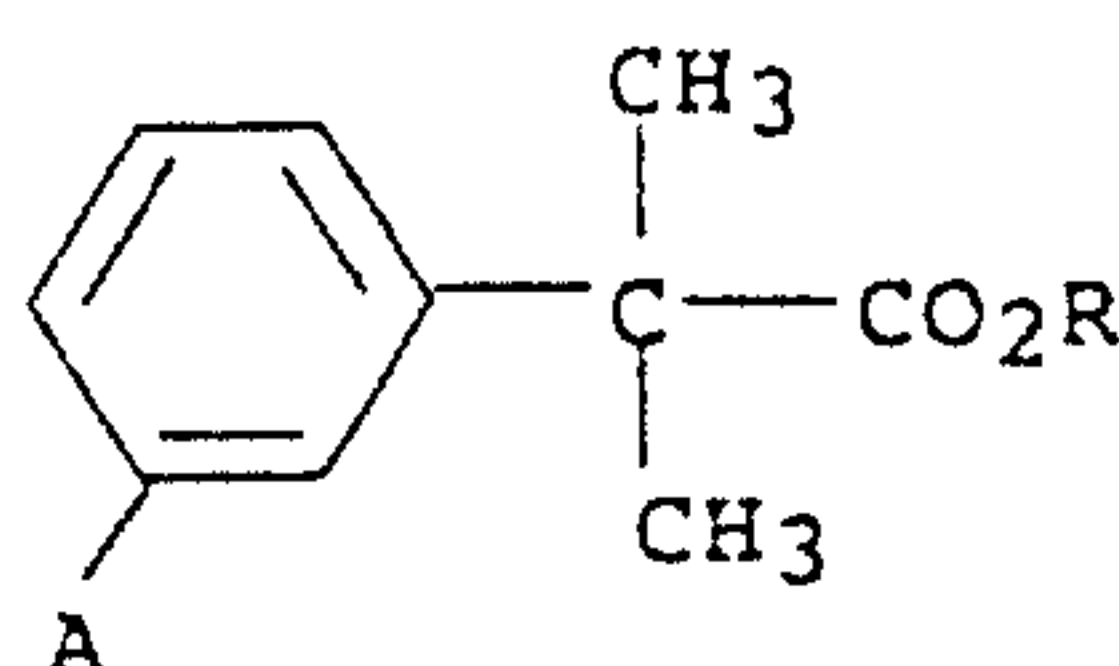
35 A is hydrogen or hydroxy; and

pharmaceutically acceptable salts thereof comprising the steps of:

AMENDED SHEET

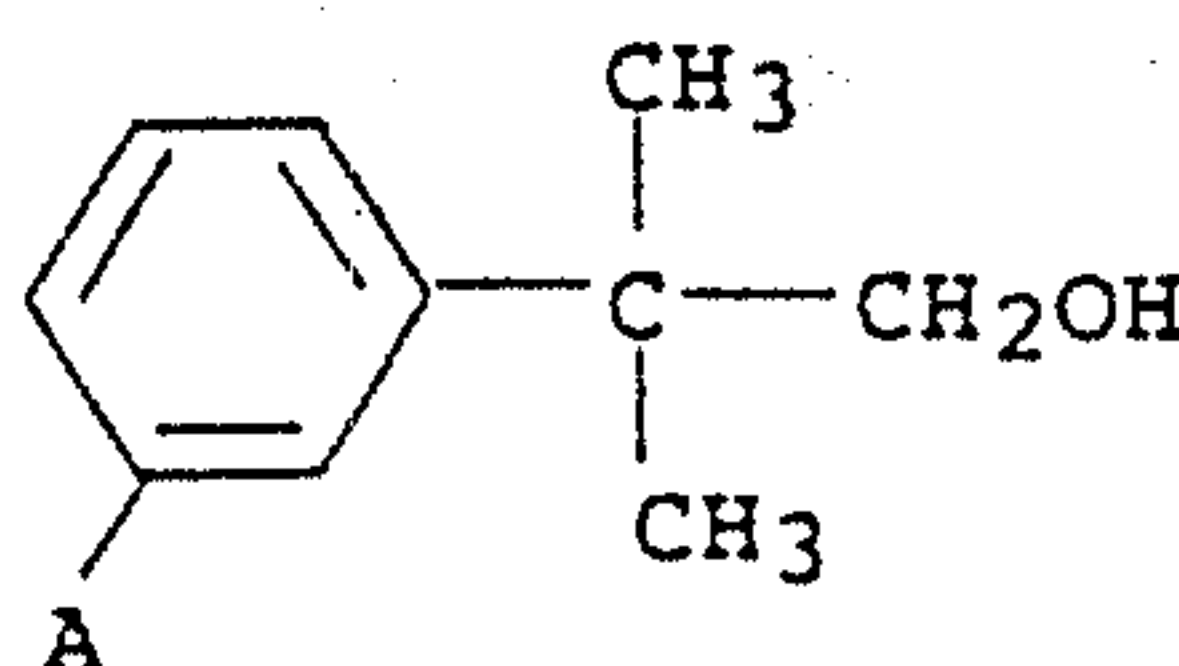
(a) reacting a benzeneacetic acid compound of the formula

5



10 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, 15 diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

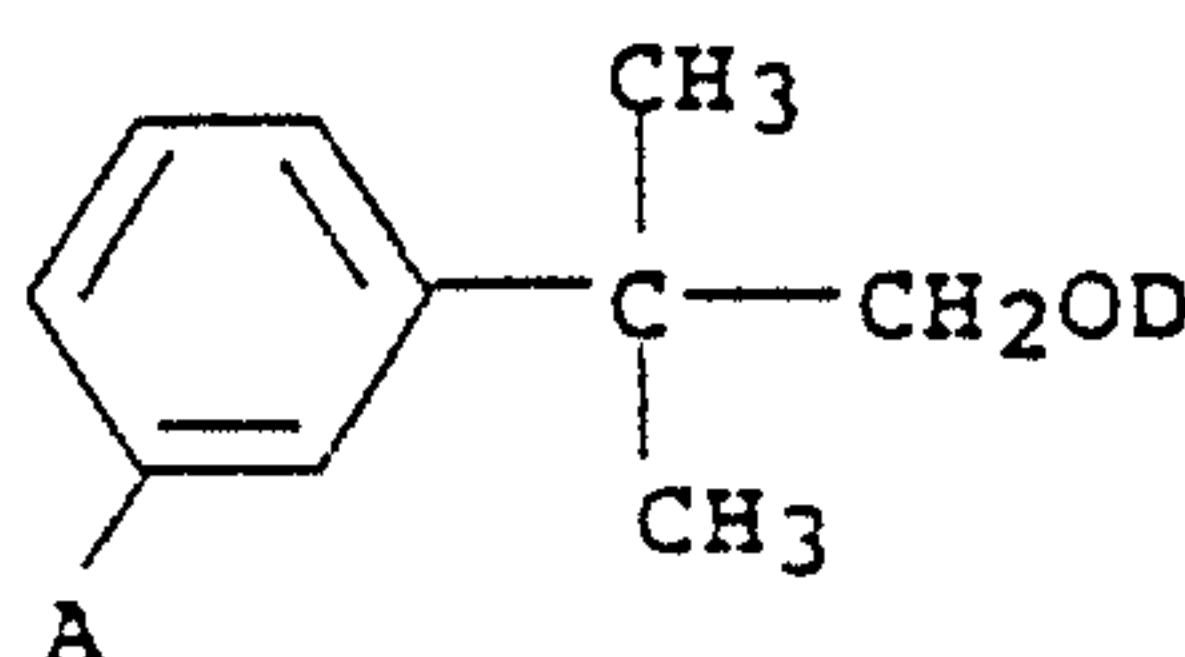
20



25 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine 30 to give a protected phenethyl alcohol of the formula

35



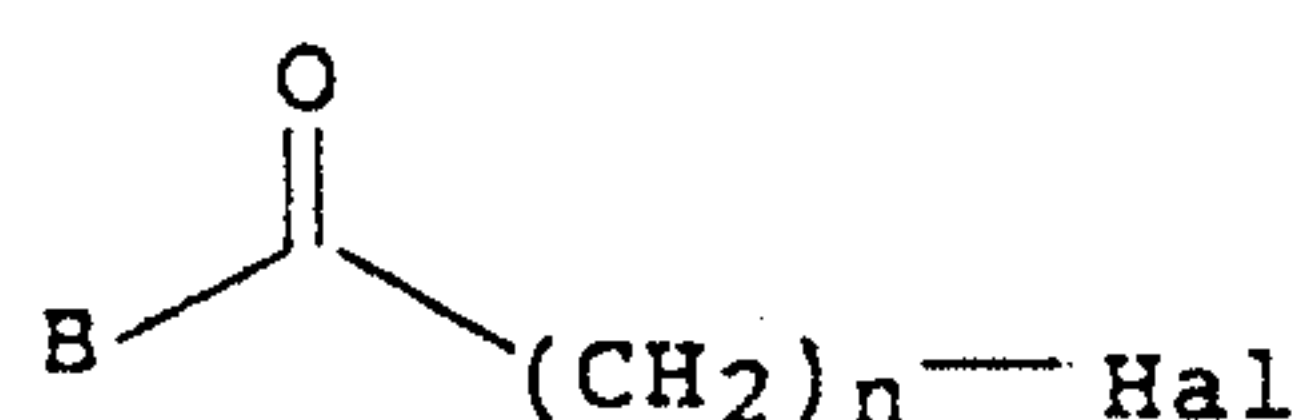
-109-

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is $C(=O)CH_3$ or $C(=O)C_6H_5$;

5

(c) reacting the protected phenethyl alcohol with a ω -halo compound of the formula

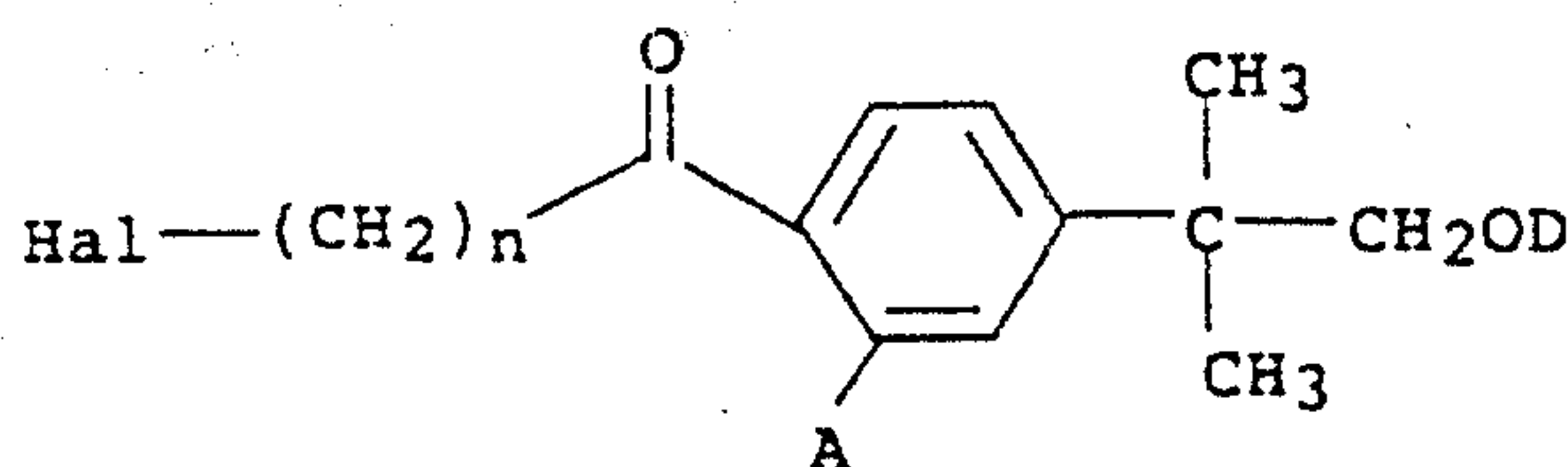
10



15

wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula

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25

wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

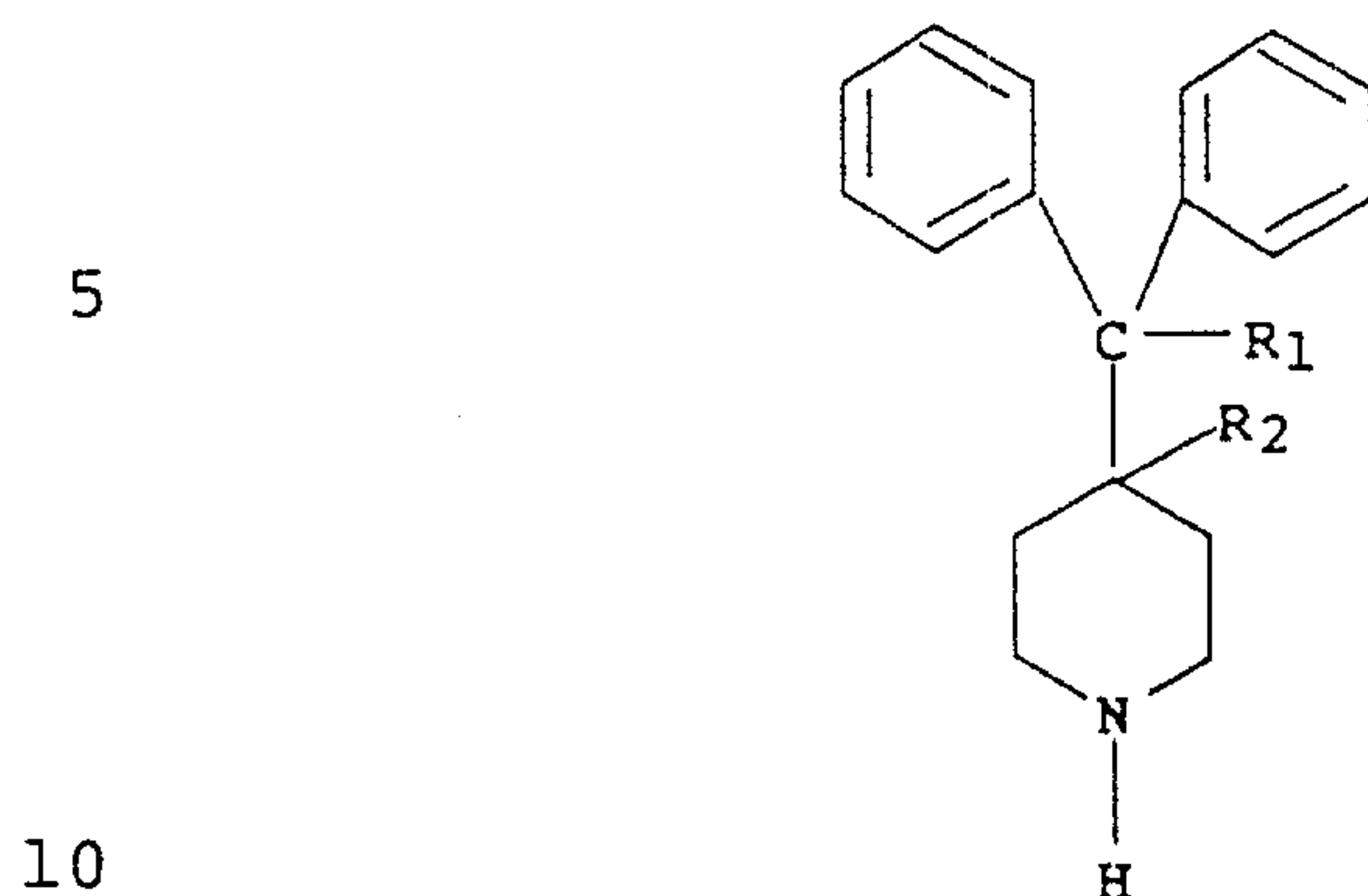
30

(d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

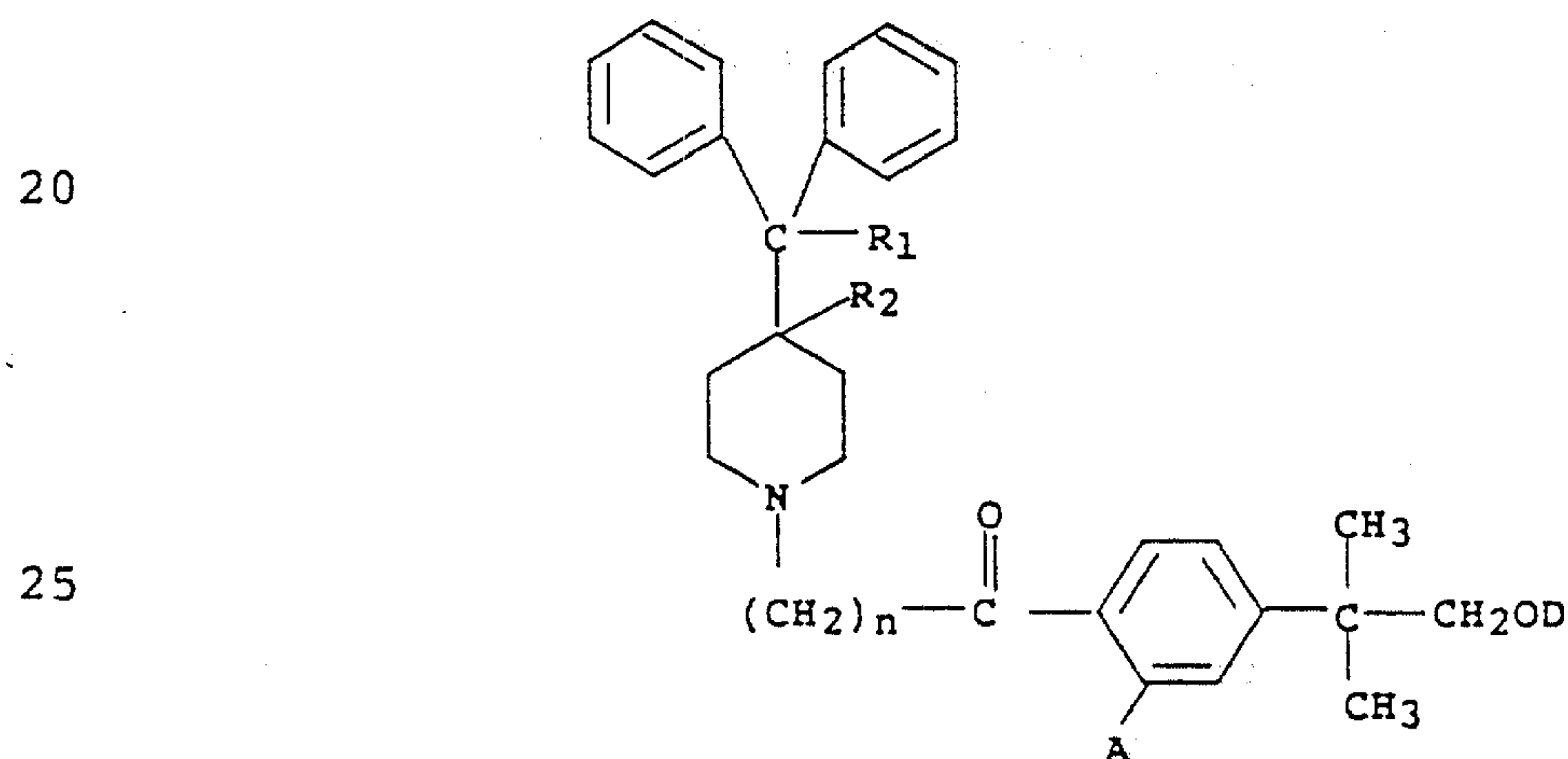
35

AMENDED SHEET

-110-



wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylketone of the formula

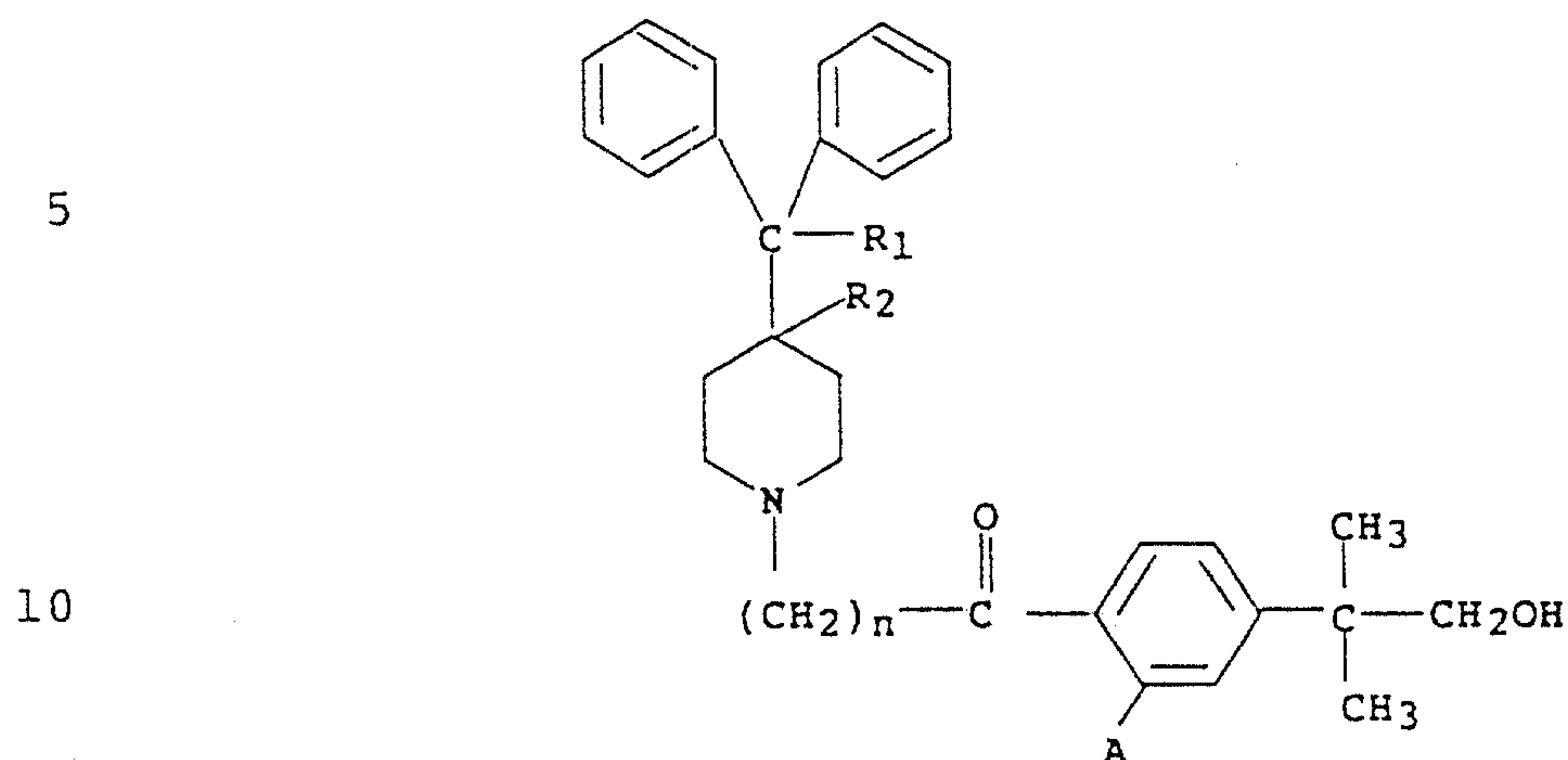


wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(e) reacting the piperidine protected hydroxyethylphenylketone with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylketone of the formula

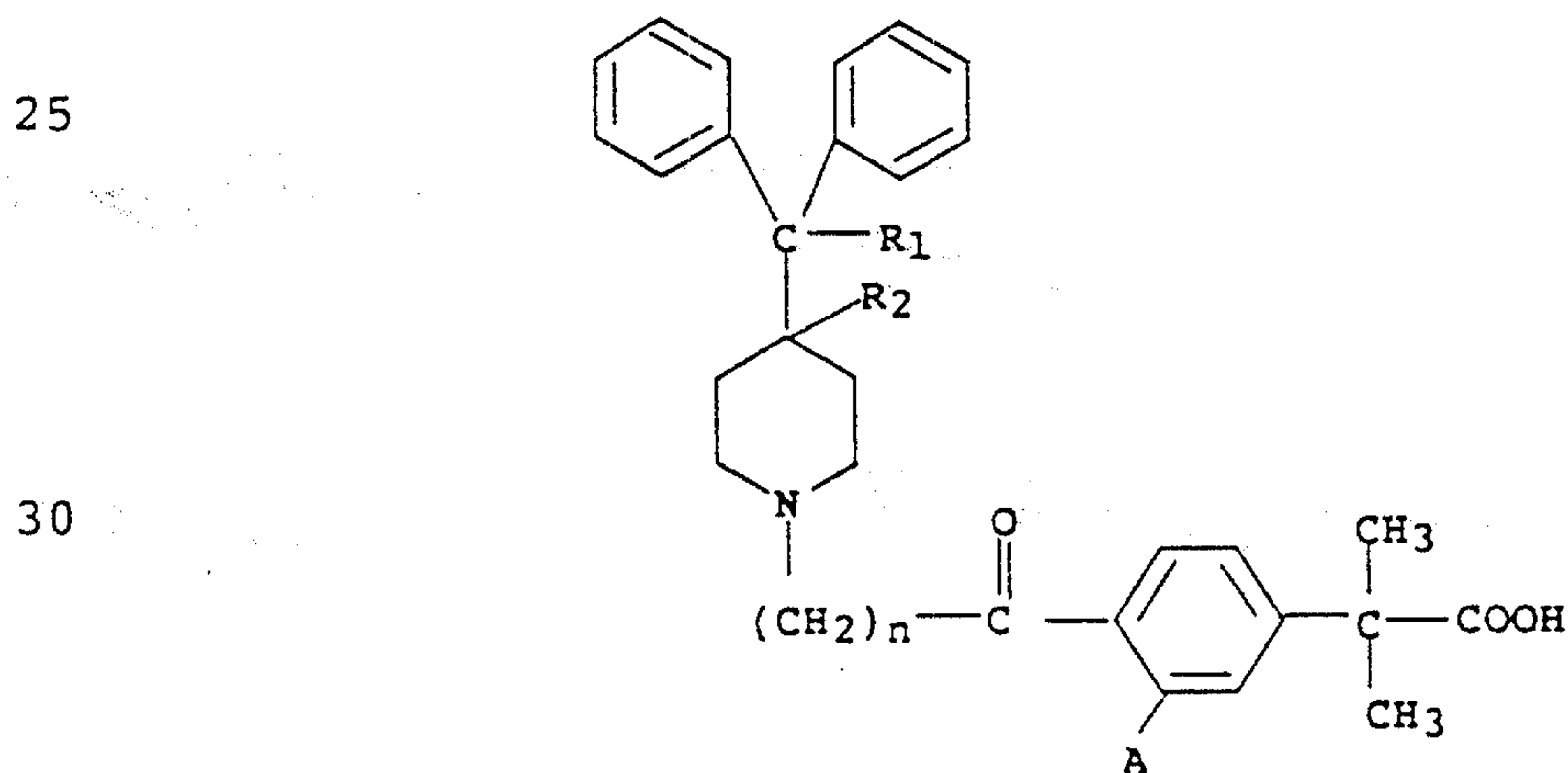
AMENDED SHEET

-111-



15 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(f) reacting the piperidine hydroxyethylphenylketone with chromium (IV) oxide, potassium permanganate, nitric acid, nitrogen dioxide, ruthenium (VIII) oxide, nickel
20 peroxide, silver oxide, t-butyl chromate or xenic acid to produce a piperidine carboxyphenylketone of the formula



-112-

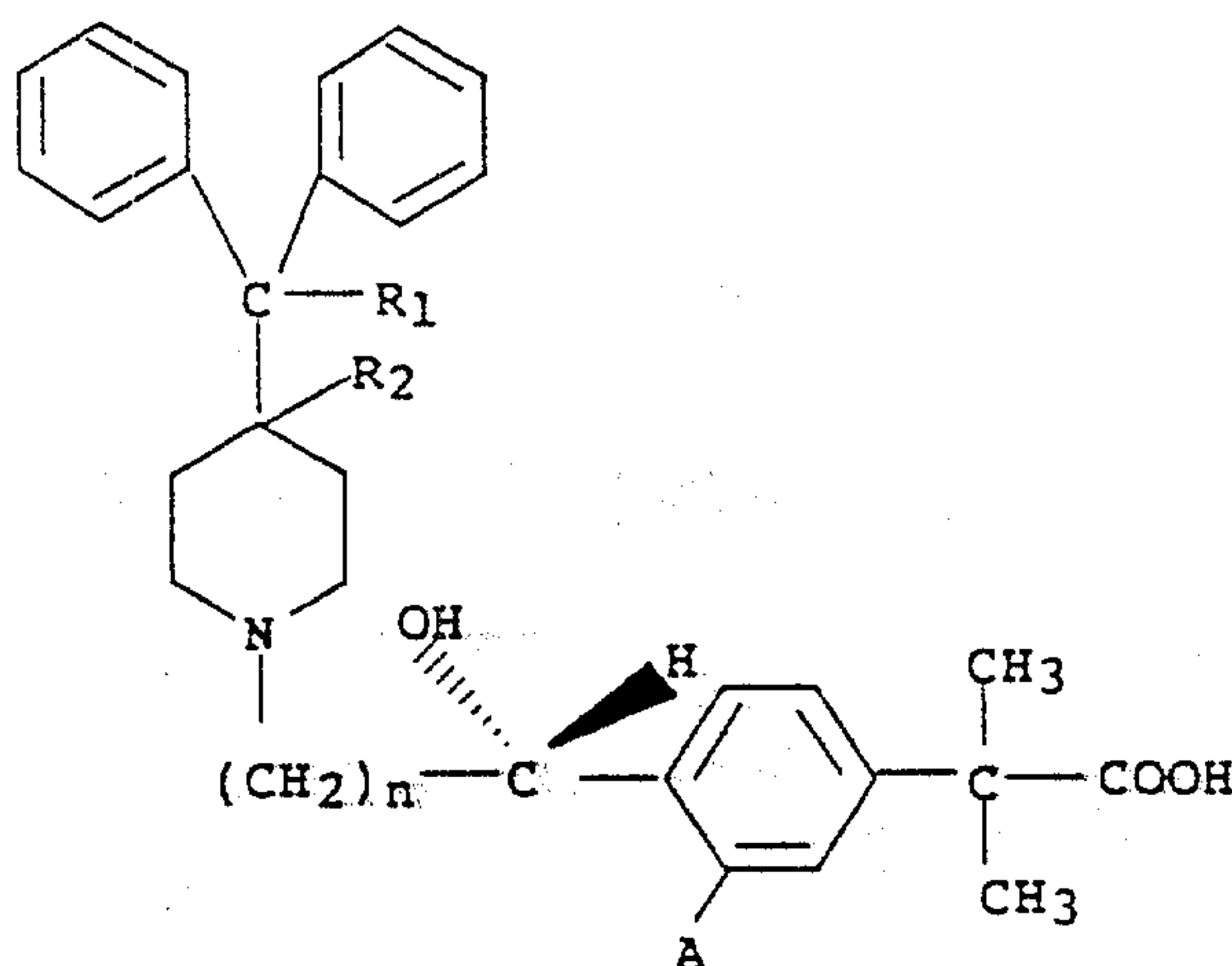
wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

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(g) reacting the piperidine carboxyphenylketone with (-)-B-chlorodiisopinocampheylborane to produce a piperidine carboxyphenylalcohol of the formula

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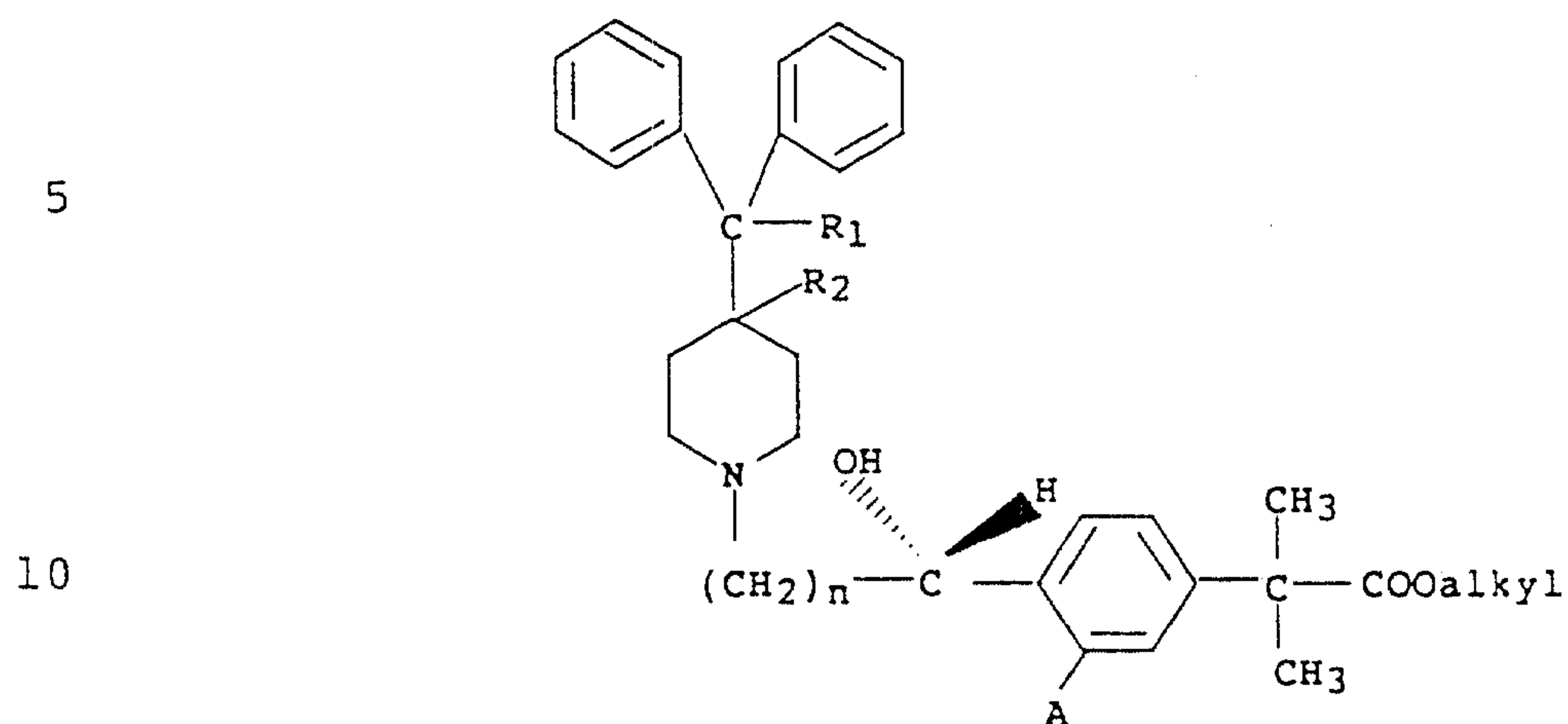
wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

25

(h) optionally reacting the piperidine carboxyphenylalcohol with diazomethane or 2,2-dimethoxypropane or with thionyl chloride followed by an alcohol of the formula HOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched to form a piperidine carboxyphenylalcohol ester of the formula

30

35



wherein R_1 , R_2 , n and alkyl are defined above and A is
 15 hydrogen or hydroxy with the proviso that when A is
 hydroxy, A may be optionally protected or unprotected; and

(i) optionally reacting the piperidine
 carboxyphenylalcohols or the piperidine
 20 carboxyphenylalcohol esters in which A is a protected
 hydroxy with mineral acids, strong organic acids, Lewis
 acids, aqueous mineral bases or catalytic hydrogenation to
 produce the unprotected piperidine carboxyphenylalcohols or
 the piperidine carboxyphenylalcohol esters.

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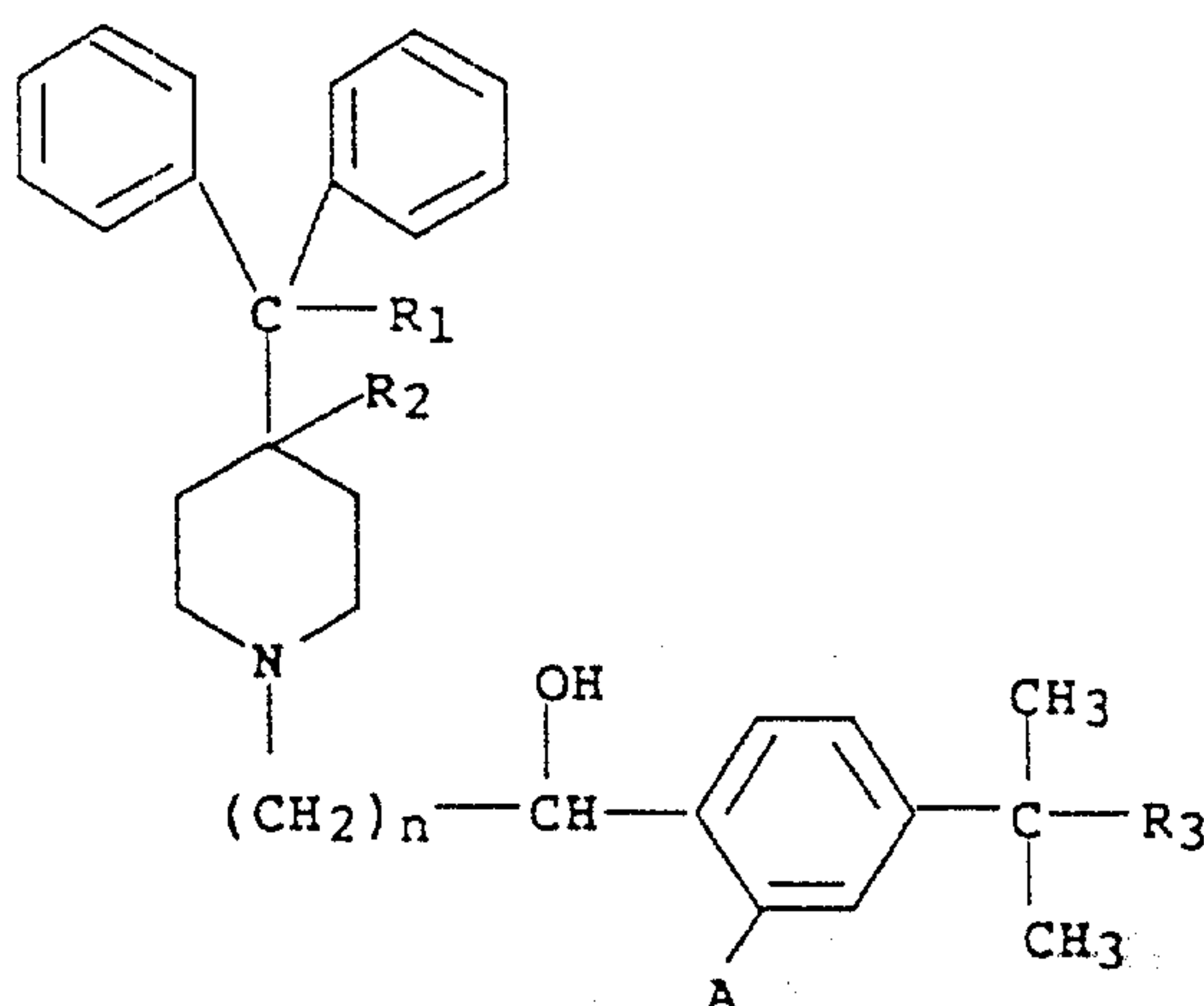
-114-

20. A process for preparing a compound of the formula

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wherein:

R₁ represents hydrogen or hydroxy;

R₂ represents hydrogen; or

20

R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;

n is an integer of from 1 to 5;

R₃ is -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

25

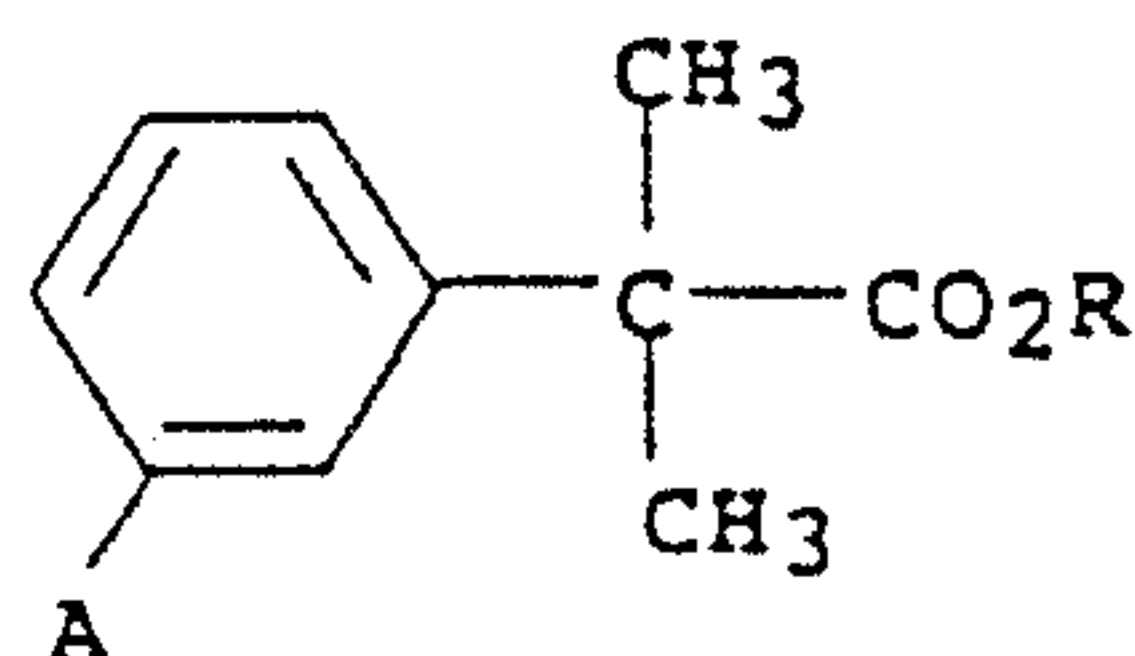
A is hydrogen or hydroxy; and

pharmaceutically acceptable salts thereof comprising the steps of:

30

(a) reacting a benzeneacetic acid compound of the formula

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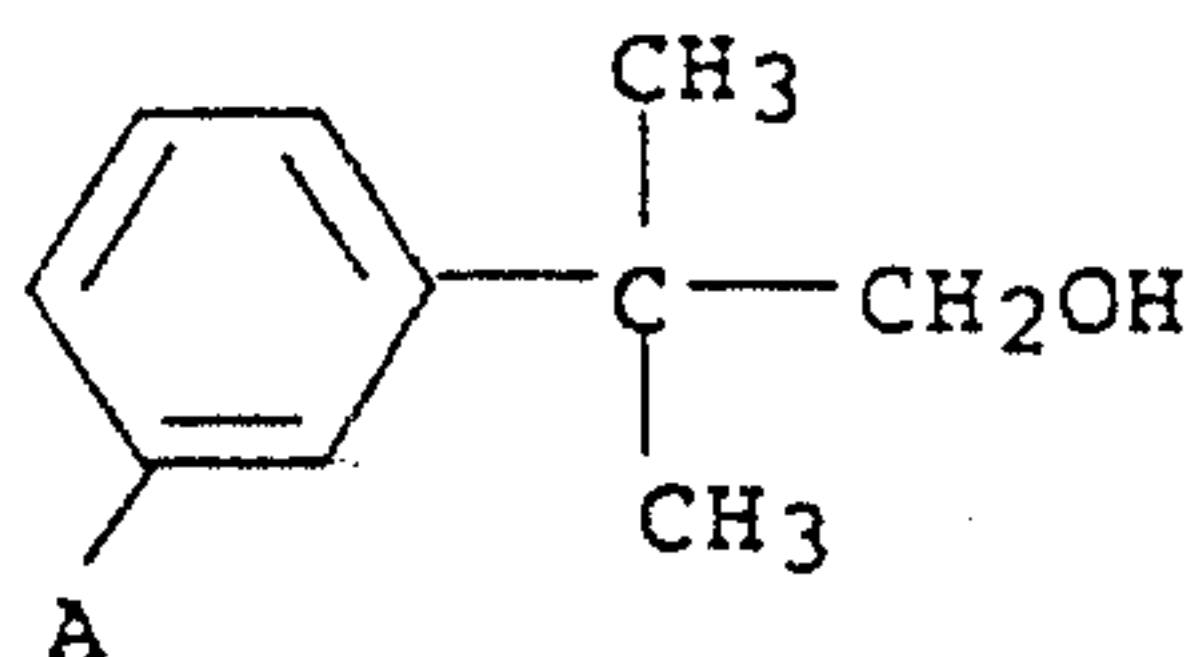


AMENDED SHEET

-115-

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

10

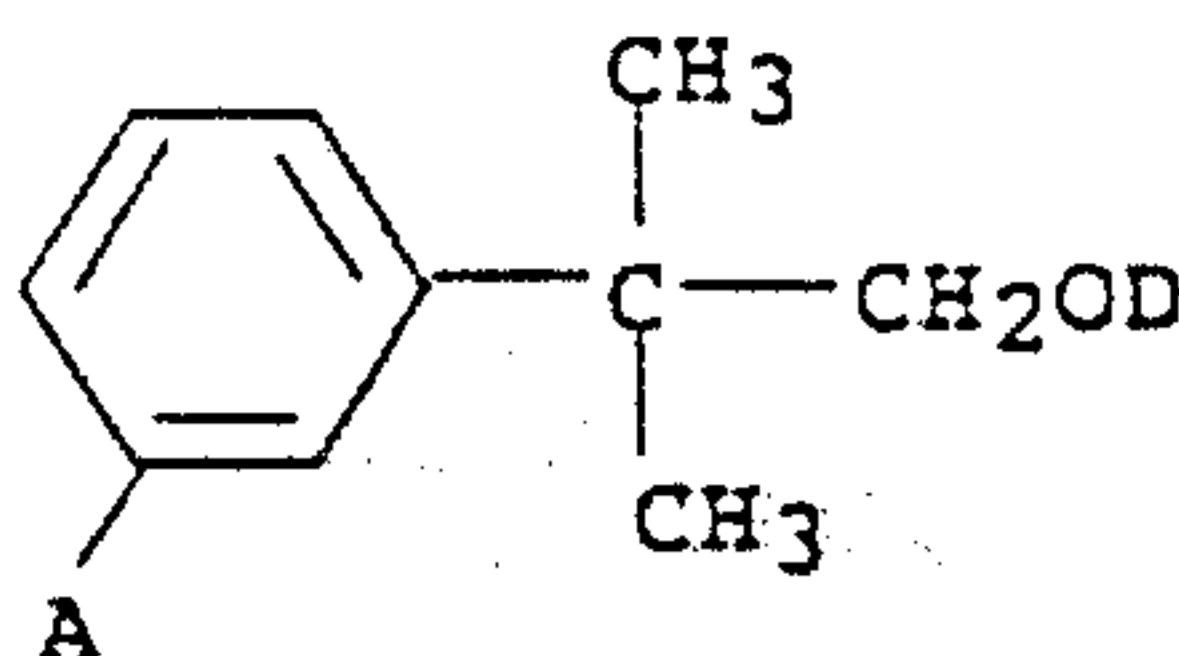


15

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(b) reacting the phenethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

25



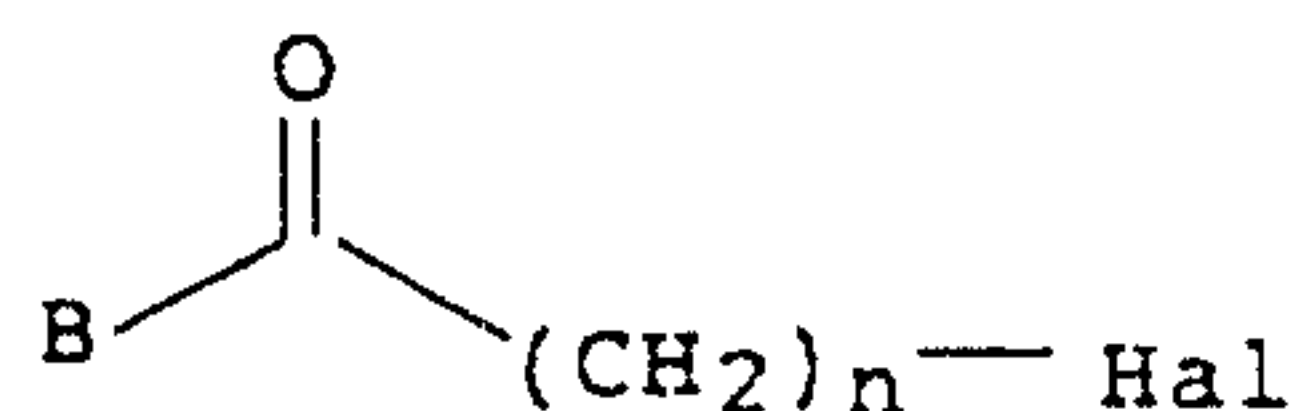
30

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is C(=O)CH₃ or C(=O)C₆H₅;

(c) reacting the protected phenethyl alcohol with a ω-halo compound of the formula

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-116-

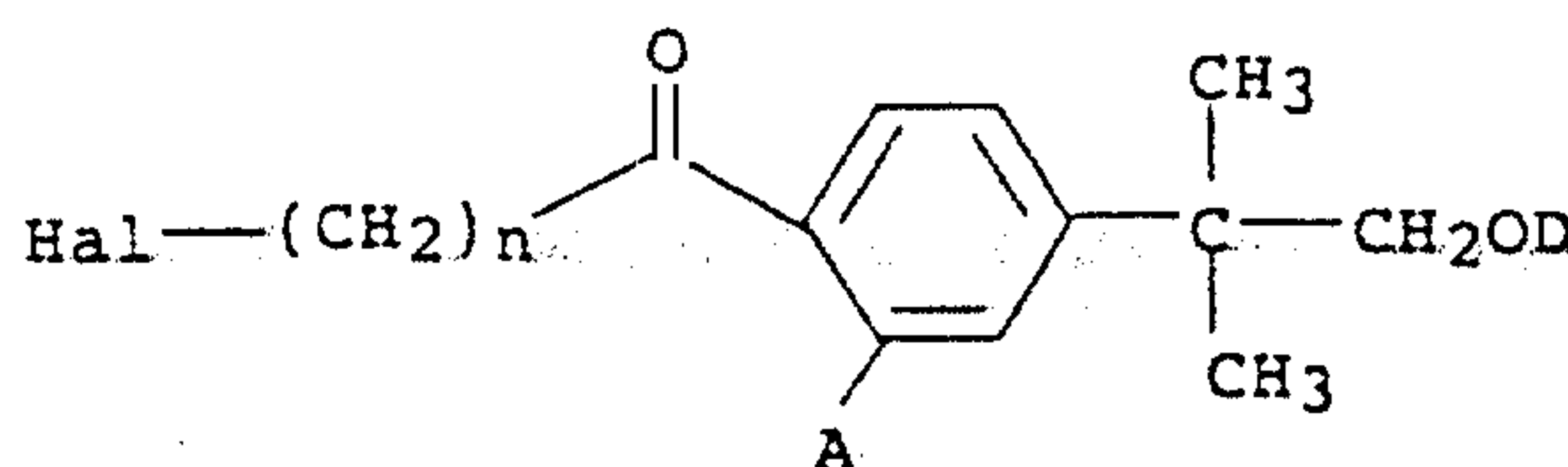


5

wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula

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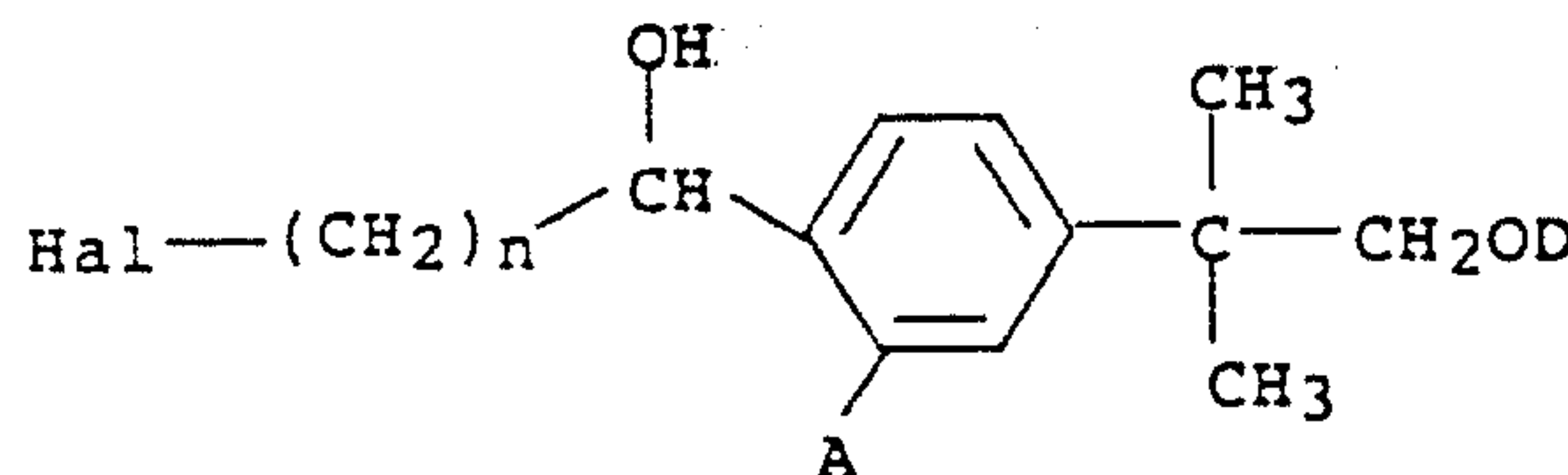
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wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

25

(d) reacting the ω -halo protected hydroxyethylphenylketone with sodium borohydride, potassium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, lithium tri-tert-butylaluminumhydride, diisobutylaluminum hydride or catalytic hydrogenation to produce a ω -halo protected hydroxyethylphenylalcohol of the formula

30



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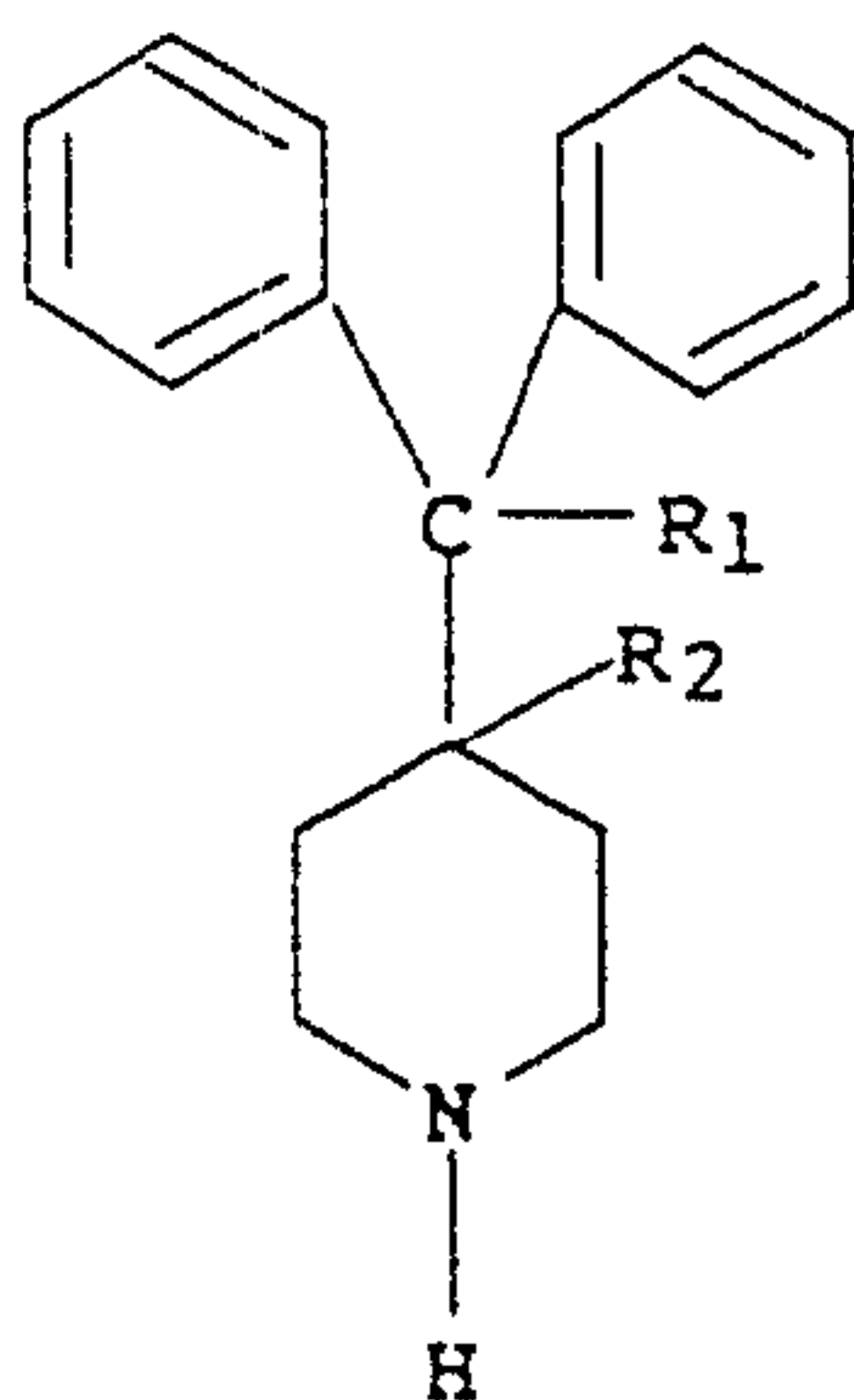
wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

-117-

(e) reacting the ω -halo protected hydroxyethylphenylalcohol with a piperidine compound of the formula

5

10



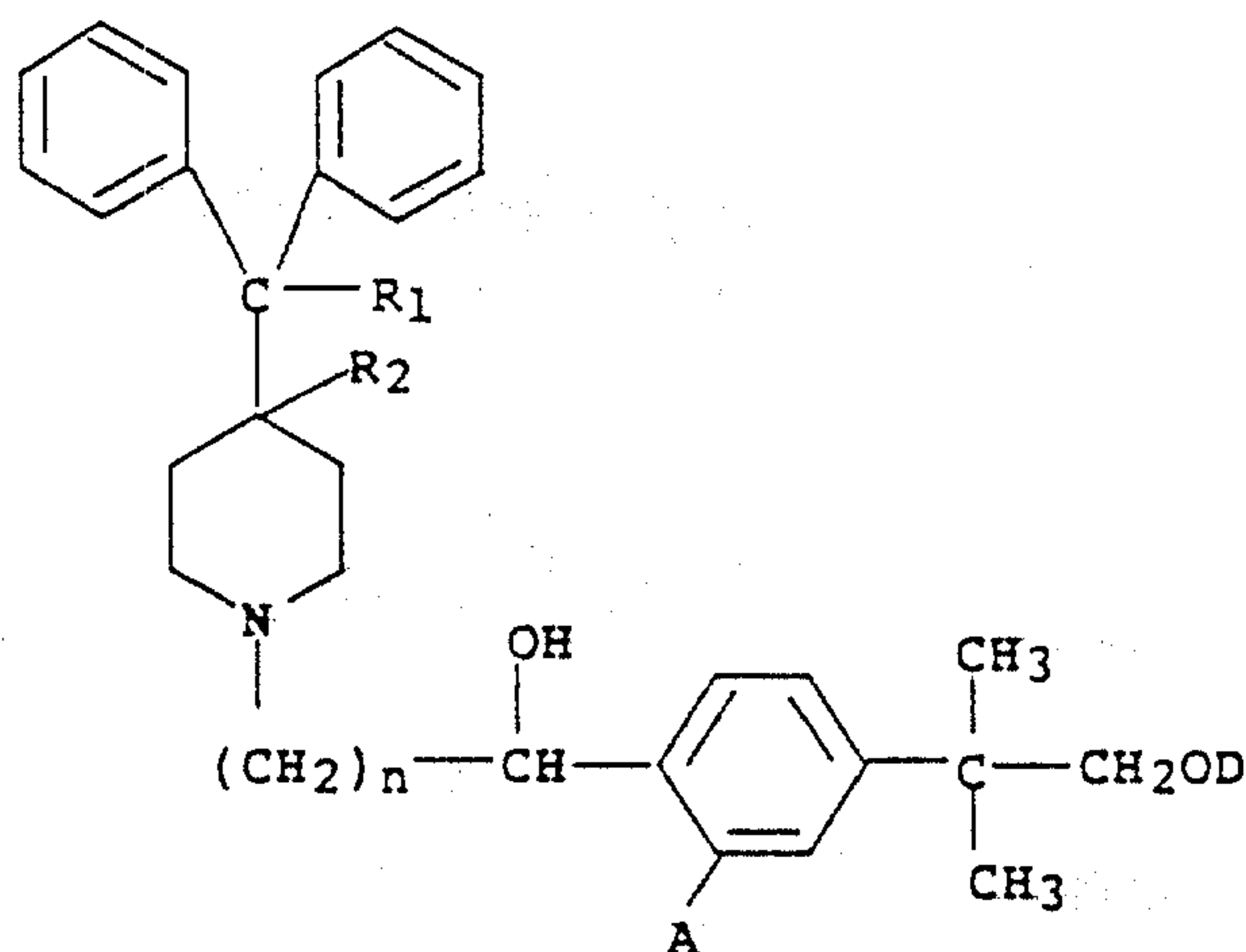
15

wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylalcohol of the formula

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25

30



wherein R_1 , R_2 , n and D are defined above and A may be hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

35

(f) reacting the piperidine protected hydroxyethylphenylalcohol with sodium methoxide in methanol, potassium carbonate in methanol, methanolic

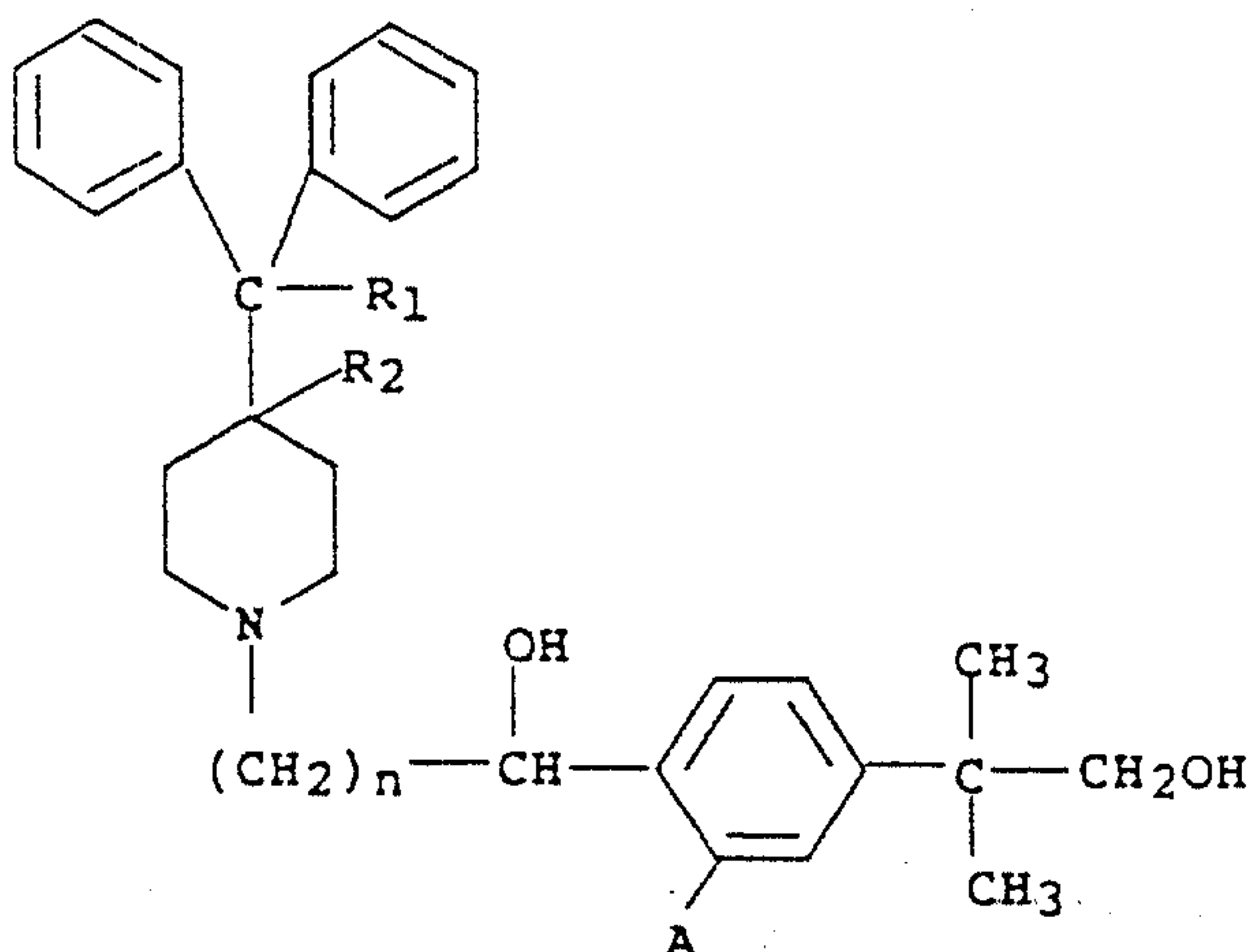
-118-

ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylalcohol of the formula

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10

15



wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

20

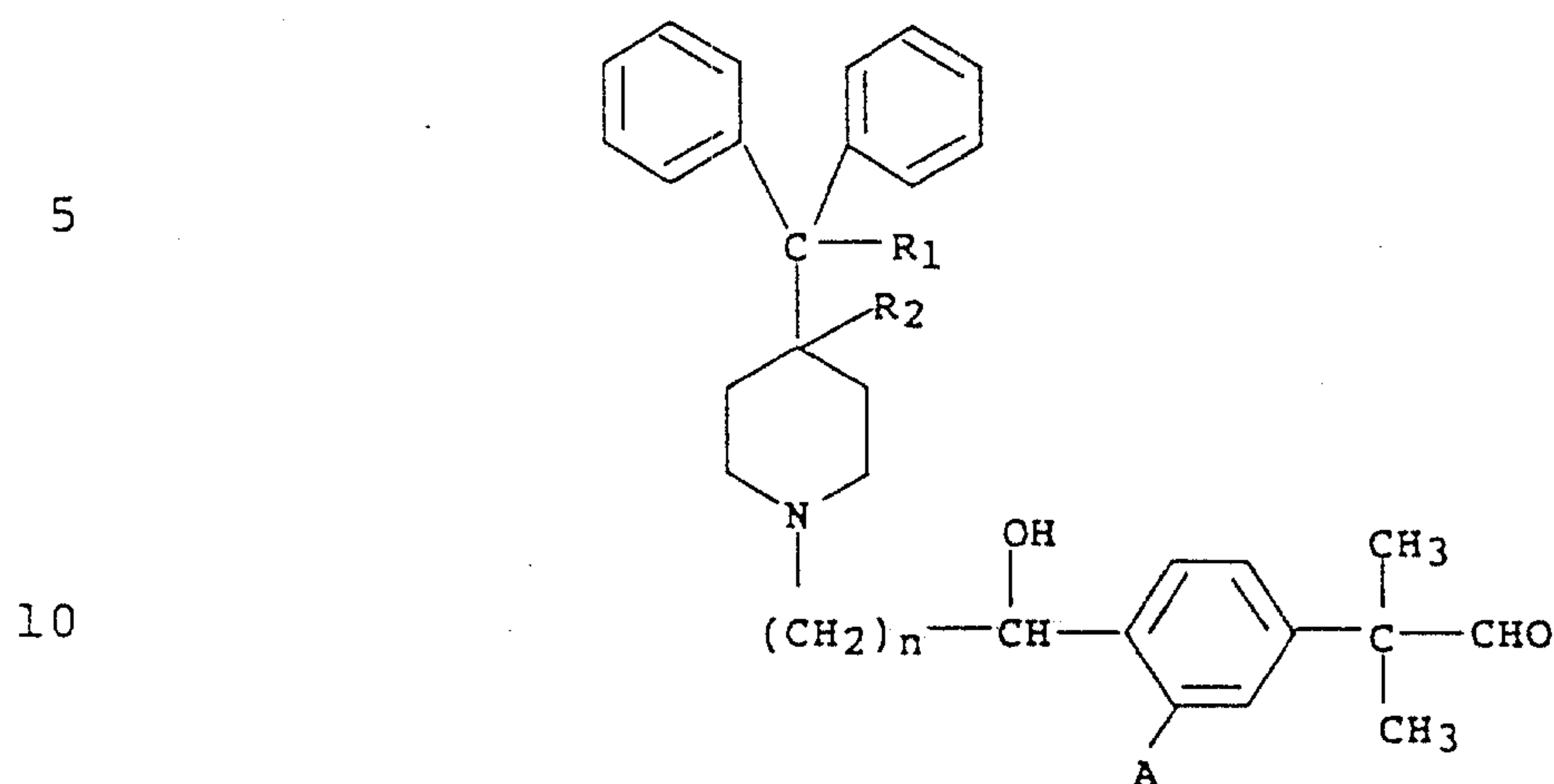
25

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(g) reacting the piperidine hydroxyethylphenylalcohol with dimethyl sulfoxide, oxyallyl chloride and triethylamine or with Dess-Martin reagent, chromium (IV) oxide, nickel peroxide, sodium dichromate, potassium dichromate, t-butyl chromate, silver oxide, argentic picolinate manganese dioxide lead tetraacetate, dicyclohexylcarbodiimide, 2,3-dichloro-5,6-dicyanoquinone, tetrachloro-1,2-benzoquinone, 2,2,6,6-tetramethylpiperidiny-1-oxyl (TEMPO) or quinolinium chlorochromate to produce a piperidine formylphenylalcohol of the formula

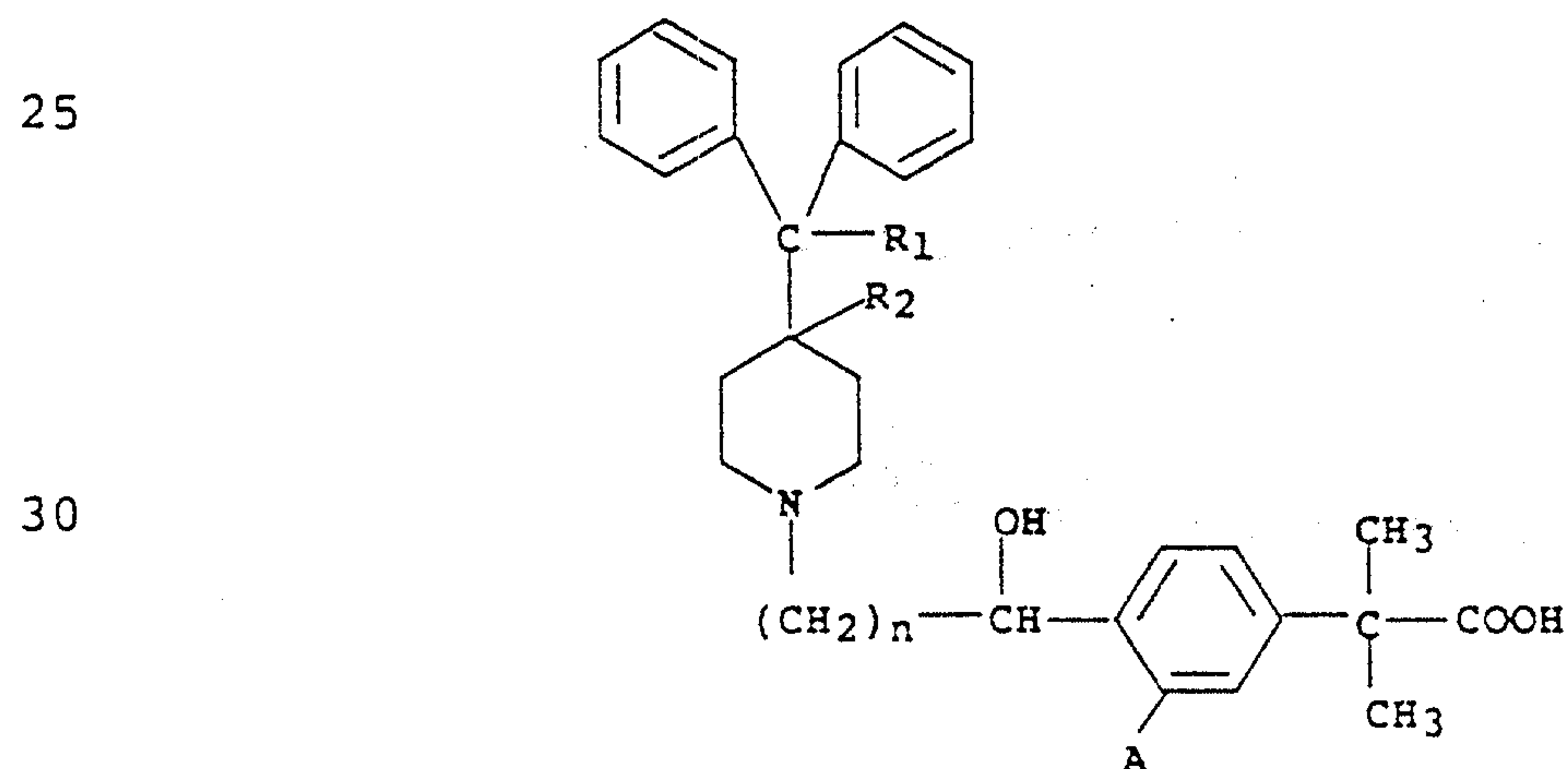
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-119-



15 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

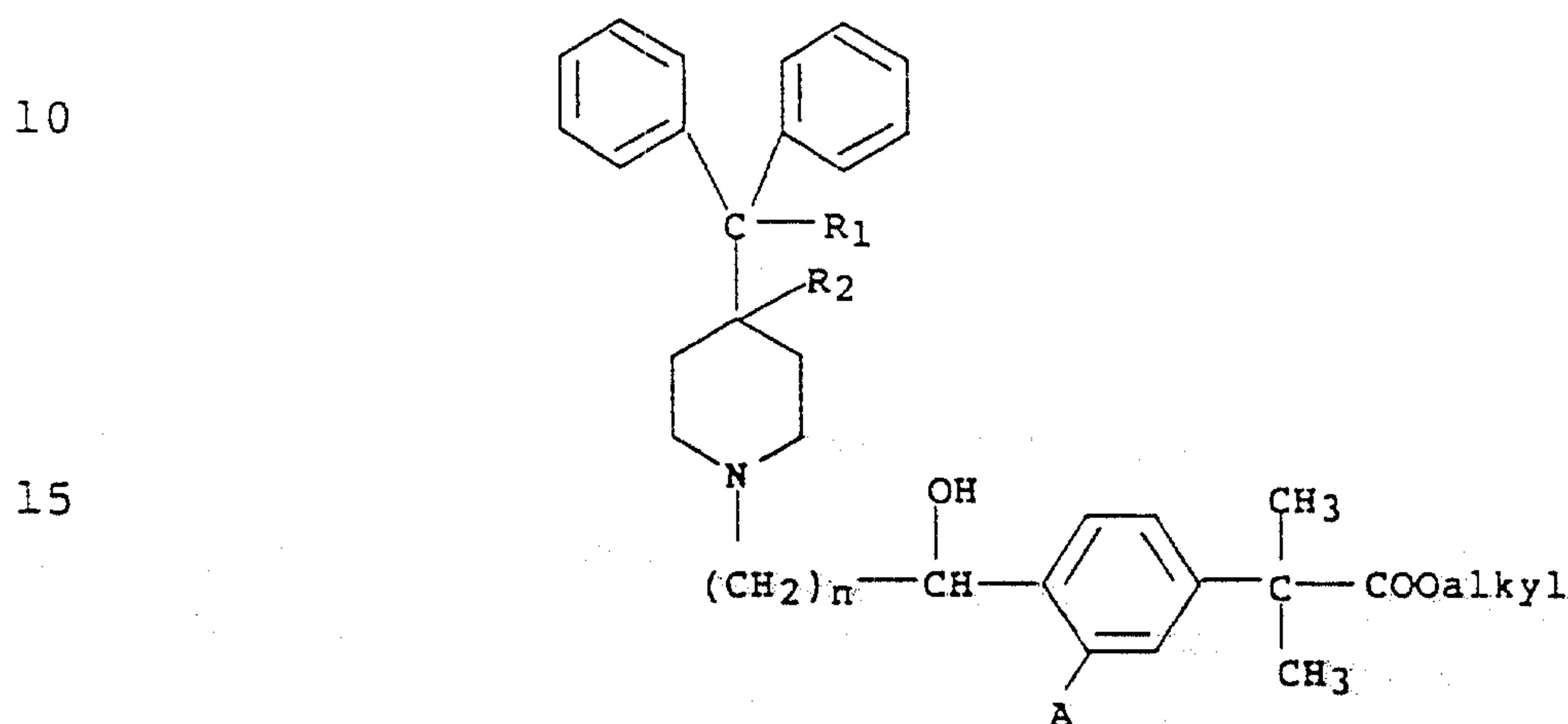
20 (h) reacting the piperidine formylphenylalcohol with potassium permanganate, chromium (IV) oxide, silver (I) oxide, silver oxide, argentic picolinate, peroxide, nitric acid, m-chloroperbenzoic acid and peracetic acid to produce a piperidine carboxyphenylketone of the formula



35 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

-120-

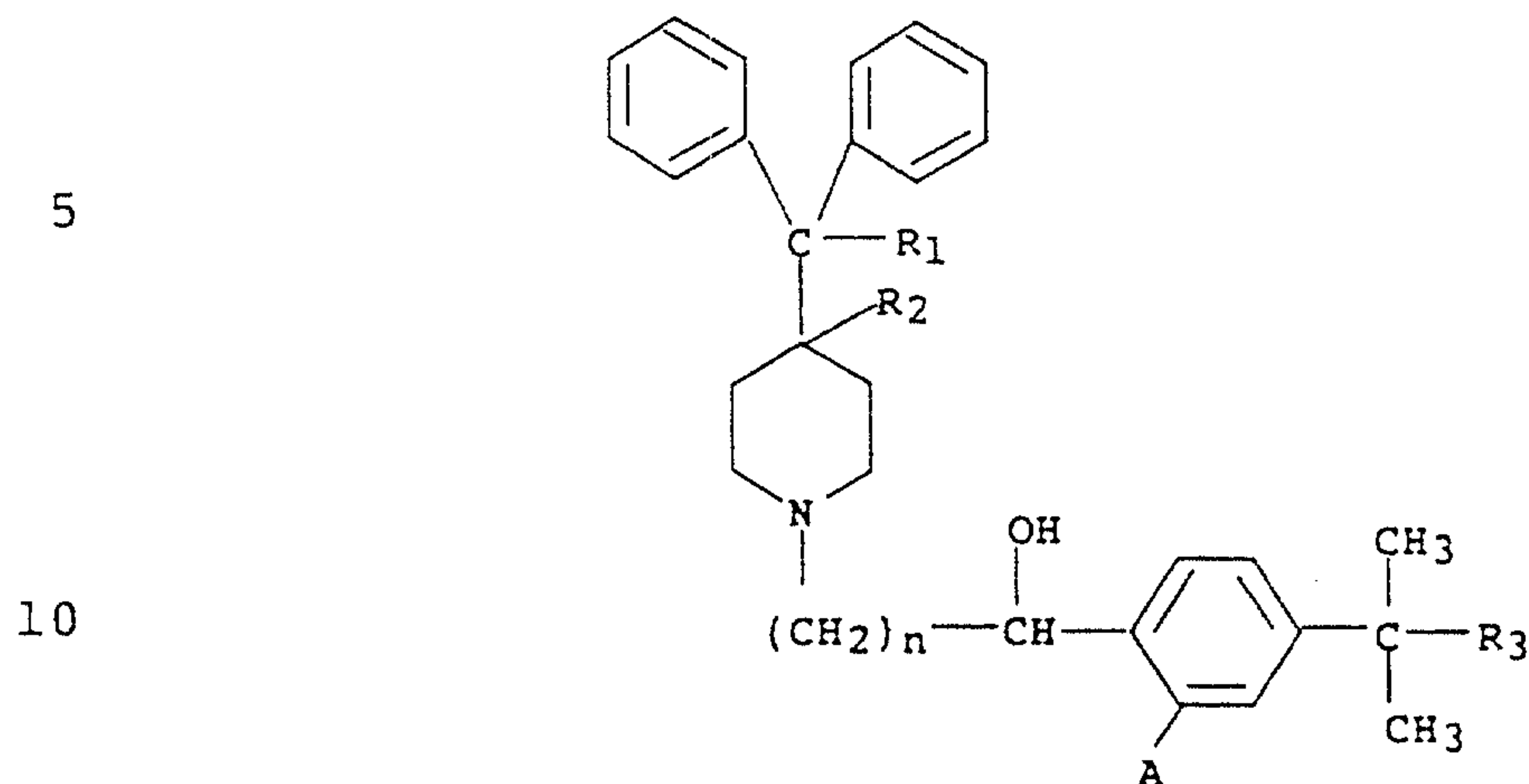
(i) optionally reacting the piperidine carboxyphenylalcohol with diazomethane or 2,2-dimethoxypropane or with thionyl chloride followed by an alcohol of the formula HOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched to form a piperidine carboxyphenylalcohol ester of the formula



(j) optionally reacting the piperidine carboxyphenylalcohols or the piperidine carboxyphenylalcohol esters which bear hydroxy protecting groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine carboxyphenylalcohols or the piperidine carboxyphenylalcohol esters.

21. A process for preparing a compound of the formula

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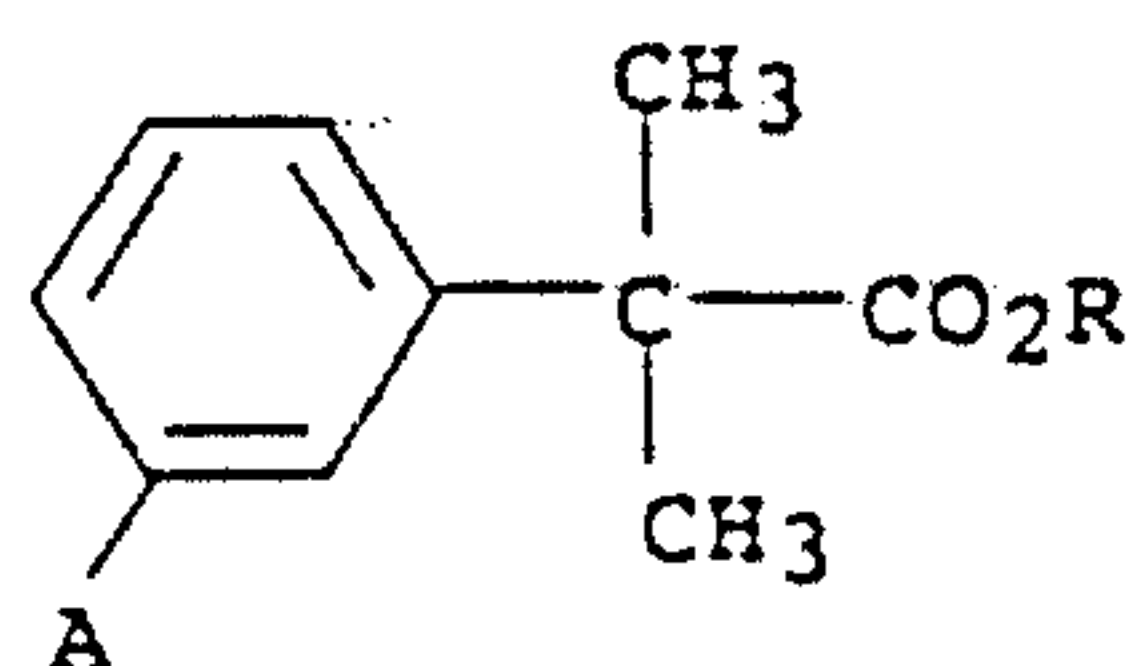
wherein

- 15 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the
carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;
20 R_3 is $-\text{COOH}$ or $-\text{COOalkyl}$ wherein the alkyl moiety has
from 1 to 6 carbon atoms and is straight or branched;
 A is hydrogen or hydroxy; and
pharmaceutically acceptable salts thereof comprising
the steps of:

25

(a) reacting a benzeneacetic acid compound of the
formula

30



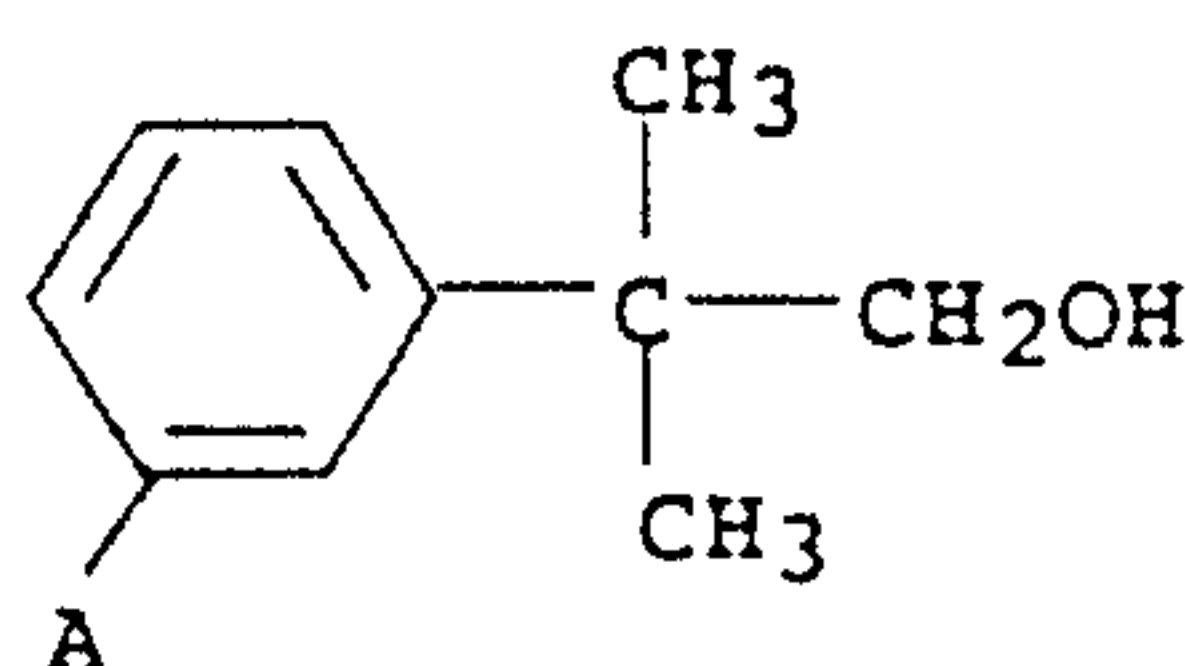
35

wherein A is hydrogen or hydroxy with the proviso that when
 A is hydroxy, A may be optionally protected or unprotected
and R is hydrogen or $\text{C}_1\text{-C}_6$ alkyl with sodium bis(2-
methoxyethoxy)aluminum hydride, lithium aluminum hydride,
diborane, lithium borohydride, lithium triethylborohydride

-122-

and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

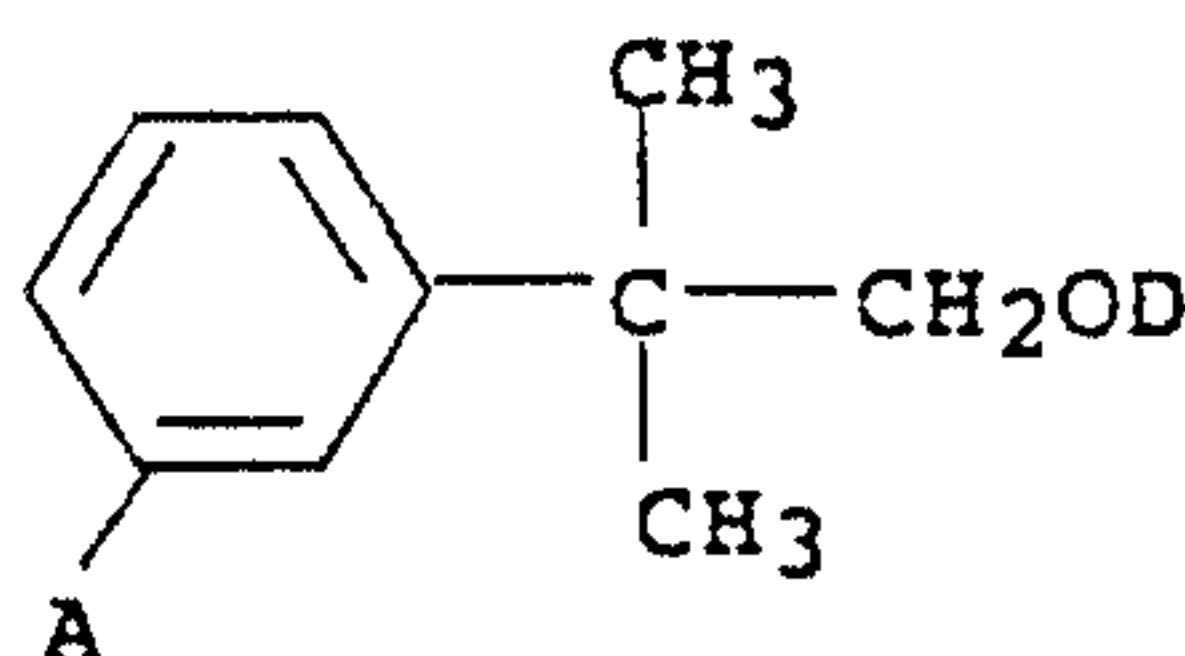
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10 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

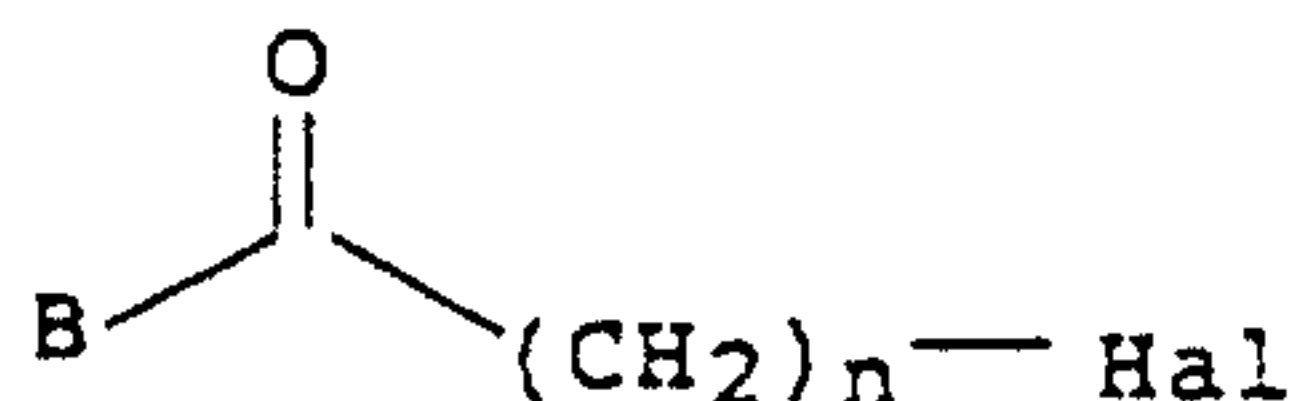
15 (b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

20



25 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is C(=O)CH₃ or C(=O)C₆H₅;

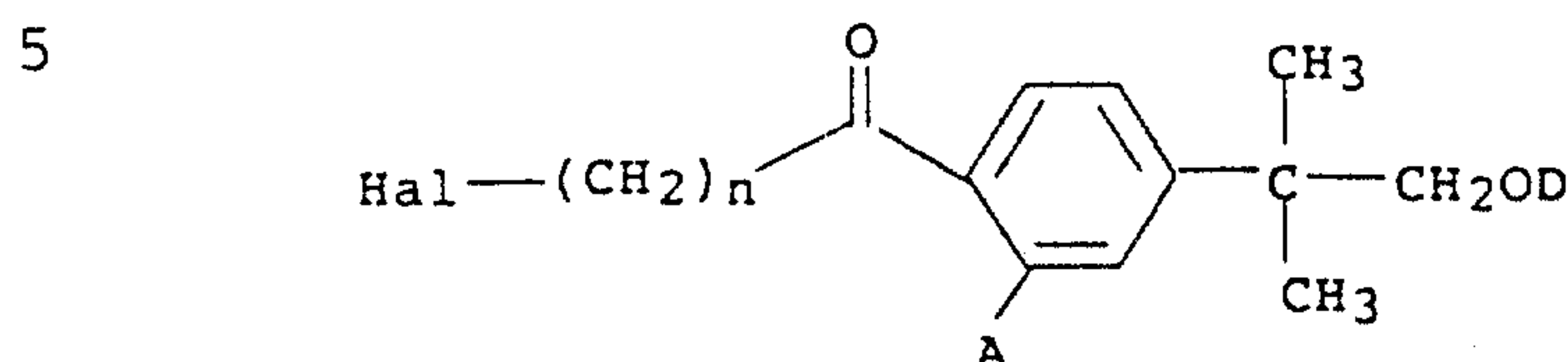
30 (c) reacting the protected phenethyl alcohol with a ω-halo compound of the formula



35 wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron

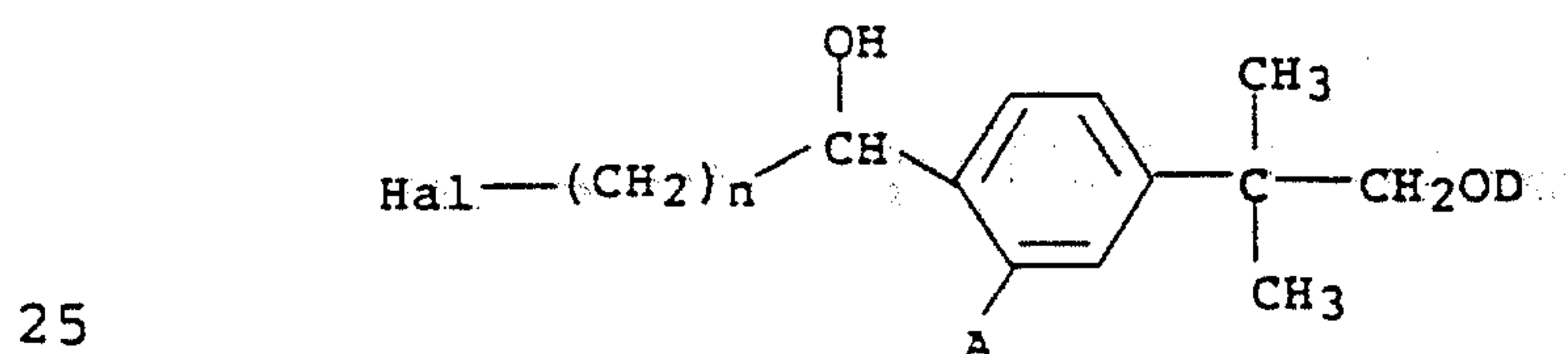
-123-

trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula



10 wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(d) reacting the ω -halo protected
 15 hydroxyethylphenylketone with sodium borohydride, potassium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, lithium tri-tert-butylaluminumhydride, diisobutylaluminum hydride or catalytic hydrogenation to
 20 produce a ω -halo protected hydroxyethylphenylalcohol of the formula

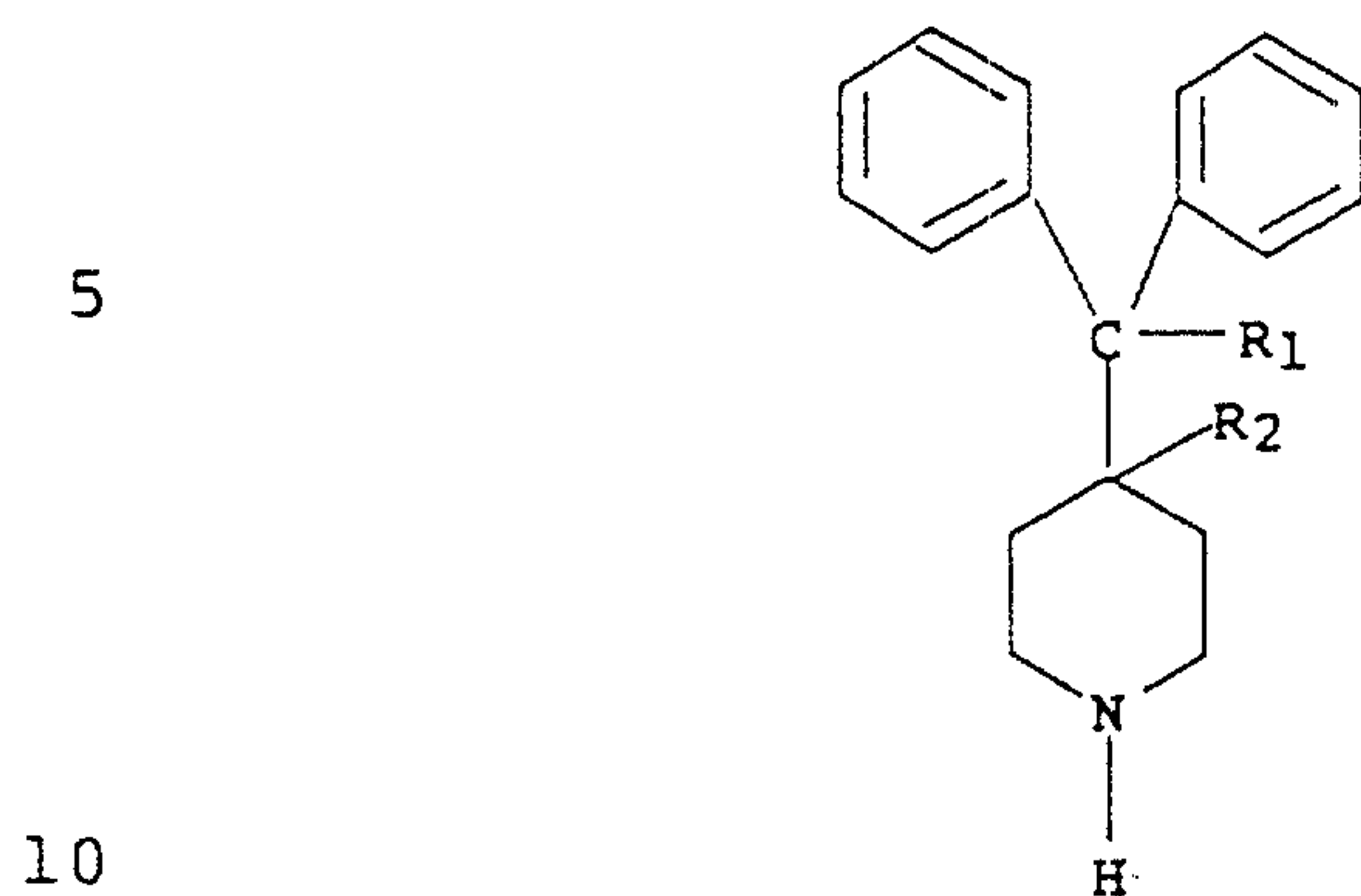


wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be
 30 optionally protected or unprotected;

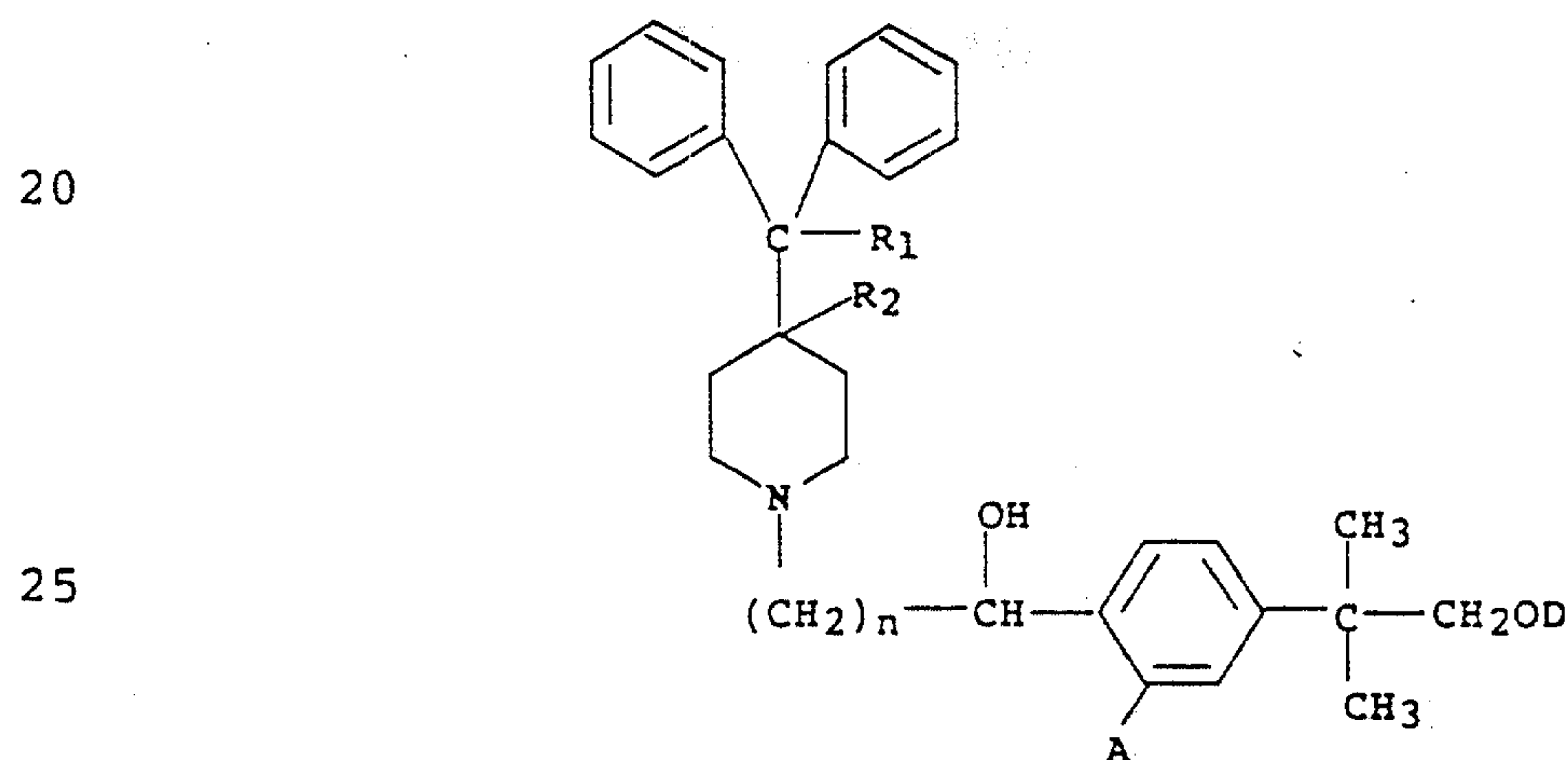
(e) reacting the ω -halo protected
 hydroxyethylphenylalcohol with a piperidine compound of the
 formula

35

-124-

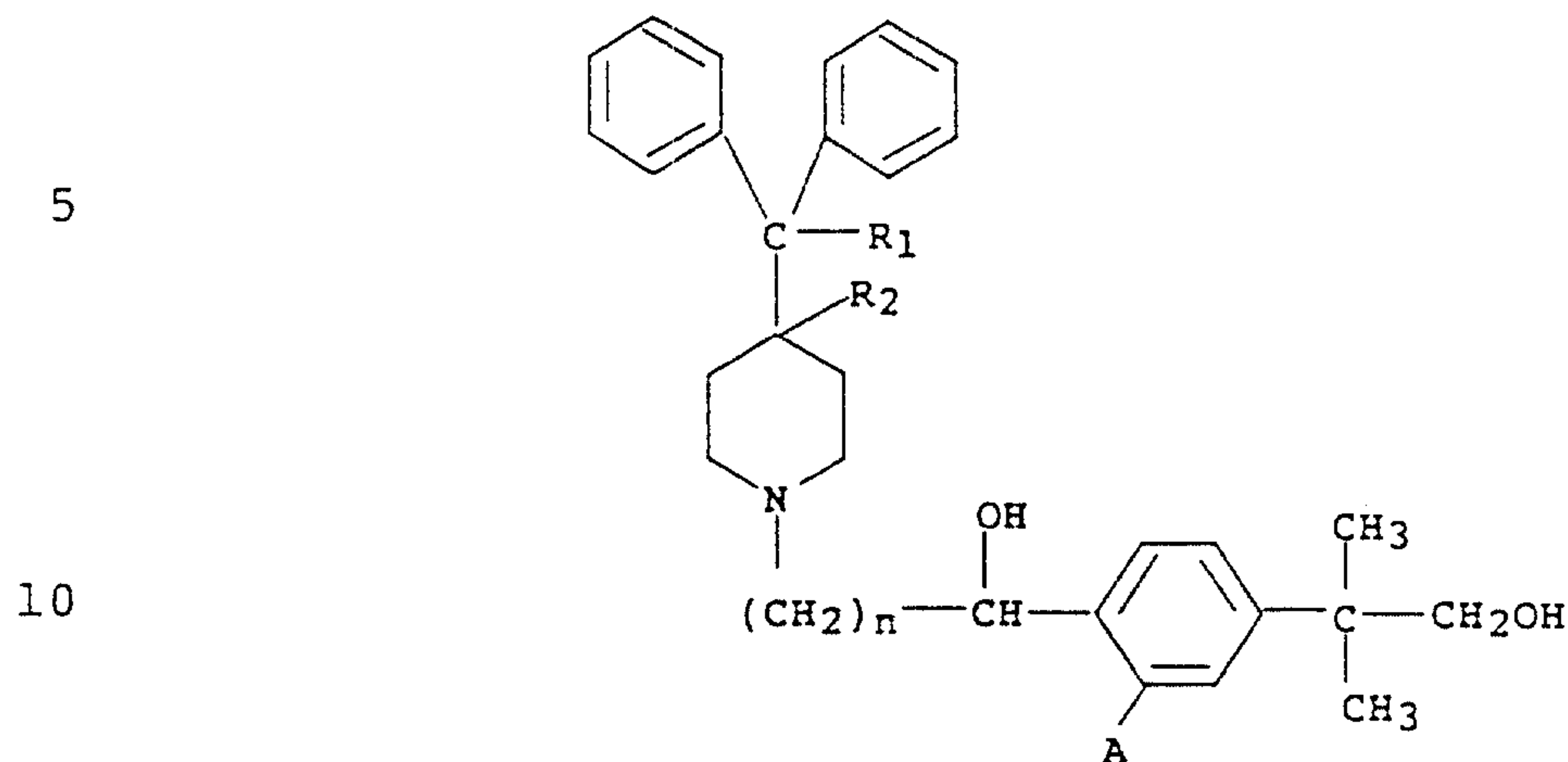


wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylalcohol of the formula



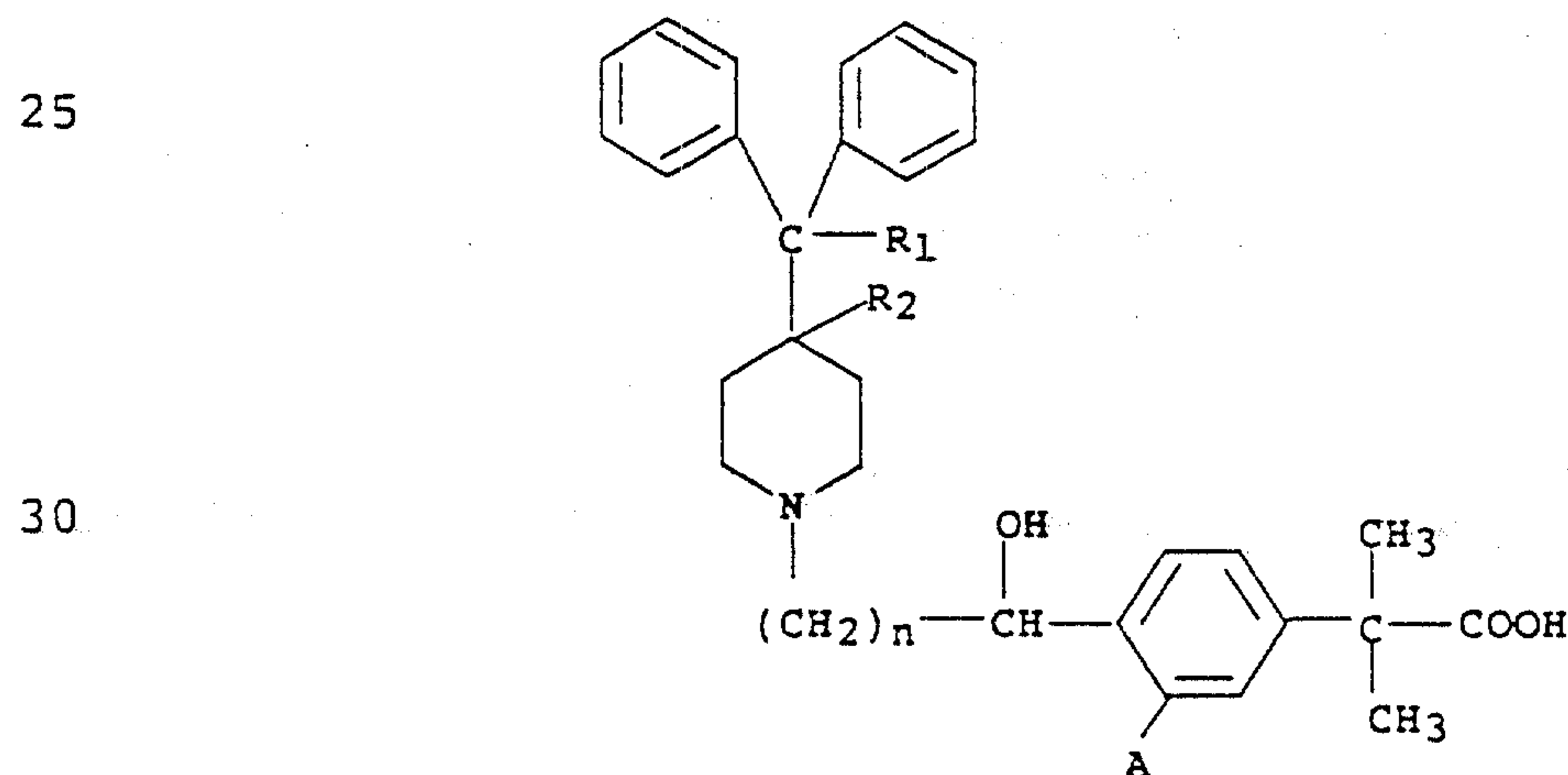
wherein R_1 , R_2 , n and D are defined above and A may be hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(f) reacting the piperidine protected hydroxyethylphenylalcohol with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylalcohol of the formula



15 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

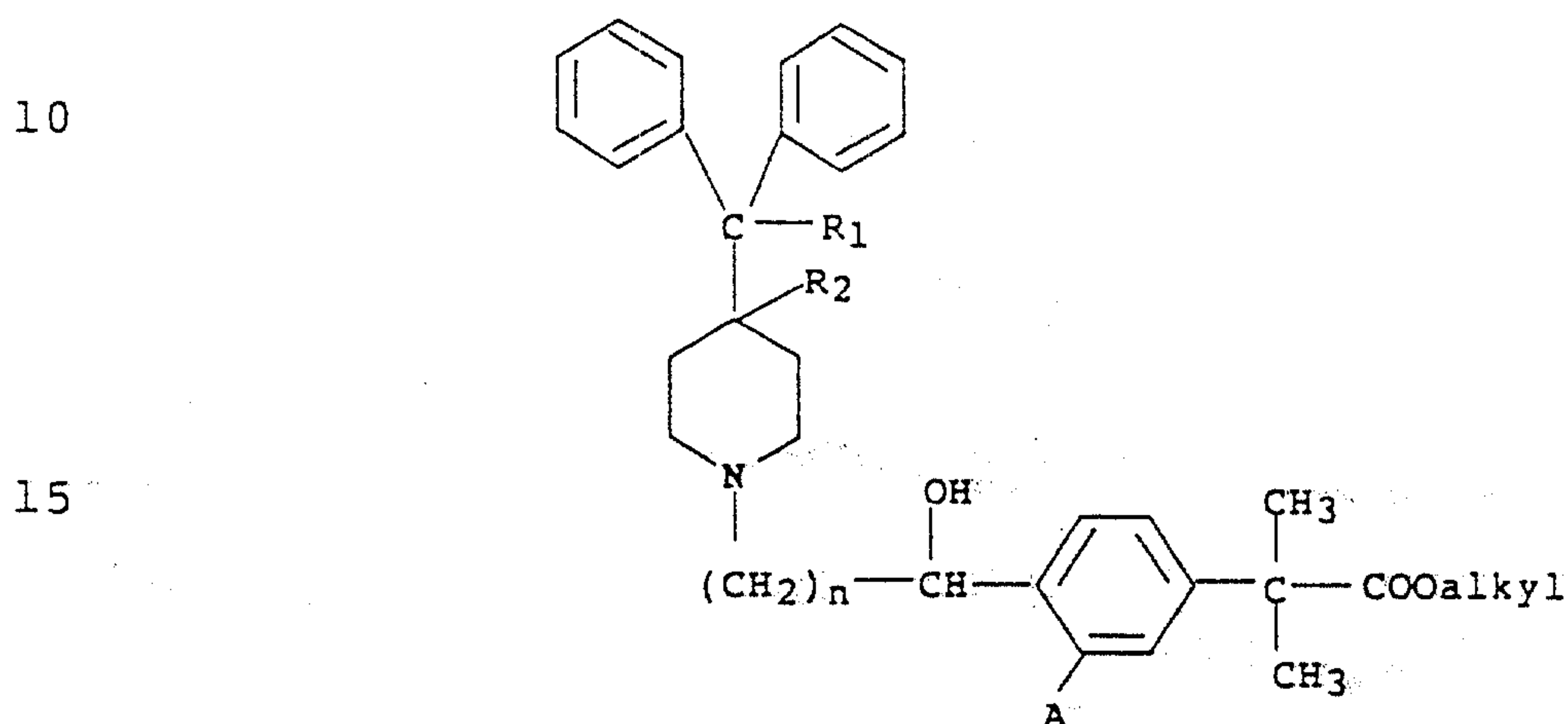
20 (g) reacting the piperidine hydroxyethylphenylalcohol with chromium (IV) oxide, potassium permanganate, nitric acid, nitrogen dioxide, ruthenium (VIII) oxide, nickel peroxide, silver oxide, t-butyl chromate or xenic acid to produce a piperidine carboxyphenylketone of the formula



35 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

-126-

(h) optionally reacting the piperidine carboxyphenylalcohol with diazomethane or 2,2-dimethoxypropane or with thionyl chloride followed by an alcohol of the formula HOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched to form a piperidine carboxyphenylalcohol ester of the formula



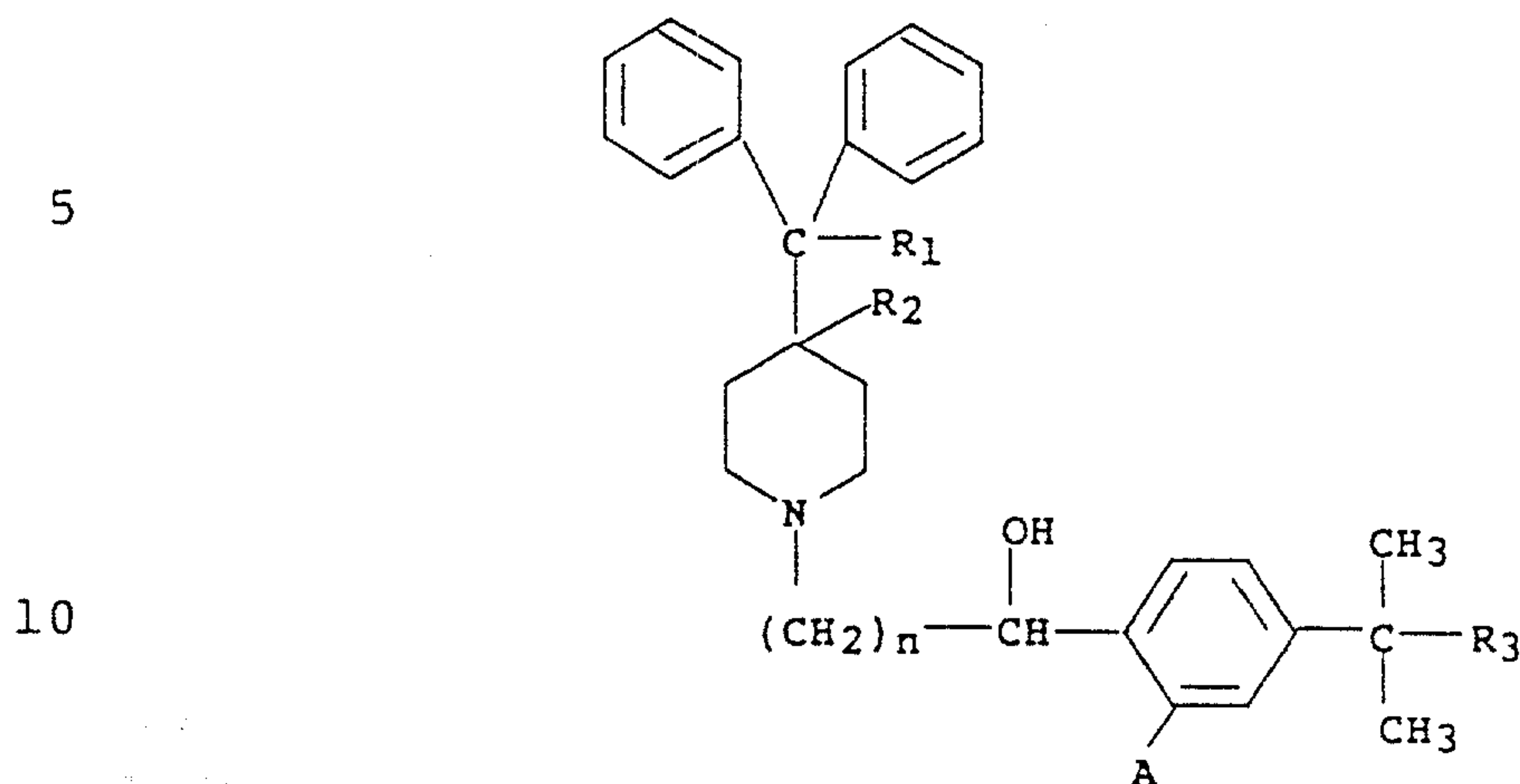
20 wherein R₁, R₂, n and alkyl are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected; and

(i) optionally reacting the piperidine
25 carboxyphenylalcohols or the piperidine
carboxyphenylalcohol esters which bear hydroxy protecting
groups with mineral acids, strong organic acids, Lewis
acids, aqueous mineral bases or catalytic hydrogenation to
produce the unprotected piperidine carboxyphenylalcohols or
30 the piperidine carboxyphenylalcohol esters.

22. A process according to Claim 21 wherein the
piperidine hydroxyphenylalcohol produced in step f is
reacted with a ruthenium (VIII) oxide to produce a
35 piperidine carboxyphenylalcohol of step g.

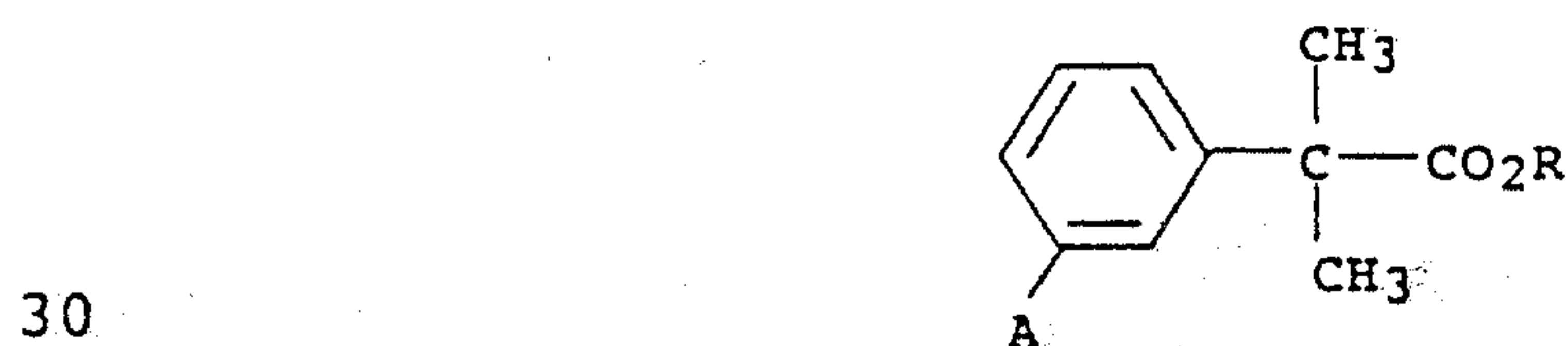
23. A process for preparing a compound of the formula
wherein

-127-



- 15 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the
carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;
 R_3 is $-\text{CH}_2\text{OH}$;
20 A is hydrogen or hydroxy; and
pharmaceutically acceptable salts thereof comprising
the steps of:

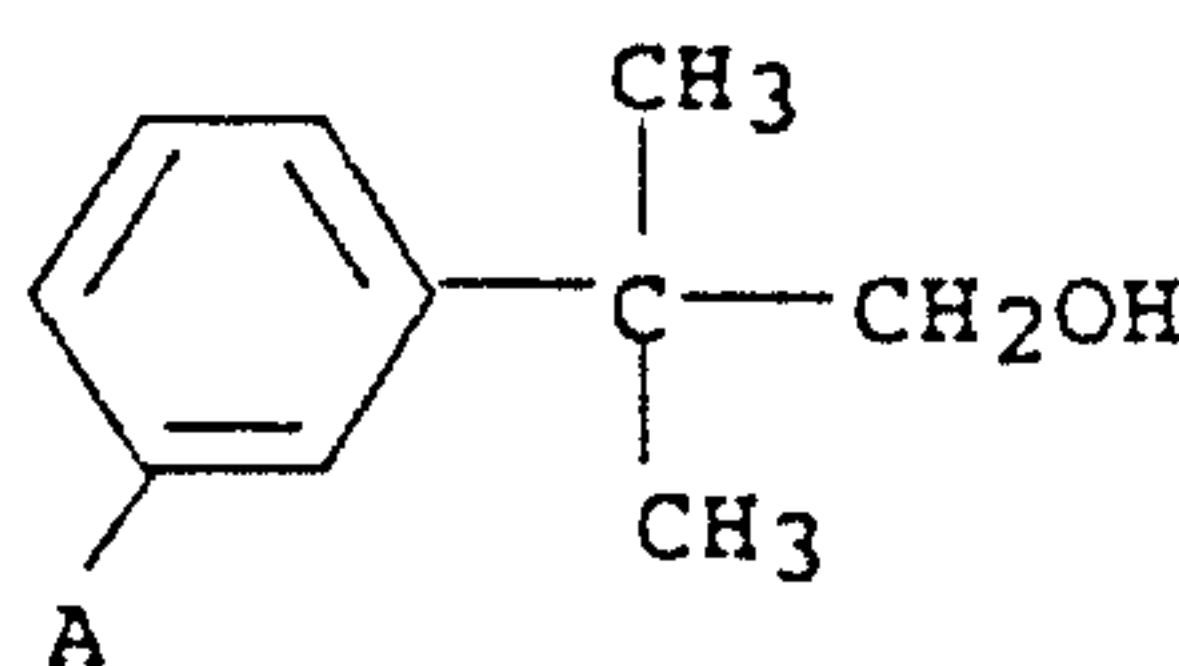
- 25 (a) reacting a benzeneacetic acid compound of the
formula



- wherein A is hydrogen or hydroxy with the proviso that when
 A is hydroxy, A may be optionally protected or unprotected
and R is hydrogen or C_1 - C_6 alkyl with sodium bis(2-
35 methoxyethoxy)aluminum hydride, lithium aluminum hydride,
diborane, lithium borohydride, lithium triethylborohydride
and lithium tri-sec-butylborohydride or aluminum hydride to
give a phenethyl alcohol of the formula

-128-

5



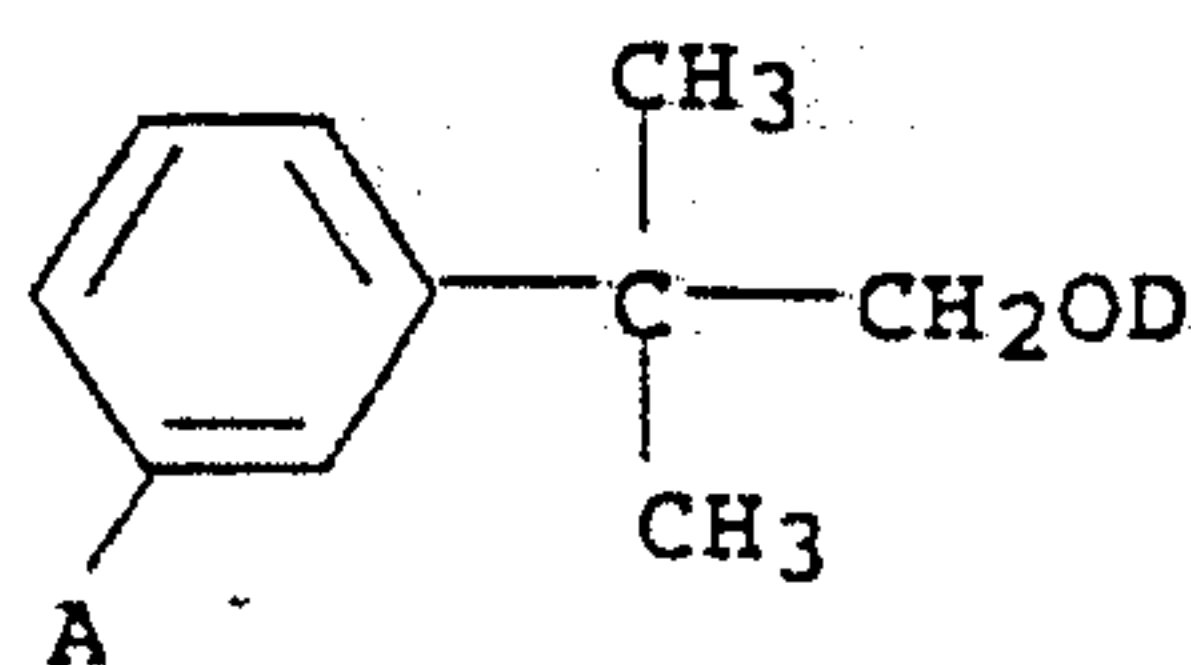
10

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

15

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

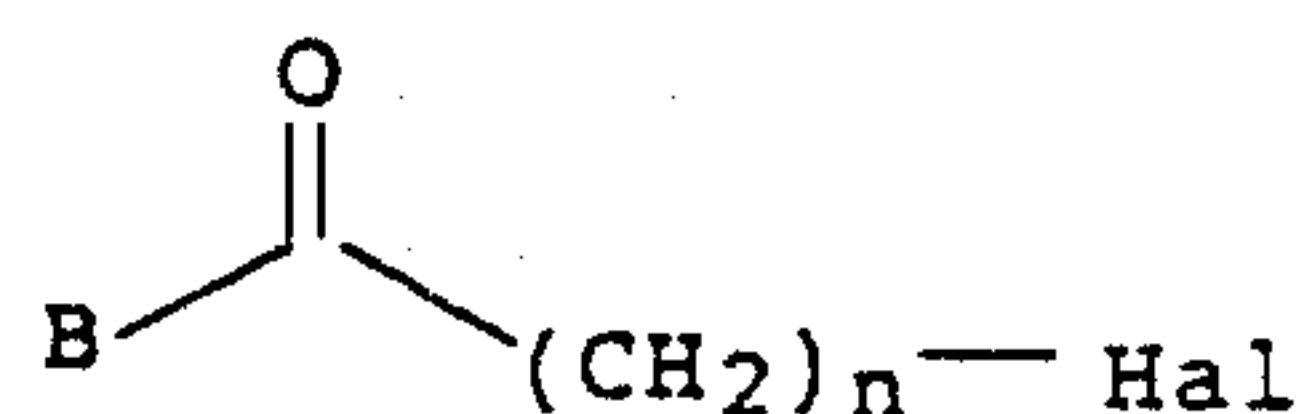
20



25

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is $C(=O)CH_3$ or $C(=O)C_6H_5$;

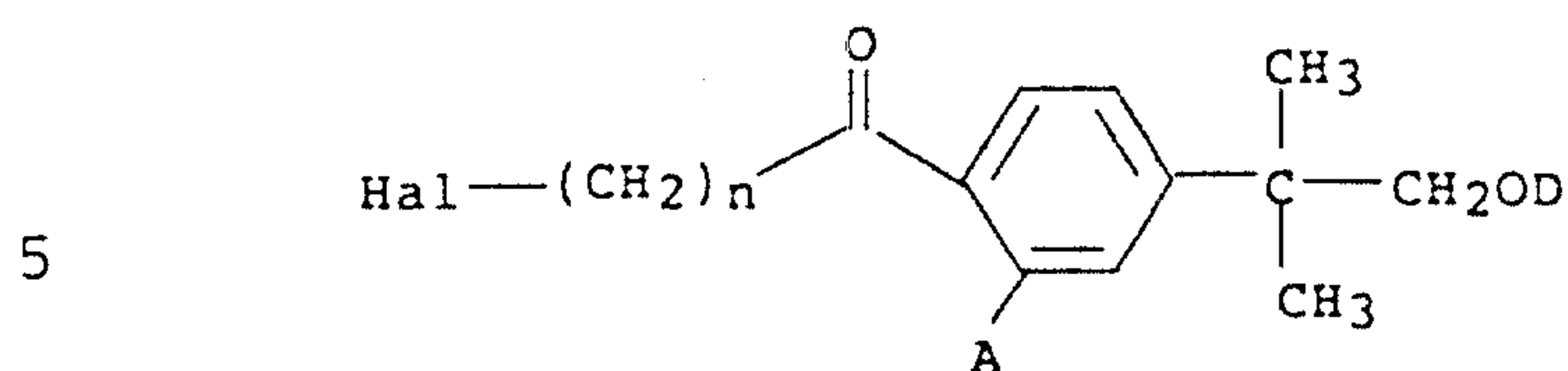
30



35

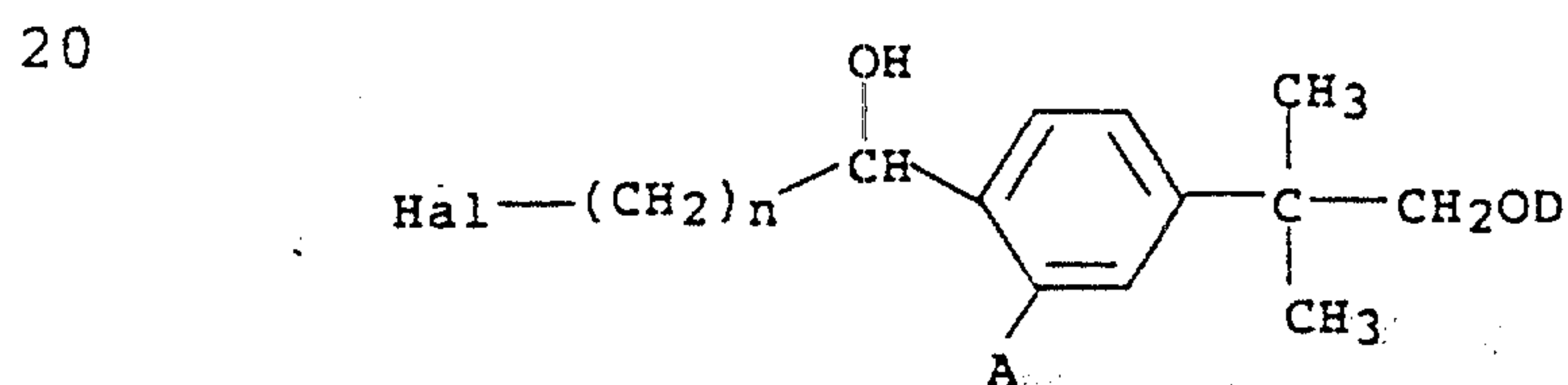
wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula

-129-



wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(d) reacting the w-halo protected hydroxyethylphenylketone with sodium borohydride, potassium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, lithium tri-tert-butylaluminumhydride, diisobutylaluminum hydride or catalytic hydrogenation to produce a w-halo protected hydroxyethylphenylalcohol of the formula

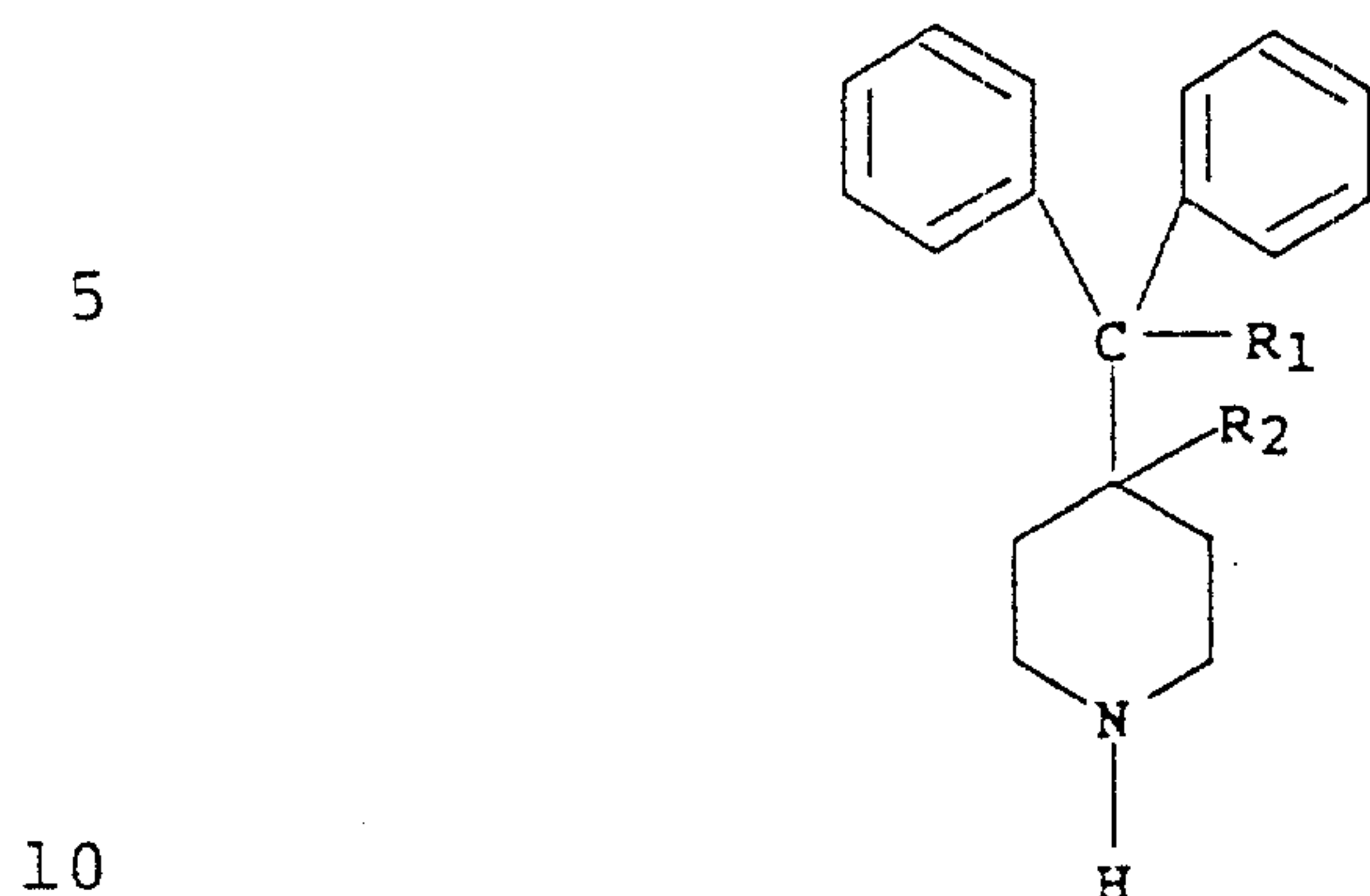


wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

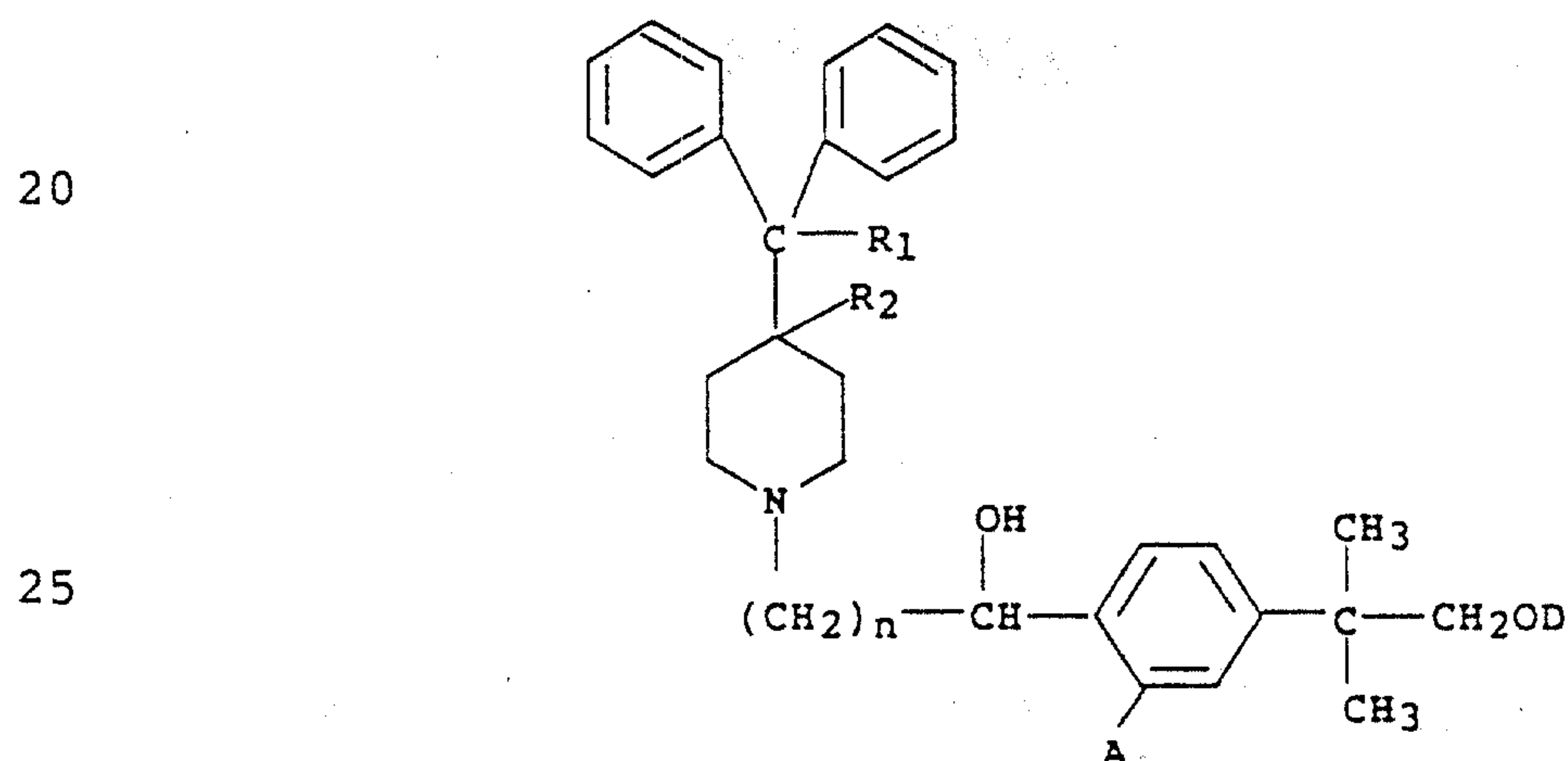
(e) reacting the w-halo protected hydroxyethylphenylalcohol with a piperidine compound of the formula

35

-130-



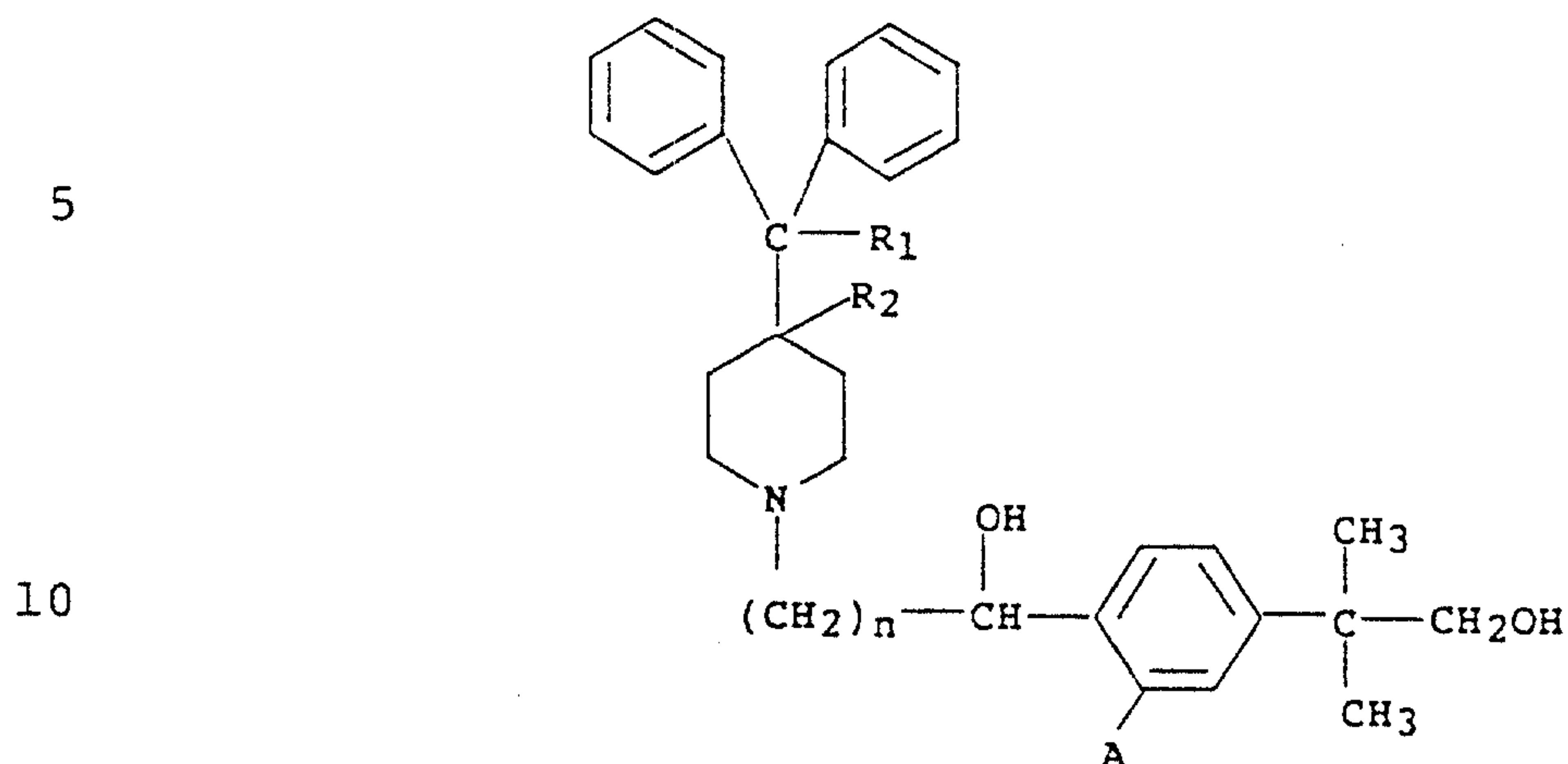
wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylalcohol of the formula



wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(f) reacting the piperidine protected hydroxyethylphenylalcohol with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylalcohol of the formula

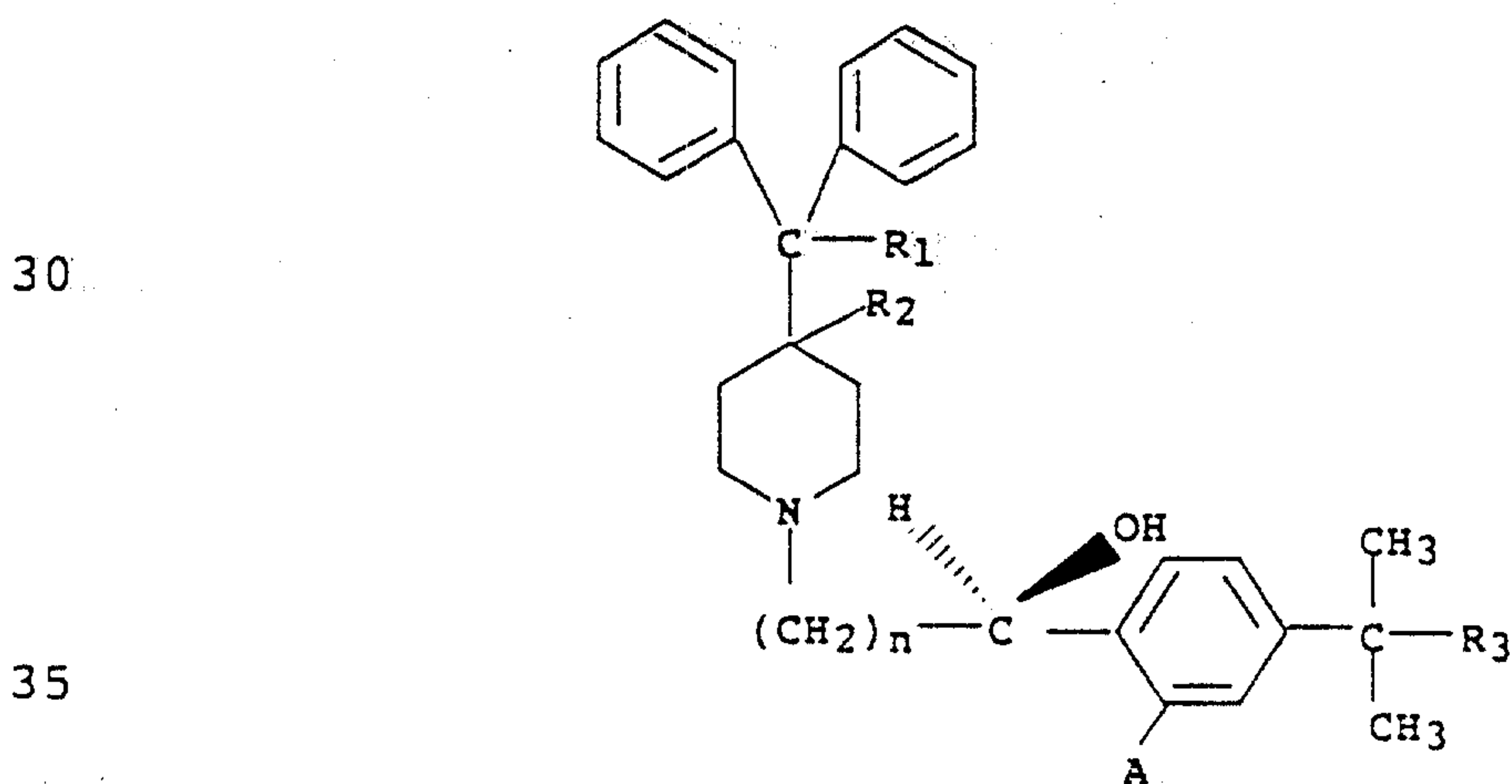
-131-



wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected; and

(g) optionally reacting the piperidine hydroxyethylphenylalcohols which bear hydroxy protecting groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine hydroxyethylphenylalcohols.

24. A process for preparing a compound of the formula



AMENDED SHEET

-132-

wherein

R₁ represents hydrogen or hydroxy;

R₂ represents hydrogen; or

5 R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;

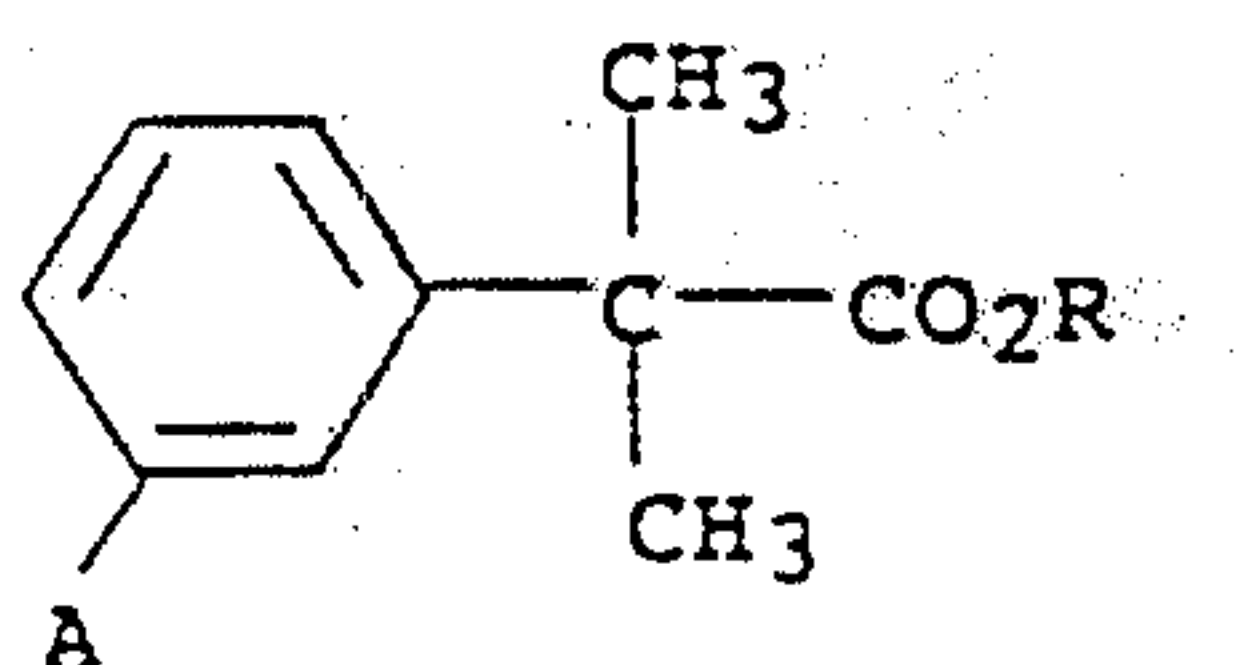
n is an integer of from 1 to 5;

R₃ is -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

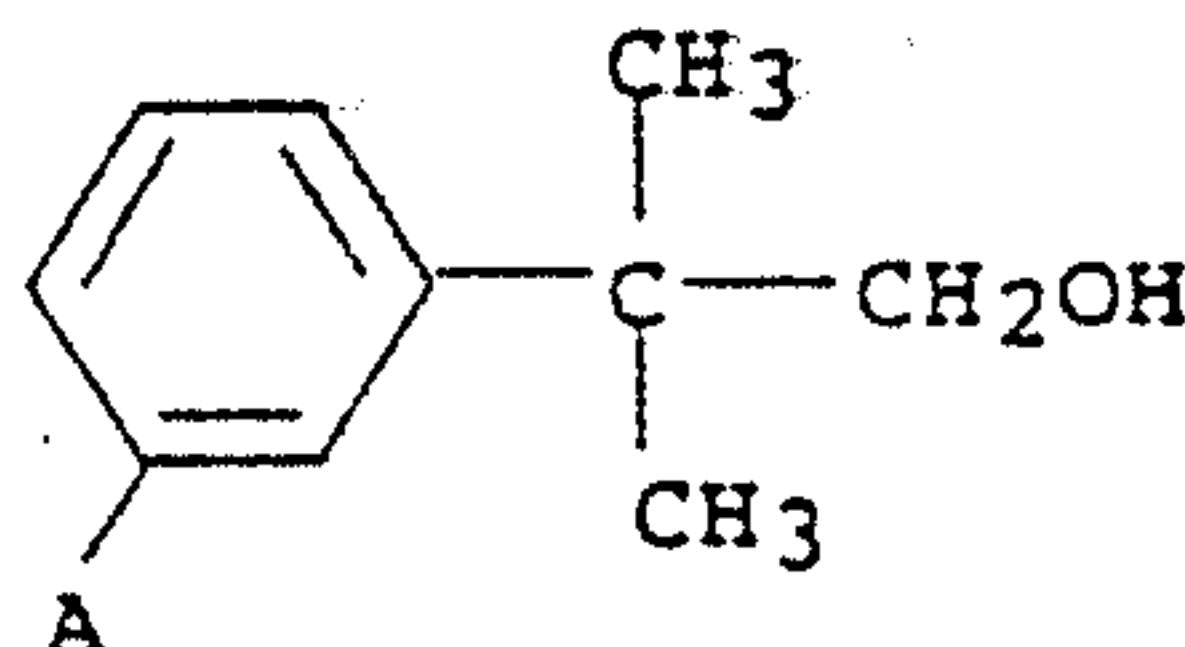
10 A is hydrogen or hydroxy; and

pharmaceutically acceptable salts thereof comprising the steps of:

(a) reacting a benzeneacetic acid compound of the
15 formula



20 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride,
25 diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula



30 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

MAILED SHEET

-133-

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

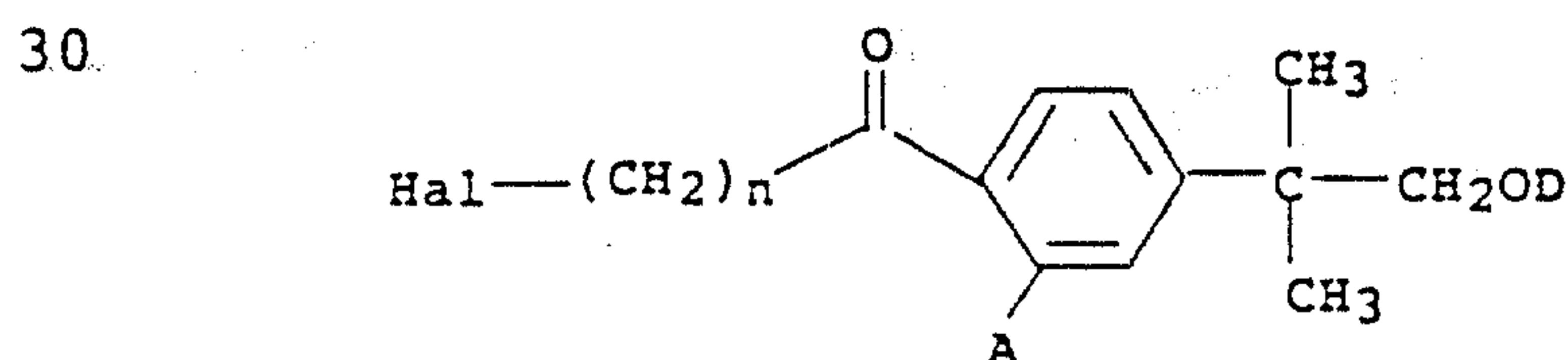


wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is C(=O)CH₃ or C(=O)C₆H₅;

(c) reacting the protected phenethyl alcohol with a ω-halo compound of the formula



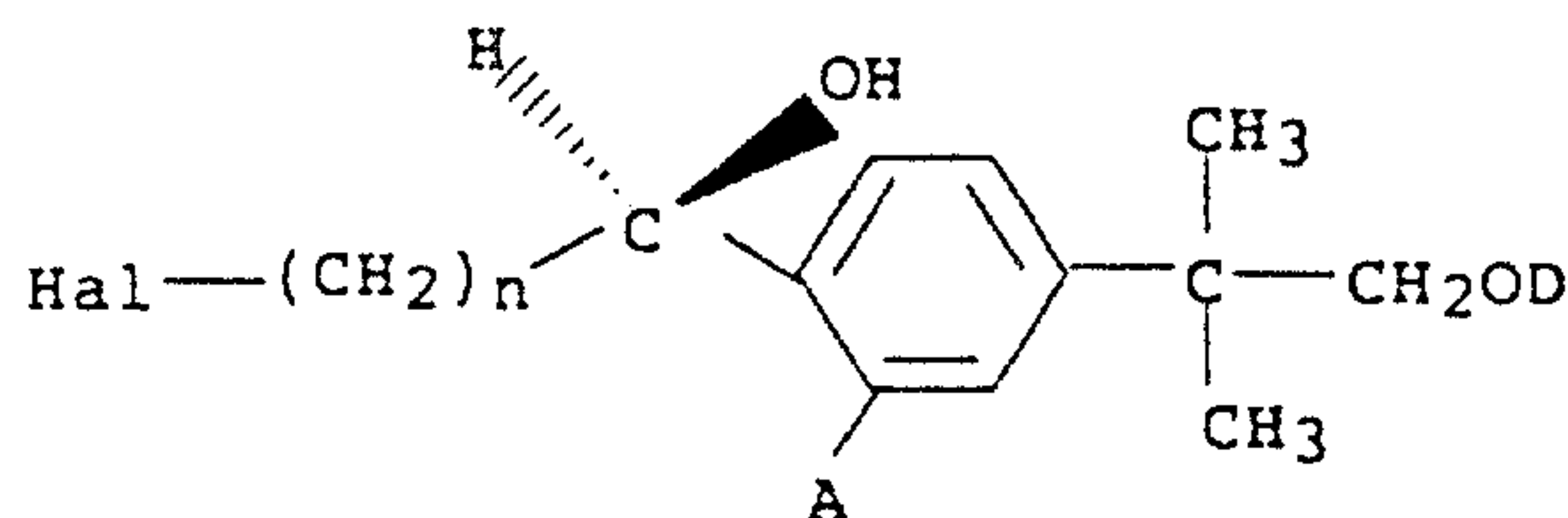
wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω-halo protected hydroxyethylphenylketone of the formula



wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

-134-

(d) reacting the ω -halo protected hydroxyethylphenylketone with (+)-B-chlorodiisopinocampheylborane to produce a ω -halo protected hydroxyethylphenylalcohol of the formula



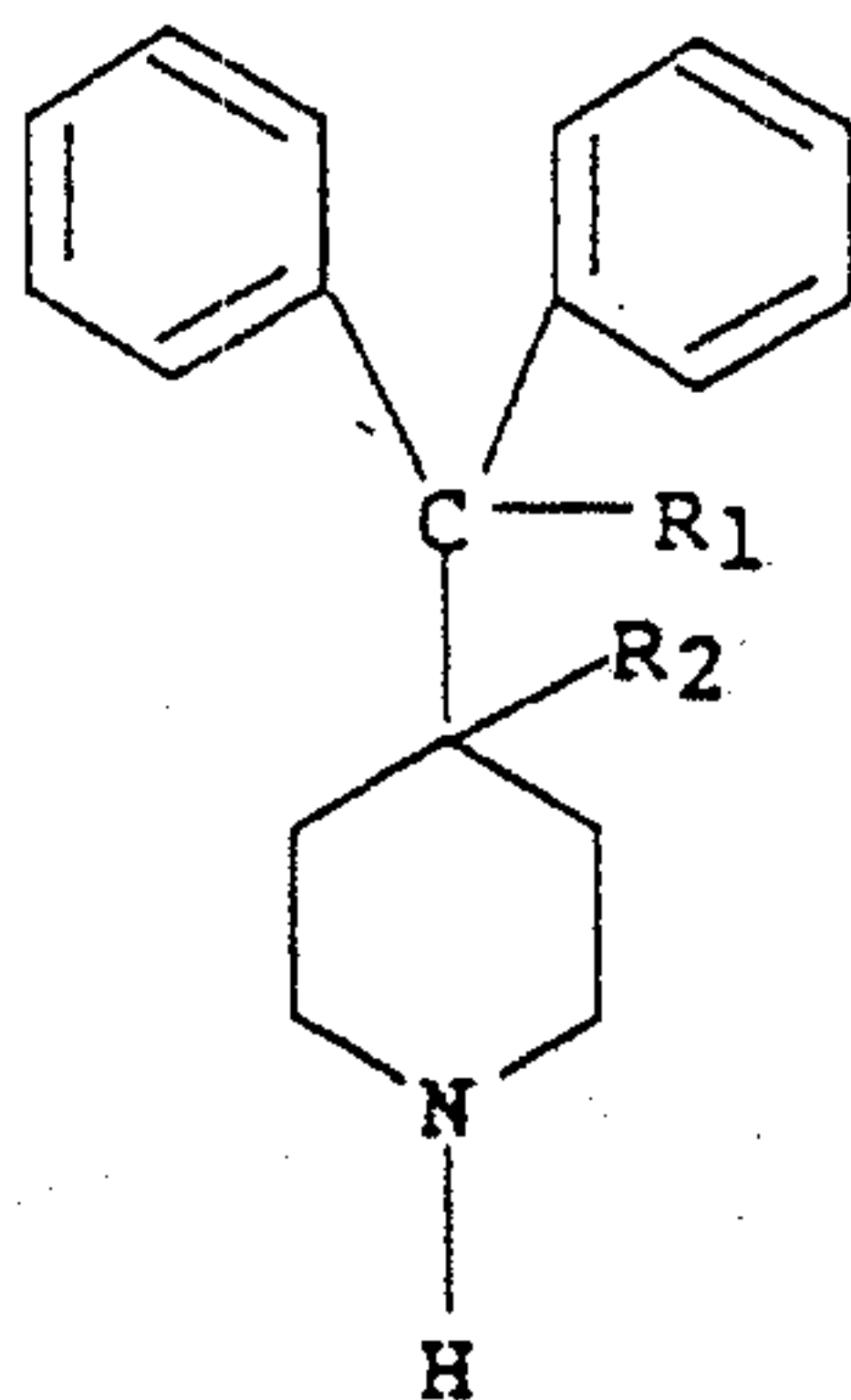
10

wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

15

(e) reacting the ω -halo protected hydroxyethylphenylalcohol with a piperidine compound of the formula

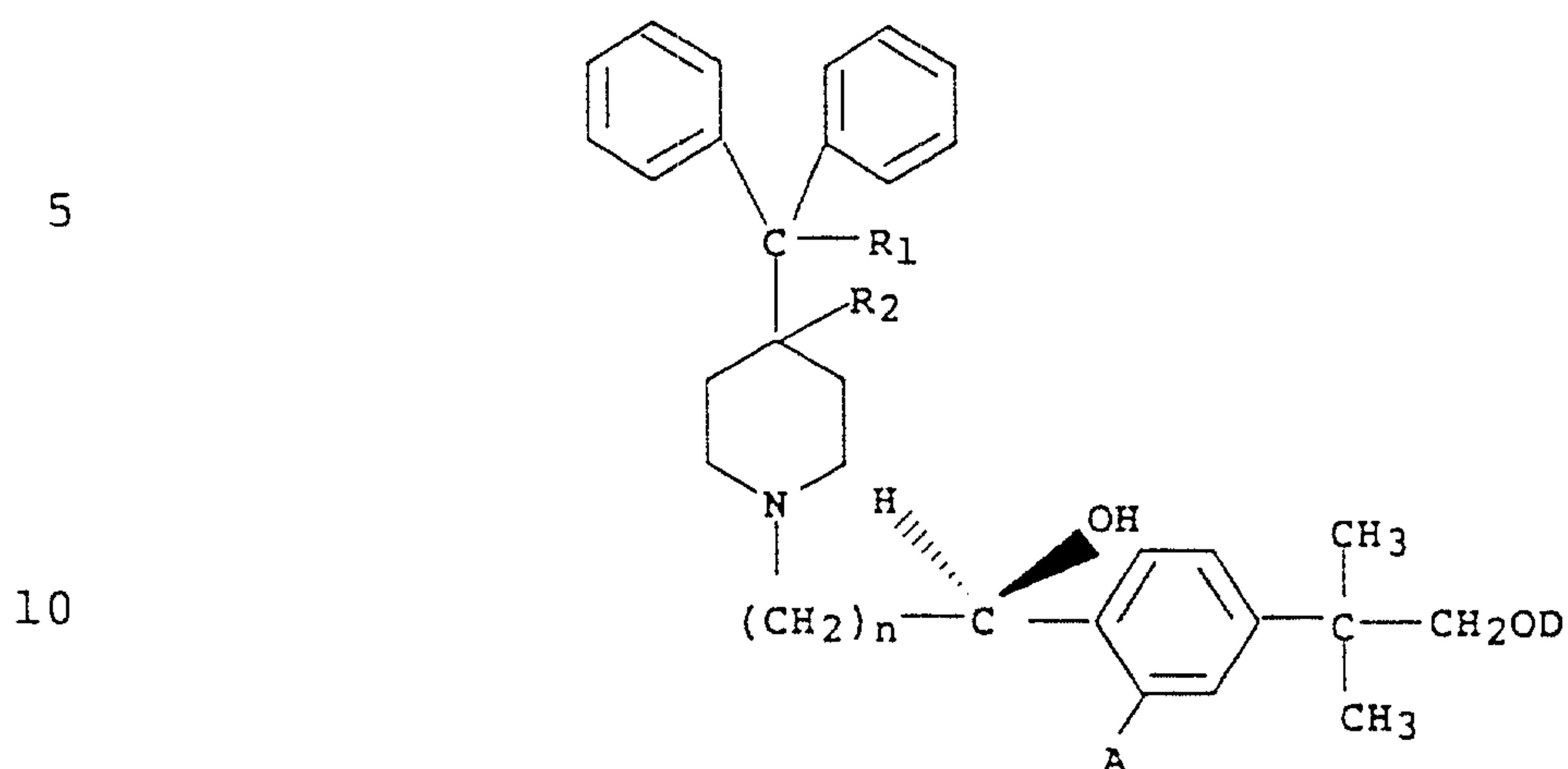
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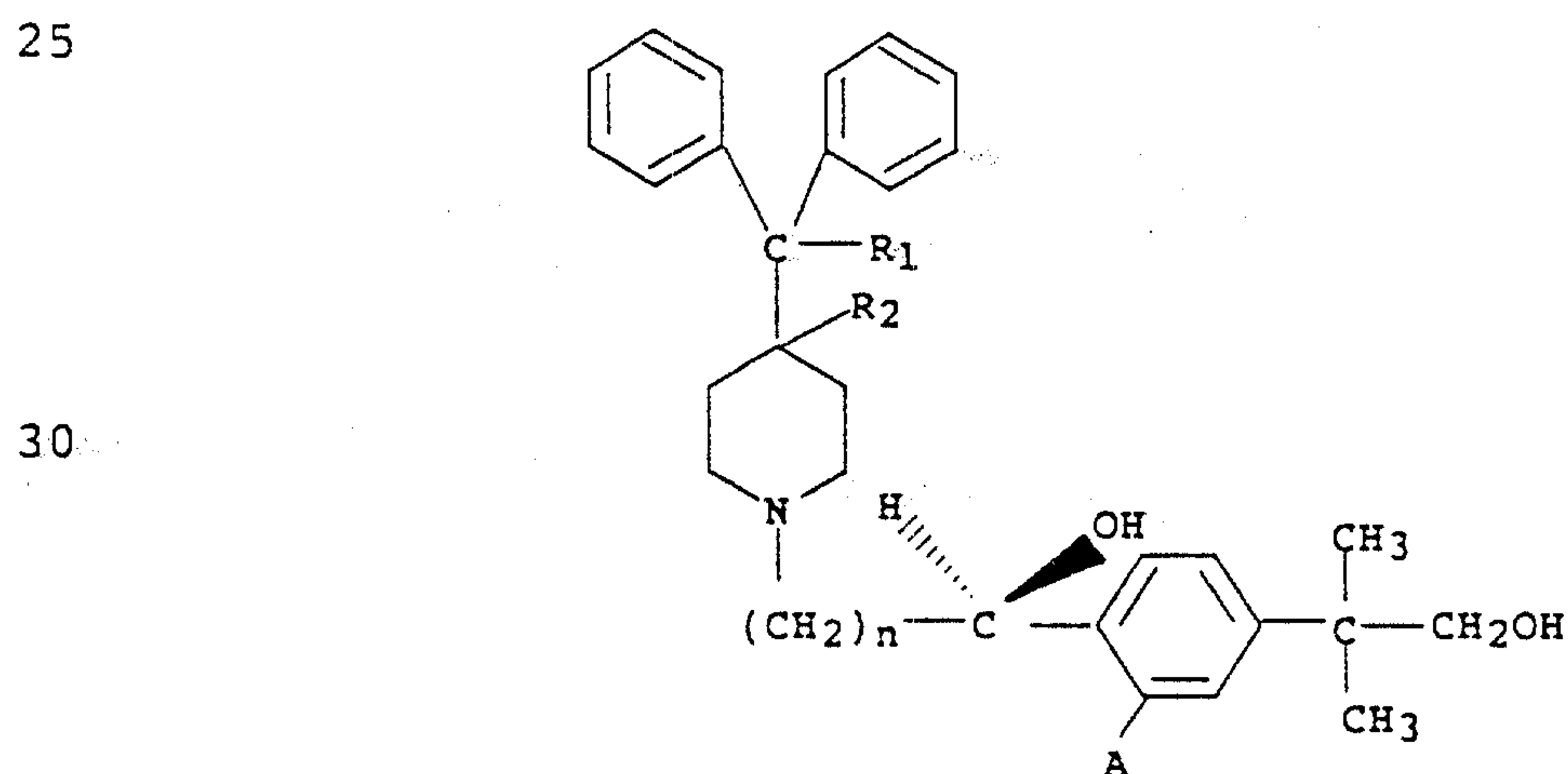
wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylalcohol of the formula

35



wherein R_1 , R_2 , n and D are defined above and A may be
 15 hydrogen or hydroxy with the proviso that when A is
 hydroxy, A may be optionally protected or unprotected;

(f) reacting the piperidine protected
 hydroxyethylphenylalcohol with sodium methoxide in
 20 methanol, potassium carbonate in methanol, methanolic
 ammonia, sodium hydroxide/pyridine in methanol and
 potassium cyanide in ethanol to produce a piperidine
 hydroxyethylphenylalcohol of the formula

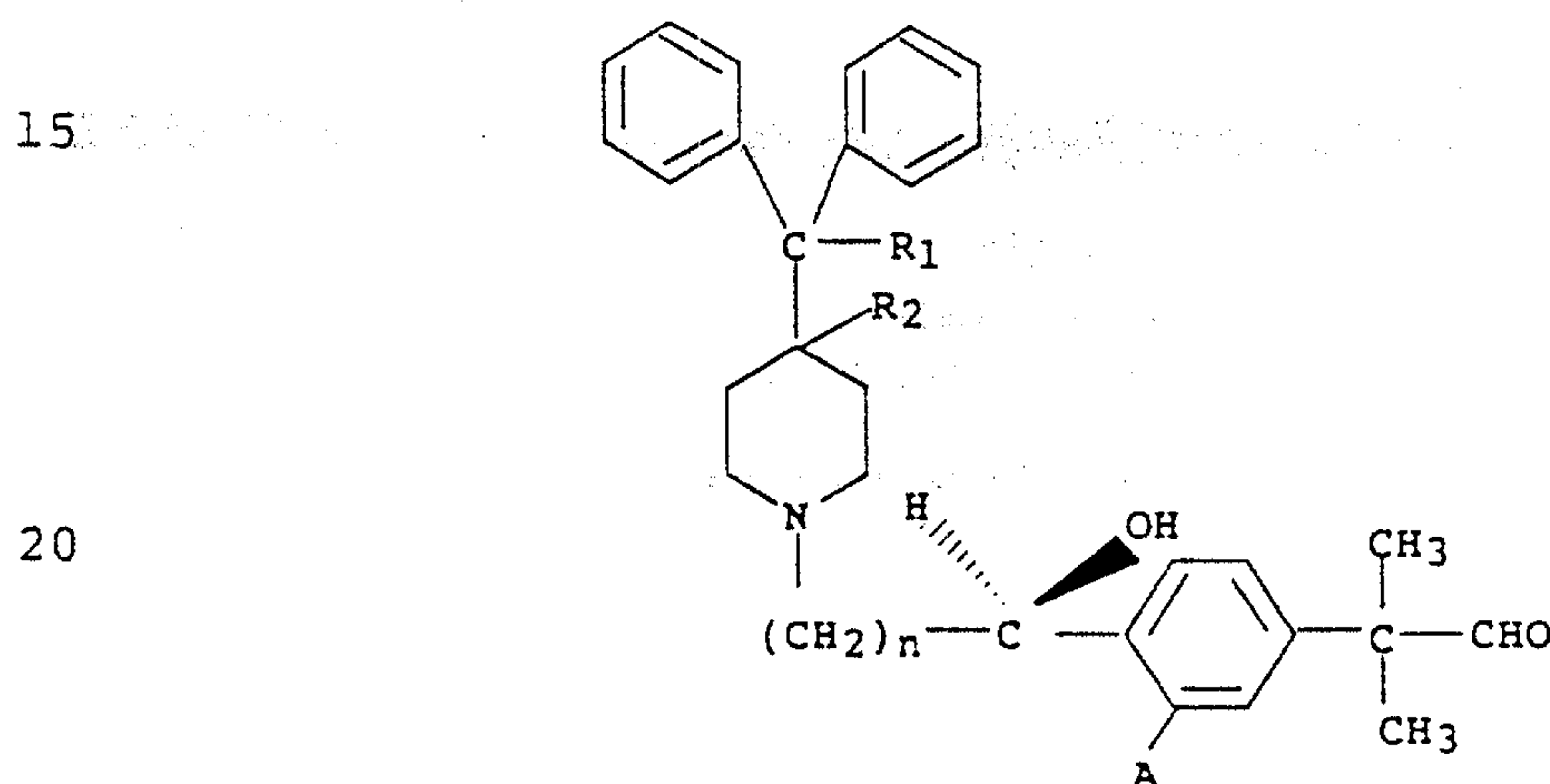


35

wherein R_1 , R_2 and n are defined above and A is hydrogen or
 hydroxy with the proviso that when A is hydroxy, A may be
 optionally protected or unprotected;

-136-

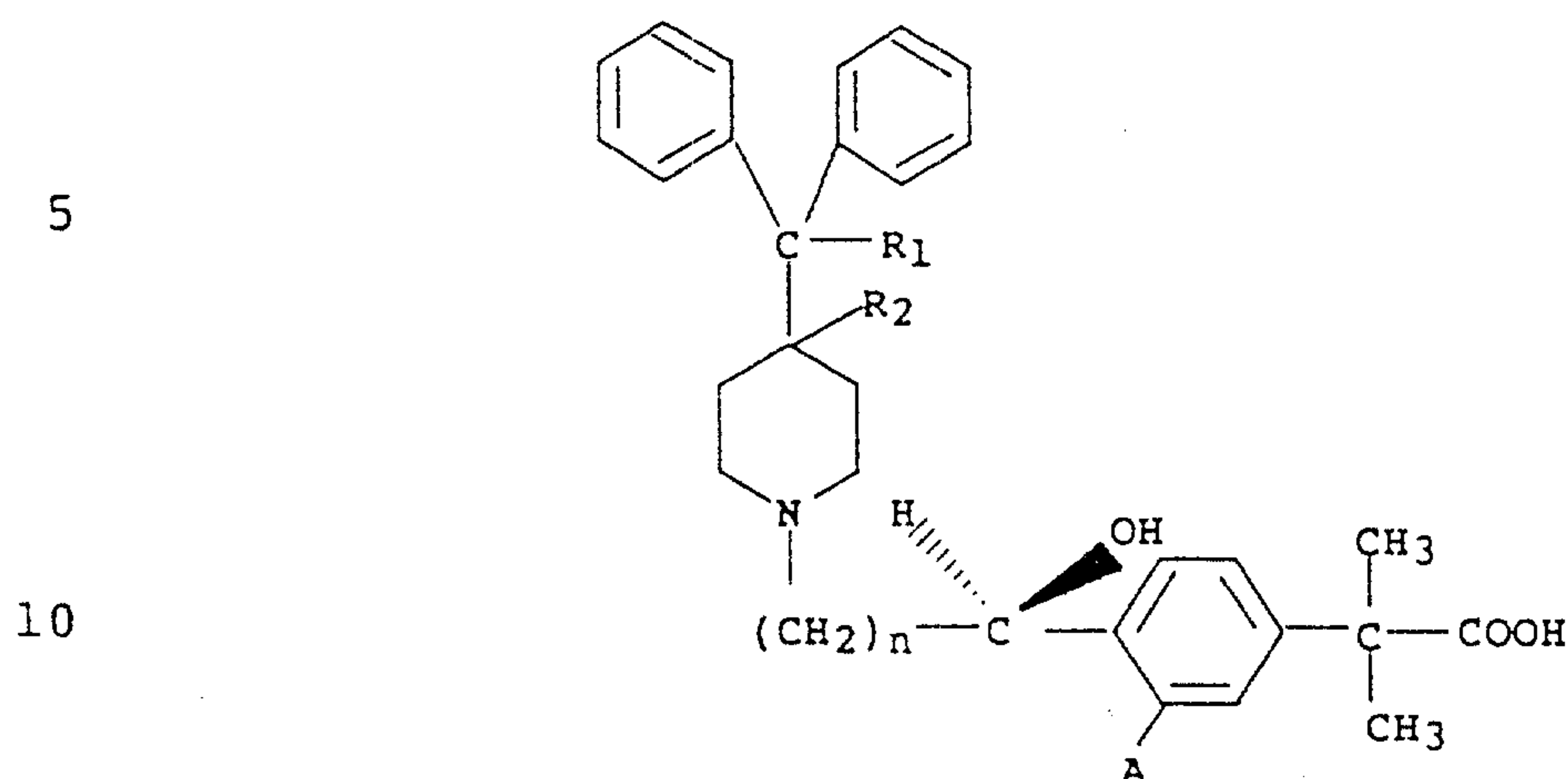
(g) reacting the piperidine hydroxyethylphenylalcohol with dimethyl sulfoxide, oxyalyl chloride and triethylamine or with Dess-Martin reagent, chromium (IV) oxide, nickel peroxide, sodium dichromate, potassium dichromate, t-butyl chromate, silver oxide, argentic picolinate manganese dioxide lead tetraacetate, dicyclohexylcarbodiimide, 2,3-dichloro-5,6-dicyanoquinone, tetrachloro-1,2-benzoquinone, 2,2,6,6-tetramethylpiperidiny-1-oxy (TEMPO) or quinolinium chlorochromate to produce a piperidine formylphenylalcohol of the formula



wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

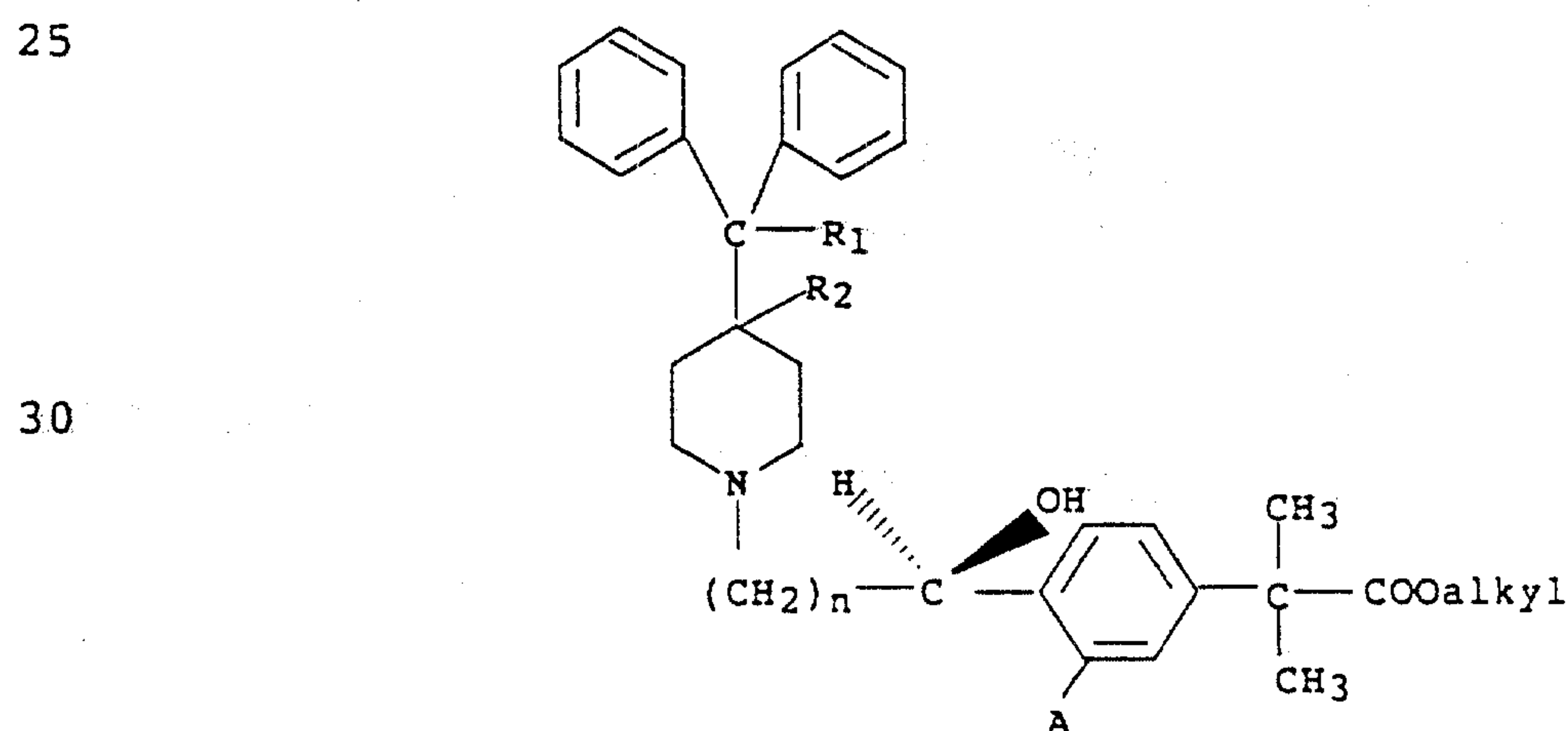
(h) reacting the piperidine formylphenylketone with potassium permanganate, chromium (IV) oxide, silver (I) oxide, silver oxide, argentic picolinate, peroxide, nitric acid, m-chloroperbenzoic acid and peracetic acid to produce a piperidine carboxyphenylalcohol of the formula

-137-



wherein R_1 , R_2 and n are defined above and A is hydrogen or
 15 hydroxy with the proviso that when A is hydroxy, A may be
 optionally protected or unprotected;

(i) optionally reacting the piperidine
 carboxyphenylalcohol with diazomethane or 2,2-
 20 dimethoxypropane or with thionyl chloride followed by an
 alcohol of the formula HOalkyl wherein the alkyl moiety has
 from 1 to 6 carbon atoms and is straight or branched to
 form a piperidine carboxyphenylalcohol ester of the formula

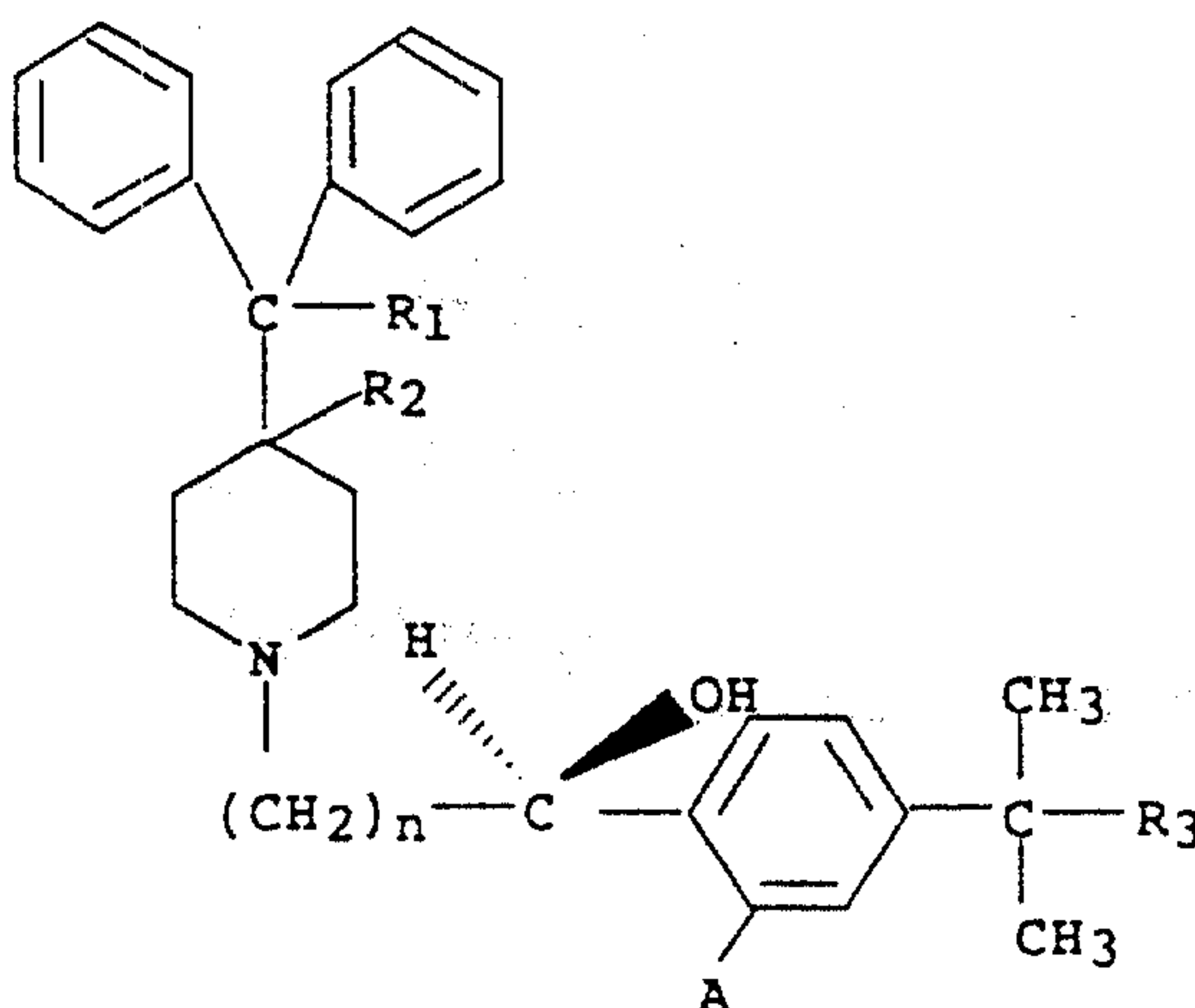


wherein R_1 , R_2 , n and alkyl are defined above and A is
 hydrogen or hydroxy with the proviso that when A is
 hydroxy, A may be optionally protected or unprotected; and

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(j) optionally reacting the piperidine carboxyphenylalcohols or the piperidine carboxyphenylalcohol esters which bear hydroxy protecting groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine carboxyphenylalcohols or the piperidine carboxyphenylalcohol esters.

25. A process for preparing a compound of the formula

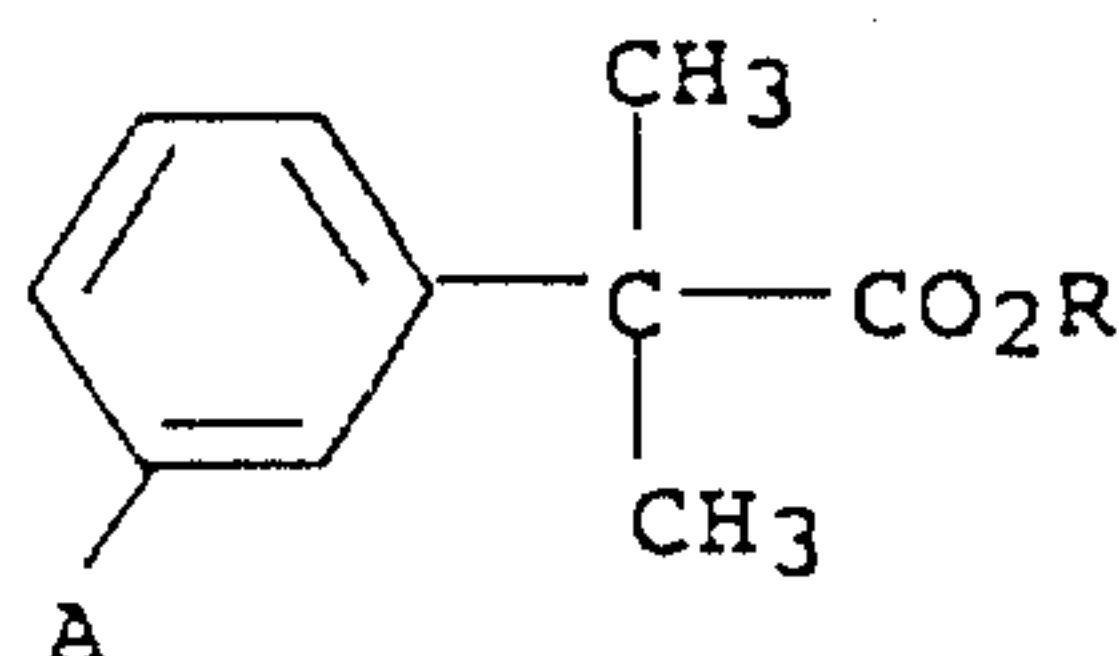


wherein

R₁ represents hydrogen or hydroxy;
 R₂ represents hydrogen; or
 R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;
 n is an integer of from 1 to 5;
 R₃ is -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;
 A is hydrogen or hydroxy; and
 pharmaceutically acceptable salts thereof comprising the steps of:

(a) reacting a benzeneacetic acid compound of the formula

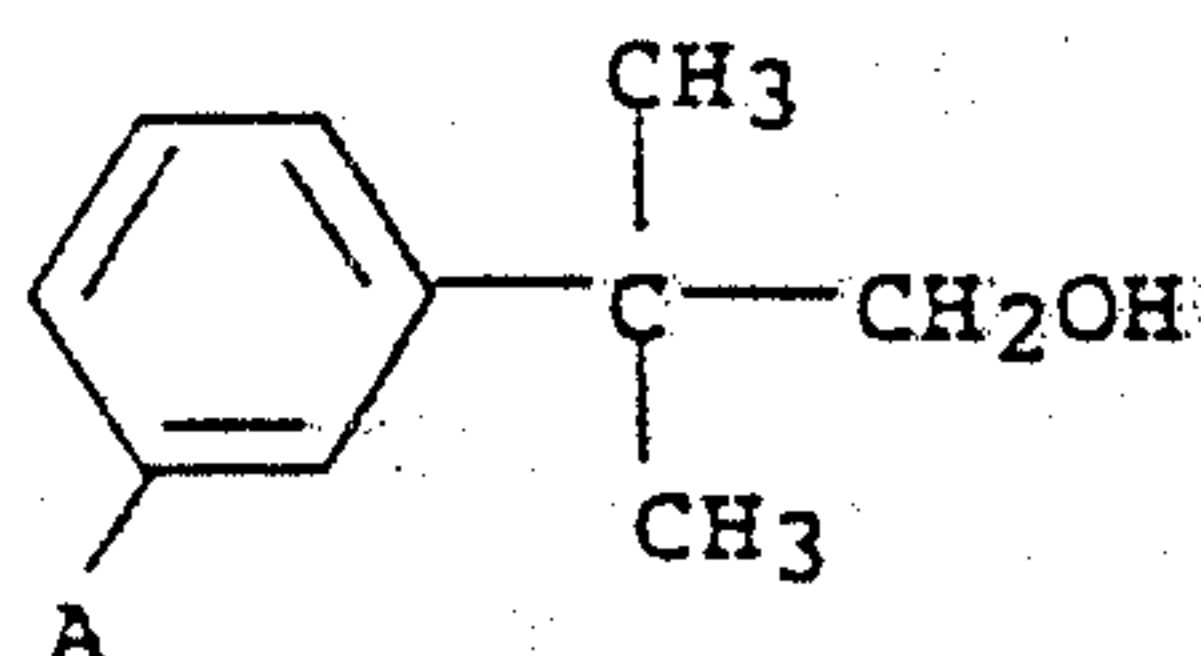
5



10

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

15



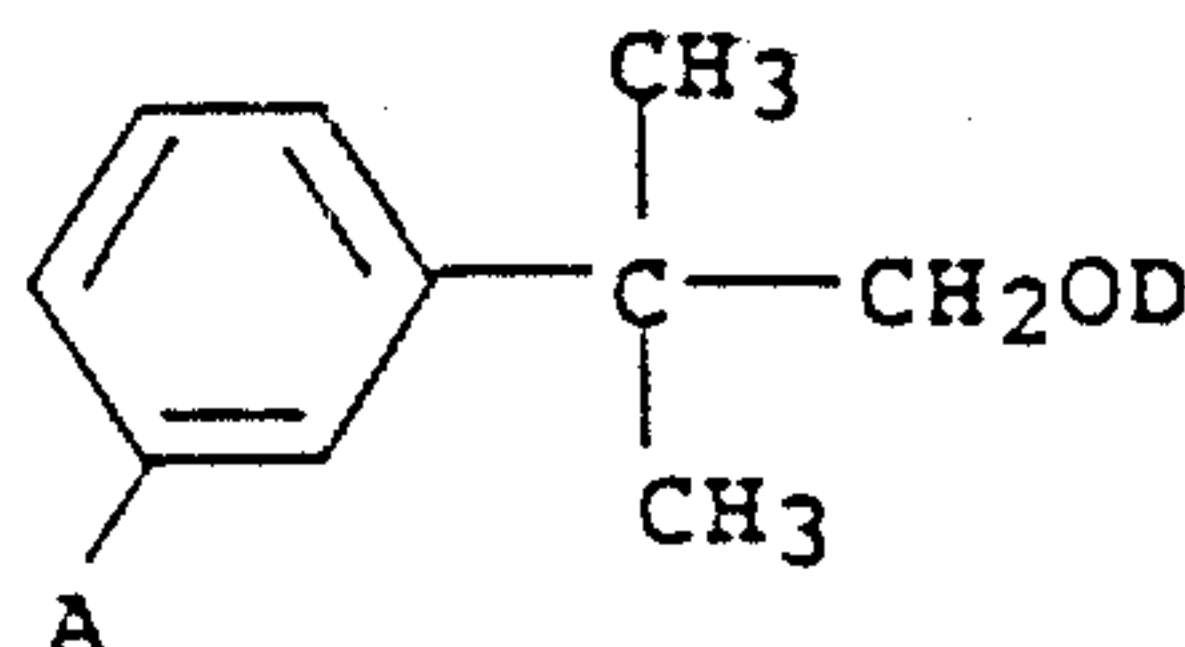
20

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

25

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

30

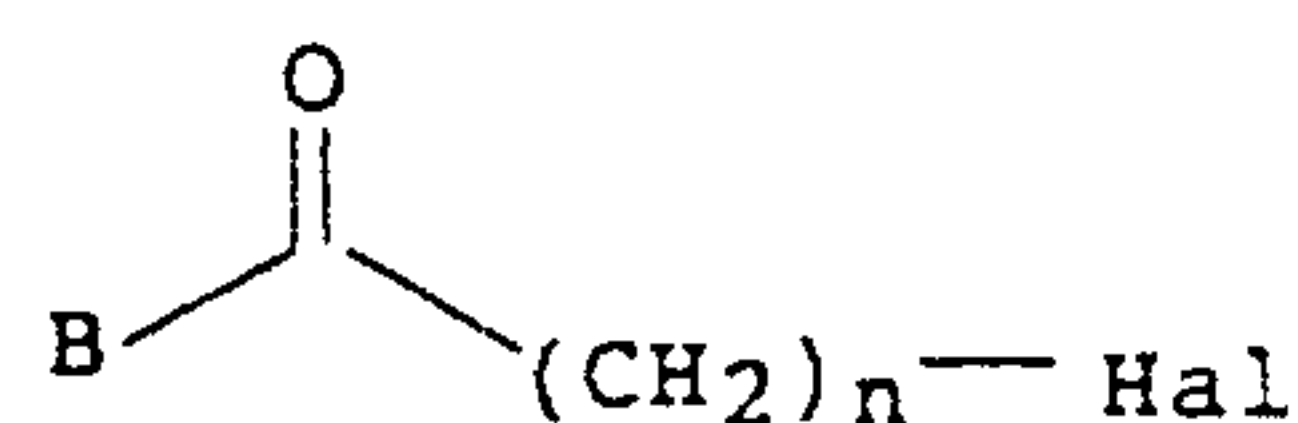


35

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is C(=O)CH₃ or C(=O)C₆H₅;

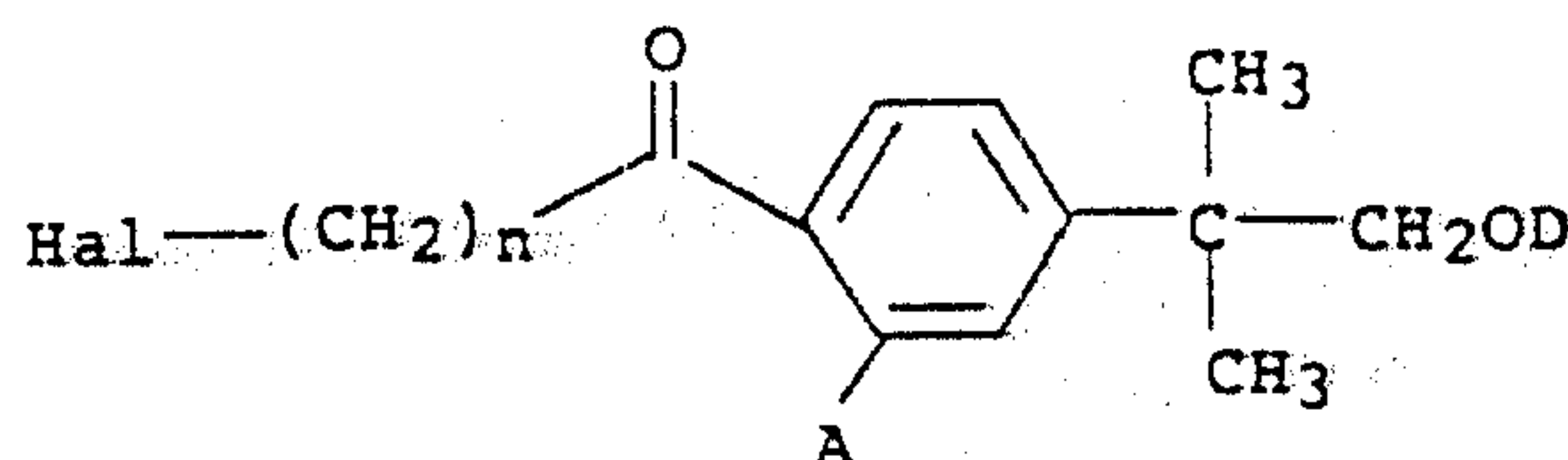
(c) reacting the protected phenethyl alcohol with a ω -halo compound of the formula

5



10 wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula

15



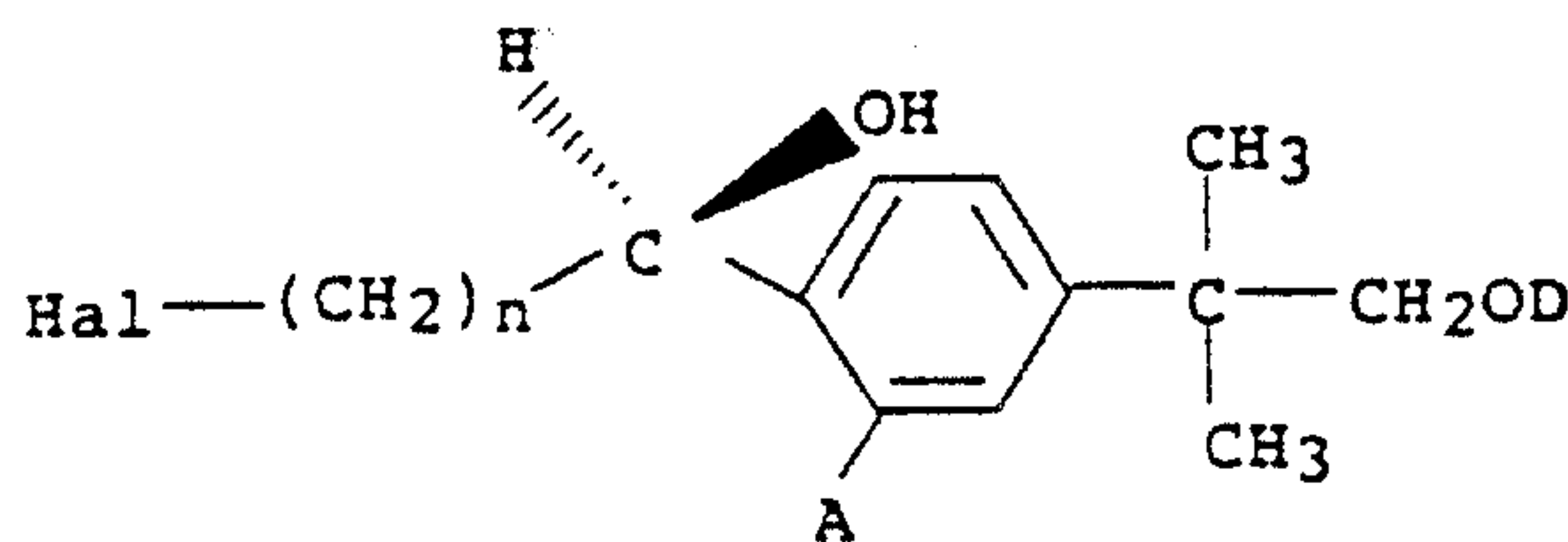
20

wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

25

(d) reacting the ω -halo protected hydroxyethylphenylketone with (+)-B-chlorodiisopinocampheylborane to produce a ω -halo protected hydroxyethylphenylalcohol of the formula

30

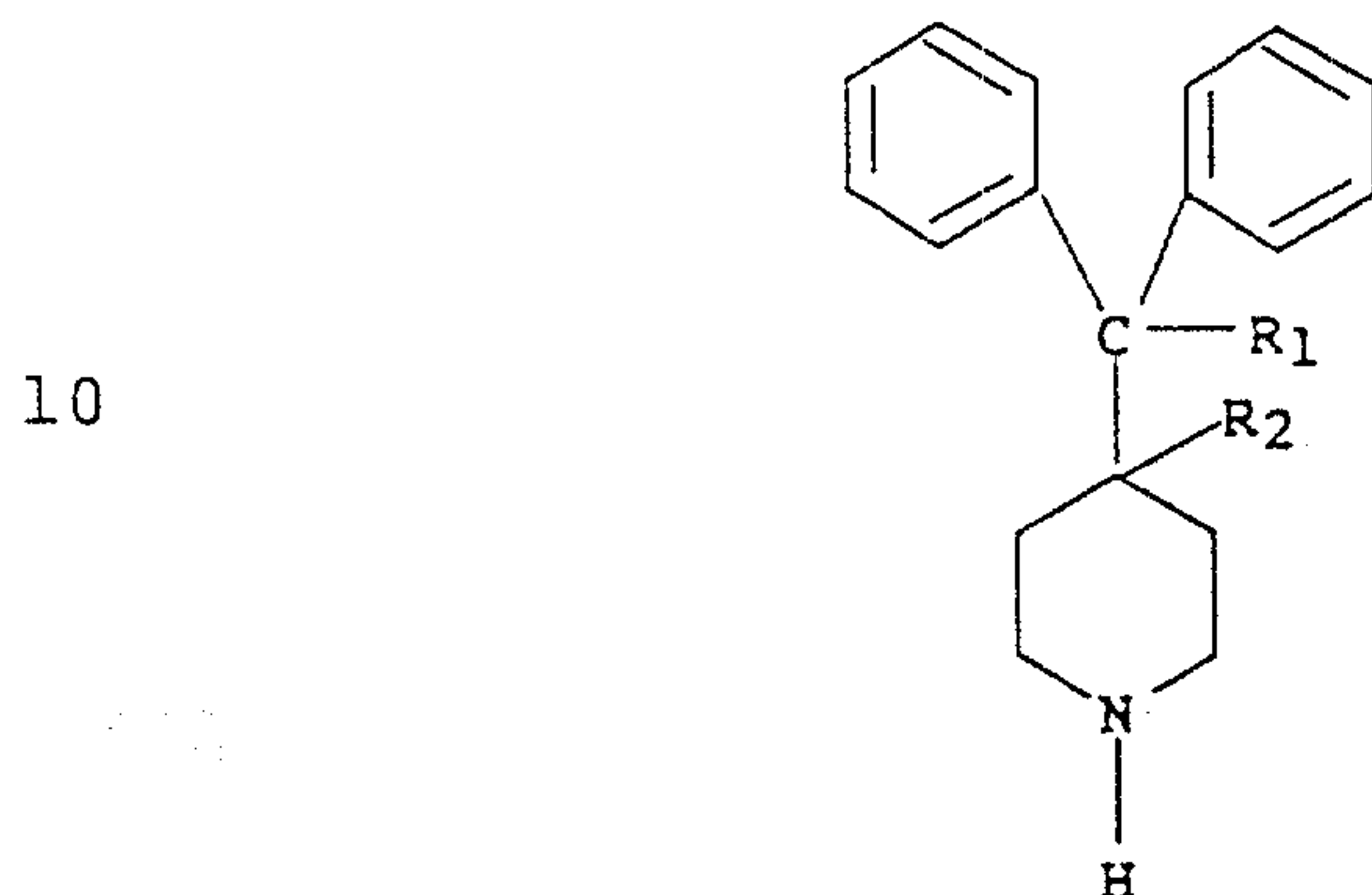


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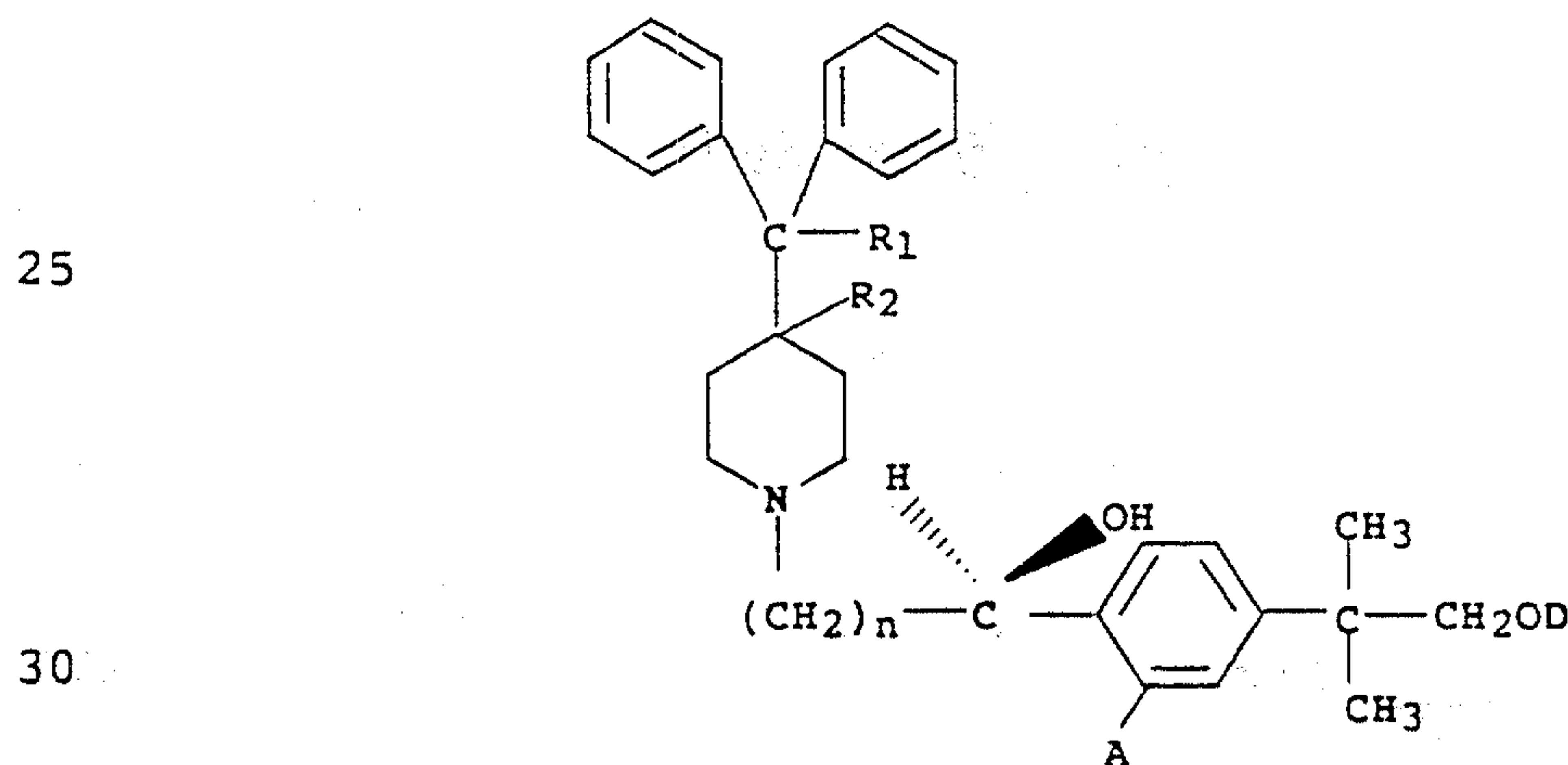
wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

-141-

(e) reacting the ω -halo protected hydroxyethylphenylalcohol with a piperidine compound of the formula



wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylalcohol of the formula



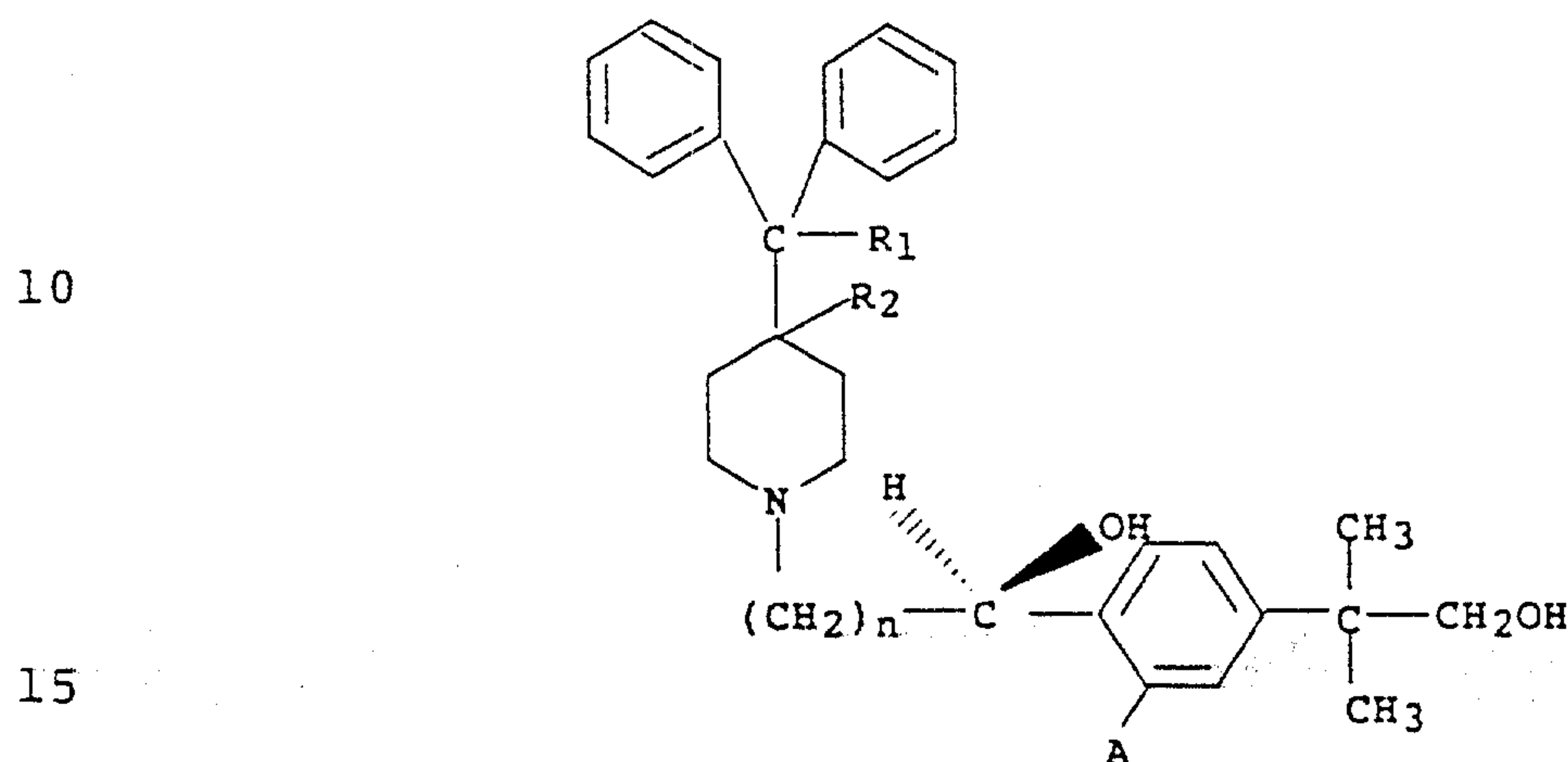
wherein R_1 , R_2 , n and D are defined above and A may be hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(f) reacting the piperidine protected hydroxyethylphenylalcohol with sodium methoxide in

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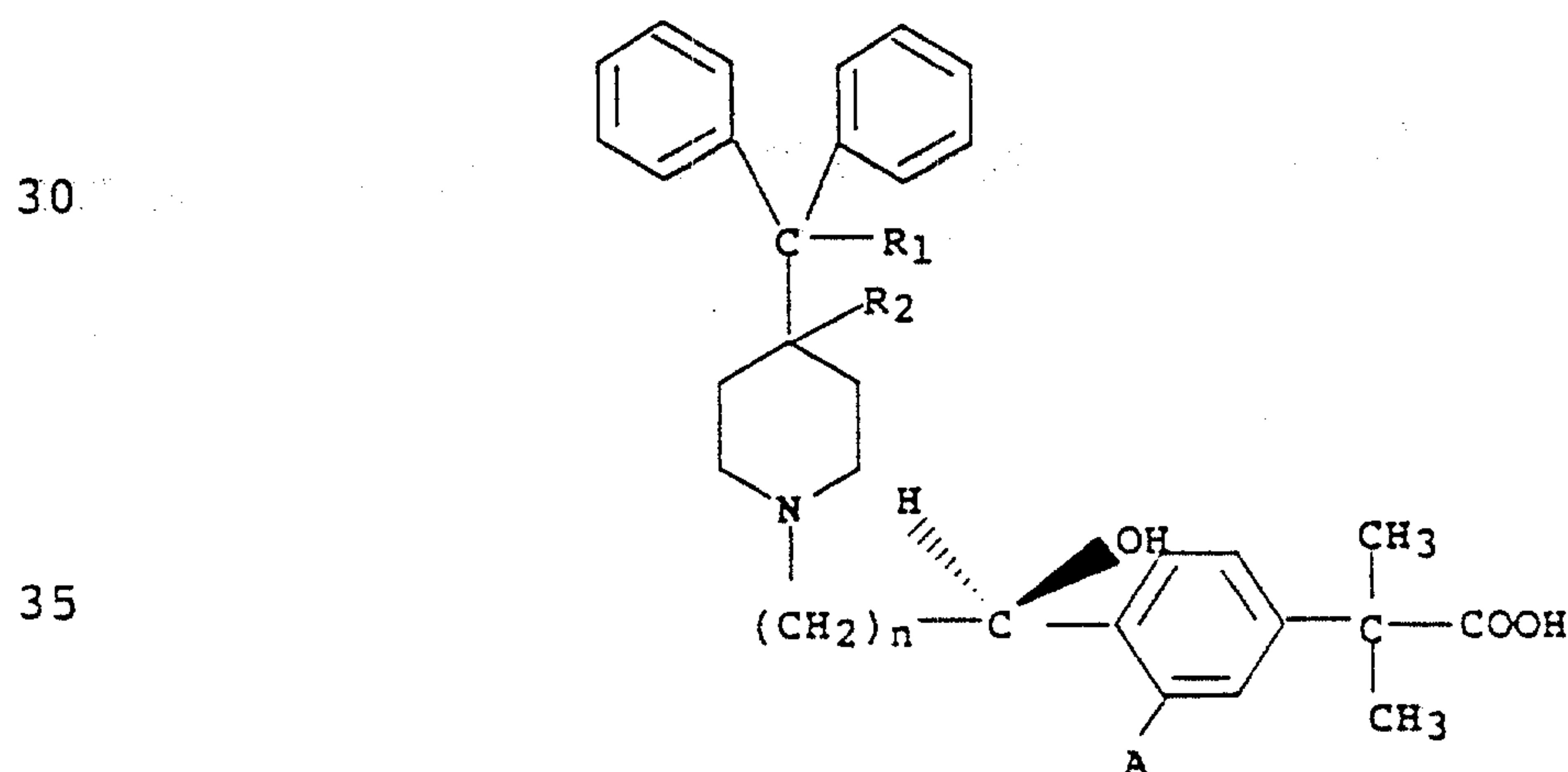
-142-

methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylalcohol of the formula



wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(g) reacting the piperidine hydroxyethylphenylalcohol with chromium (IV) oxide, potassium permanganate, nitric acid, nitrogen dioxide, ruthenium (VIII) oxide, nickel peroxide, silver oxide, t-butyl chromate or xenic acid to produce a piperidine carboxyphenylketone of the formula

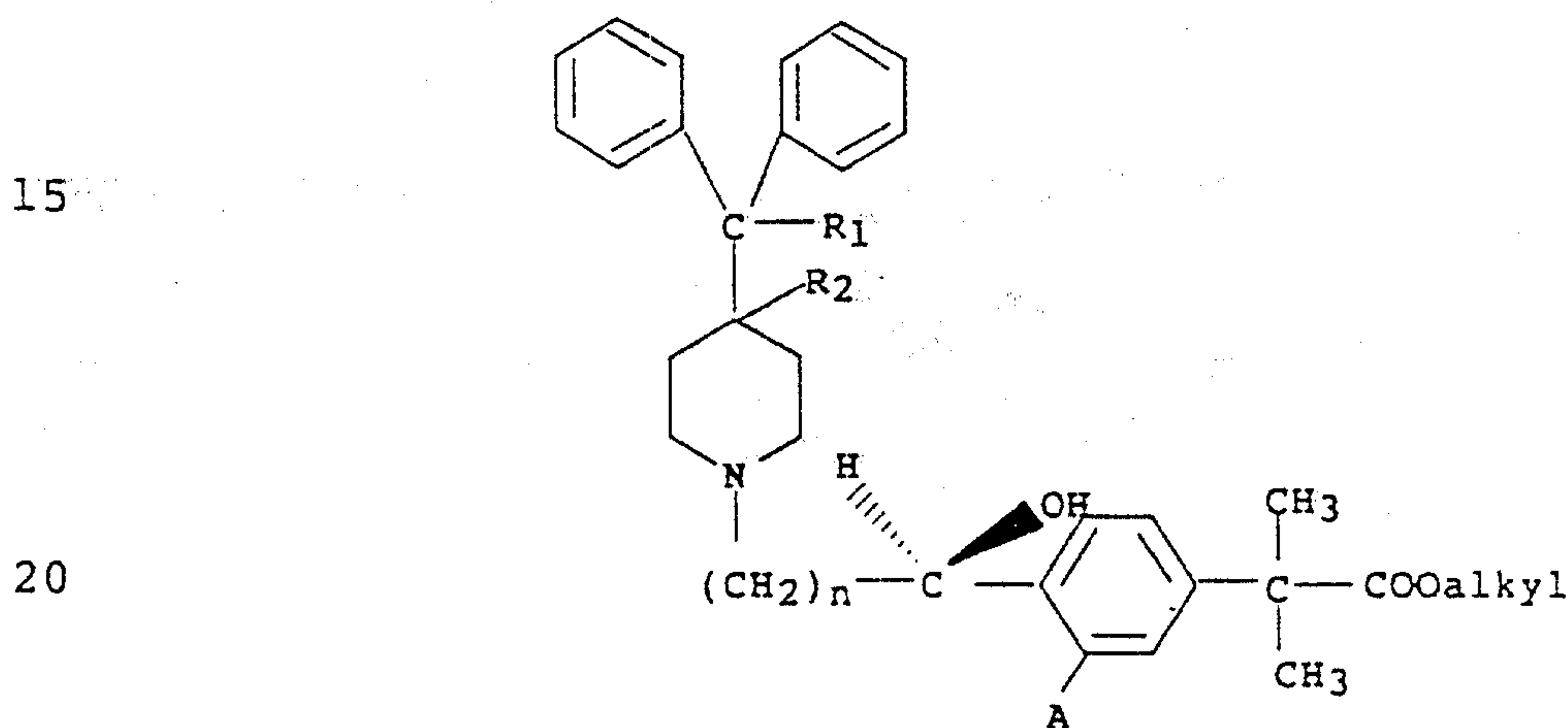


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wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

5

(h) optionally reacting the piperidine carboxyphenylalcohol with diazomethane or 2,2-dimethoxypropane or with thionyl chloride followed by an alcohol of the formula HOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched to form a piperidine carboxyphenylalcohol ester of the formula



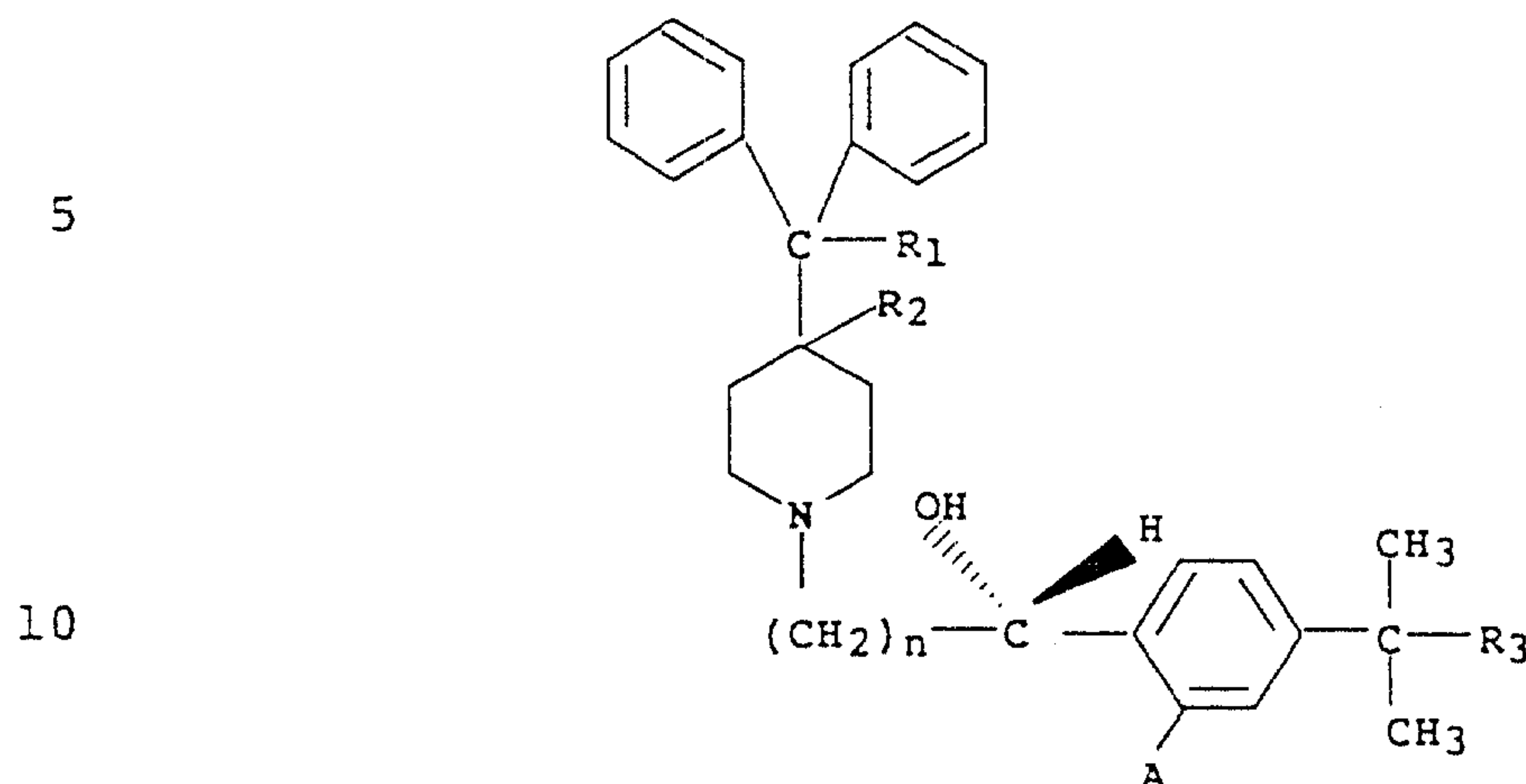
wherein R_1 , R_2 , n and alkyl are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected; and

(i) optionally reacting the piperidine carboxyphenylalcohols or the piperidine carboxyphenylalcohol esters which bear hydroxy protecting groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine carboxyphenylalcohols or the piperidine carboxyphenylalcohol esters.

35

26. A process for preparing a compound of the formula

-144-



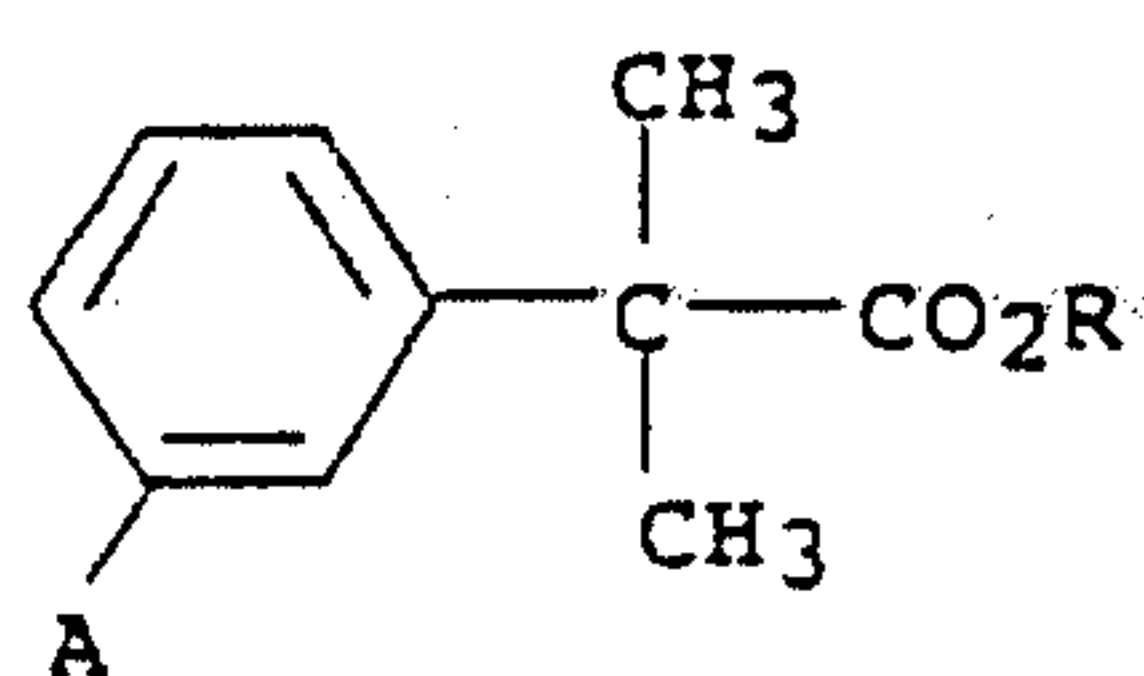
wherein

- 15 R_1 represents hydrogen or hydroxy;
- R_2 represents hydrogen; or
- R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;
- n is an integer of from 1 to 5;
- 20 R_3 is $-\text{COOH}$ or $-\text{COOalkyl}$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;
- A is hydrogen or hydroxy; and
- pharmaceutically acceptable salts thereof comprising the steps of:

25

(a) reacting a benzeneacetic acid compound of the formula

30



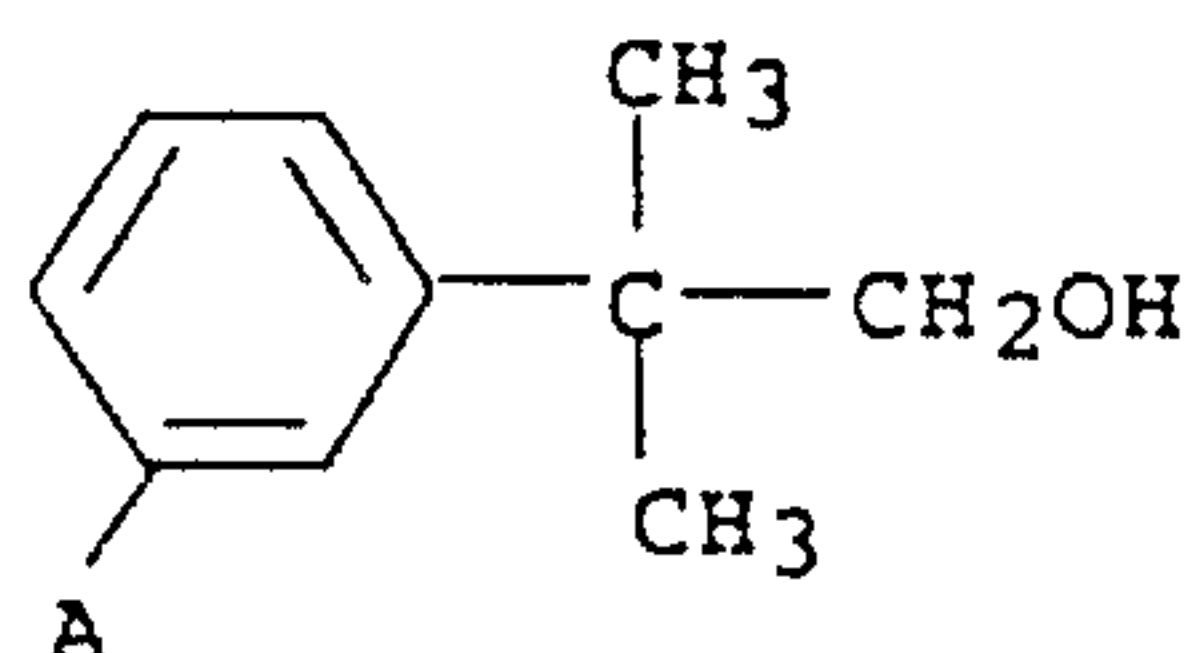
35

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and R is hydrogen or $\text{C}_1\text{-C}_6$ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, diborane, lithium borohydride, lithium triethylborohydride

-145-

and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

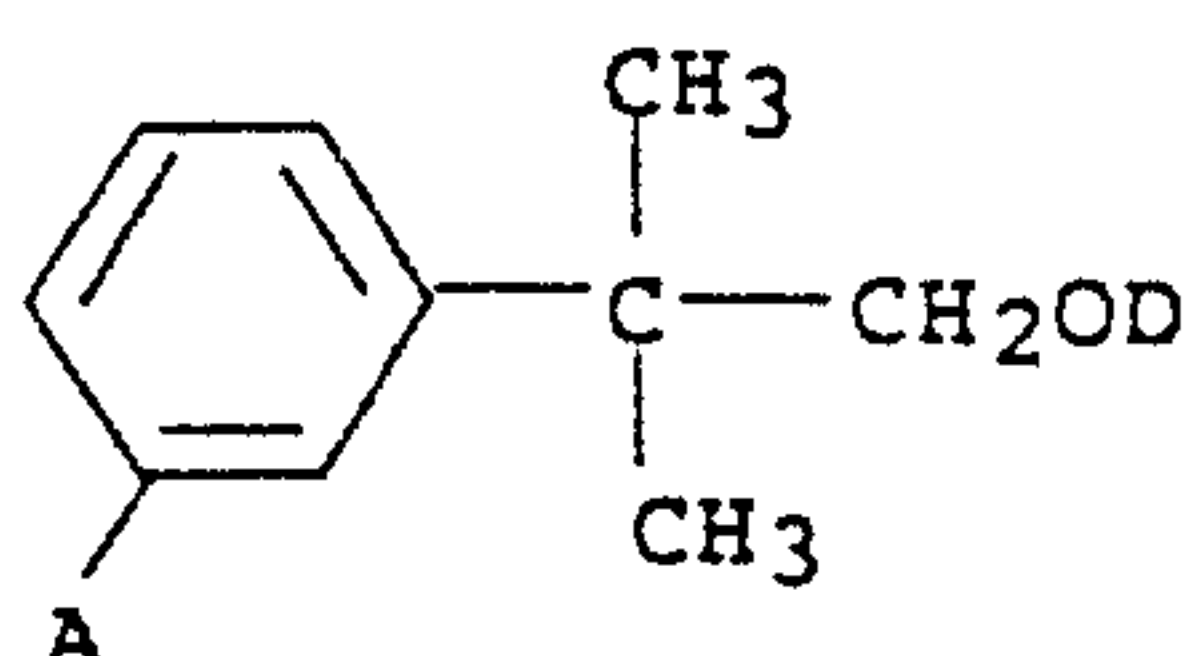
5



10 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

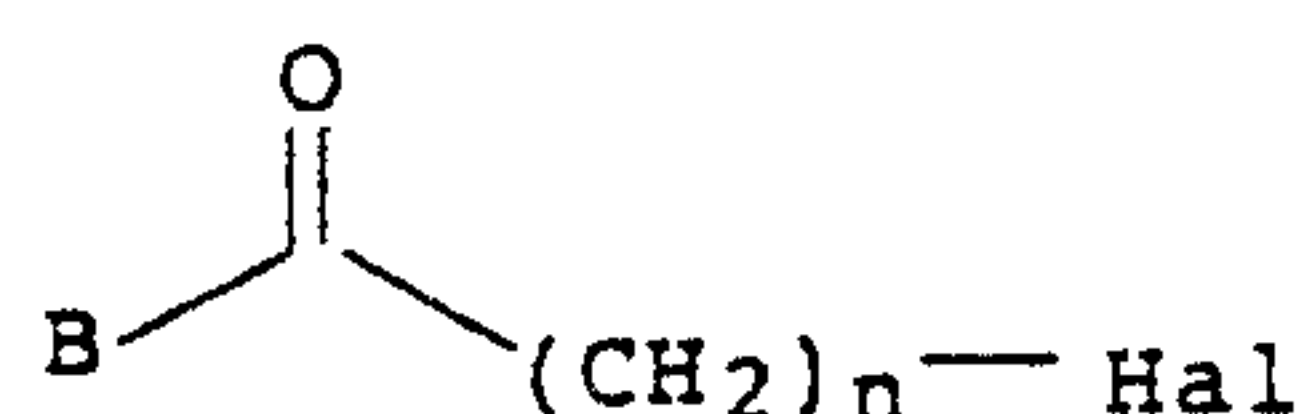
20



25 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is C(=O)CH₃ or C(=O)C₆H₅;

(c) reacting the protected phenethyl alcohol with a ω-halo compound of the formula

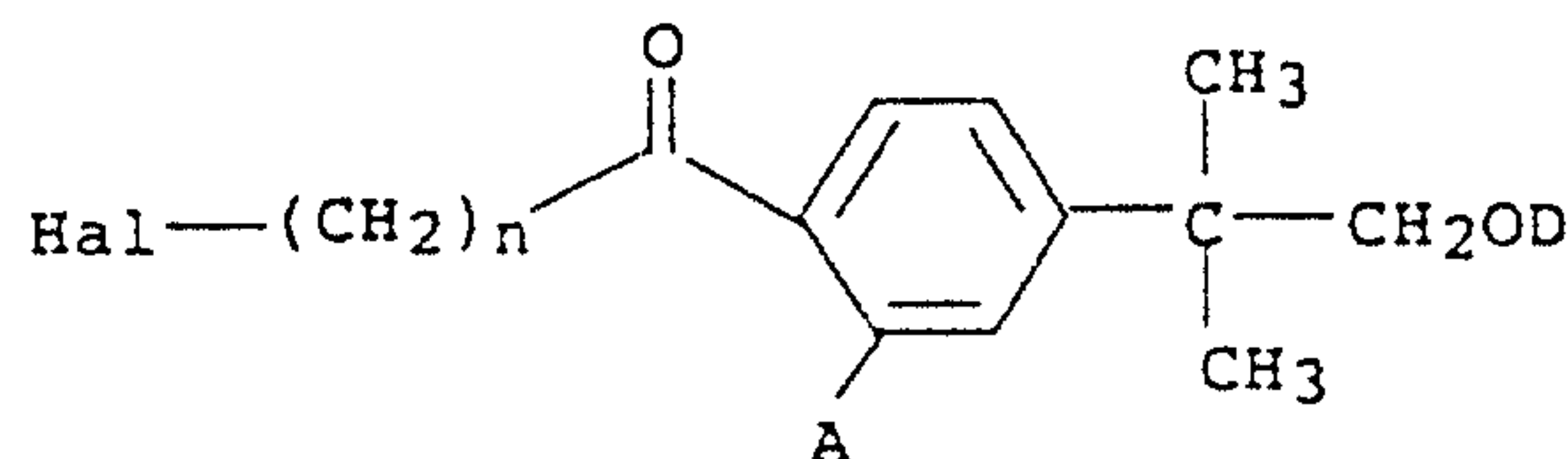
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35 wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron

trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula

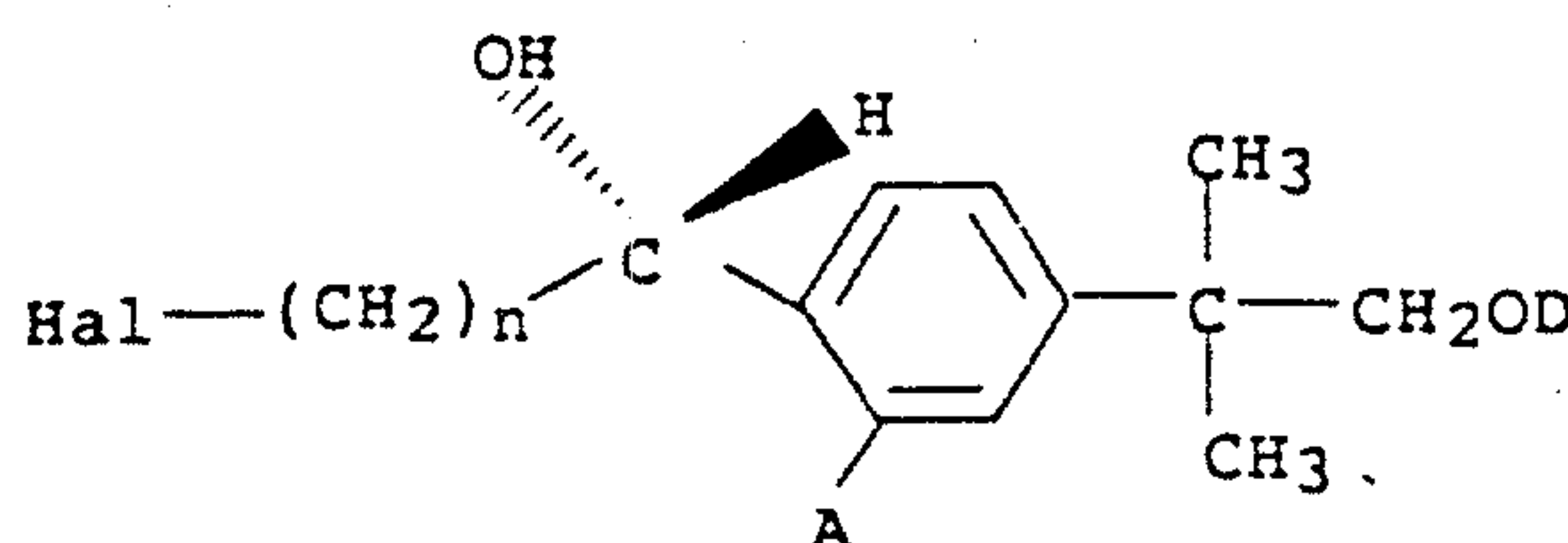
5



10 wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(d) reacting the ω -halo protected
15 hydroxyethylphenylketone with (-)-B-
chlorodiisopinocampheylborane to produce a ω -halo
protected hydroxyethylphenylalcohol of the formula

20

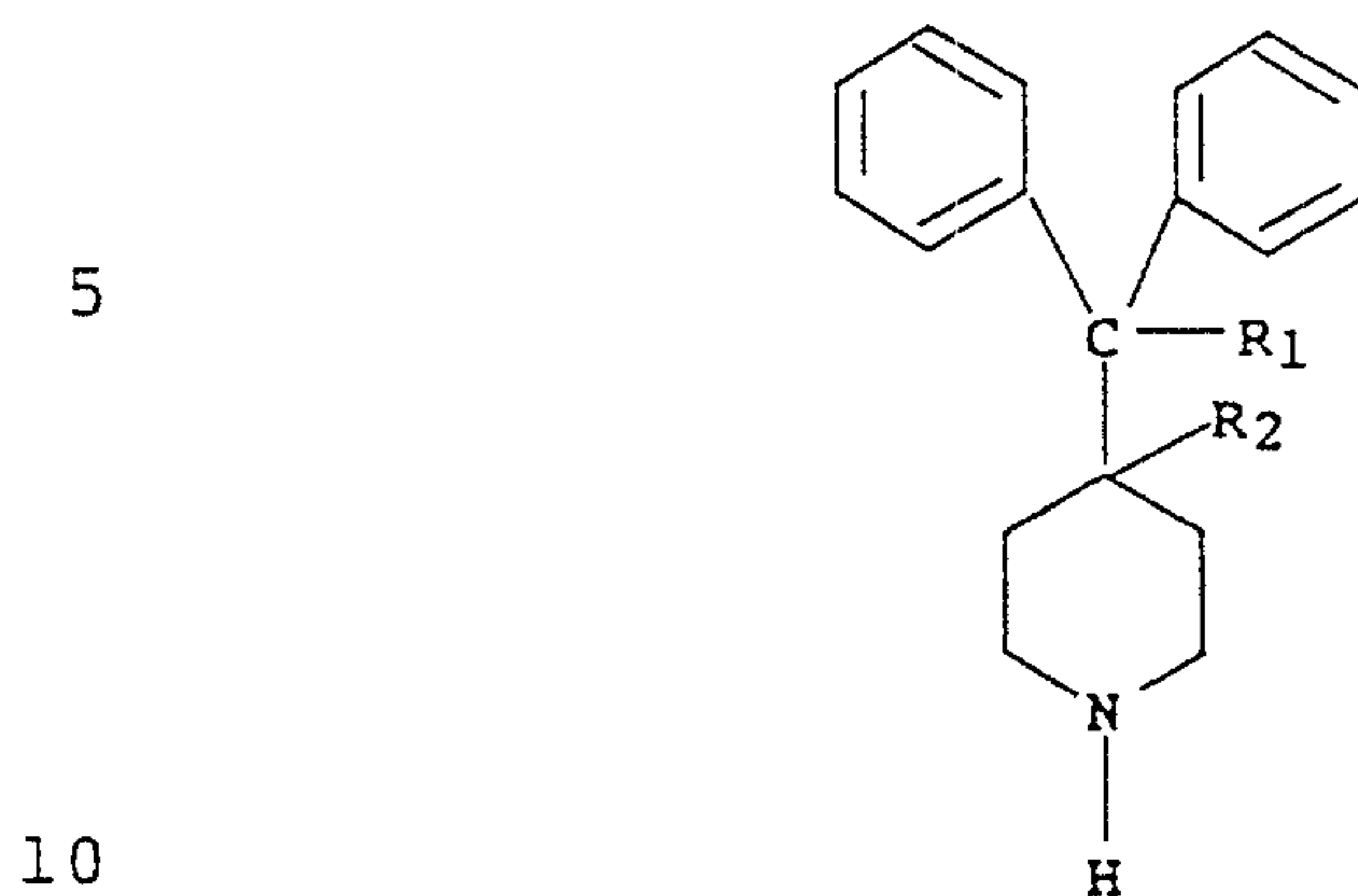


25 wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

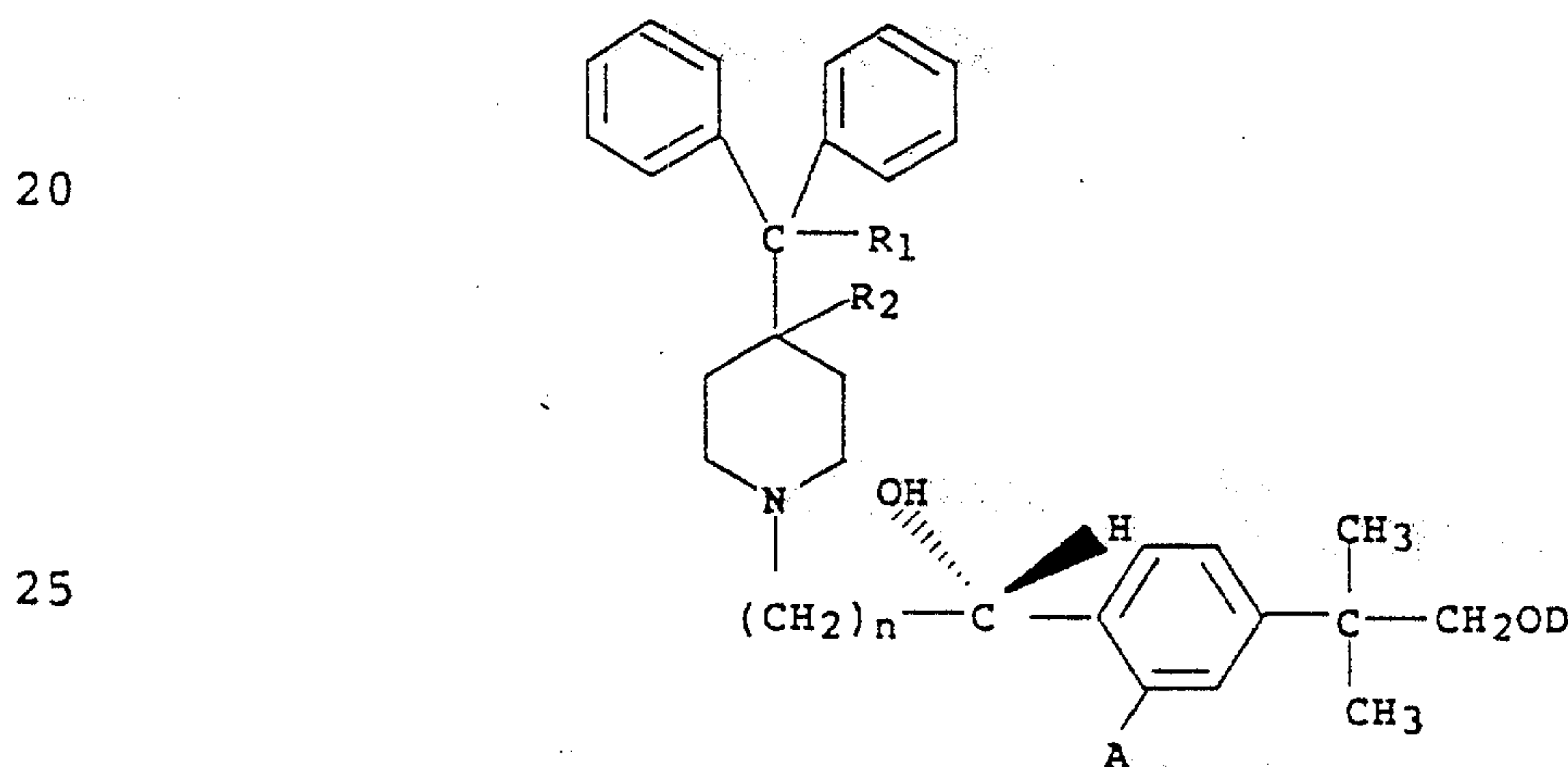
(e) reacting the ω -halo protected
30 hydroxyethylphenylalcohol with a piperidine compound of the
formula

35

-147-



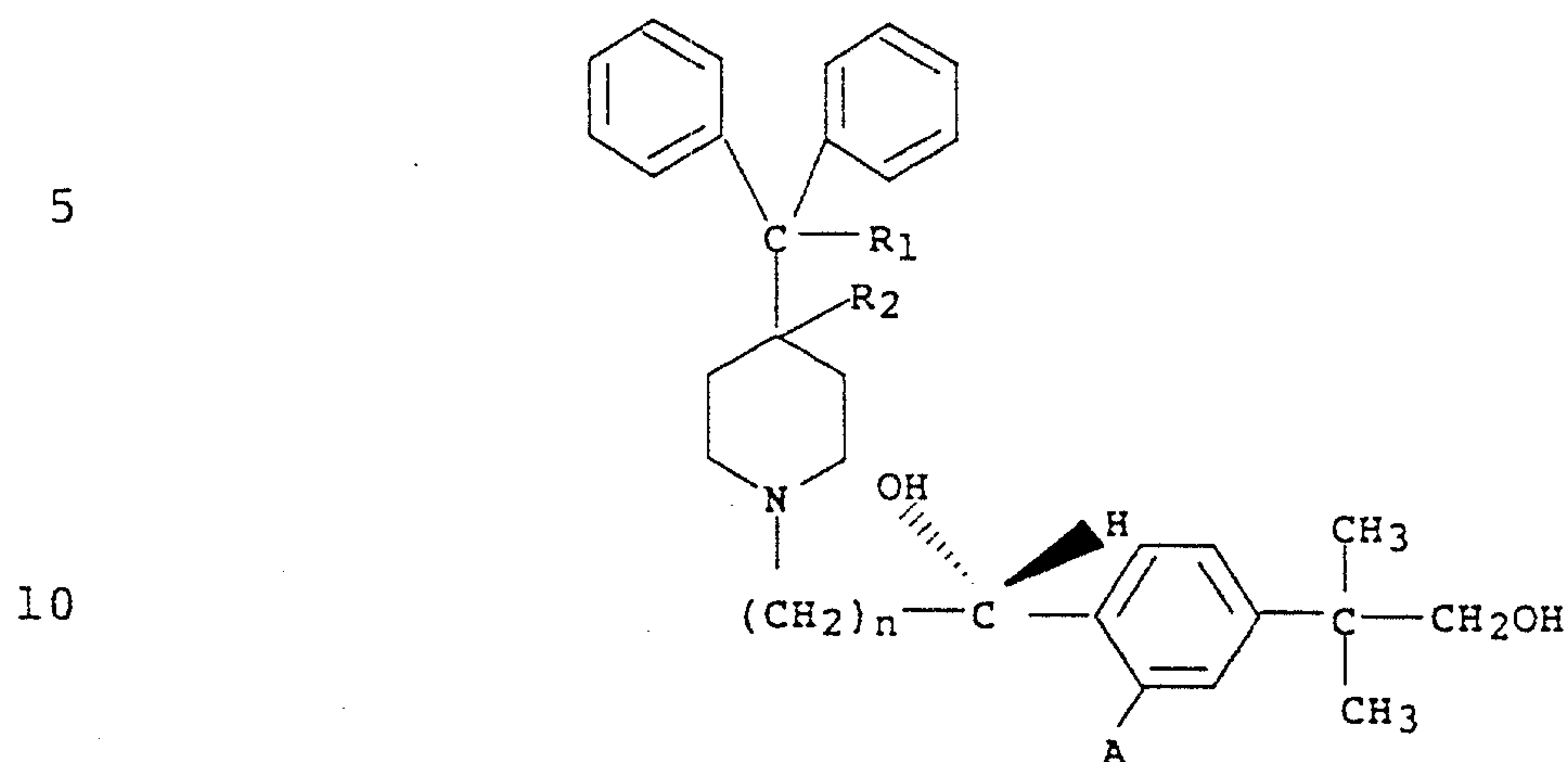
wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylalcohol of the formula



wherein R_1 , R_2 , n and D are defined above and A may be hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(f) reacting the piperidine protected hydroxyethylphenylalcohol with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylalcohol of the formula

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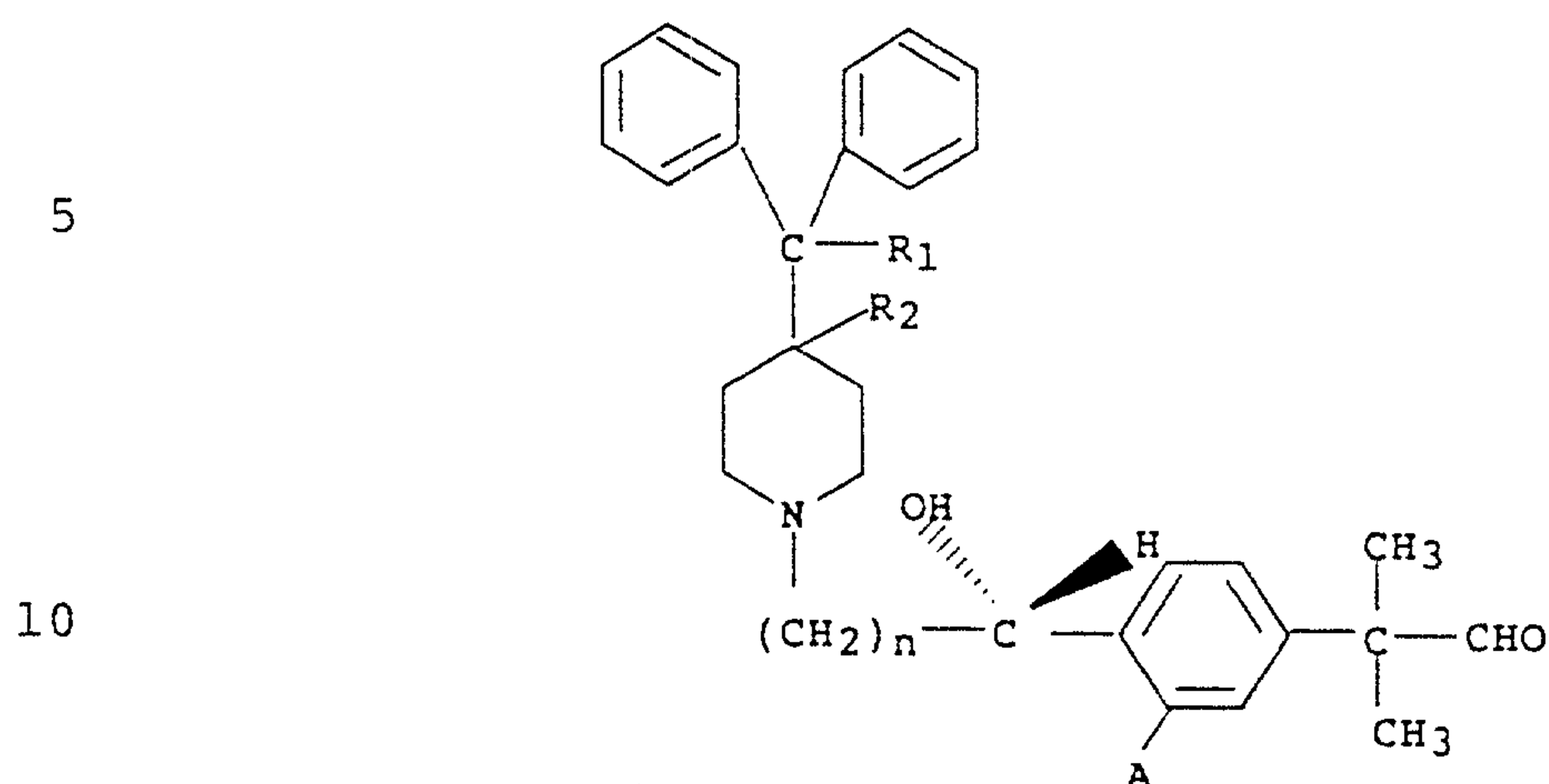


wherein R₁, R₂ and n are defined above and A is hydrogen or
 15 hydroxy with the proviso that when A is hydroxy, A may be
 optionally protected or unprotected;

(g) reacting the piperidine hydroxyethylphenylalcohol
 with dimethyl sulfoxide, oxyalyl chloride and triethylamine
 20 or with Dess-Martin reagent, chromium (IV) oxide, nickel
 peroxide, sodium dichromate, potassium dichromate, t-butyl
 chromate, silver oxide, argentic picolinate manganese
 dioxide lead tetraacetate, dicyclohexylcarbodiimide, 2,3-
 dichloro-5,6-dicyanoquinone, tetrachloro-1,2-benzoquinone,
 25 2,2,6,6-tetramethylpiperidiny-1-oxy (TEMPO) or quinolinium
 chlorochromate to produce a piperidine formylphenylalcohol
 of the formula

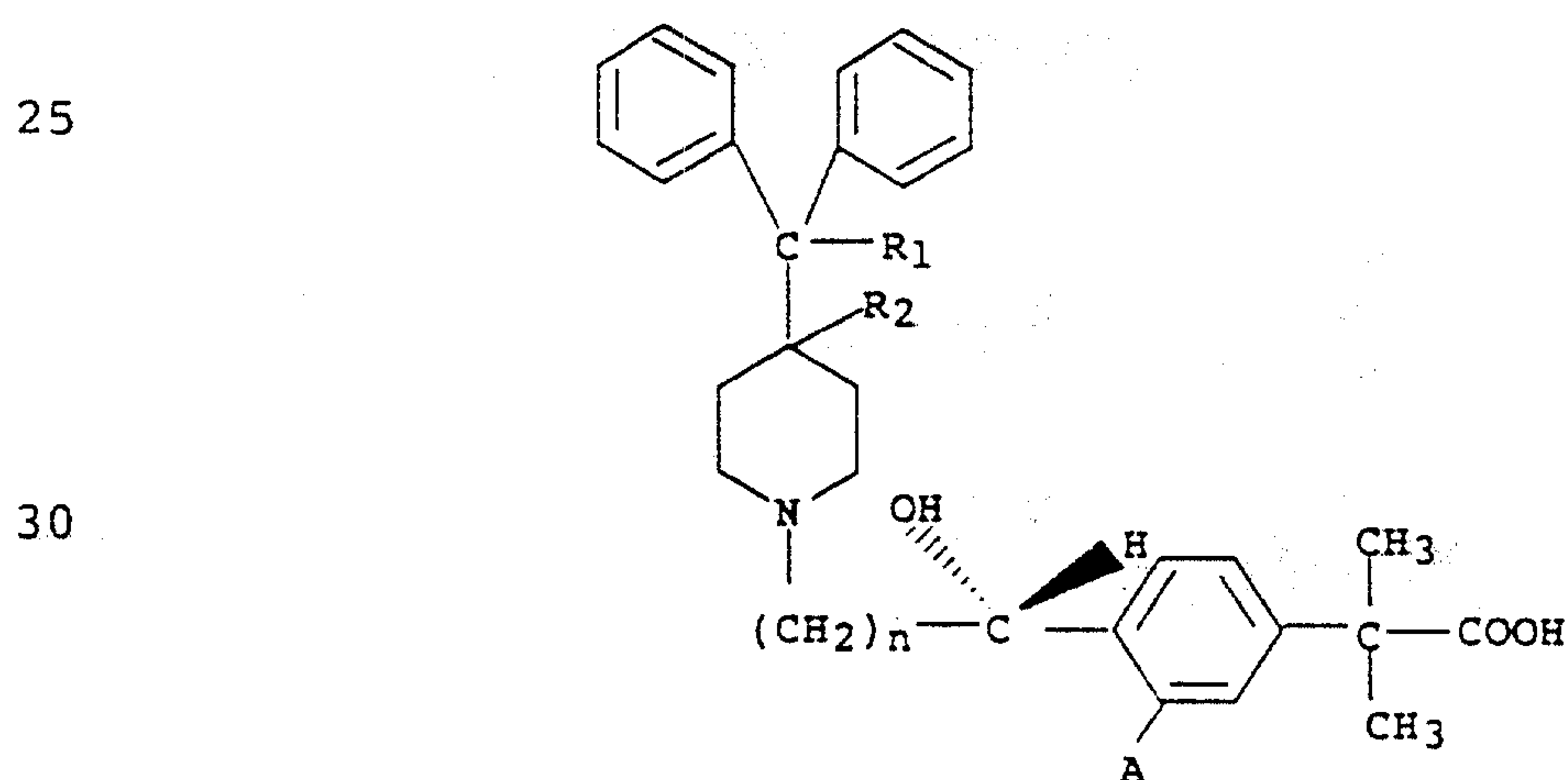
30

35



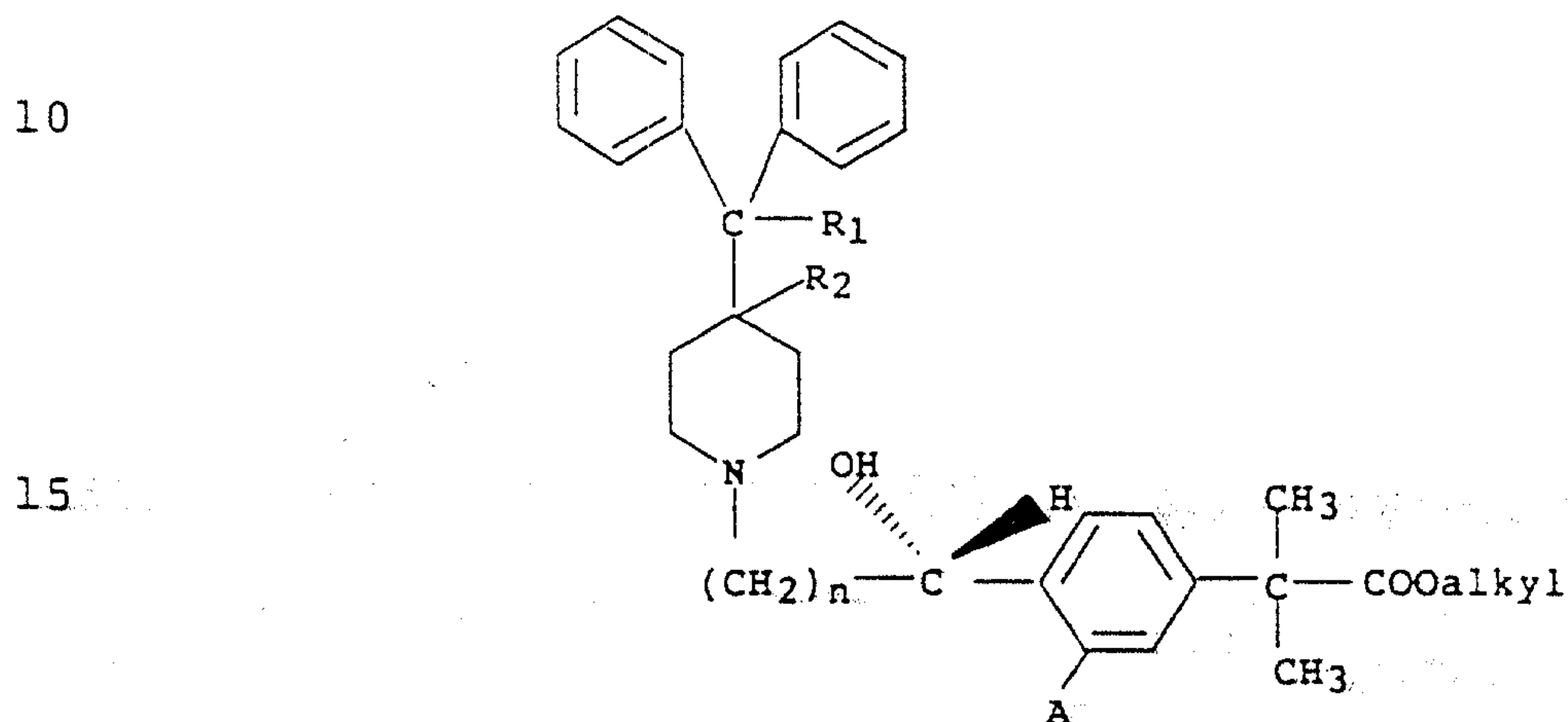
wherein R_1 , R_2 and n are defined above and A is hydrogen or
 15 hydroxy with the proviso that when A is hydroxy, A may be
 optionally protected or unprotected;

(h) reacting the piperidine formylphenylketone with
 potassium permanganate, chromium (IV) oxide, silver (I)
 20 oxide, silver oxide, argentic picolinate, peroxide, nitric
 acid, m-chloroperbenzoic acid and peracetic acid to produce
 a piperidine carboxyphenylalcohol of the formula



35 wherein R_1 , R_2 and n are defined above and A is hydrogen or
 hydroxy with the proviso that when A is hydroxy, A may be
 optionally protected or unprotected;

- (i) optionally reacting the piperidine carboxyphenylalcohol with diazomethane or 2,2-dimethoxypropane or with thionyl chloride followed by an alcohol of the formula HOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched to form a piperidine carboxyphenylalcohol ester of the formula

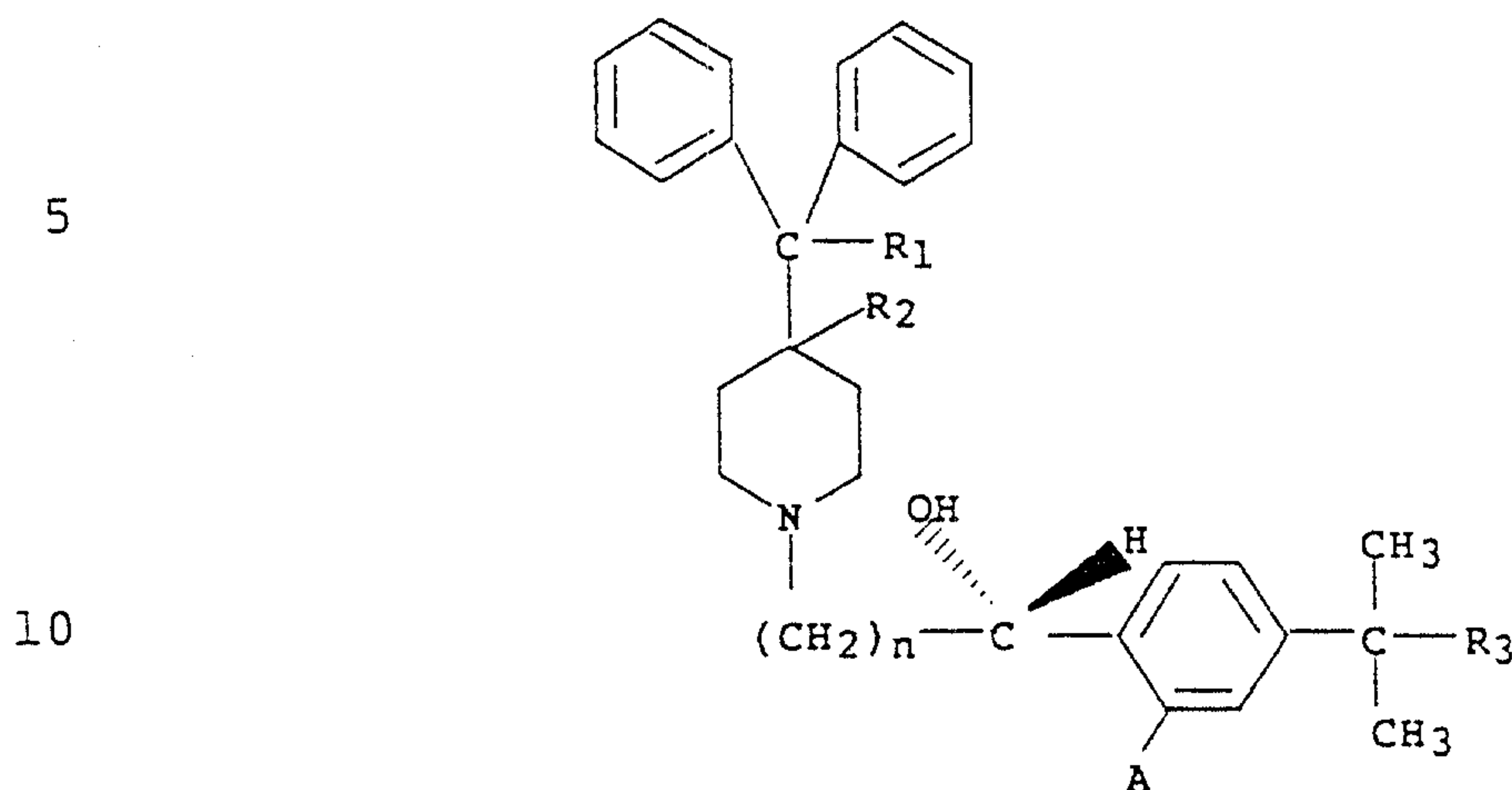


- 20 wherein R₁, R₂, n and alkyl are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected; and

- (j) optionally reacting the piperidine carboxyphenylalcohols or the piperidine carboxyphenylalcohol esters which bear hydroxy protecting groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine carboxyphenylalcohols or the piperidine carboxyphenylalcohol esters.

27. A process for preparing a compound of the formula

-151-



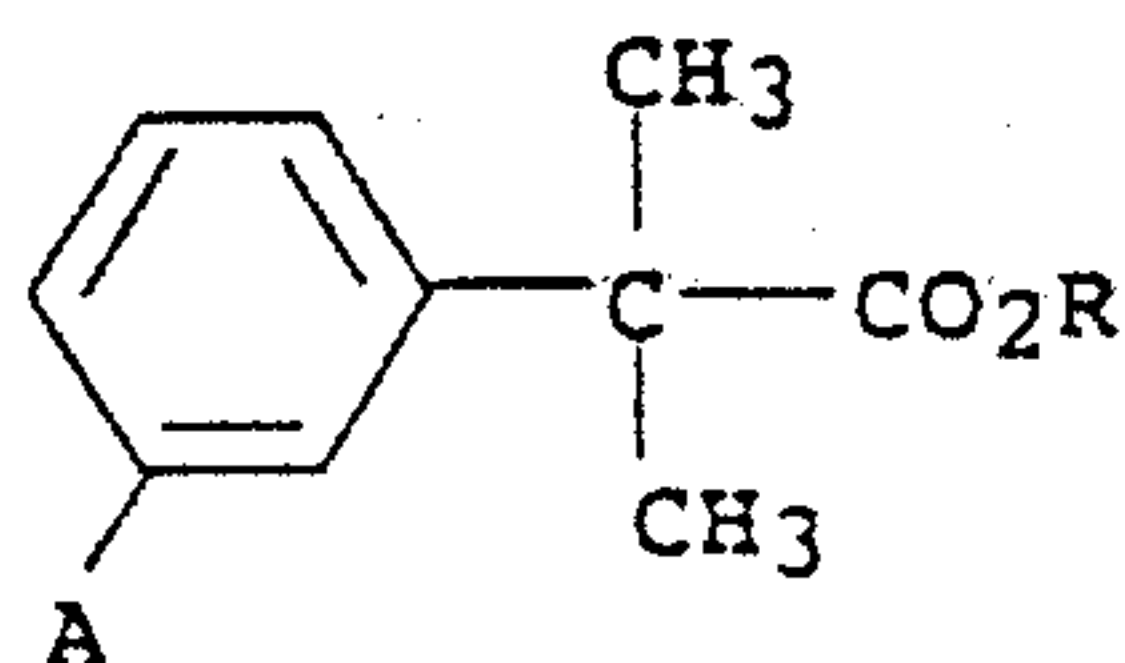
wherein

- 15 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the
carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;
20 R_3 is $-\text{COOH}$ or $-\text{COOalkyl}$ wherein the alkyl moiety has
from 1 to 6 carbon atoms and is straight or branched;
 A is hydrogen or hydroxy; and
pharmaceutically acceptable salts thereof comprising
the steps of:

25

(a) reacting a benzeneacetic acid compound of the
formula

30



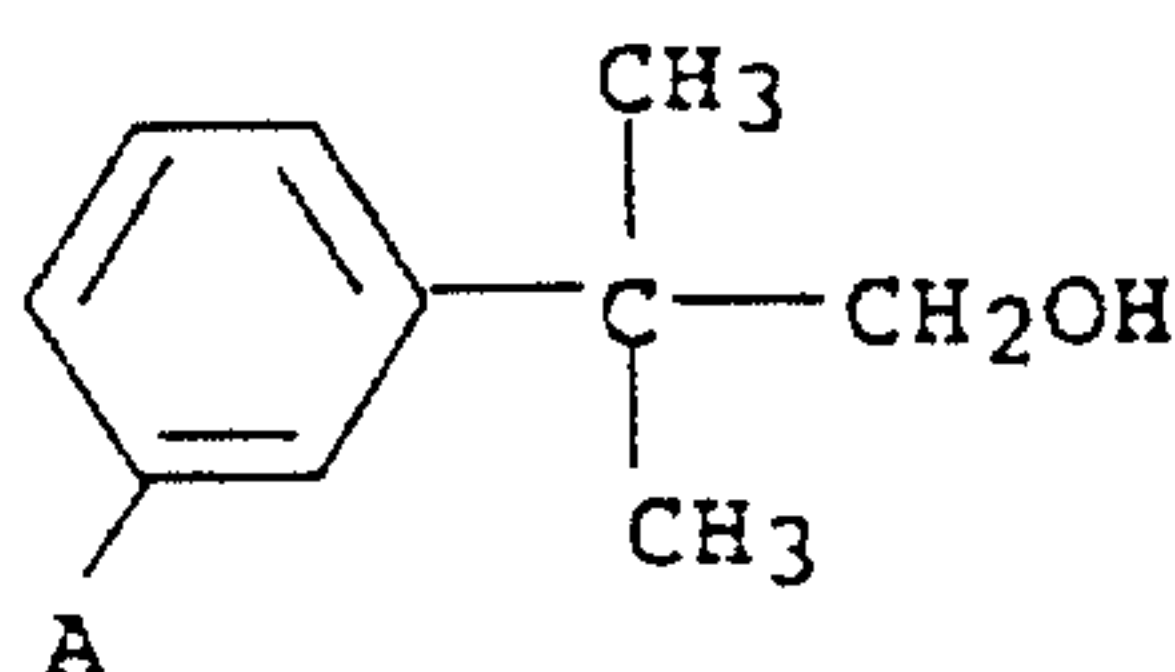
35

wherein A is hydrogen or hydroxy with the proviso that when
 A is hydroxy, A may be optionally protected or unprotected
and R is hydrogen or $\text{C}_1\text{-C}_6$ alkyl with sodium bis(2-
methoxyethoxy)aluminum hydride, lithium aluminum hydride,
diborane, lithium borohydride, lithium triethylborohydride

-152-

and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

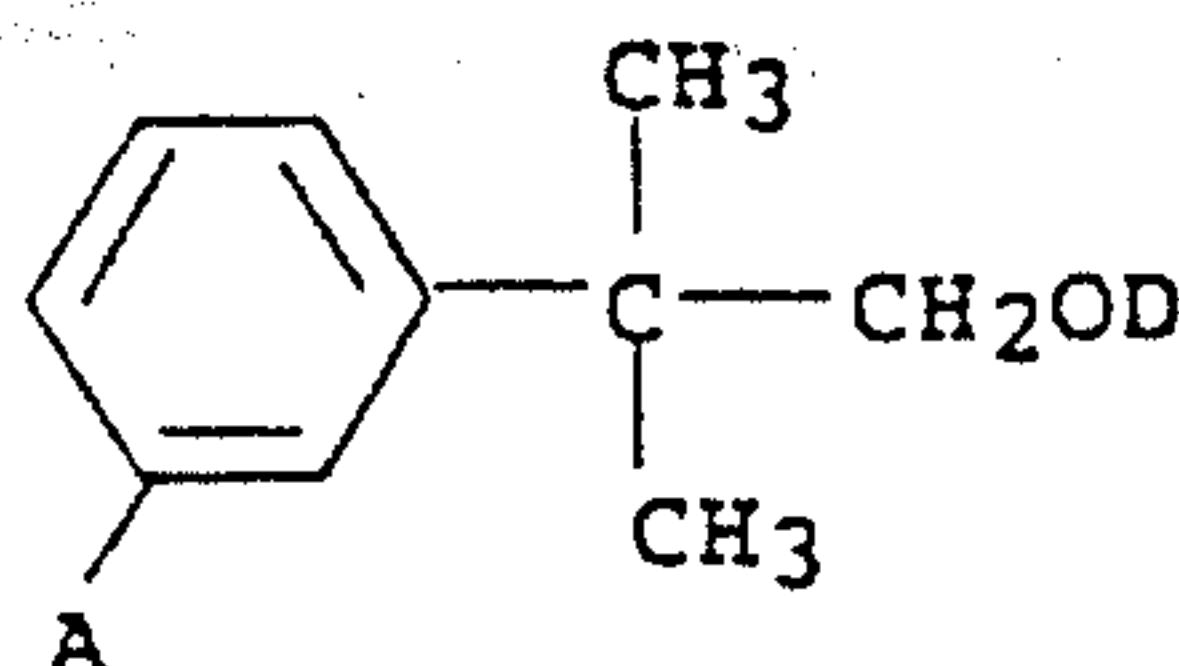
5



10 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

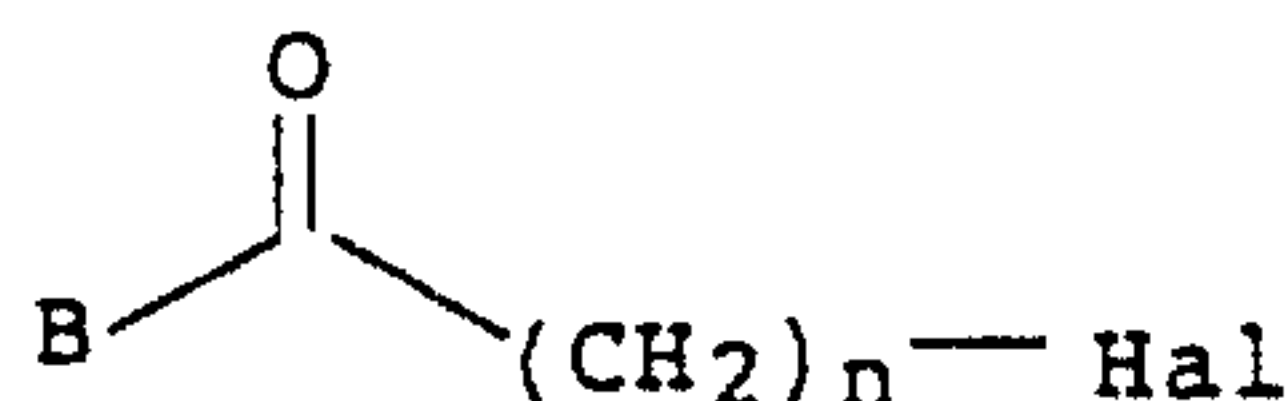
20



25 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is C(=O)CH₃ or C(=O)C₆H₅;

(c) reacting the protected phenethyl alcohol with a ω-halo compound of the formula

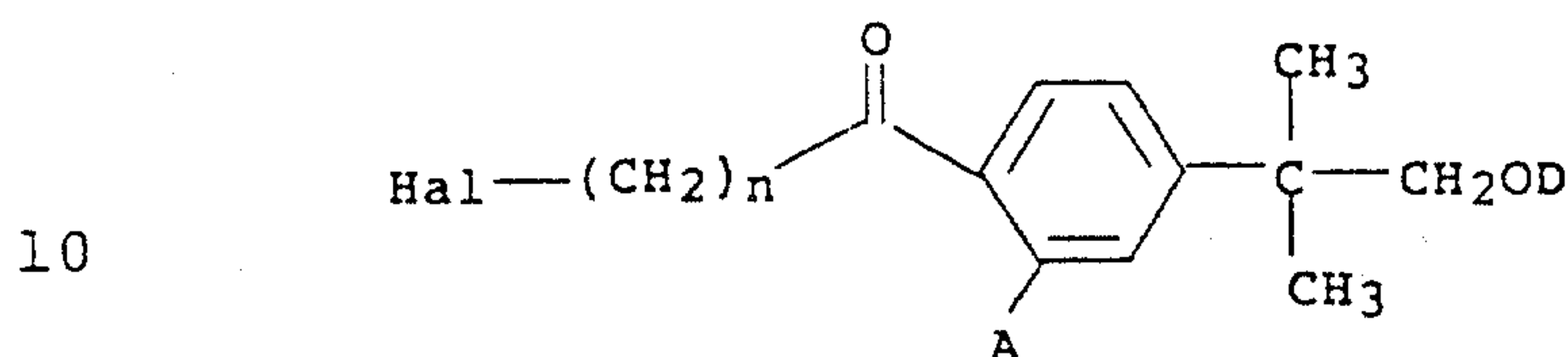
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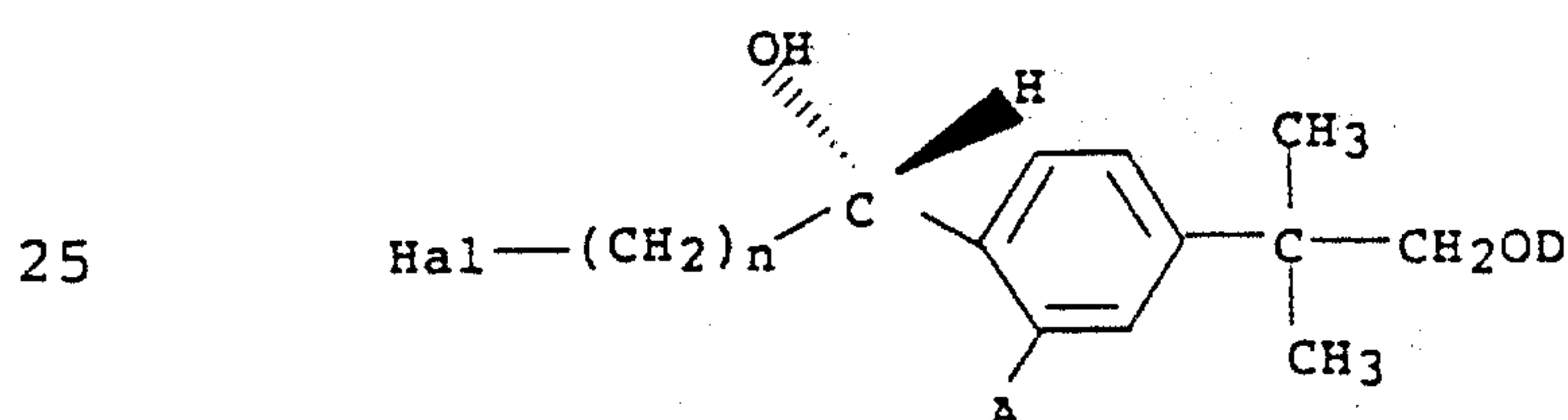
-153-

wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula



wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

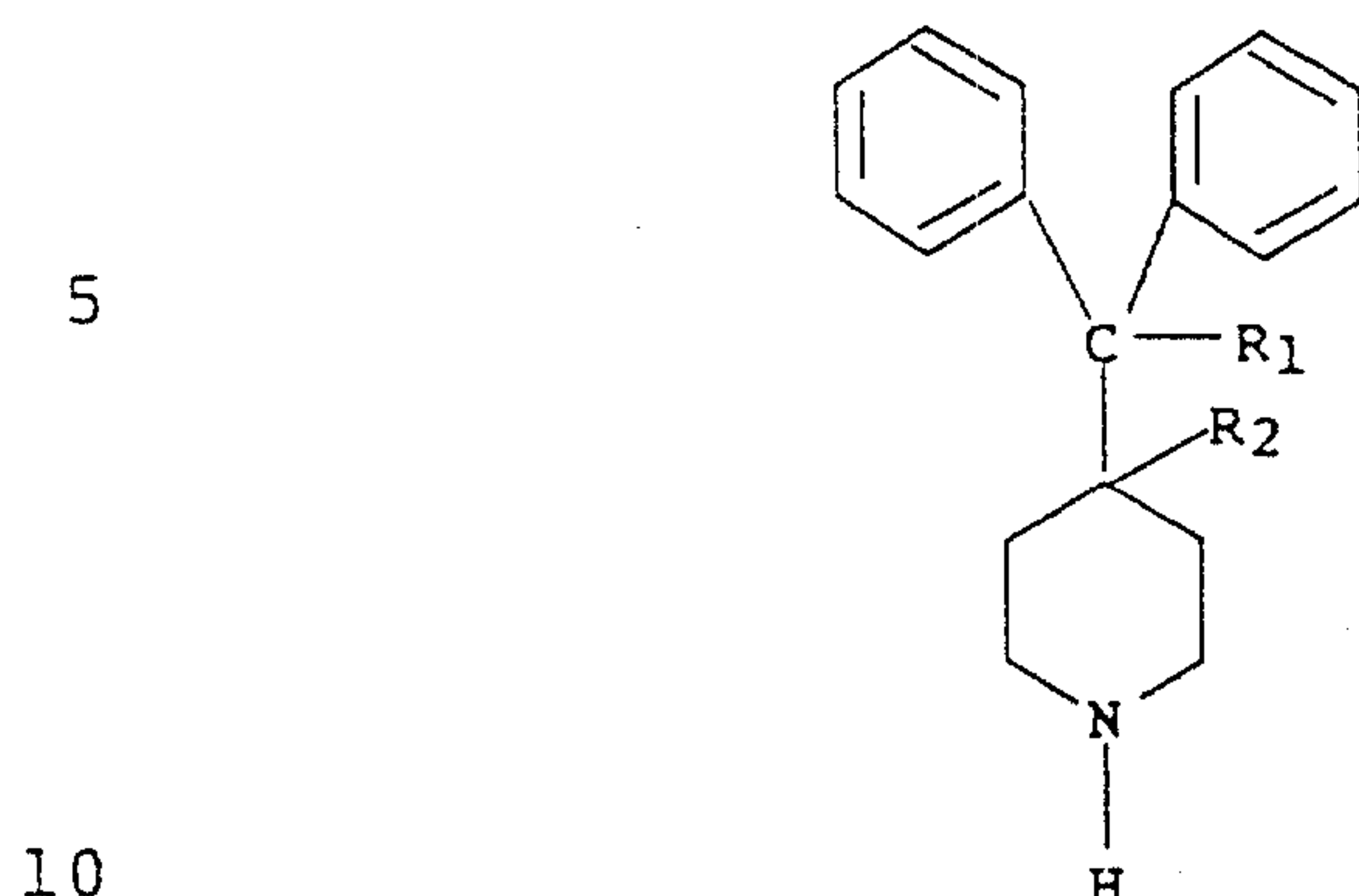
(d) reacting the ω -halo protected hydroxyethylphenylketone with (-)-B-chlorodiisopinocampheylborane to produce a ω -halo protected hydroxyethylphenylalcohol of the formula



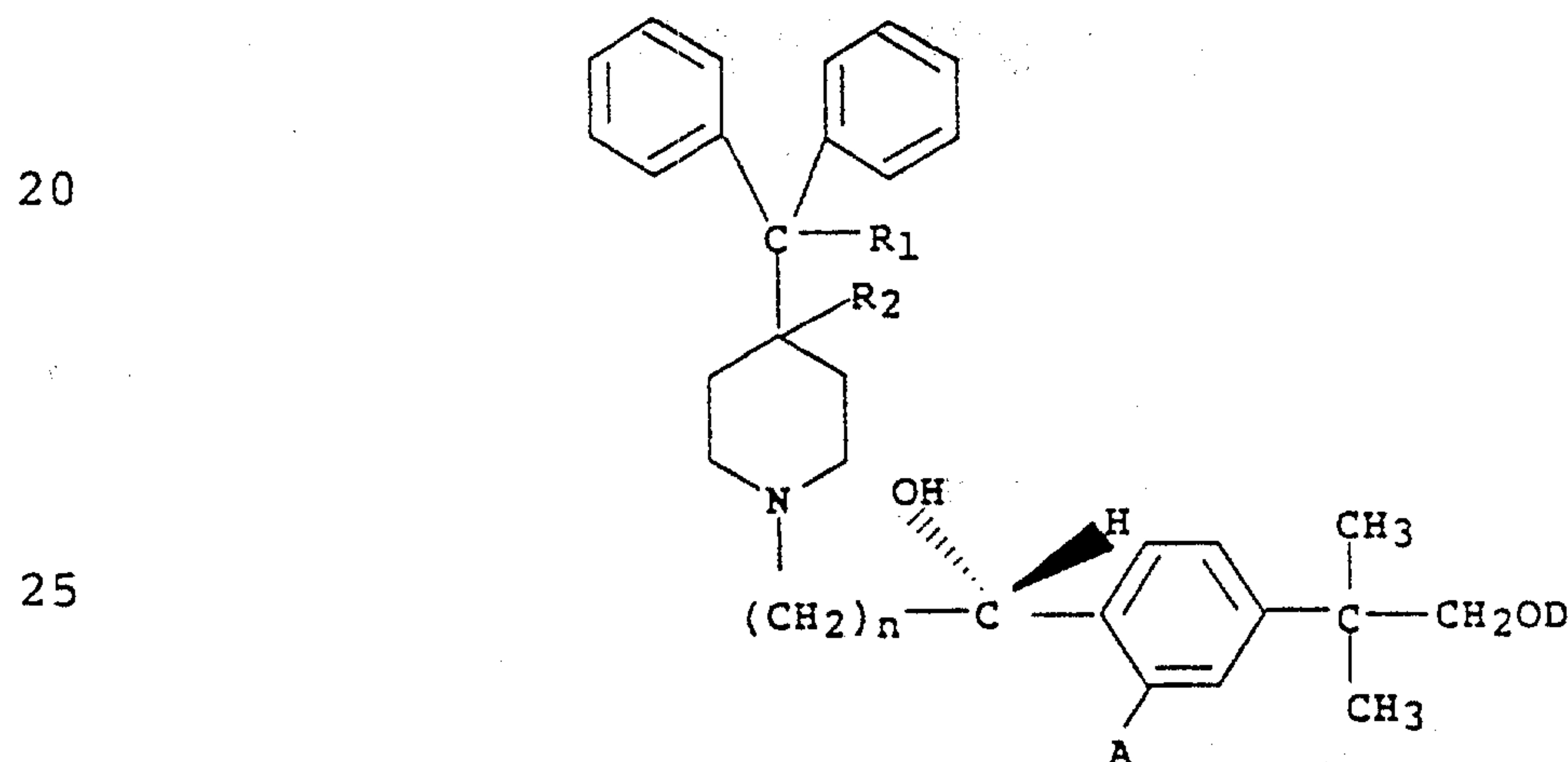
wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(e) reacting the ω -halo protected hydroxyethylphenylalcohol with a piperidine compound of the formula

-154-



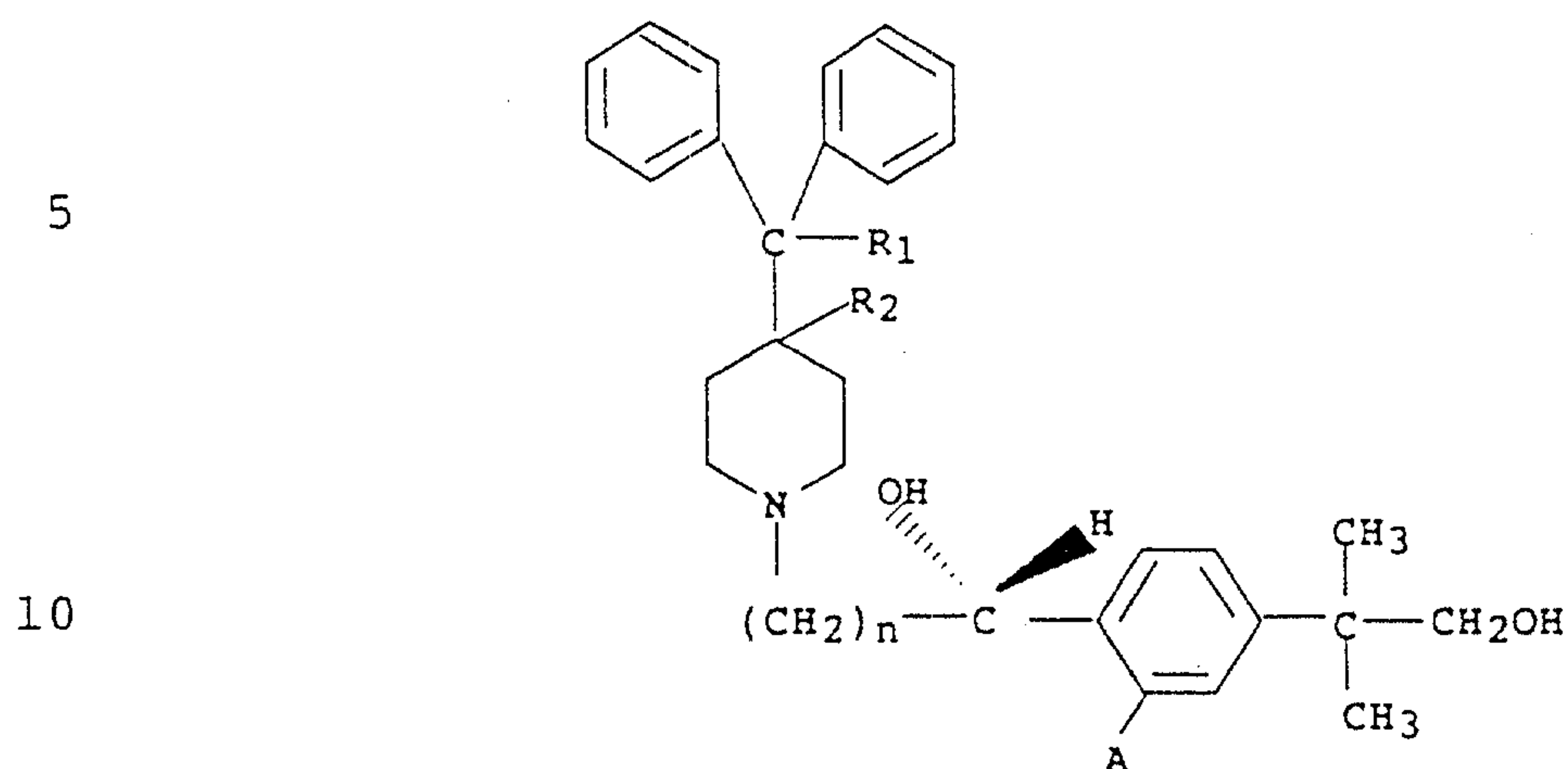
wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylalcohol of the formula



wherein R_1 , R_2 , n and D are defined above and A may be hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

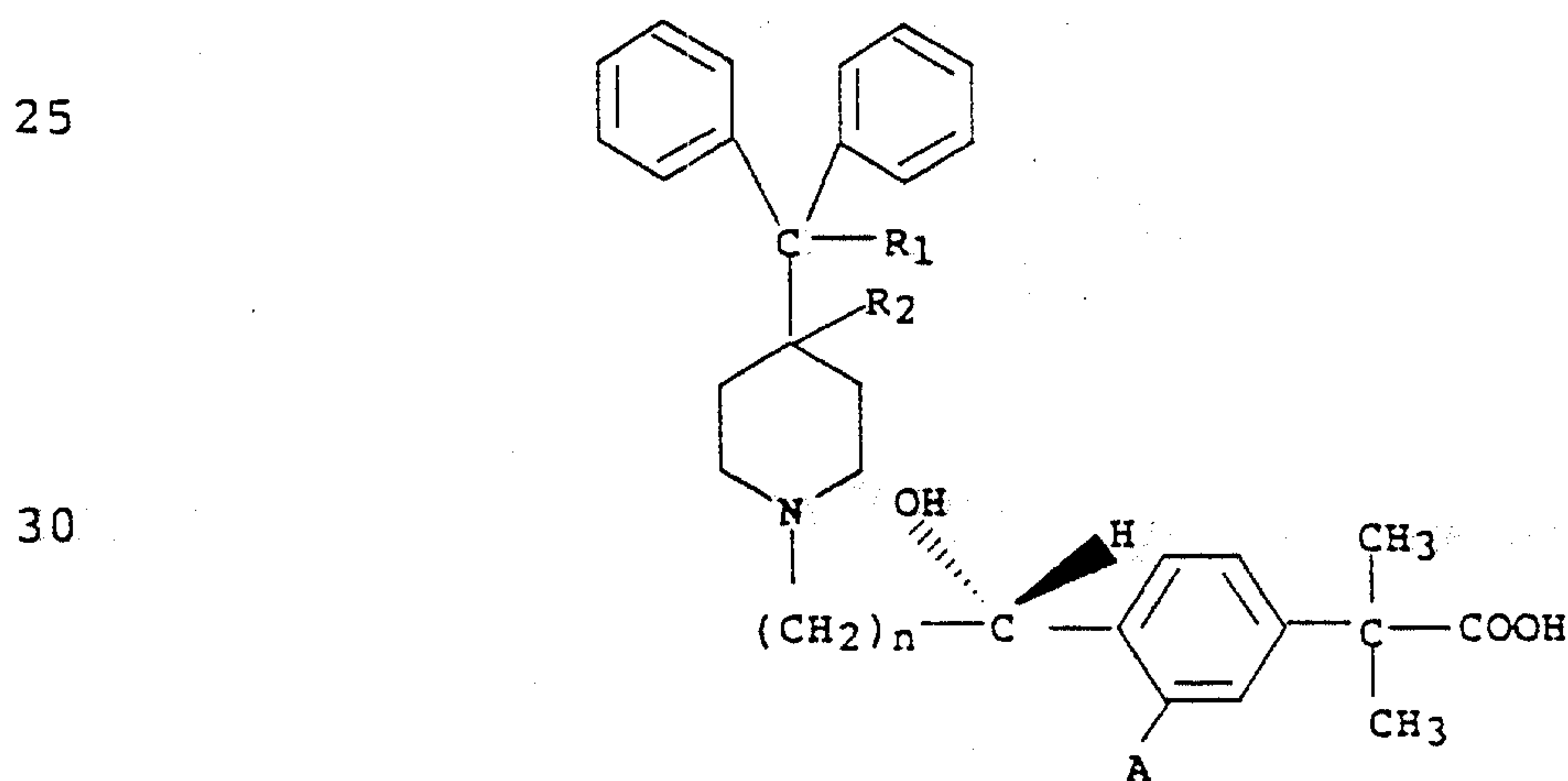
(f) reacting the piperidine protected hydroxyethylphenylalcohol with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylalcohol of the formula

-155-



wherein R_1 , R_2 and n are defined above and A is hydrogen or
 15 hydroxy with the proviso that when A is hydroxy, A may be
 optionally protected or unprotected;

(g) reacting the piperidine hydroxyethylphenylalcohol
 with chromium (IV) oxide, potassium permanganate, nitric
 20 acid, nitrogen dioxide, ruthenium (VIII) oxide, nickel
 peroxide, silver oxide, t-butyl chromate or xenic acid to
 produce a piperidine carboxyphenylketone of the formula



35

-156-

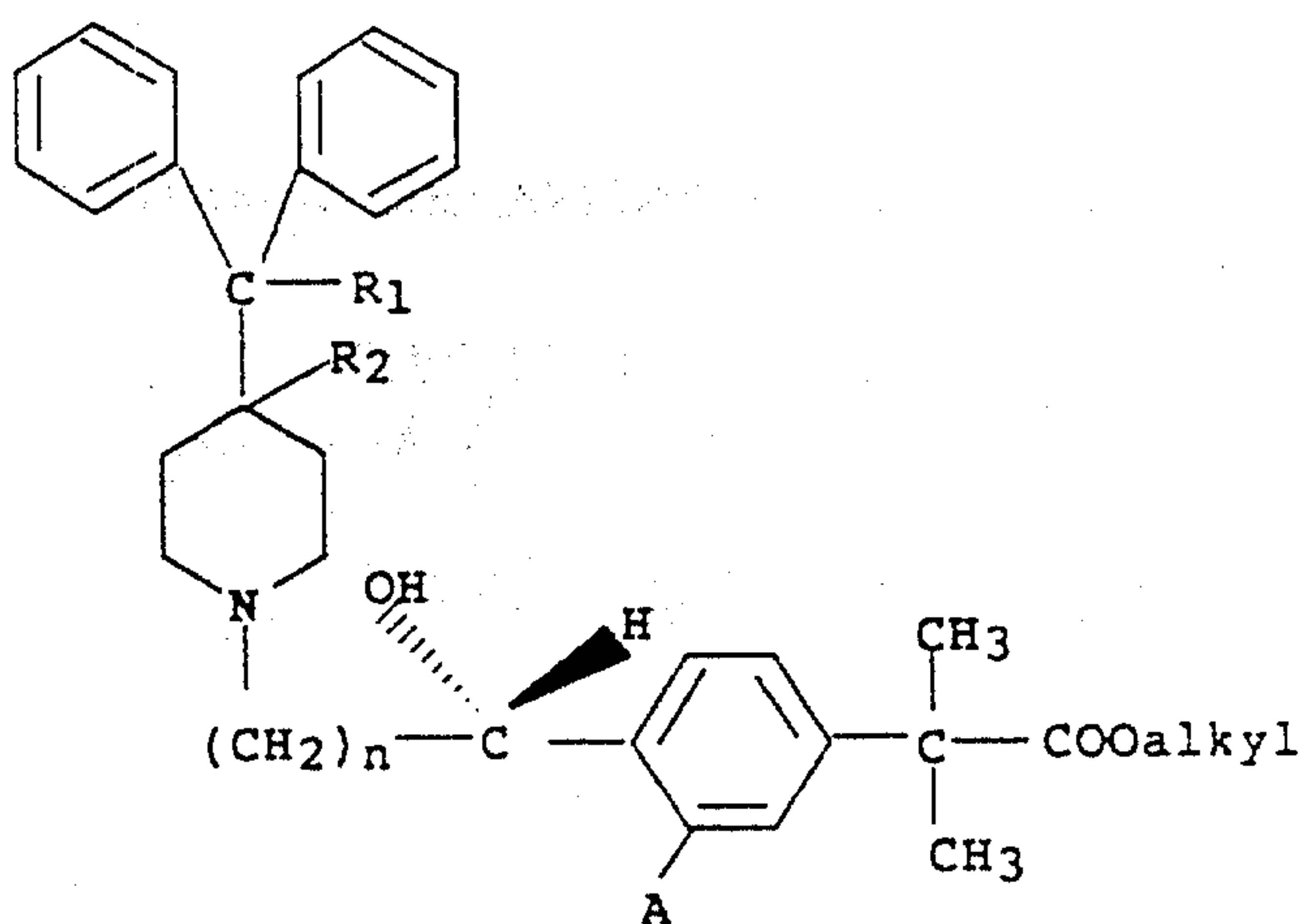
wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

5

(h) optionally reacting the piperidine carboxyphenylalcohol with diazomethane or 2,2-dimethoxypropane or with thionyl chloride followed by an alcohol of the formula HOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched to form a piperidine carboxyphenylalcohol ester of the formula

15

20



wherein R_1 , R_2 , n and alkyl are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected; and

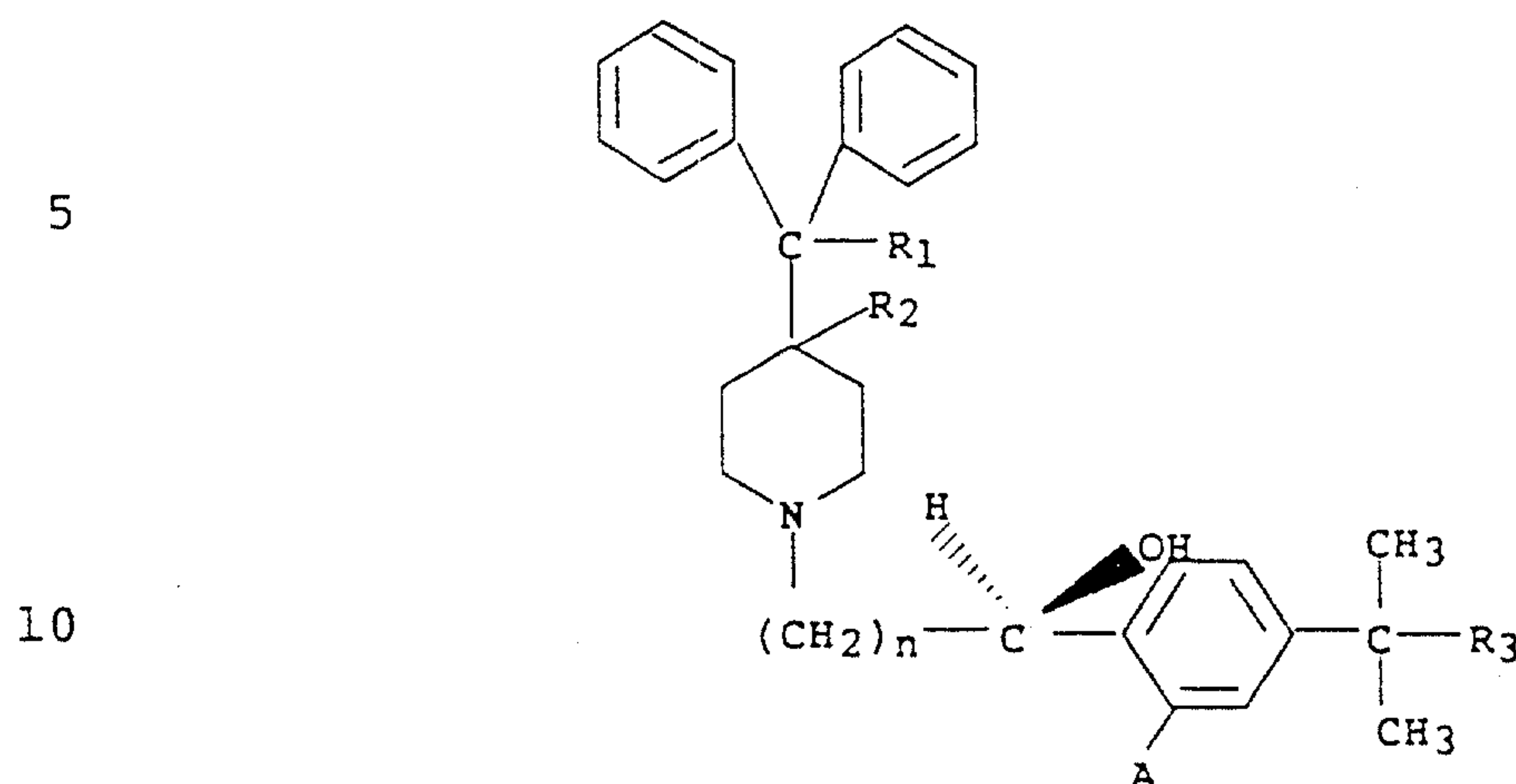
25

(i) optionally reacting the piperidine carboxyphenylalcohols or the piperidine carboxyphenylalcohol esters which bear hydroxy protecting groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine carboxyphenylalcohols or the piperidine carboxyphenylalcohol esters.

35

28. A process for preparing a compound of the formula

-157-



wherein

- 15 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the
carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;
20 R_3 is $-\text{CH}_2\text{OH}$;
 A is hydrogen or hydroxy; and
pharmaceutically acceptable salts thereof comprising
the steps of:

- 25 (a) reacting a benzeneacetic acid compound of the
formula

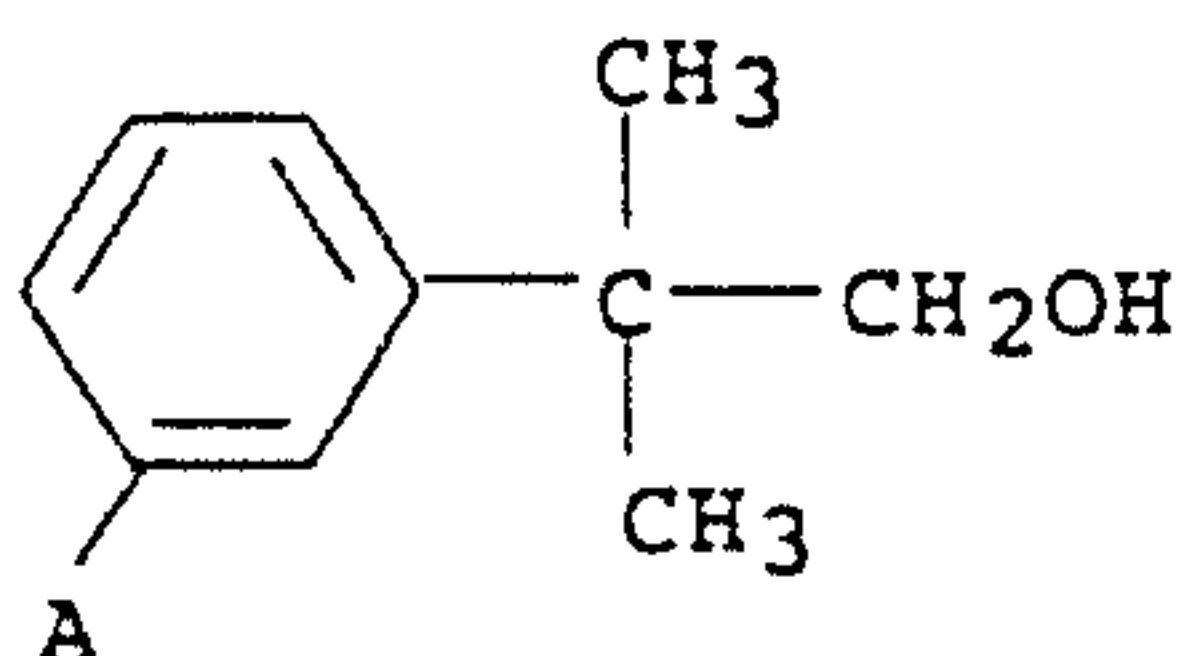


- 35 wherein A is hydrogen or hydroxy with the proviso that when
 A is hydroxy, A may be optionally protected or unprotected
and R is hydrogen or $\text{C}_1\text{-C}_6$ alkyl with sodium bis(2-
methoxyethoxy)aluminum hydride, lithium aluminum hydride,
diborane, lithium borohydride, lithium triethylborohydride

-158-

and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

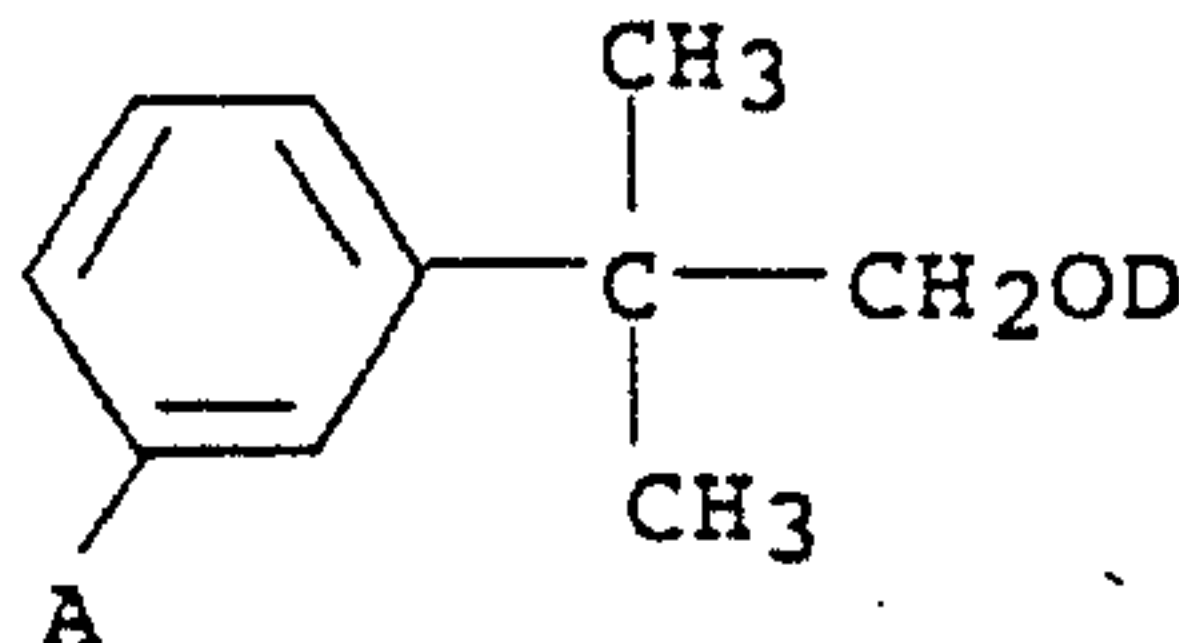
5



10 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

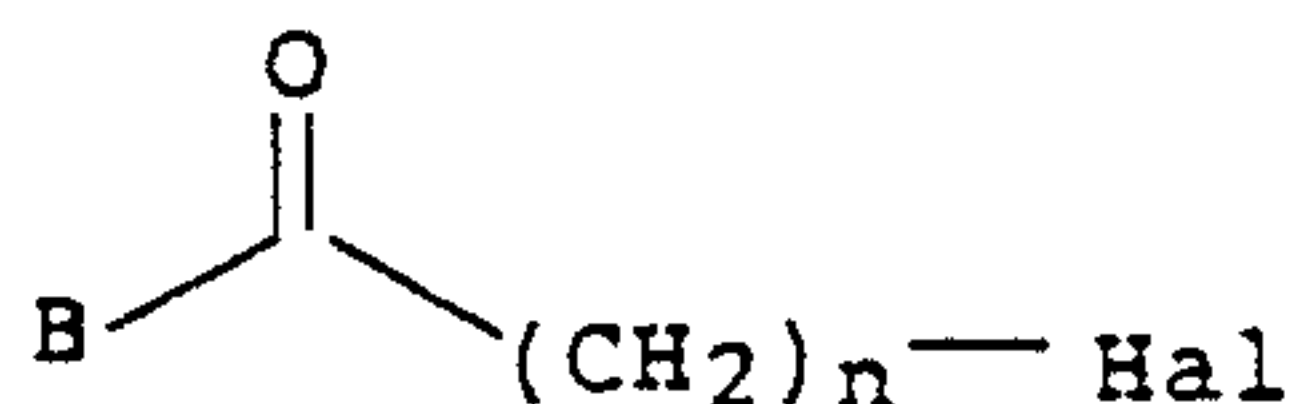
15 (b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

20



25 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is $\text{C}(=\text{O})\text{CH}_3$ or $\text{C}(=\text{O})\text{C}_6\text{H}_5$;

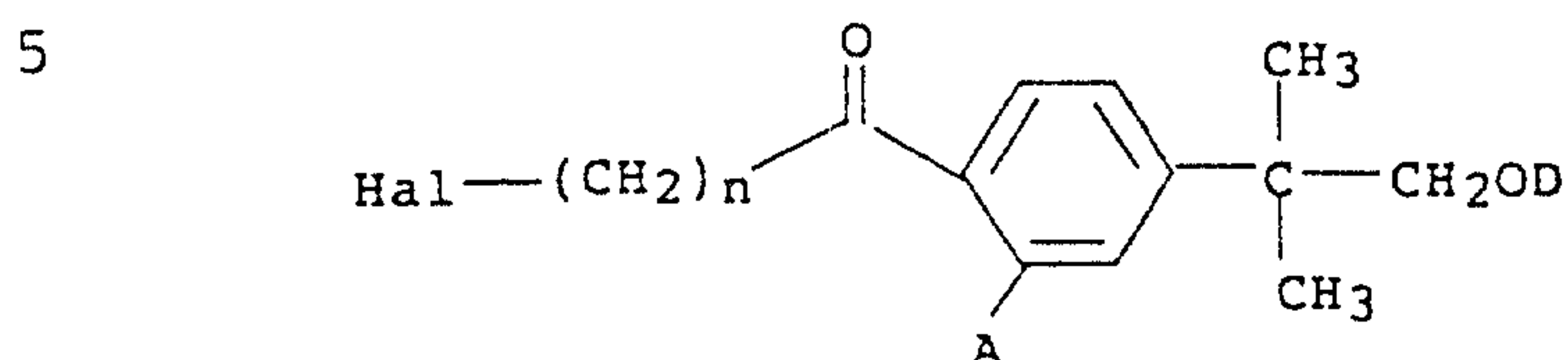
30 (c) reacting the protected phenethyl alcohol with a ω -halo compound of the formula



35 wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron

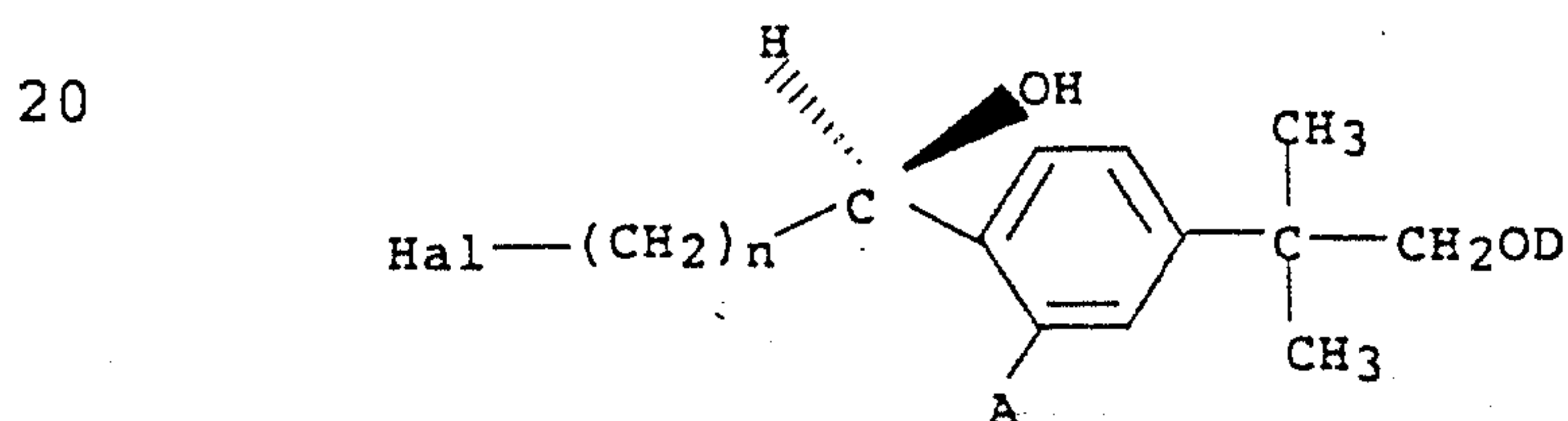
-159-

trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula



10 wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

15 (d) reacting the ω -halo protected hydroxyethylphenylketone with (+)-B-chlorodiisopinocampheylborane a ω -halo protected hydroxyethylphenylalcohol of the formula

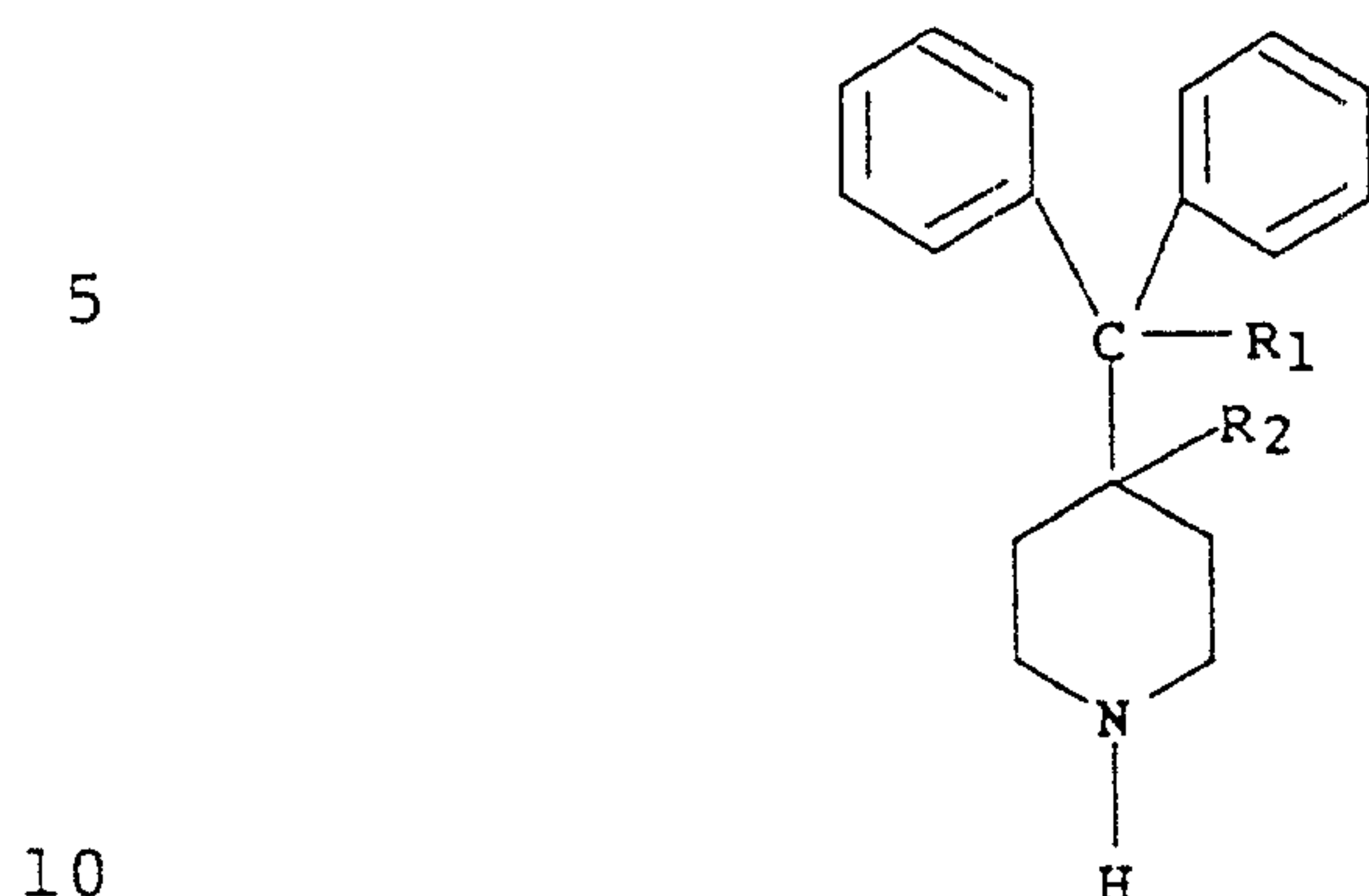


25 wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

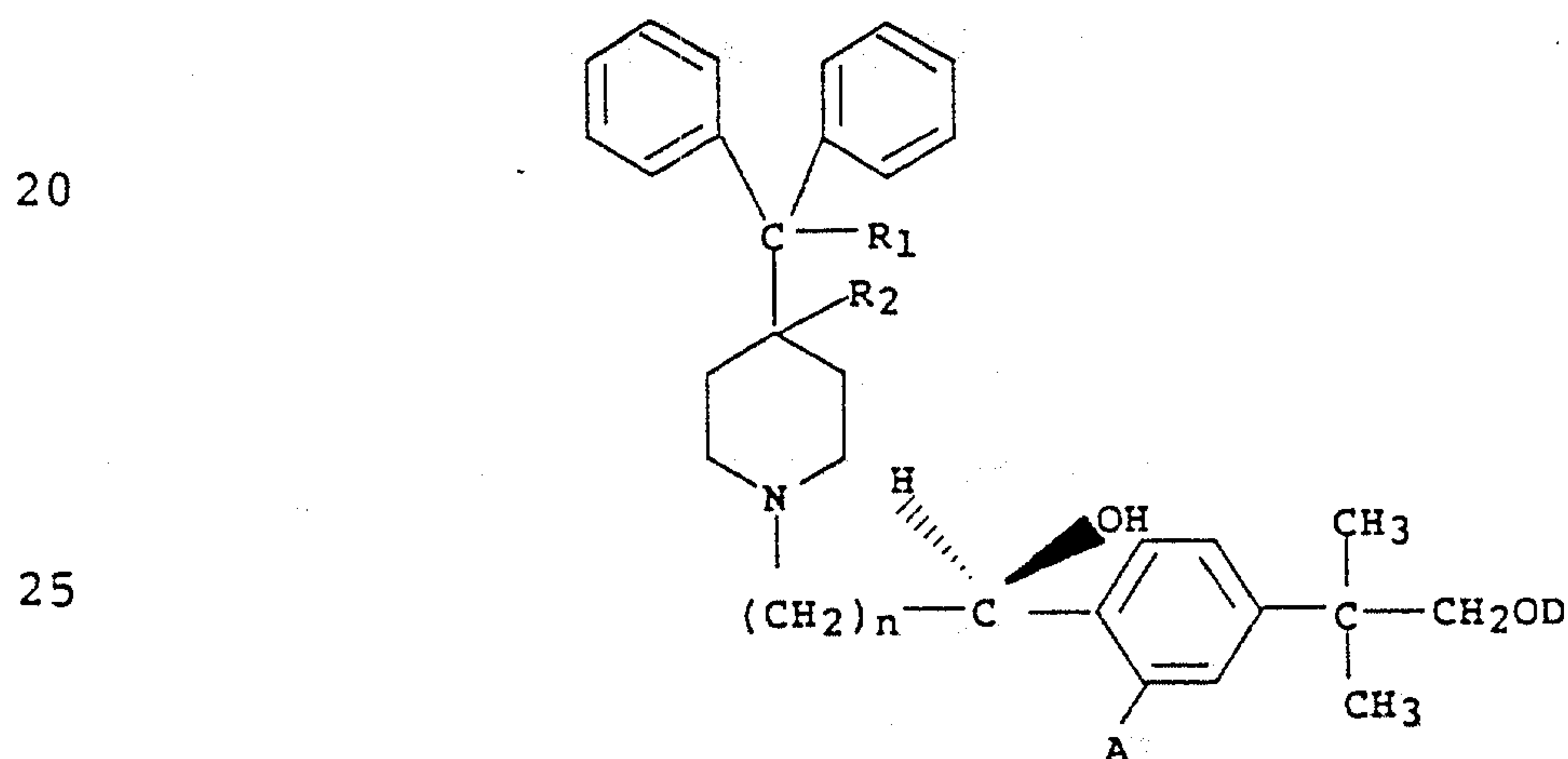
30 (e) reacting the ω -halo protected hydroxyethylphenylalcohol with a piperidine compound of the formula

35

-160-



wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylalcohol of the formula

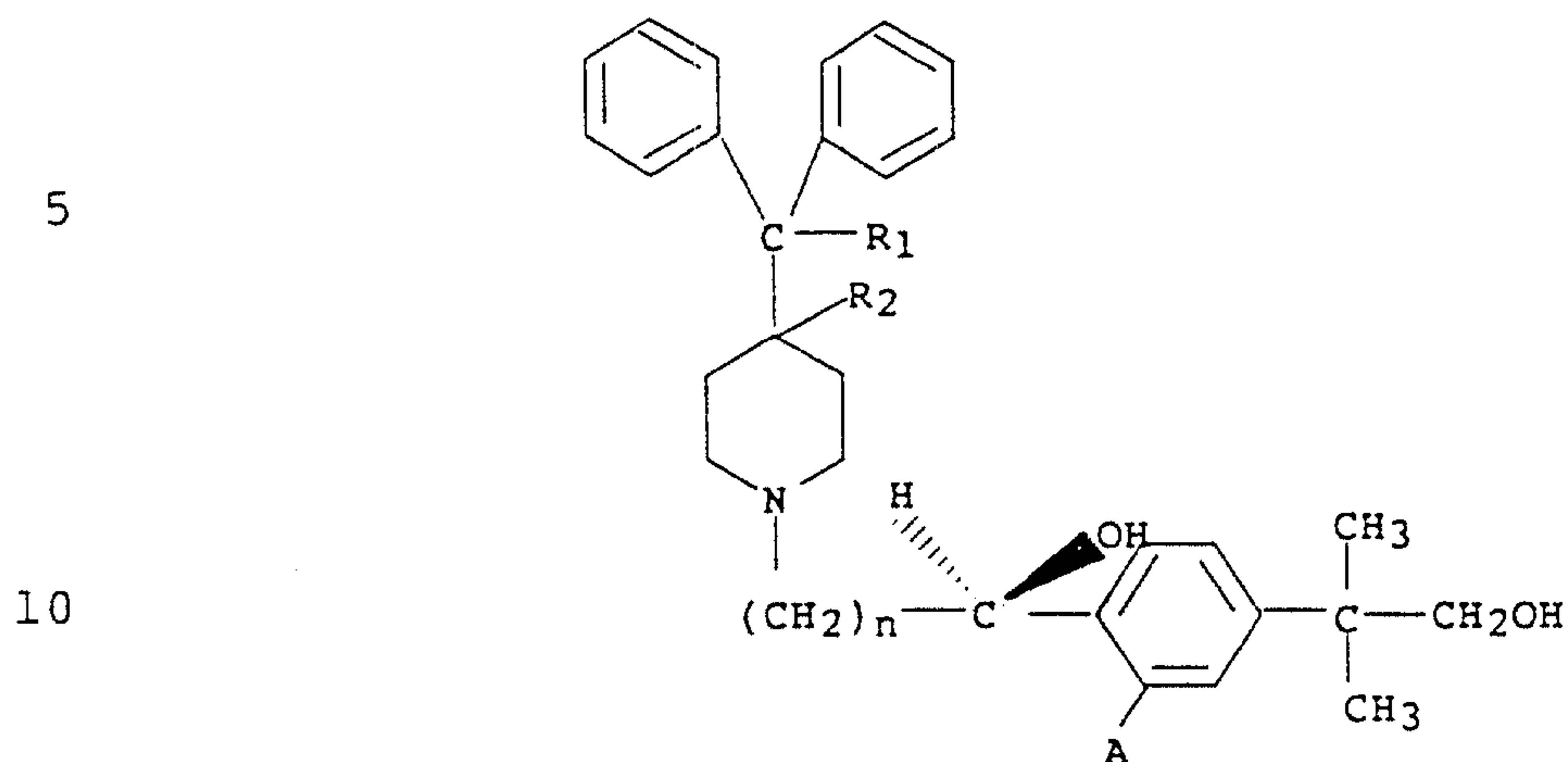


wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(f) reacting the piperidine protected hydroxyethylphenylalcohol with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylalcohol of the formula

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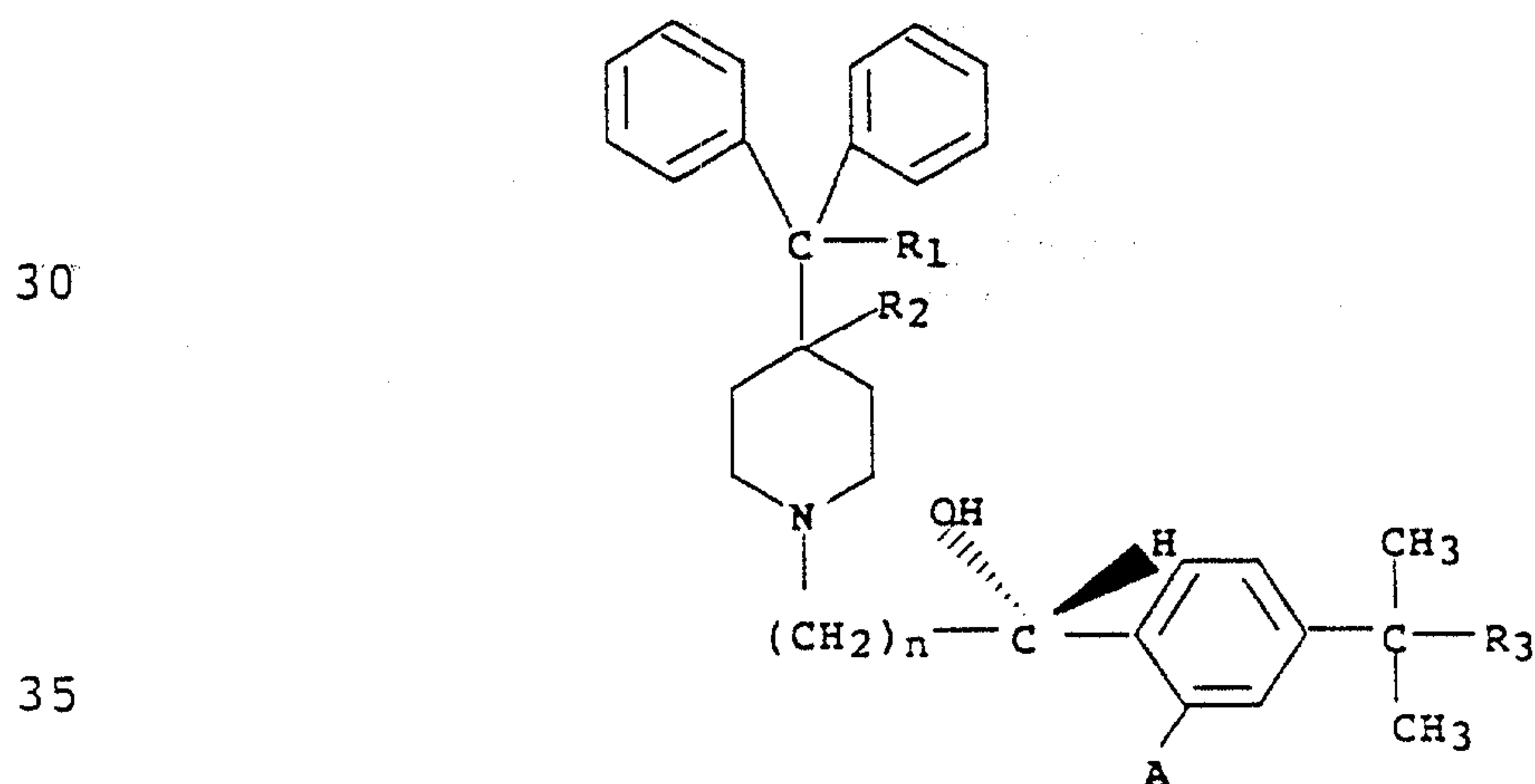
-161-



15 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected; and

20 (g) optionally reacting the piperidine hydroxyethylphenylalcohols which bear hydroxy protecting groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine hydroxyethylphenylalcohols.

25 29. A process for preparing a compound of the formula



wherein

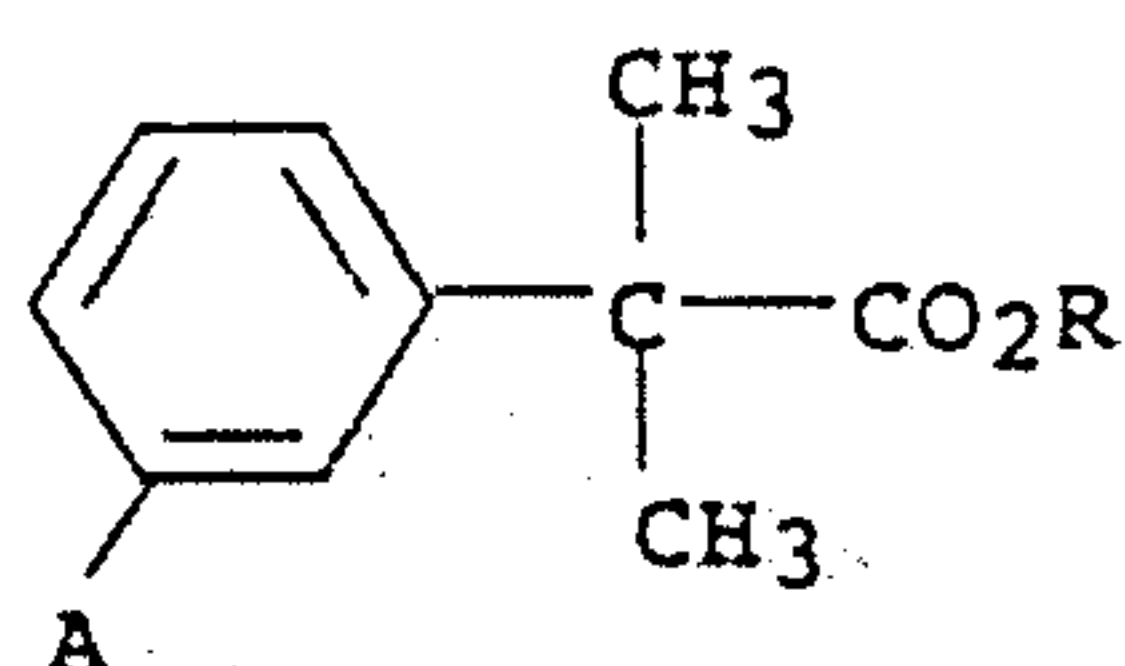
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-162-

R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the
 5 carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;
 R_3 is $-\text{CH}_2\text{OH}$;
 A is hydrogen or hydroxy; and
 pharmaceutically acceptable salts thereof comprising
 10 the steps of:

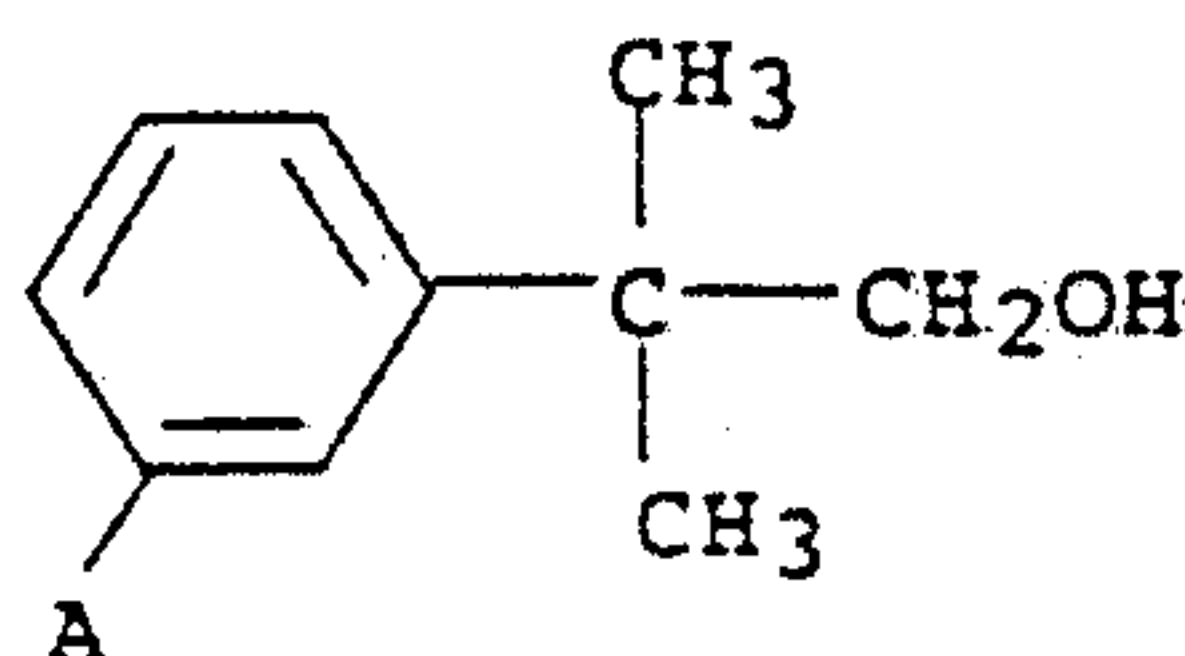
(a) reacting a benzeneacetic acid compound of the
 formula

15



20 wherein A is hydrogen or hydroxy with the proviso that when
 A is hydroxy, A may be optionally protected or unprotected
 and R is hydrogen or $\text{C}_1\text{-C}_6$ alkyl with sodium bis(2-
 methoxyethoxy)aluminum hydride, lithium aluminum hydride,
 diborane, lithium borohydride, lithium triethylborohydride
 25 and lithium tri-sec-butylborohydride or aluminum hydride to
 give a phenethyl alcohol of the formula

30



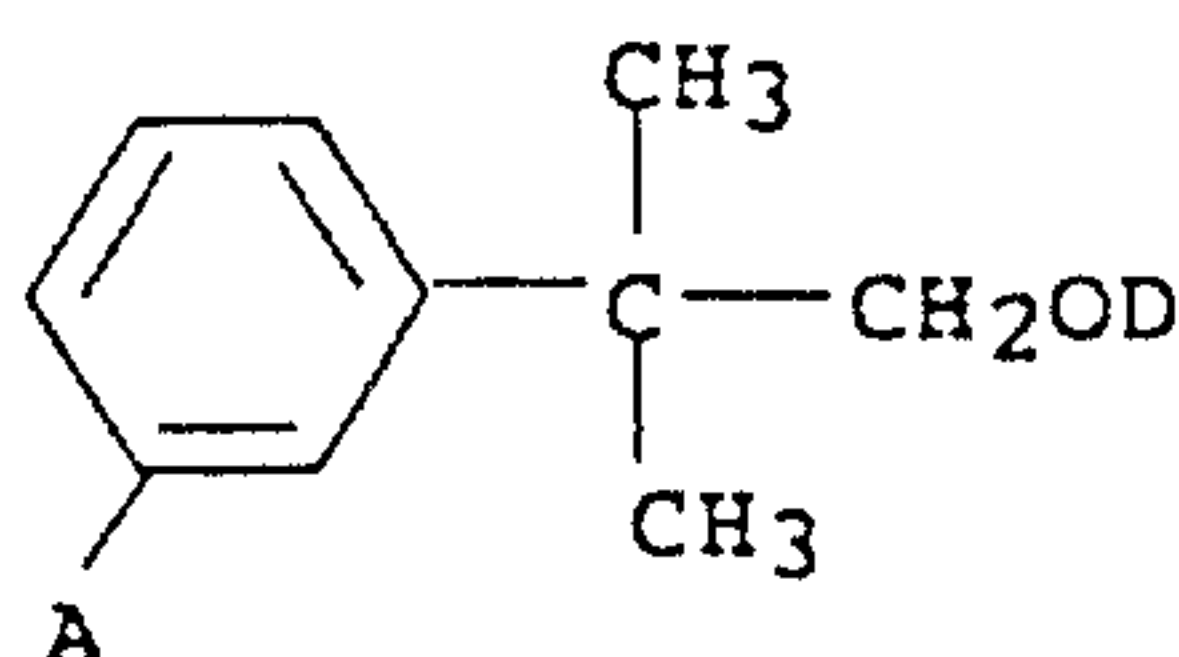
wherein A is hydrogen or hydroxy with the proviso that when
 A is hydroxy, A may be optionally protected or unprotected;
 35

(b) reacting the phenylethyl alcohol with acetyl
 chloride, acetic anhydride, benzoyl chloride or benzoic
 anhydride in the presence of sodium bicarbonate, potassium

-163-

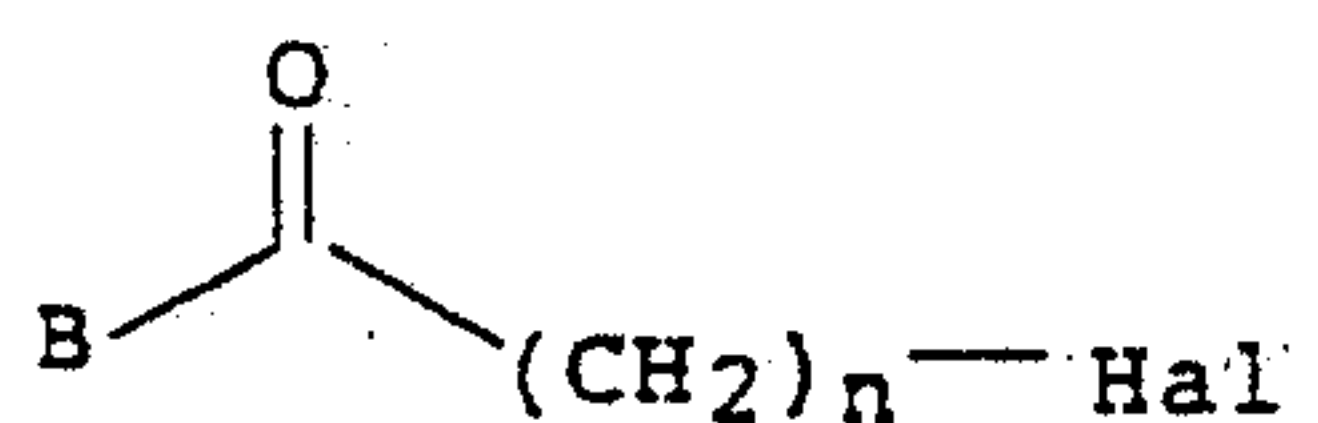
carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

5



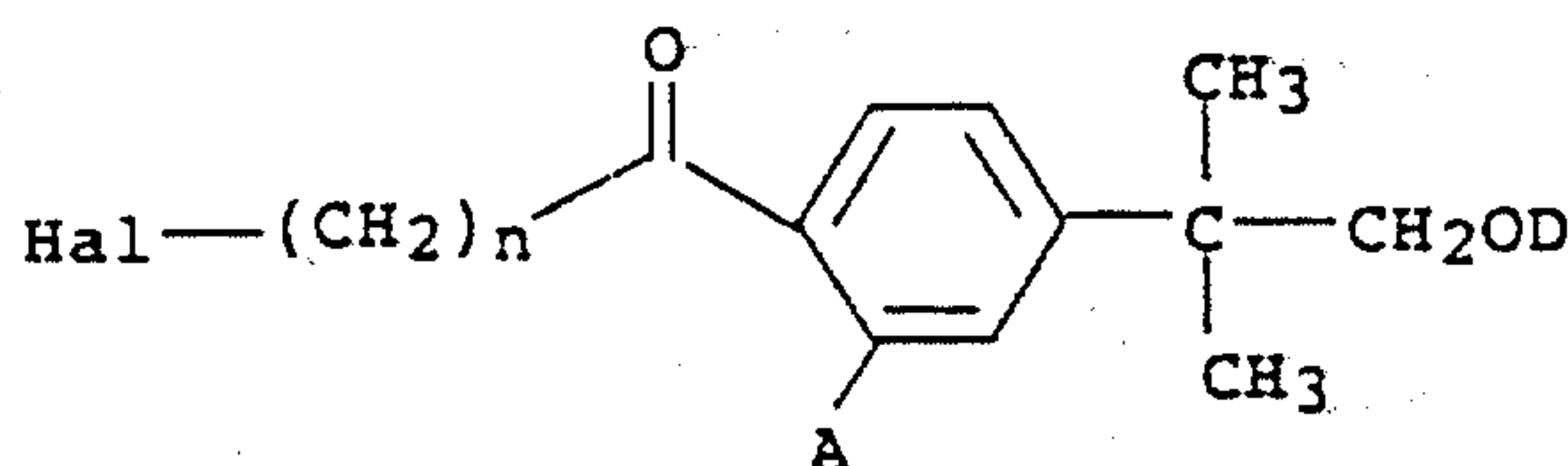
10 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is $\text{C}(=\text{O})\text{CH}_3$ or $\text{C}(=\text{O})\text{C}_6\text{H}_5$;

15 (c) reacting the protected phenethyl alcohol with a ω -halo compound of the formula



20

wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce
25 a ω -halo protected hydroxyethylphenylketone of the formula



30

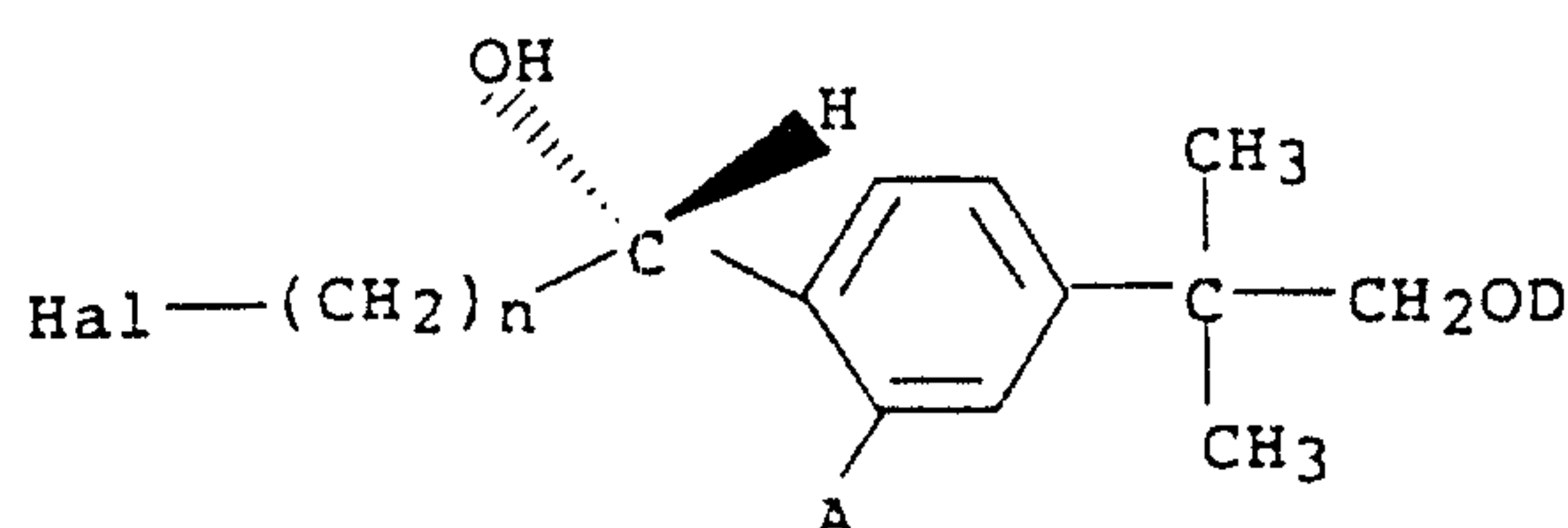
wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

35

(d) reacting the ω -halo protected hydroxyethylphenylketone with (-)-B-

-164-

chlorodiisopinocampheylborane to produce a ω -halo protected hydroxyethylphenylalcohol of the formula

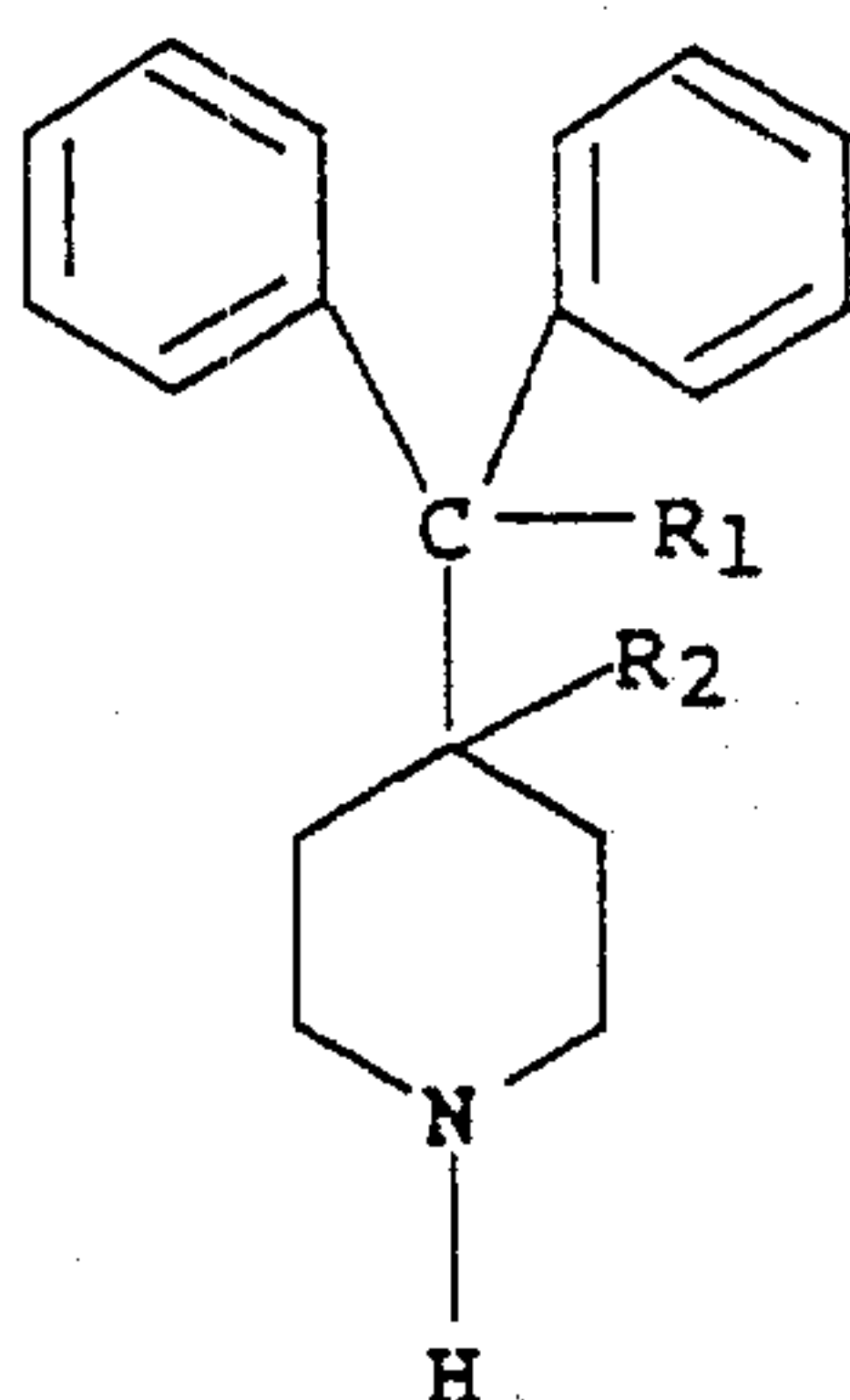


10

wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

15

(e) reacting the ω -halo protected hydroxyethylphenylalcohol with a piperidine compound of the formula



25

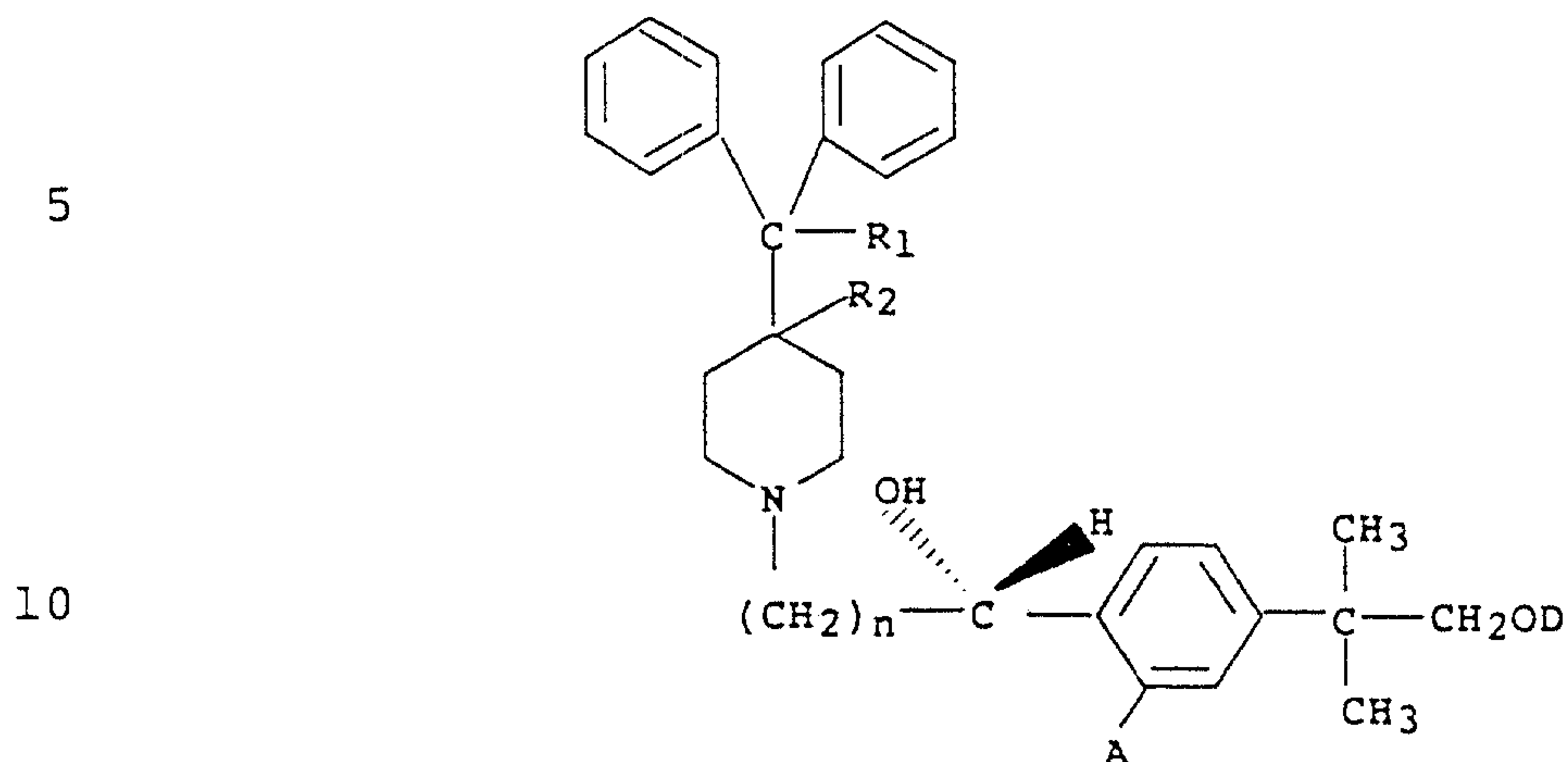
wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the

30

piperidine compound may be used to produce a piperidine protected hydroxyethylphenylalcohol of the formula

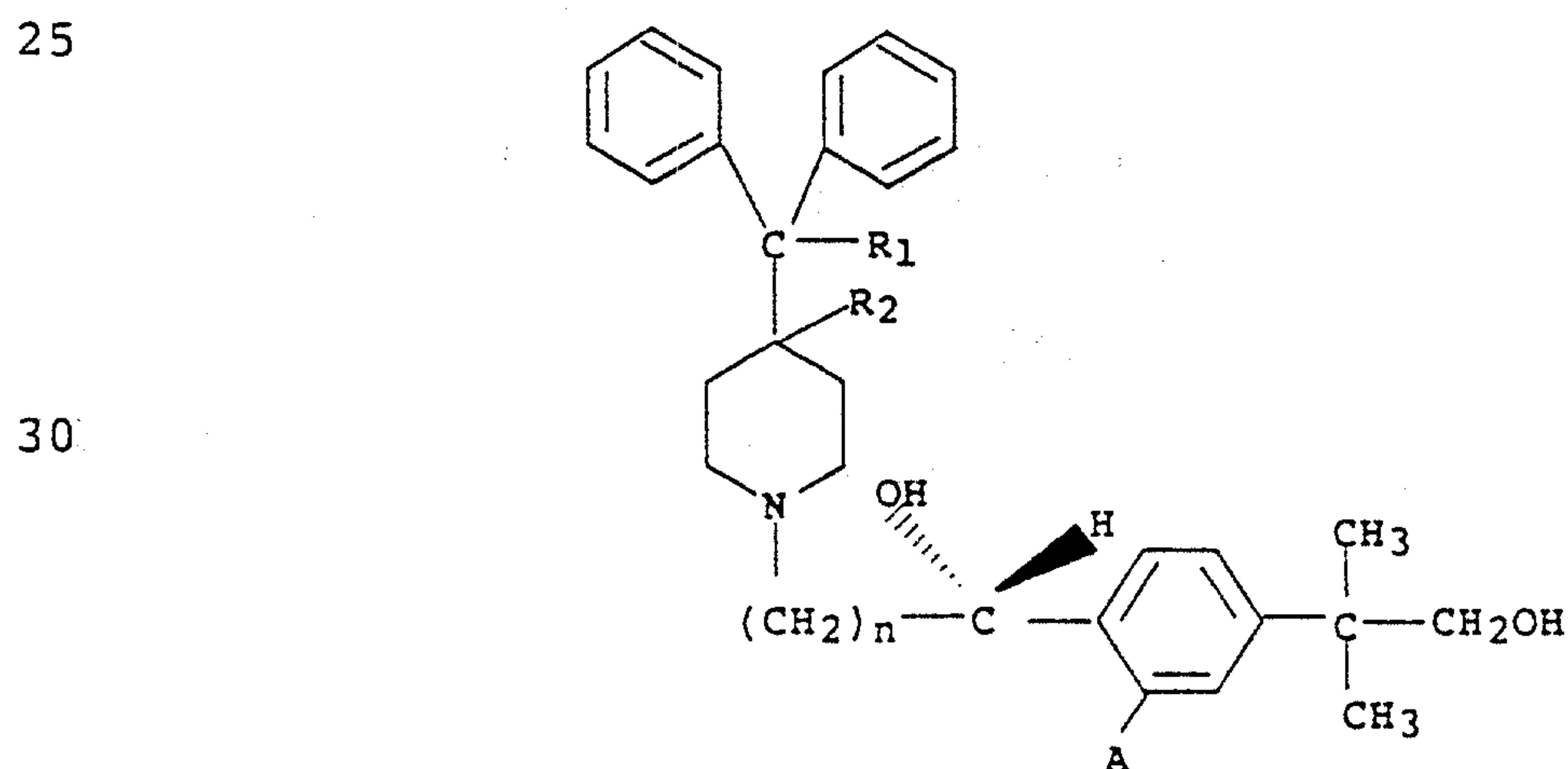
35

-165-



wherein R_1 , R_2 , n and D are defined above and A is hydrogen
 15 or hydroxy with the proviso that when A is hydroxy, A may
 be optionally protected or unprotected;

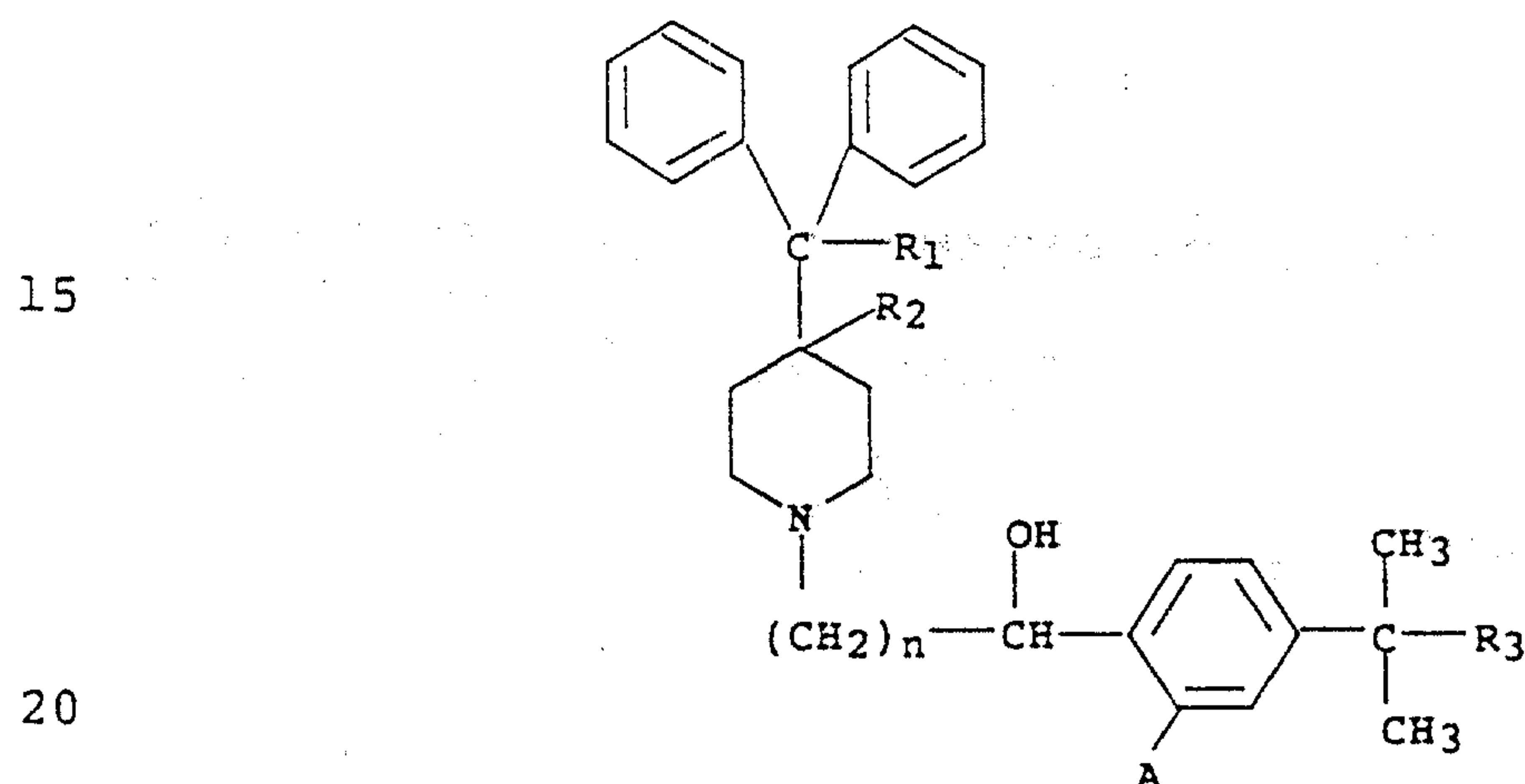
(f) reacting the piperidine protected
 hydroxyethylphenylalcohol with sodium methoxide in
 20 methanol, potassium carbonate in methanol, methanolic
 ammonia, sodium hydroxide/pyridine in methanol and
 potassium cyanide in ethanol to produce a piperidine
 hydroxyethylphenylalcohol of the formula



35 wherein R_1 , R_2 and n are defined above and A is hydrogen or
 hydroxy with the proviso that when A is hydroxy, A may be
 optionally protected or unprotected; and

(g) optionally reacting the piperidine hydroxyethylphenylalcohols which bear hydroxy protecting groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine hydroxyethylphenylalcohols.

10 30. A process for preparing a compound of the formula



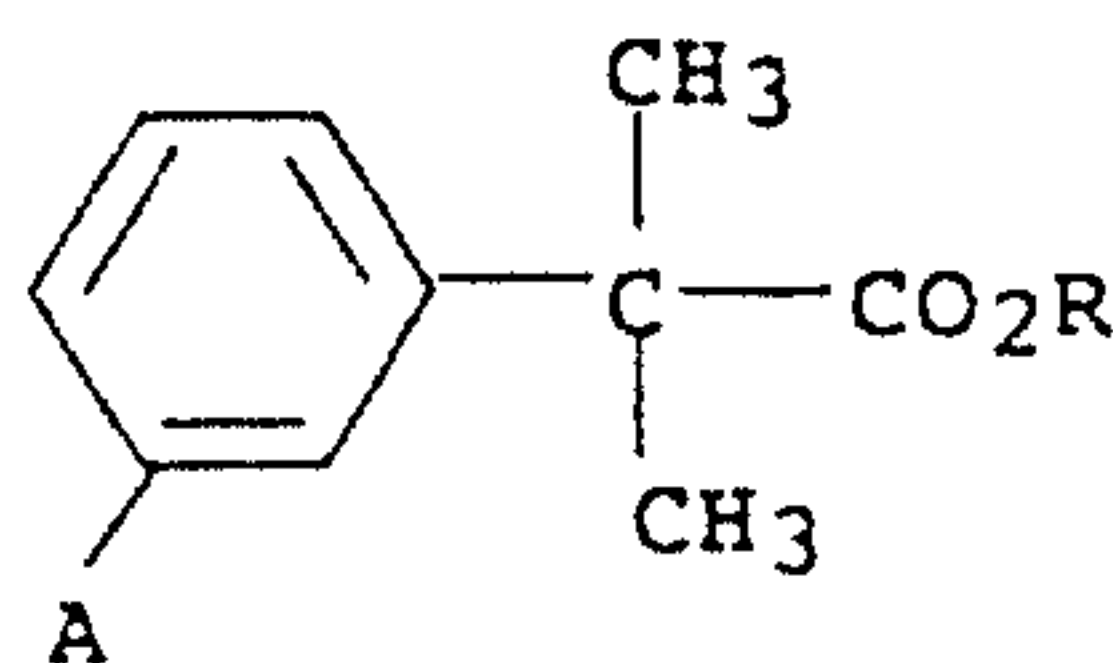
wherein:

25 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;
 R_3 is $-\text{COOH}$ or $-\text{COOalkyl}$ wherein the alkyl moiety has
 30 from 1 to 6 carbon atoms and is straight or branched;
 A is hydrogen or hydroxy; and
 pharmaceutically acceptable salts thereof comprising the steps of:

35 (a) reacting a benzeneacetic acid compound of the formula

-167-

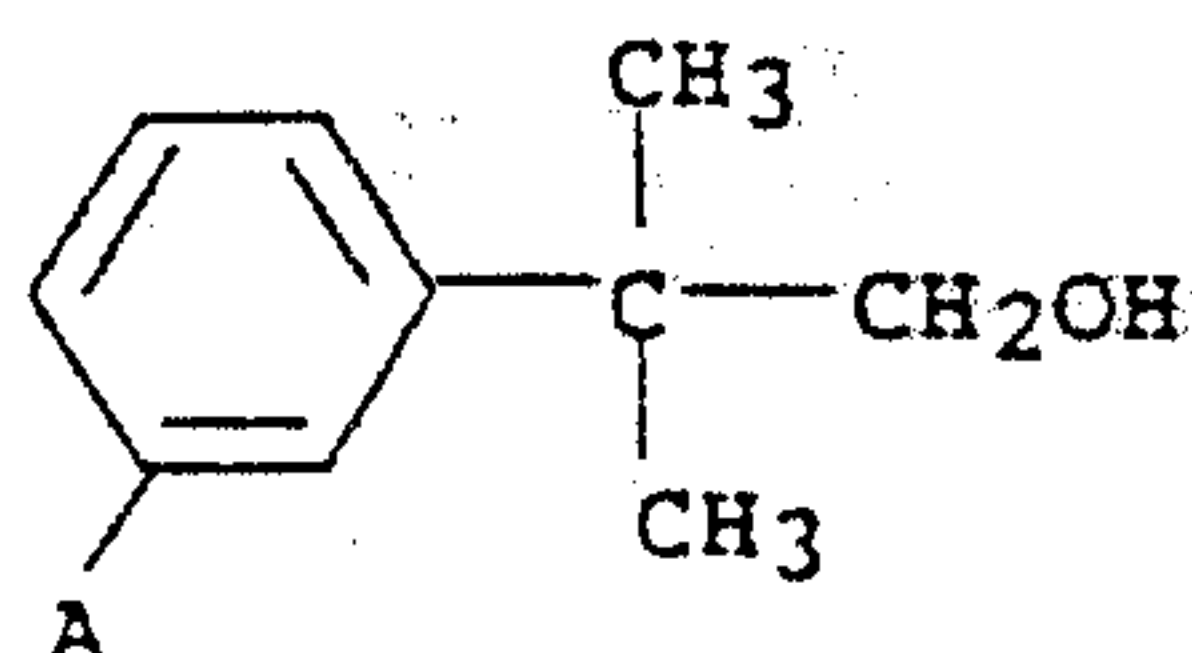
5



10

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

15



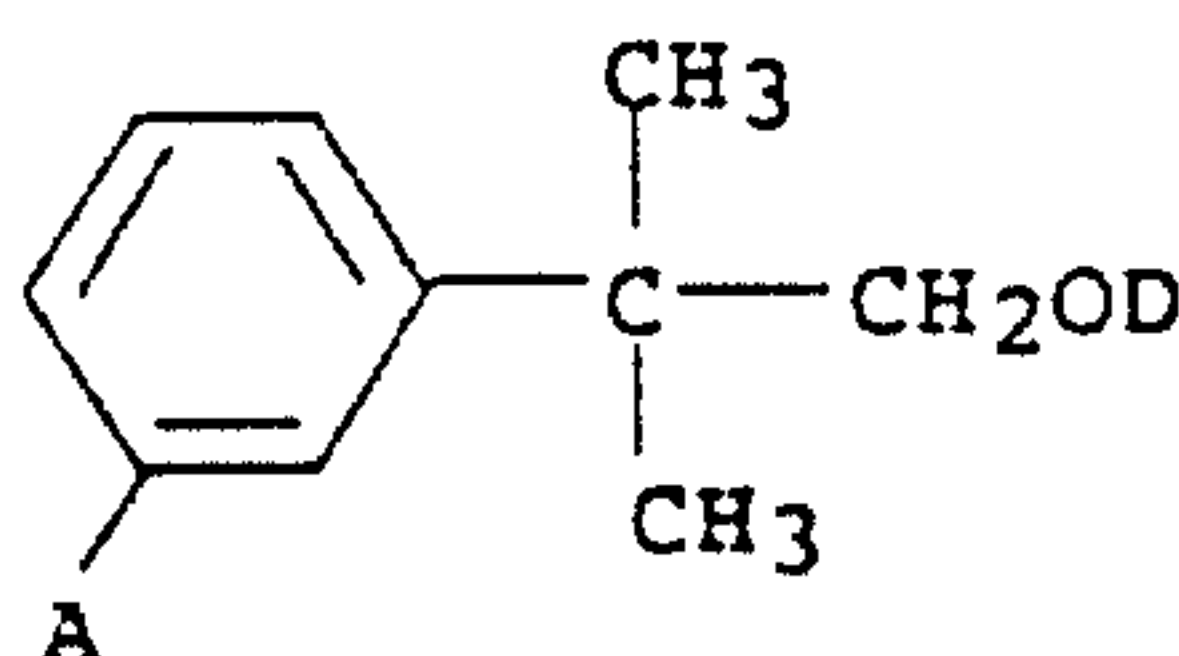
20

wherein A is hydrogen or hydroxy, with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

25

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

30



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-168-

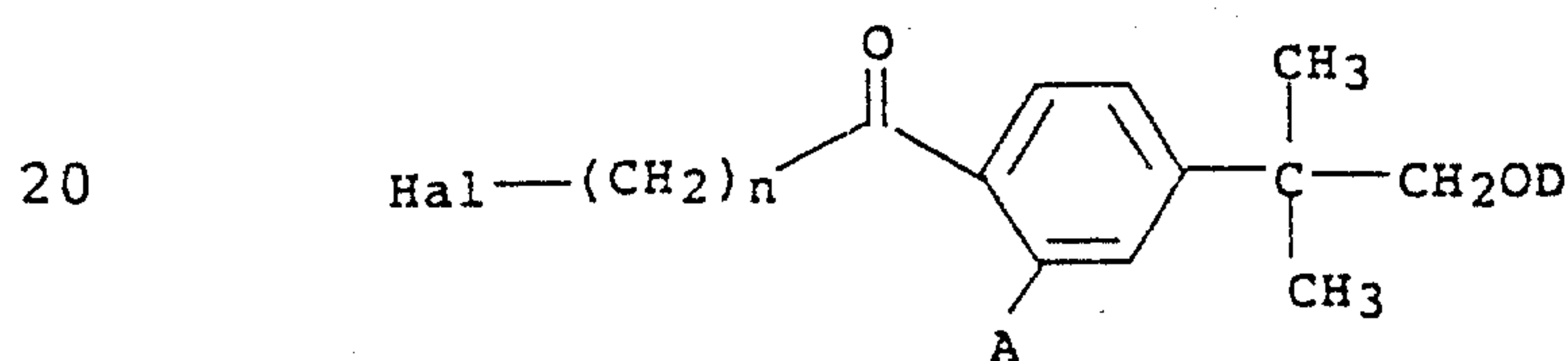
wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is $C(=O)CH_3$ or $C(=O)C_6H_5$;

5

(c) reacting the protected phenethyl alcohol with a ω -halo compound of the formula



wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula

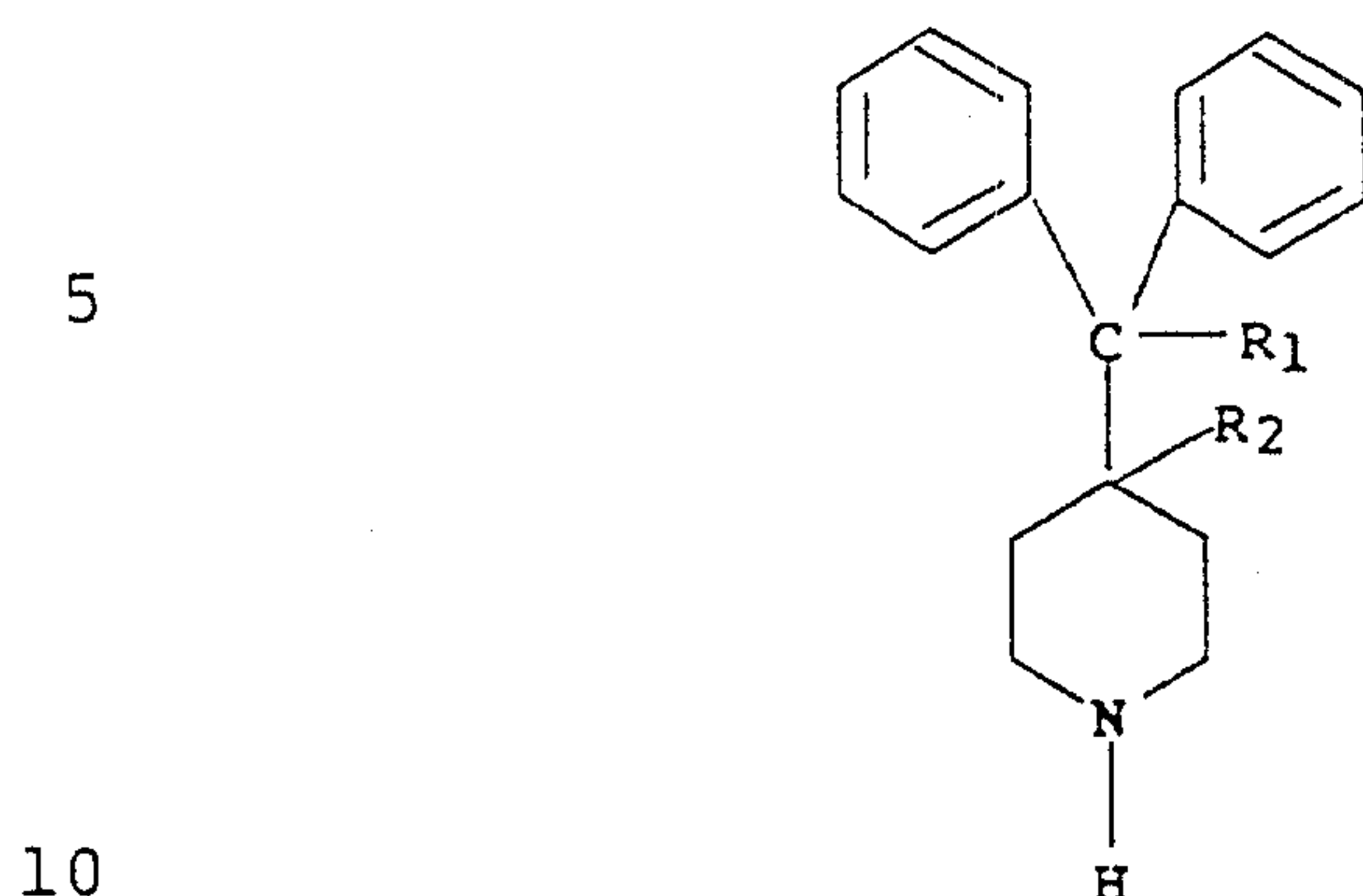


wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

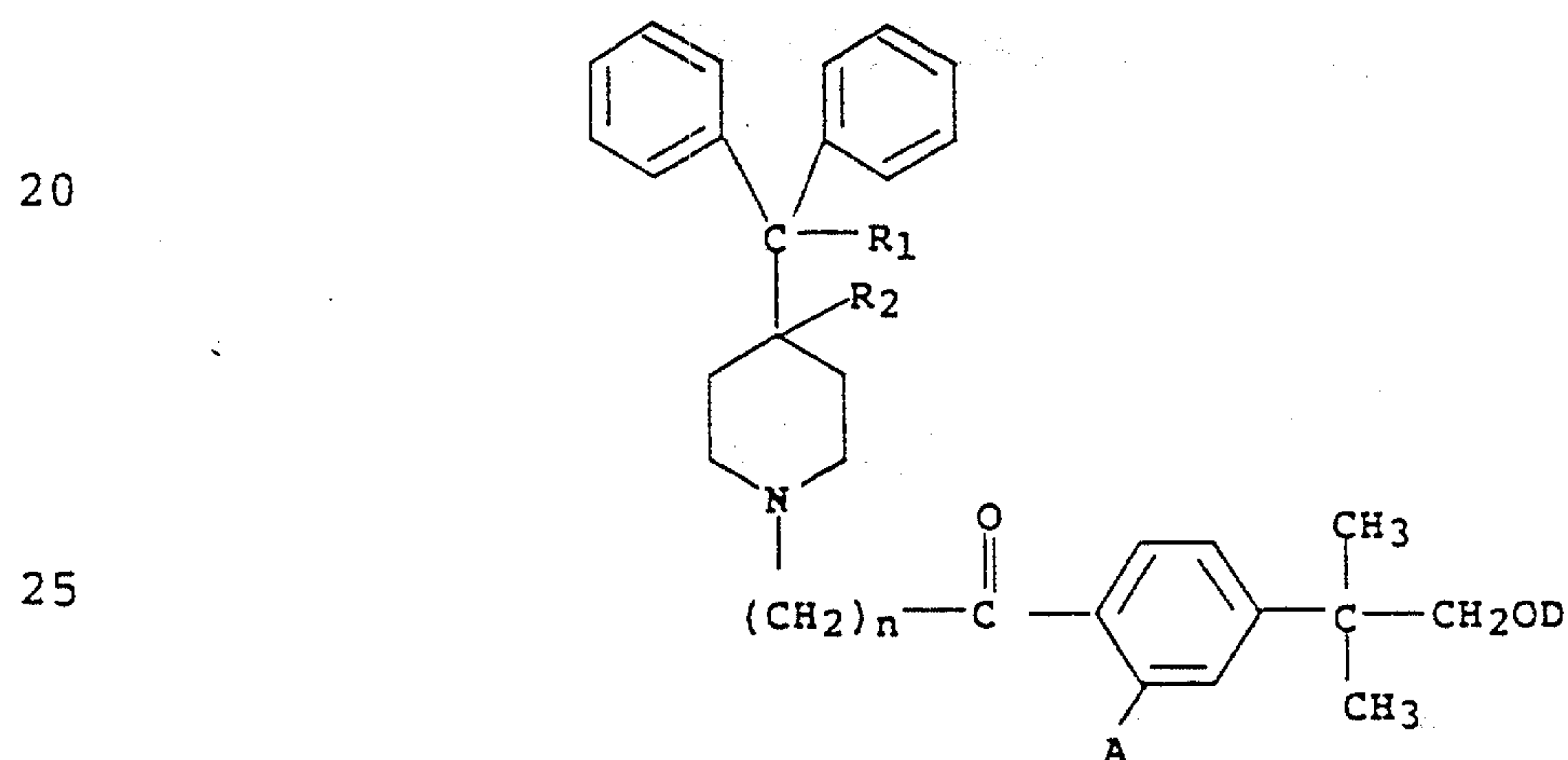
(d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

35

-169-



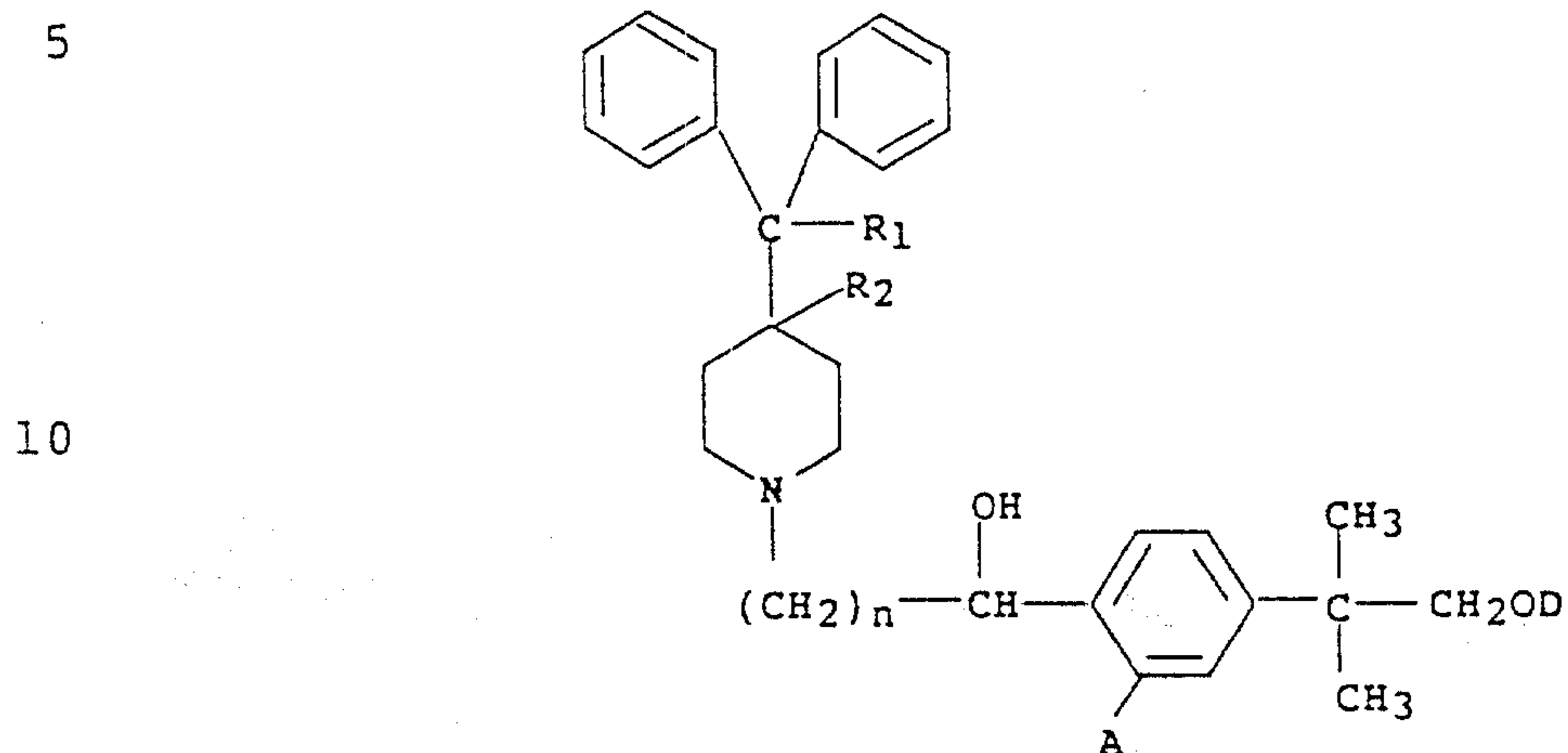
wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylketone of the formula



wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

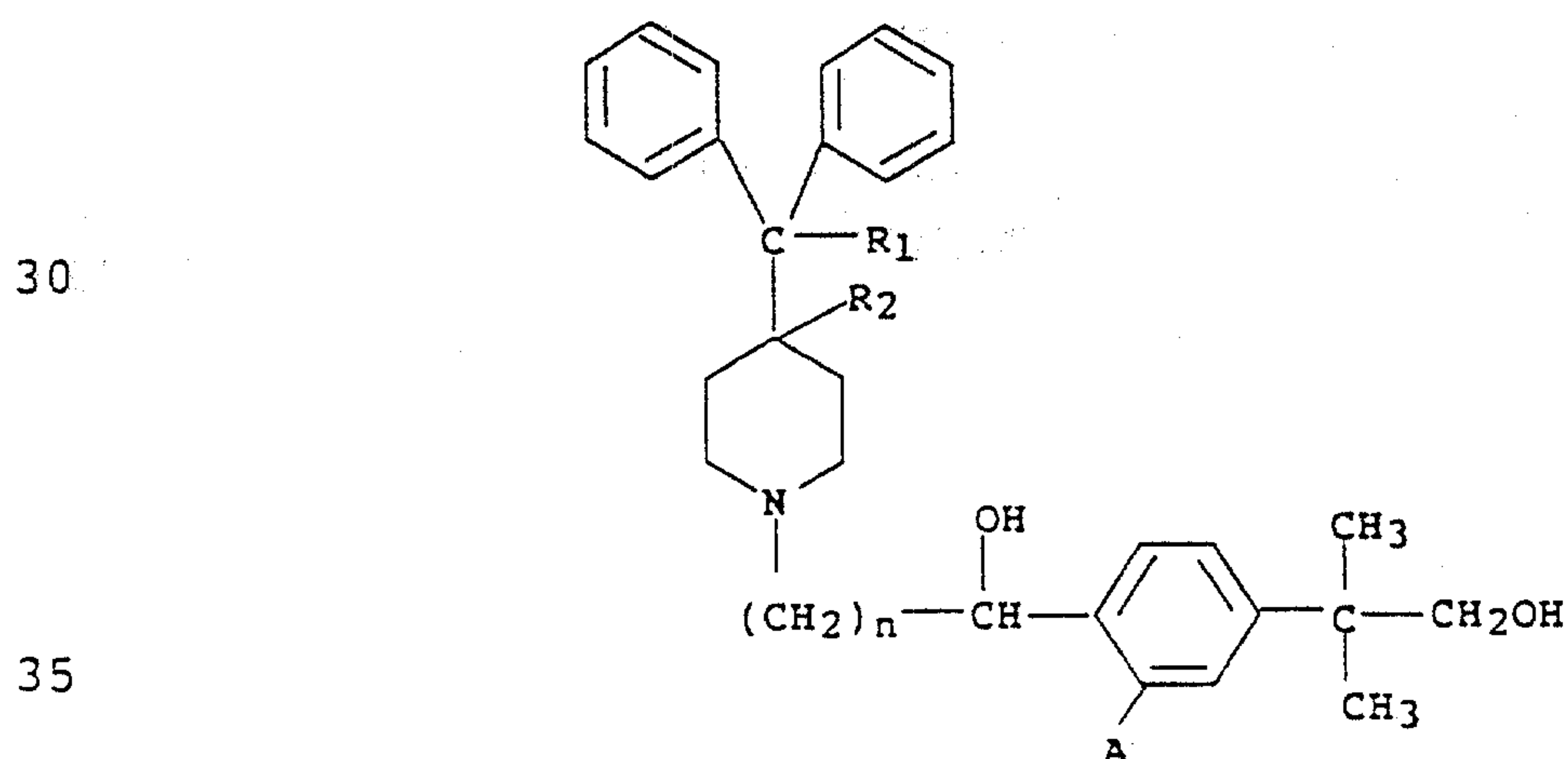
(e) reacting the piperidine protected hydroxyethylphenylketone with sodium borohydride, potassium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, lithium tri-tert-butylaluminumhydride, diisobutylaluminum hydride or catalytic hydrogenation to

produce a piperidine protected hydroxyethylphenylalcohol of the formula



wherein R_1 , R_2 , D and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

- 20 (f) reacting the piperidine protected hydroxyethylphenylalcohol with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine
- 25 hydroxyethylphenylalcohol of the formula



-171-

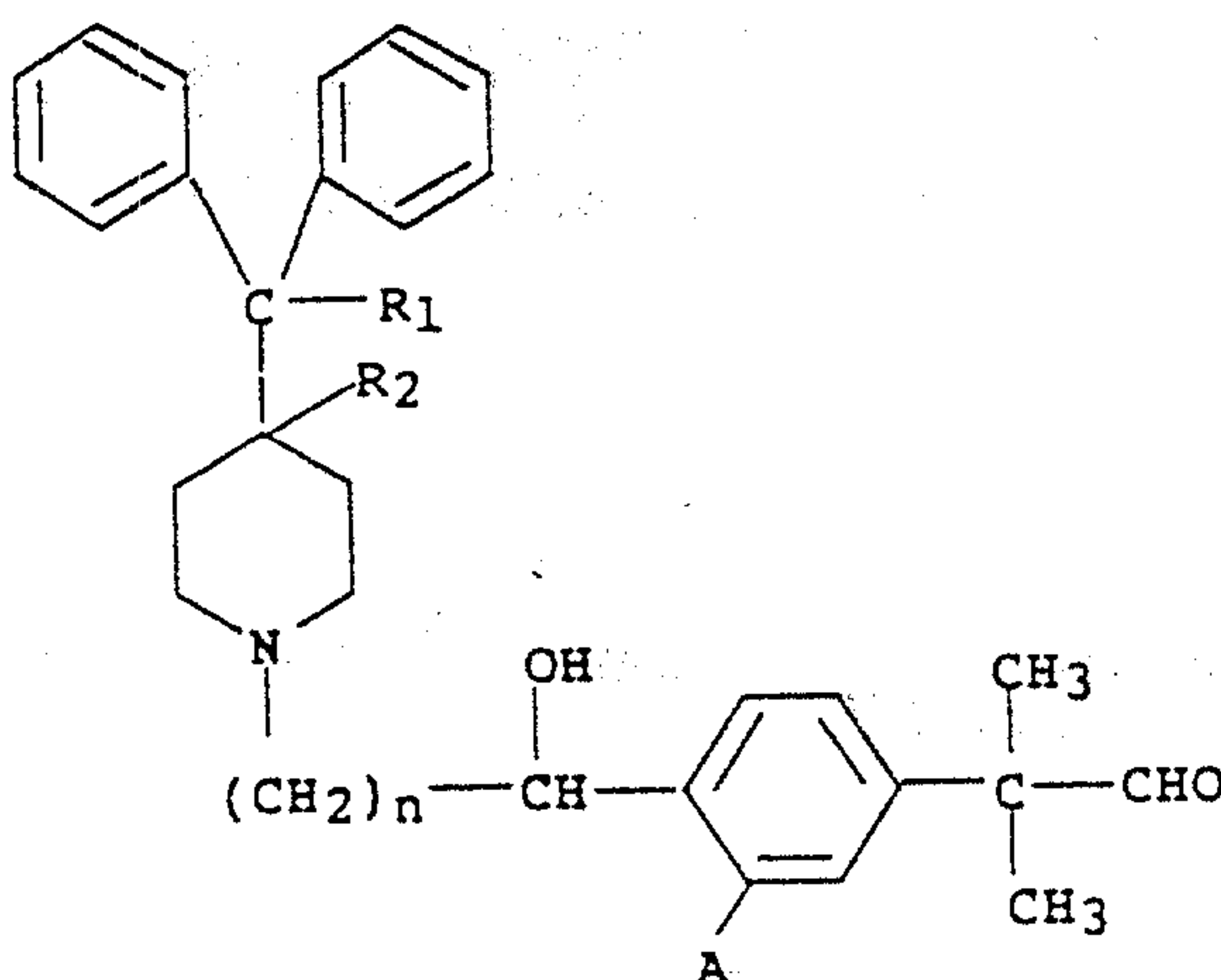
wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

5

(g) reacting the piperidine hydroxyethylphenylalcohol with dimethyl sulfoxide, oxyalyl chloride and triethylamine or with Dess-Martin reagent, chromium (IV) oxide, nickel peroxide, sodium dichromate, potassium dichromate, t-butyl chromate, silver oxide, argentic picolinate manganese dioxide lead tetraacetate, dicyclohexylcarbodiimide, 2,3-dichloro-5,6-dicyanoquinone, tetrachloro-1,2-benzoquinone, 2,2,6,6-tetramethylpiperidiny-1-oxy (TEMPO) or quinolinium chlorochromate to produce a piperidine formylphenylalcohol
15 of the formula

20

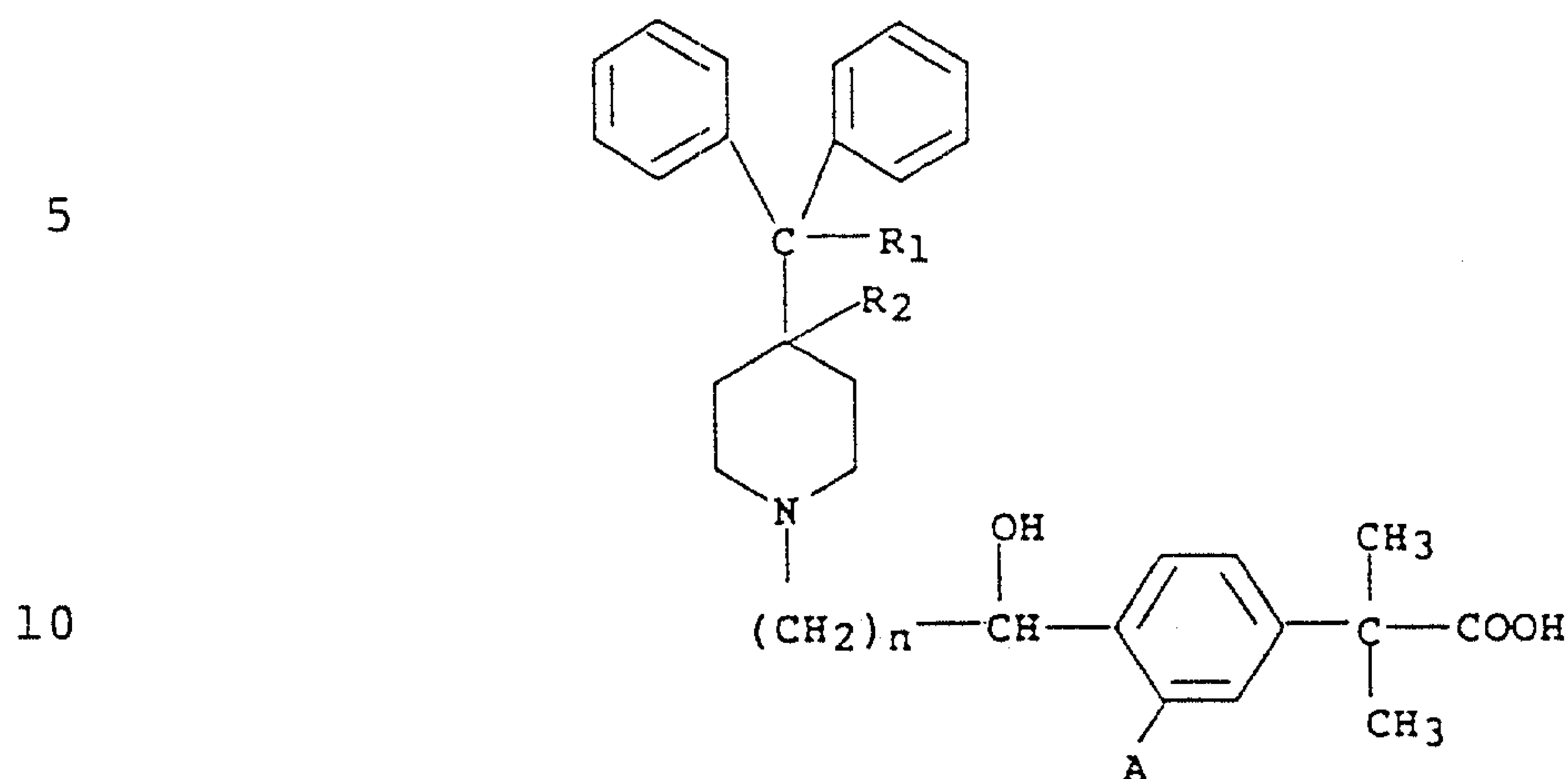
25



wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be
30 optionally protected or unprotected;

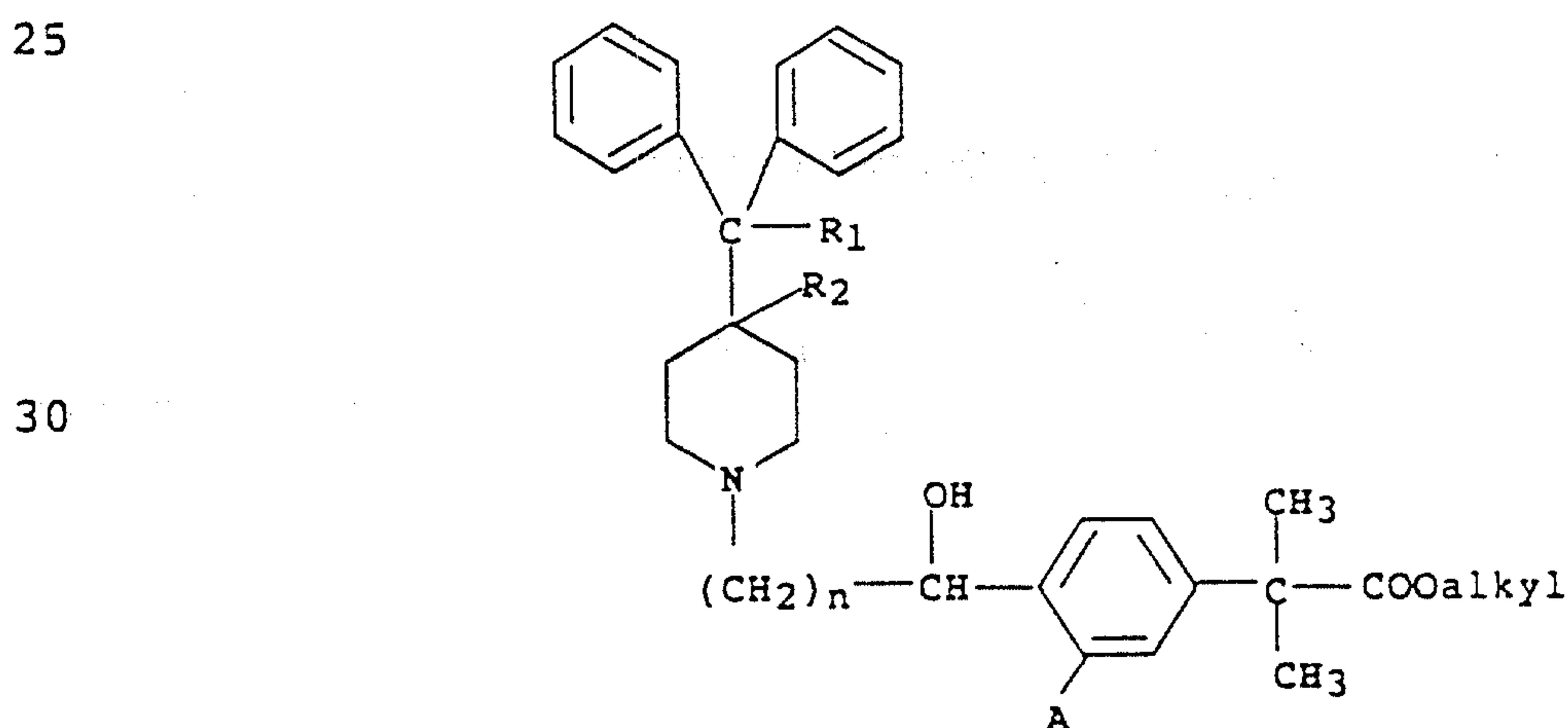
(h) reacting the piperidine formylphenylalcohol with potassium permanganate, chromium (IV) oxide, silver (I) oxide, silver oxide, argentic picolinate, peroxide, nitric
35 acid, m-chloroperbenzoic acid and peracetic acid to produce a piperidine carboxyphenylalcohol of the formula

-172-



wherein R₁, R₂ and n are defined above and A is hydrogen or
 15 hydroxy with the proviso that when A is hydroxy, A may be
 optionally protected or unprotected;

(i) optionally reacting the piperidine
 carboxyphenylalcohol with diazomethane or 2,2-
 20 dimethoxypropane or with thionyl chloride followed by an
 alcohol of the formula HOalkyl wherein the alkyl moiety has
 from 1 to 6 carbon atoms and is straight or branched to
 form a piperidine carboxyphenylalcohol ester of the formula



35

wherein R₁, R₂, n and alkyl are defined above and A is
 hydrogen or hydroxy with the proviso that when A is
 hydroxy, A may be optionally protected or unprotected; and

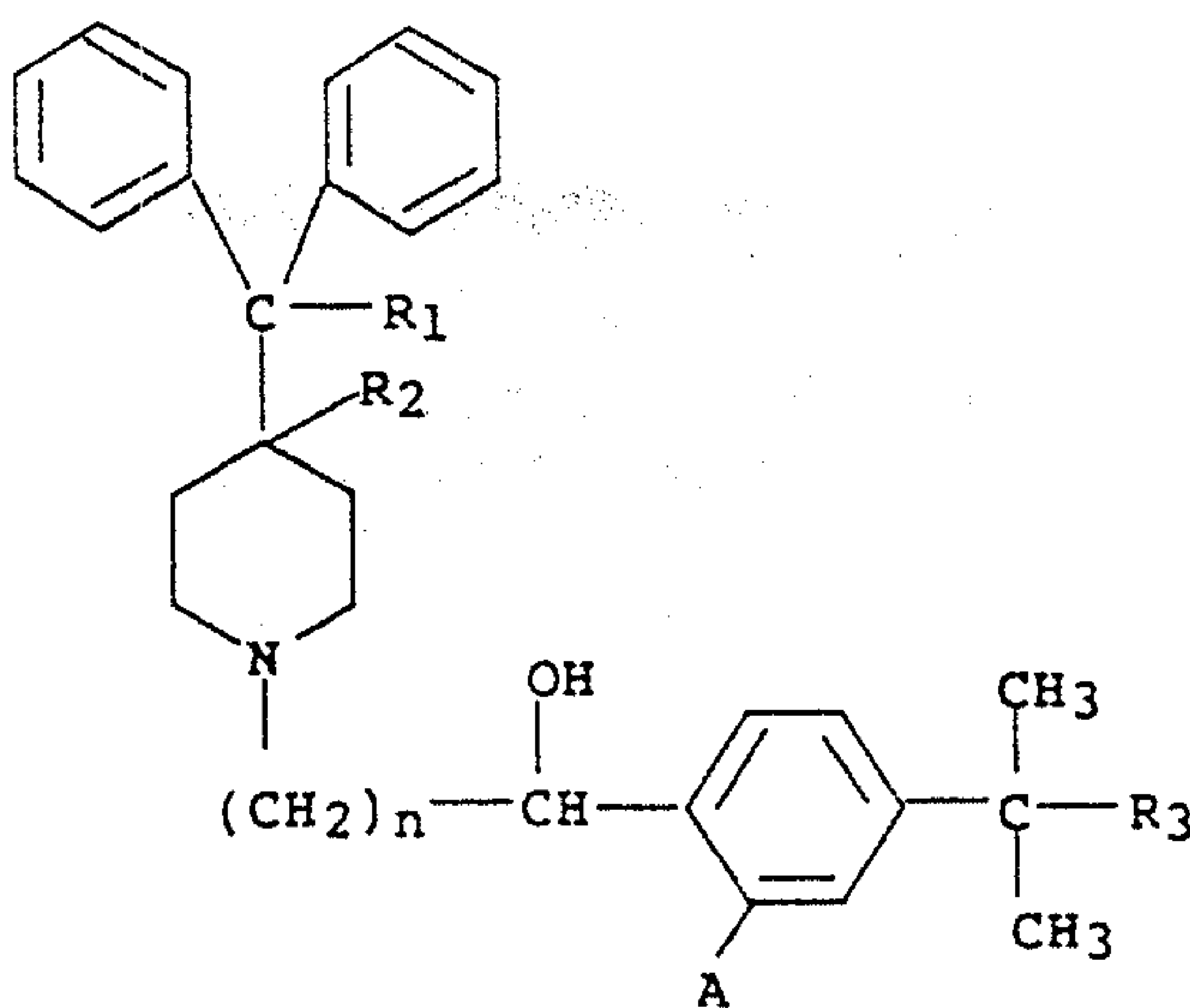
(j) optionally reacting the piperidine
 carboxyphenylalcohols or the piperidine
 5 carboxyphenylalcohol esters which bear hydroxy protecting
 groups with mineral acids, strong organic acids, Lewis
 acids, aqueous mineral bases or catalytic hydrogenation to
 produce the unprotected piperidine carboxyphenylalcohols or
 the piperidine carboxyphenylalcohol esters.

10

31. A process for preparing a compound of the formula

15

20



wherein

25

R₁ represents hydrogen or hydroxy;

R₂ represents hydrogen; or

R₁ and R₂ taken together form a second bond between the
 carbon atoms bearing R₁ and R₂;

n is an integer of from 1 to 5;

30

R₃ is -COOH or -COOalkyl wherein the alkyl moiety has
 from 1 to 6 carbon atoms and is straight or branched;

A is hydrogen or hydroxy; and

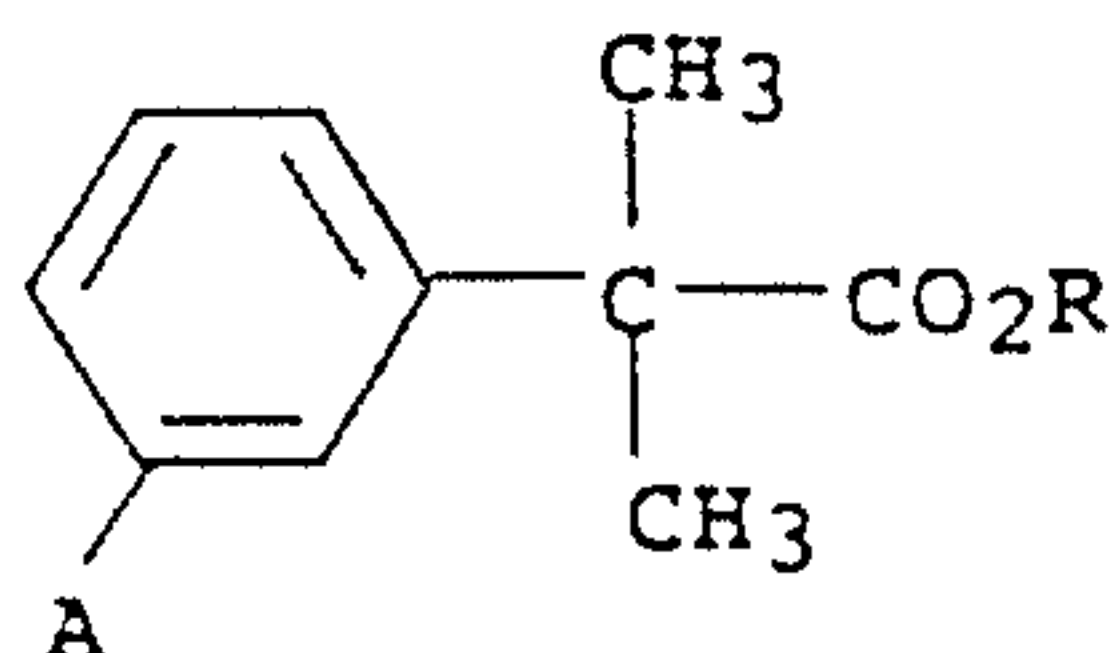
pharmaceutically acceptable salts thereof comprising
 the steps of:

35

(a) reacting a benzeneacetic acid compound of the
 formula

-174-

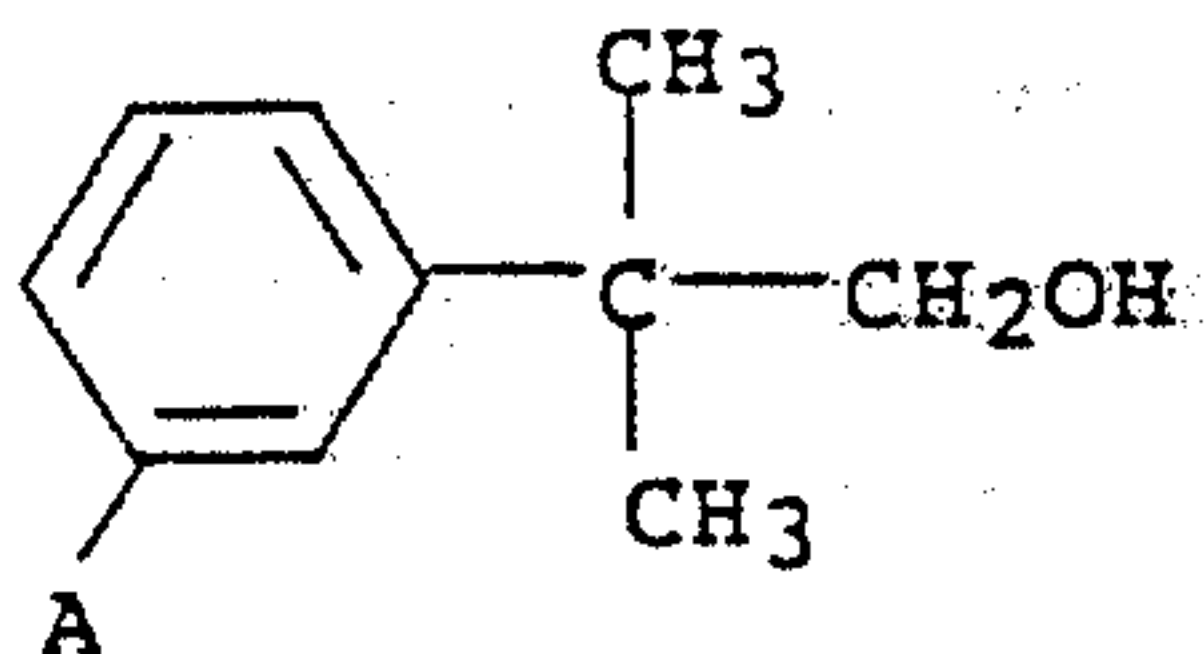
5



10

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, diborane, lithium borohydride, lithium triethylborohydride, and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

15



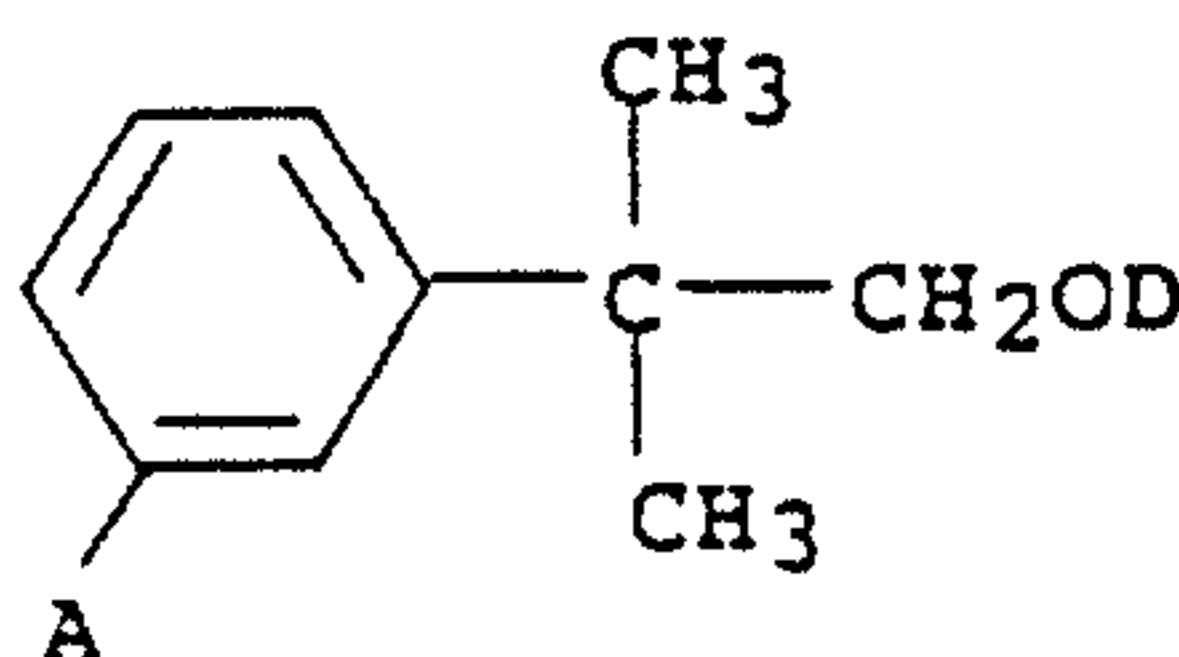
20

wherein A is hydrogen or hydroxy, with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

25

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

30



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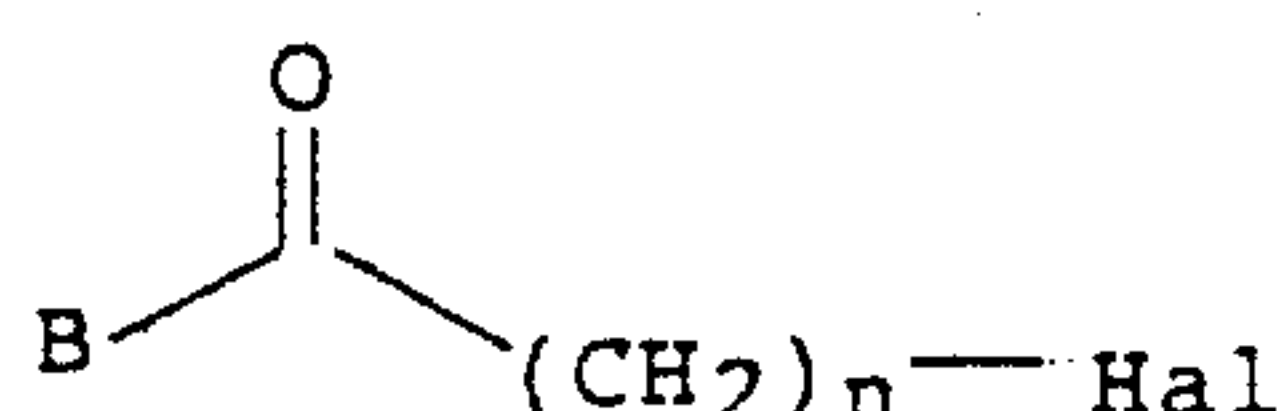
-175-

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is $C(=O)CH_3$ or $C(=O)C_6H_5$;

5

(c) reacting the protected phenethyl alcohol with a ω -halo compound of the formula

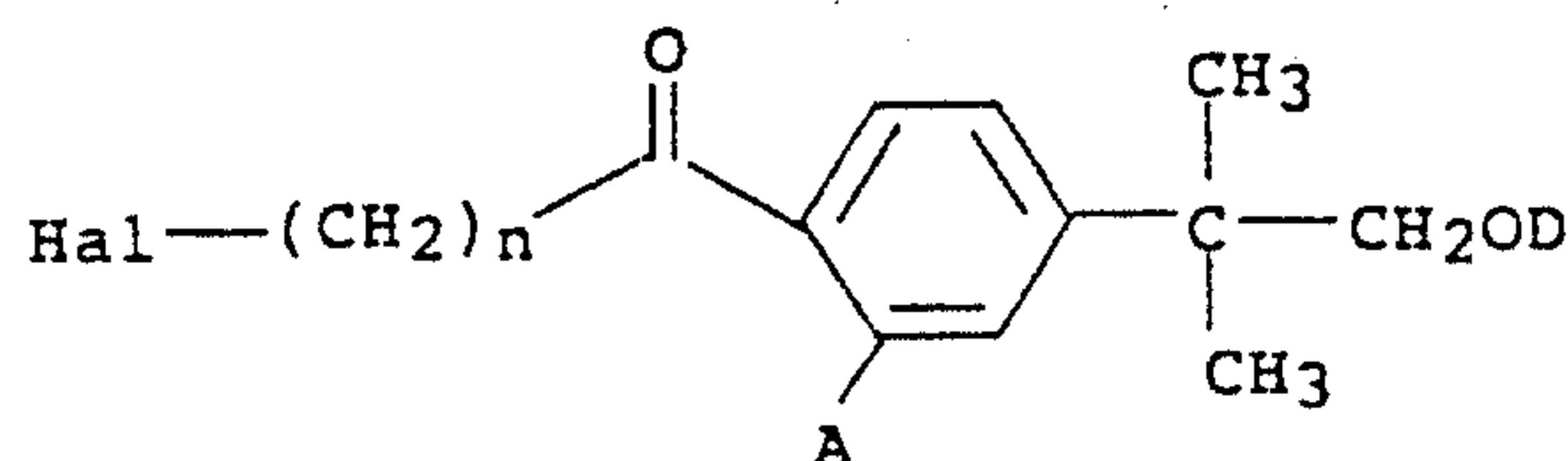
10



15

wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula

20



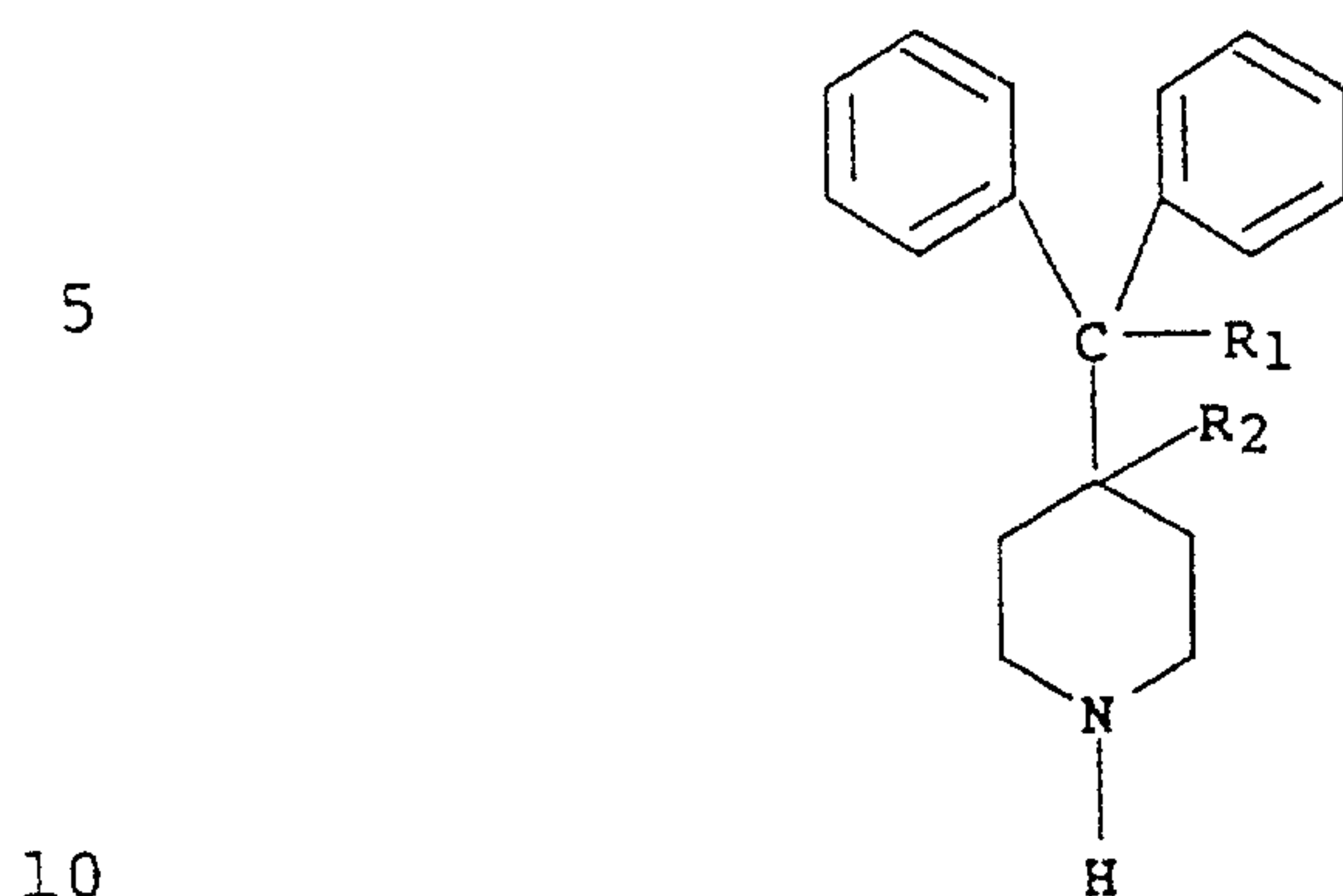
25

wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

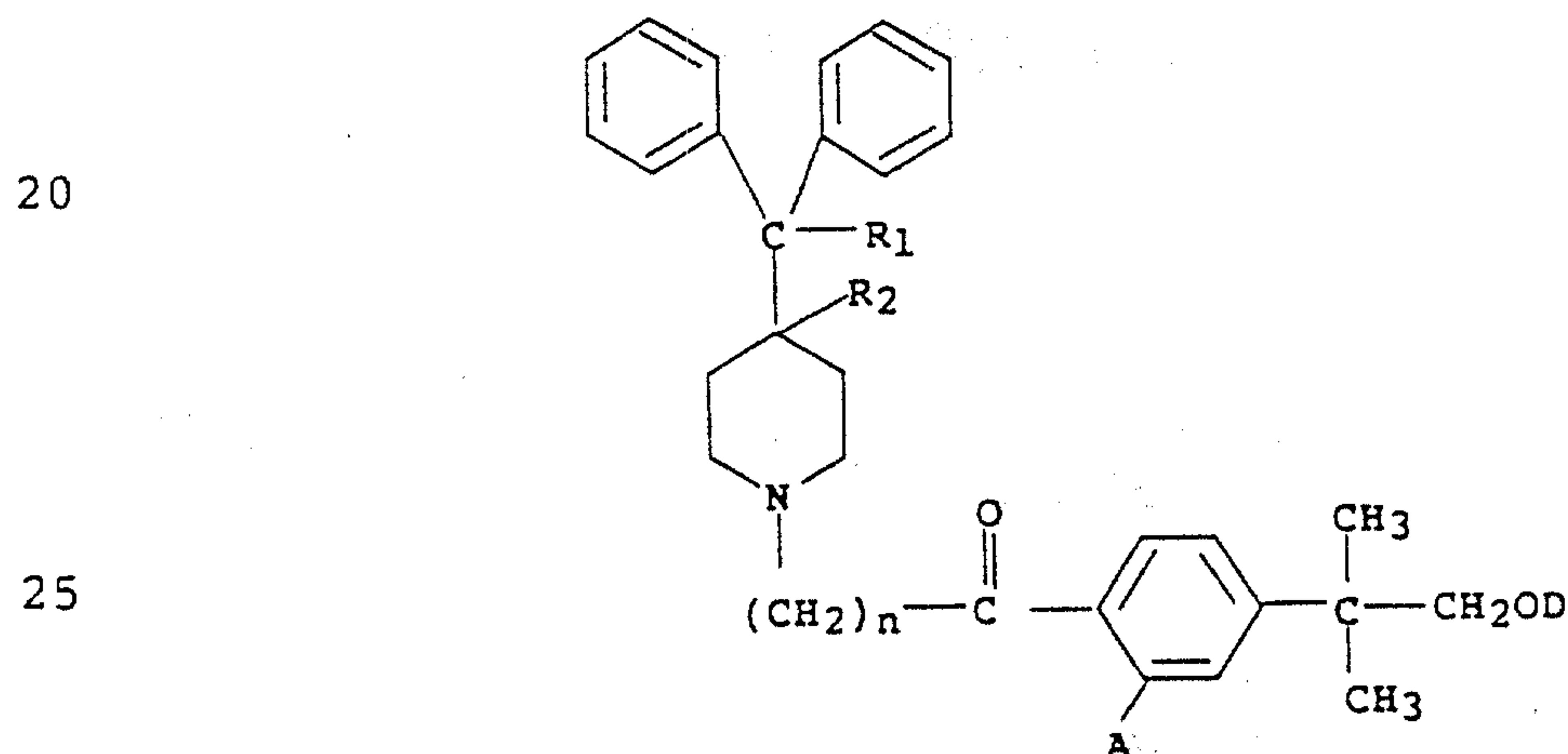
30

(d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

35



wherein R_1 and R_2 are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylketone of the formula

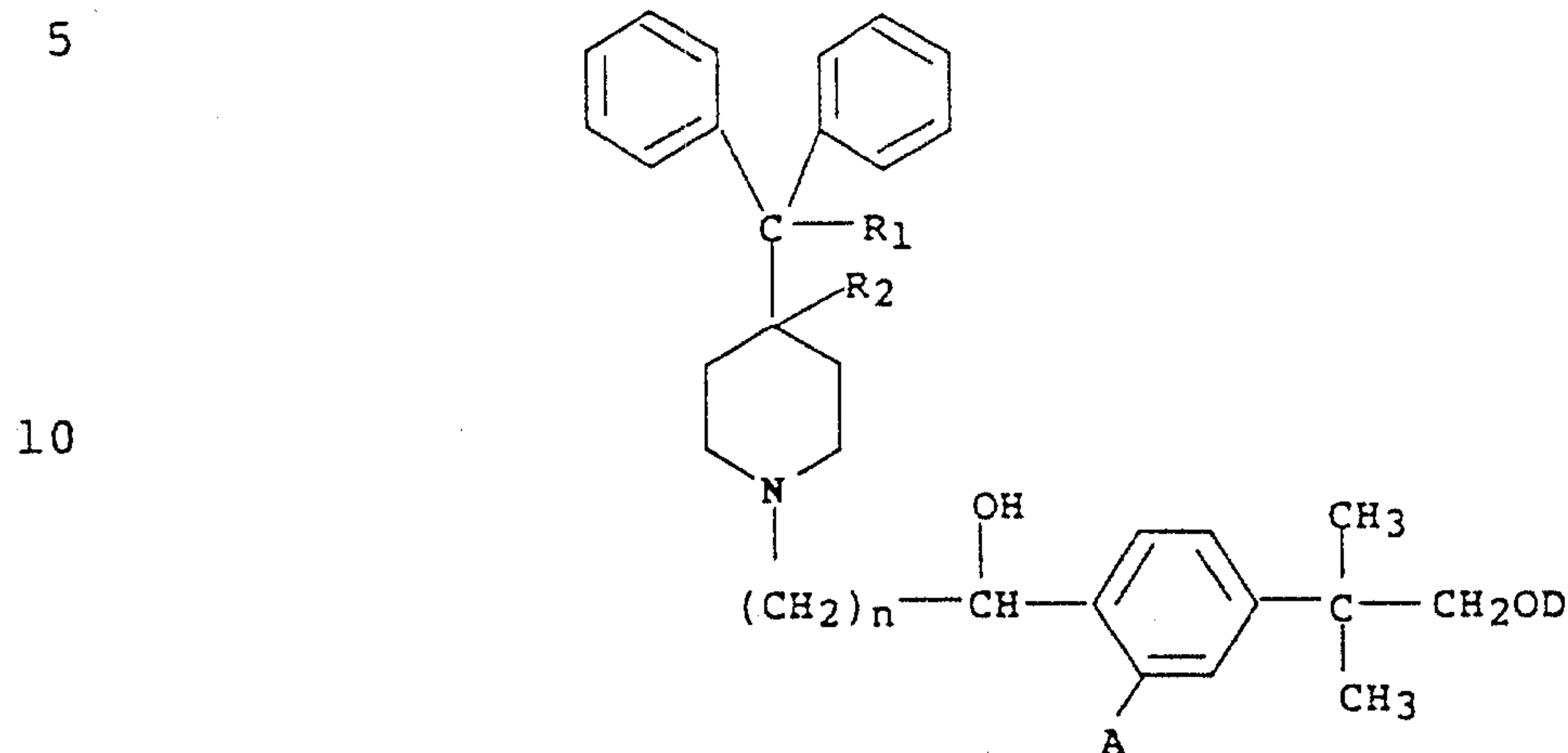


wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(e) reacting the piperidine protected hydroxyethylphenylketone with sodium borohydride, potassium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, lithium tri-tert-butylaluminumhydride, diisobutylaluminum hydride or catalytic hydrogenation to

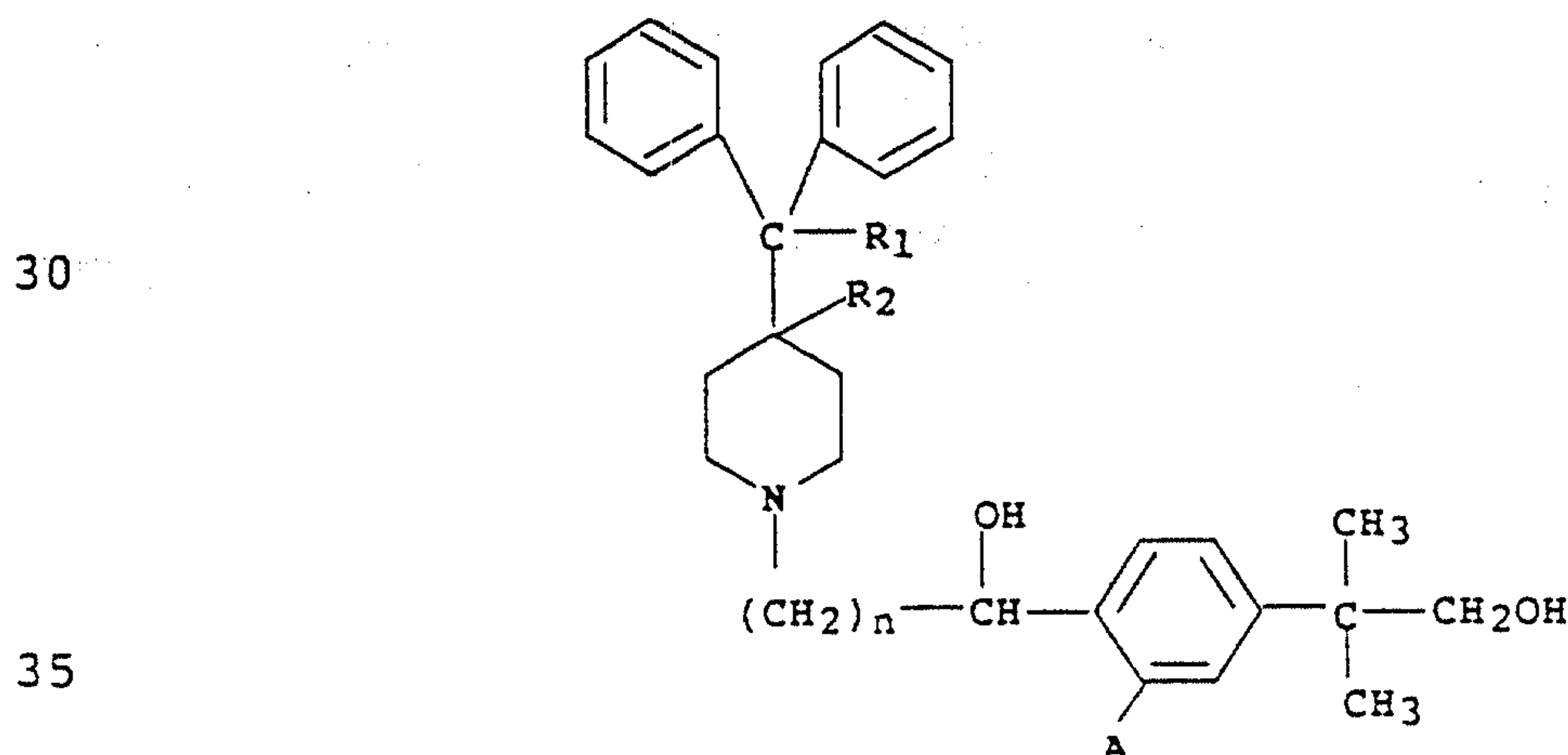
-177-

produce a piperidine protected hydroxyethylphenylalcohol of the formula



wherein R_1 , R_2 , D and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

- 20 (f) reacting the piperidine protected hydroxyethylphenylalcohol with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine
- 25 hydroxyethylphenylalcohol of the formula



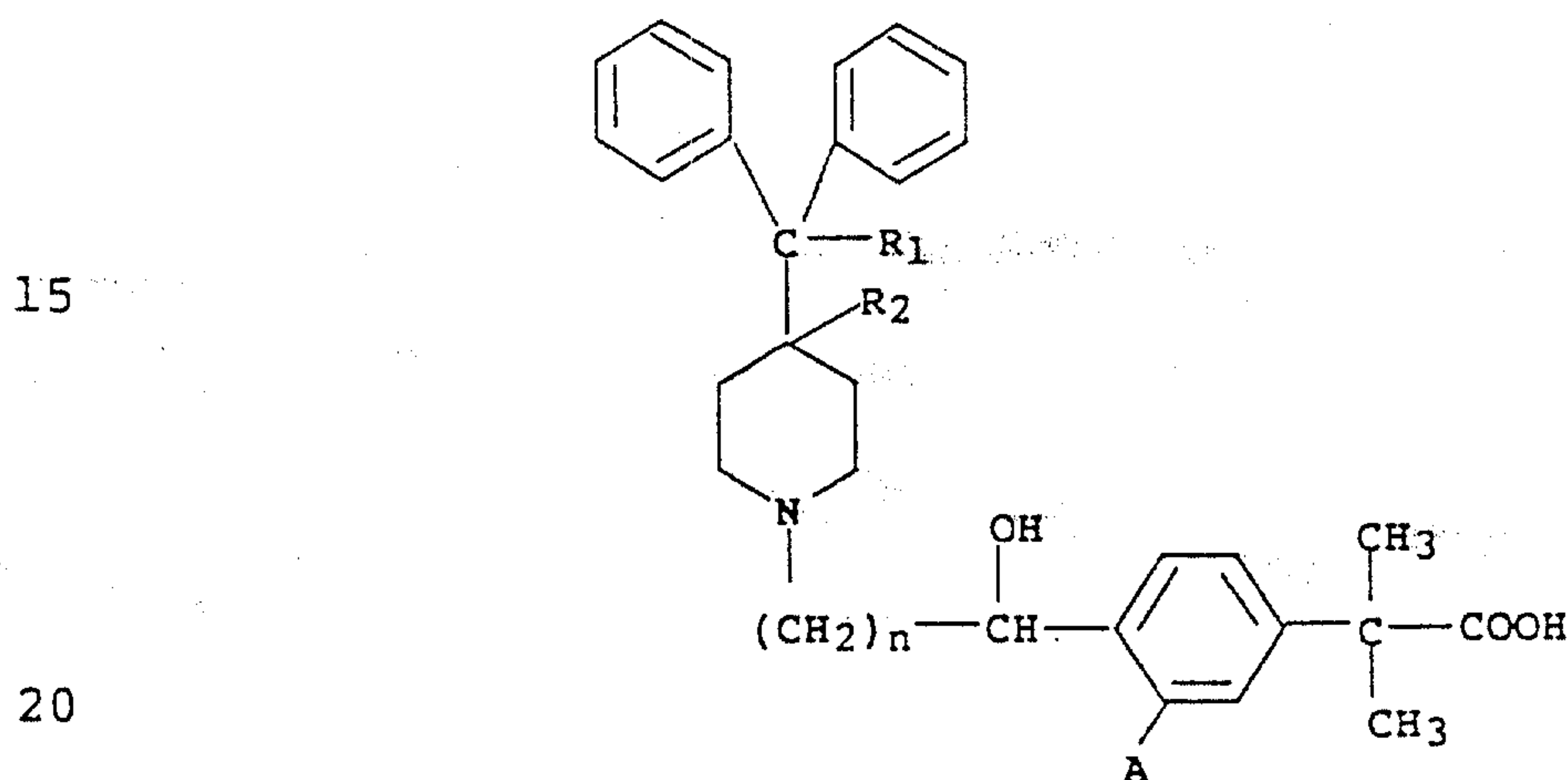
-178-

wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

5

(g) reacting the piperidine hydroxyethylphenylalcohol with chromium (IV) oxide, potassium permanganate, nitric acid, nitrogen dioxide, ruthenium (VIII) oxide, nickel peroxide, silver oxide, t-butyl chromate or xenic acid to

10 produce a piperidine carboxyphenylalcohol of the formula



wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be

25 optionally protected or unprotected;

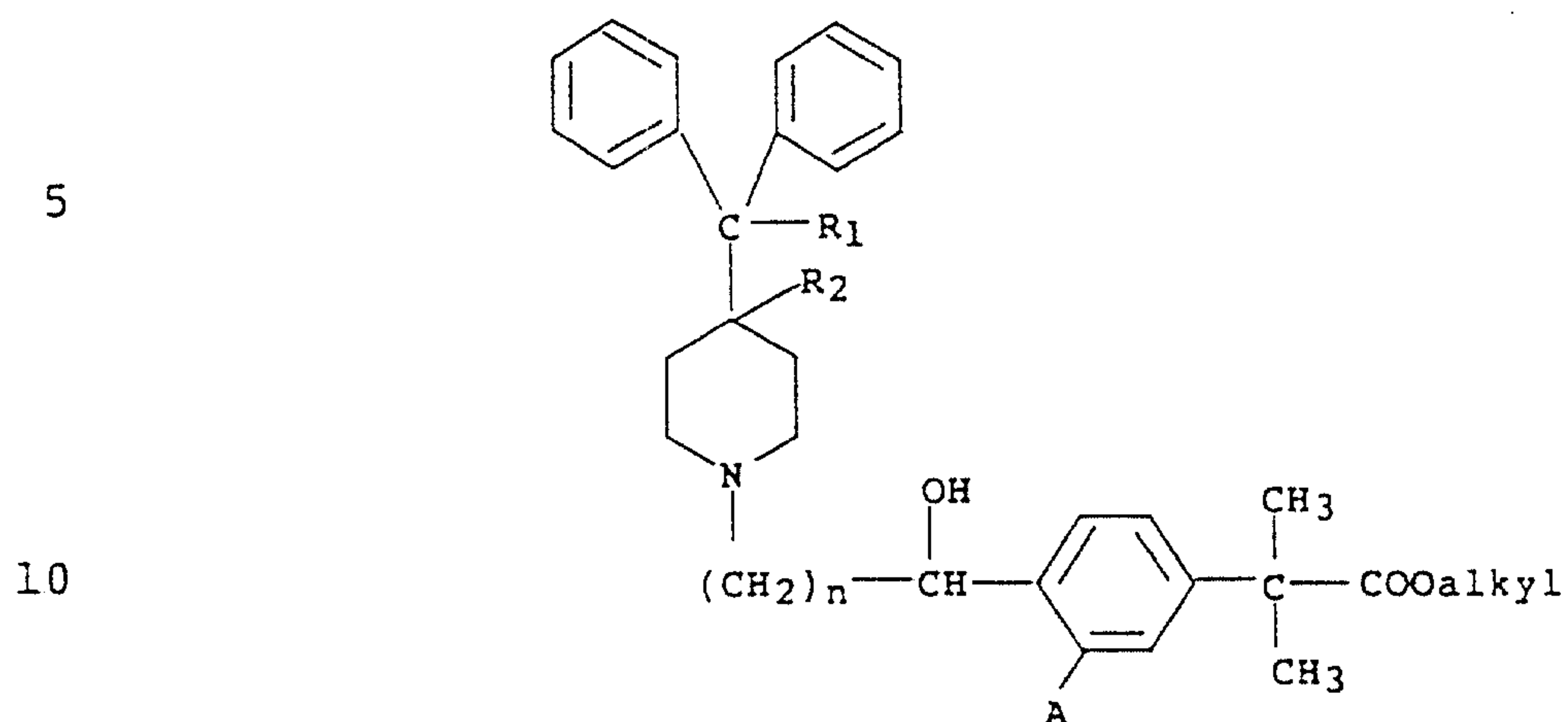
(h) optionally reacting the piperidine carboxyphenylalcohol with diazomethane or 2,2-dimethoxypropane or with thionyl chloride followed by an

30 alcohol of the formula HOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched to form a piperidine carboxyphenylalcohol ester of the formula

35

AMENDED SHEET

-179-



wherein R₁, R₂, n and alkyl are defined above and A is
 15 hydrogen or hydroxy with the proviso that when A is
 hydroxy, A may be optionally protected or unprotected; and

(i) optionally reacting the piperidine
 carboxyphenylalcohols or the piperidine
 20 carboxyphenylalcohol esters which bear hydroxy protecting
 groups with mineral acids, strong organic acids, Lewis
 acids, aqueous mineral bases or catalytic hydrogenation to
 produce the unprotected piperidine carboxyphenylalcohols or
 the piperidine carboxyphenylalcohol esters.

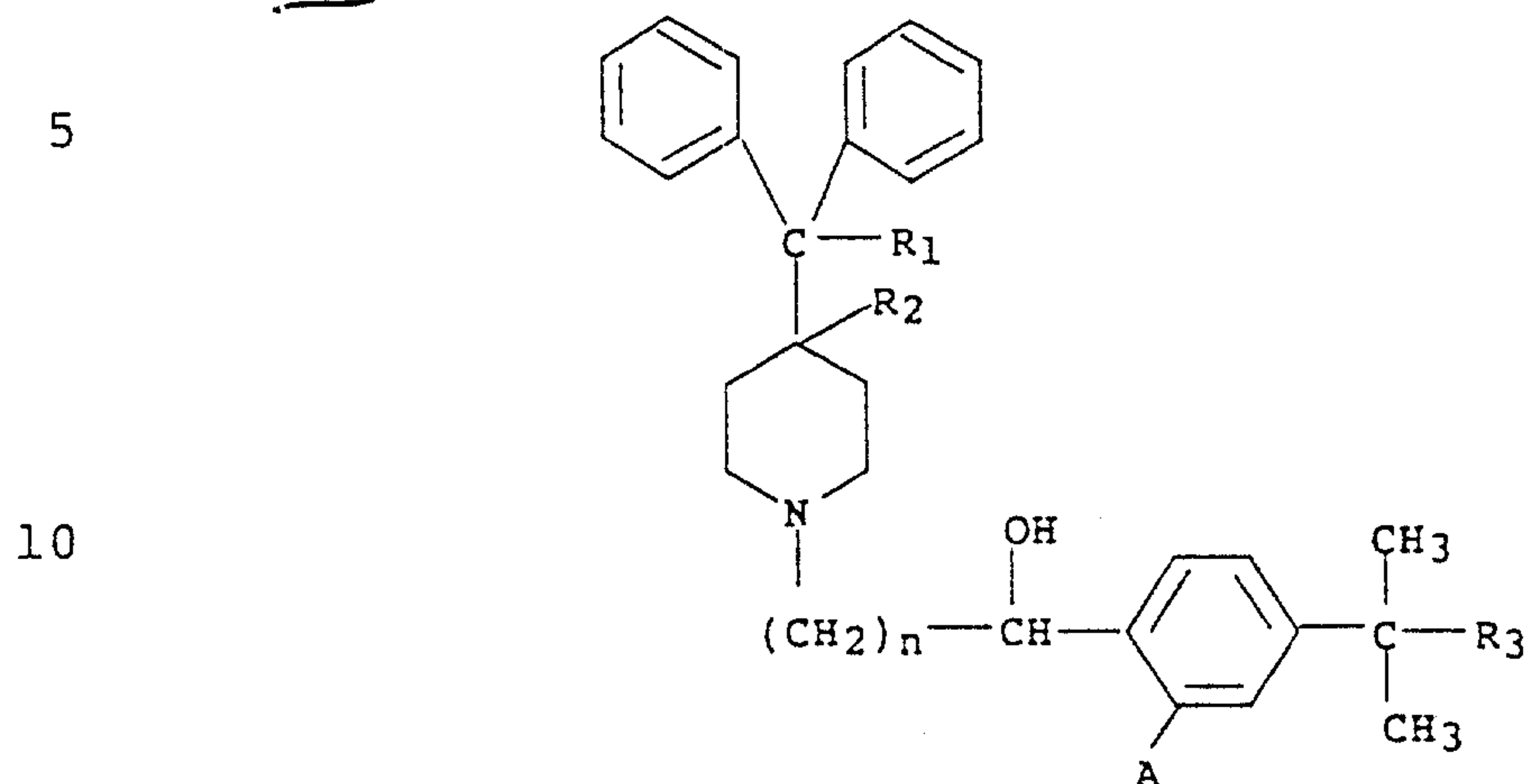
25

32. A process according to Claim 31 wherein the
 piperidine hydroxyethylphenylalcohol produced in step f is
 reacted with ruthenium (VIII) oxide to produce the
 piperidine carboxyphenylketone of step g.

30

35

33. A process for preparing a compound of the formula



wherein

R₁ represents hydrogen or hydroxy;

R₂ represents hydrogen; or

R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;

```
n is an integer of from 1 to 5;
```

A is hydrogen or hydroxy;

R₃ is -CH₂OH; and

pharmaceutically acceptable salts thereof comprising
steps of:

(a) reacting a benzeneacetic acid compound of the formula

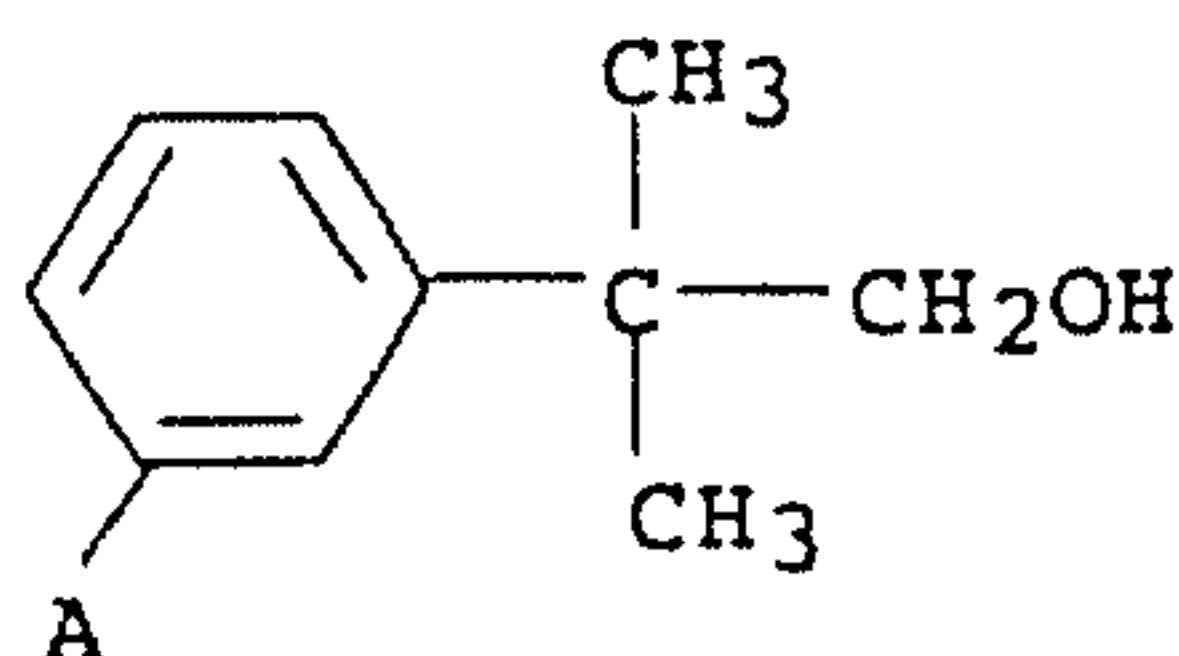


wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or deprotected and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, diborane, lithium borohydride, lithium triethylborohydride.

-181-

and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula;

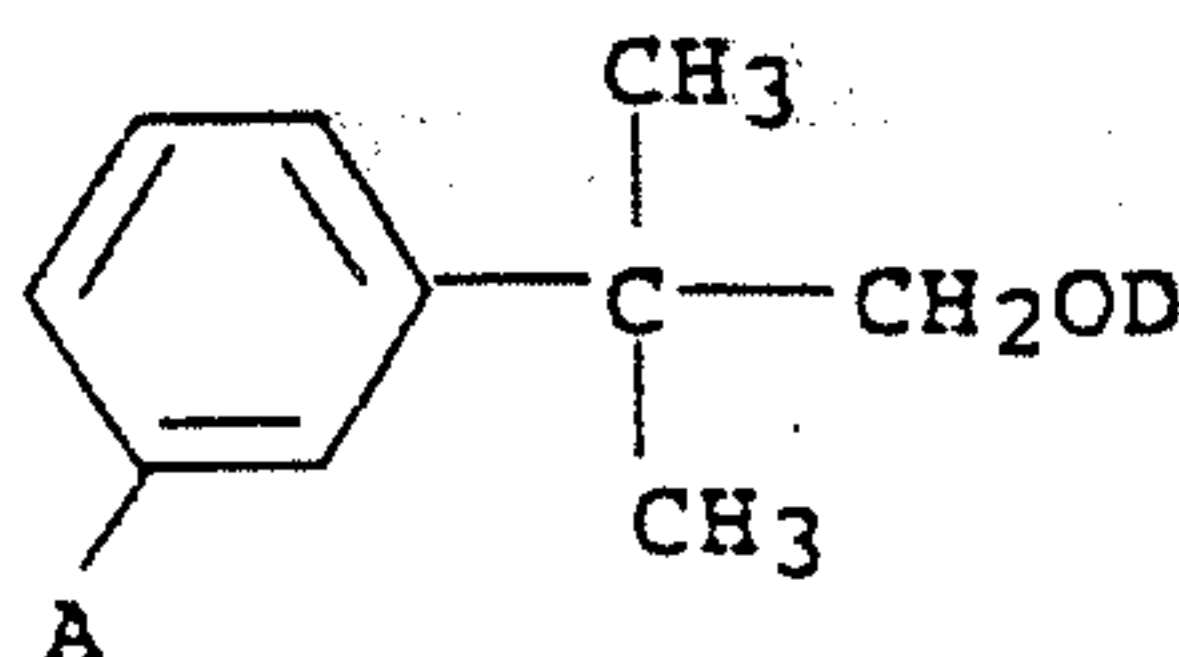
5



10

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

15



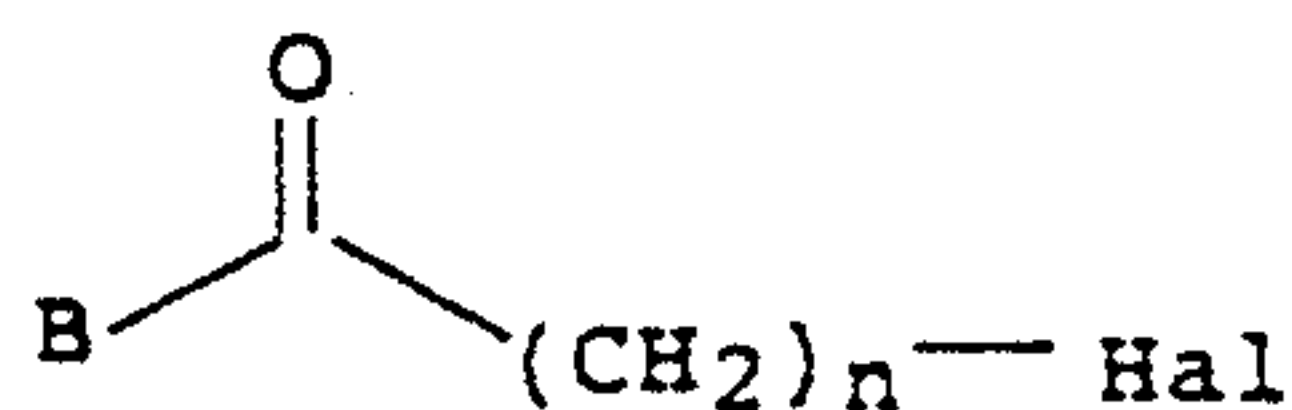
20

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or deprotected and D is C(=O)CH₃ or C(=O)C₆H₅;

25

(c) reacting the protected phenethyl alcohol with a ω-halo compound of the formula

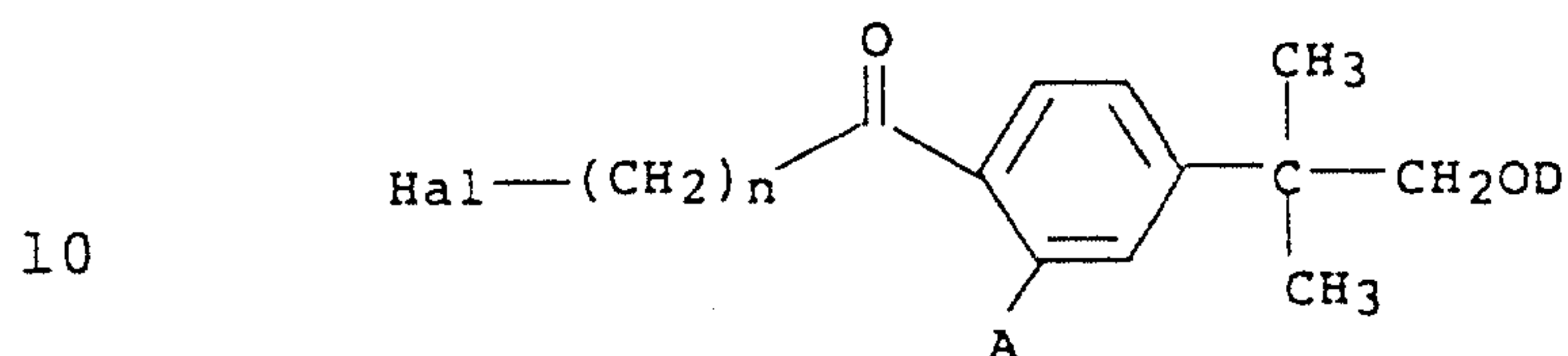
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-182-

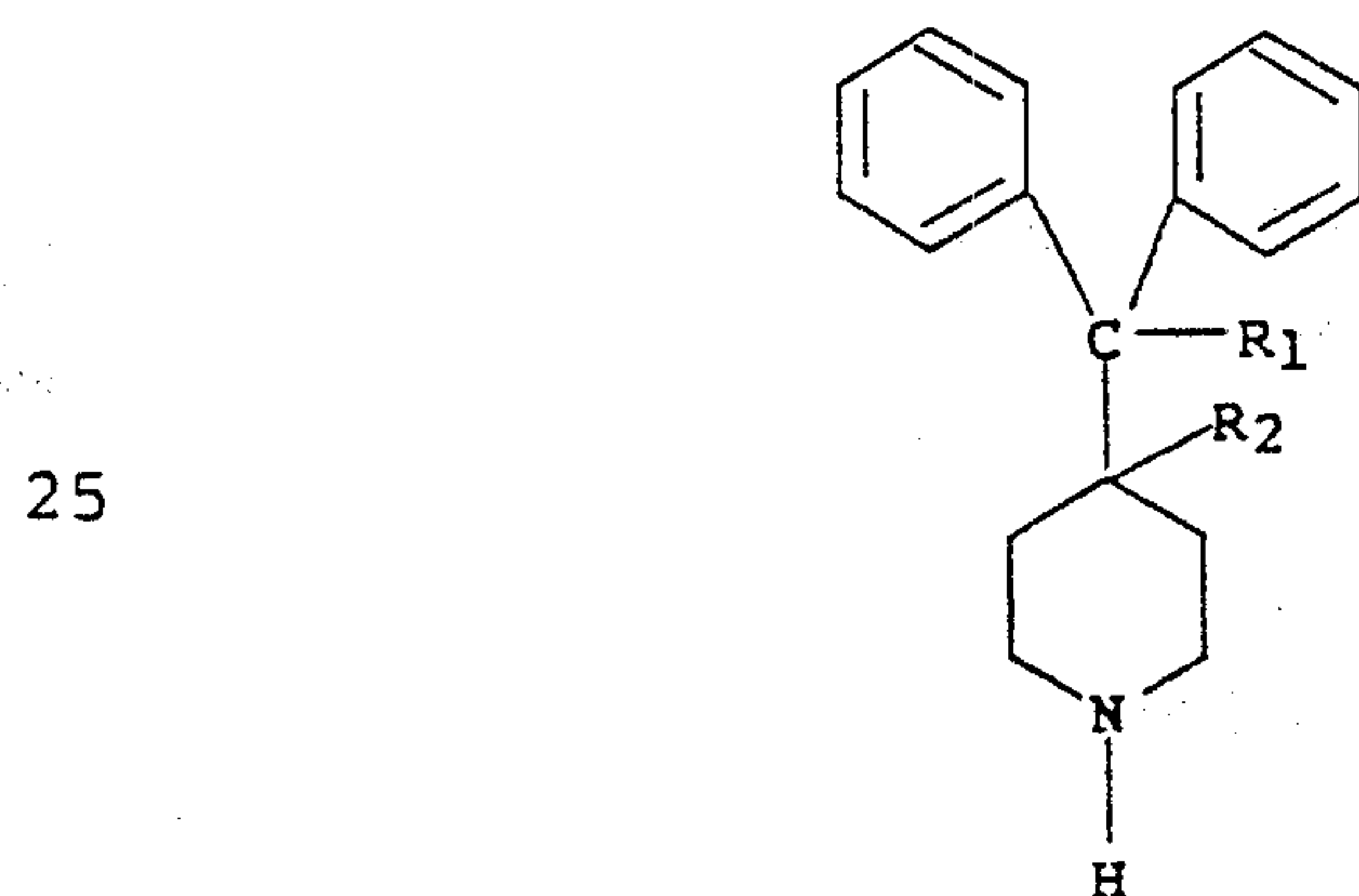
wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula



15 wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or deprotected;

(d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

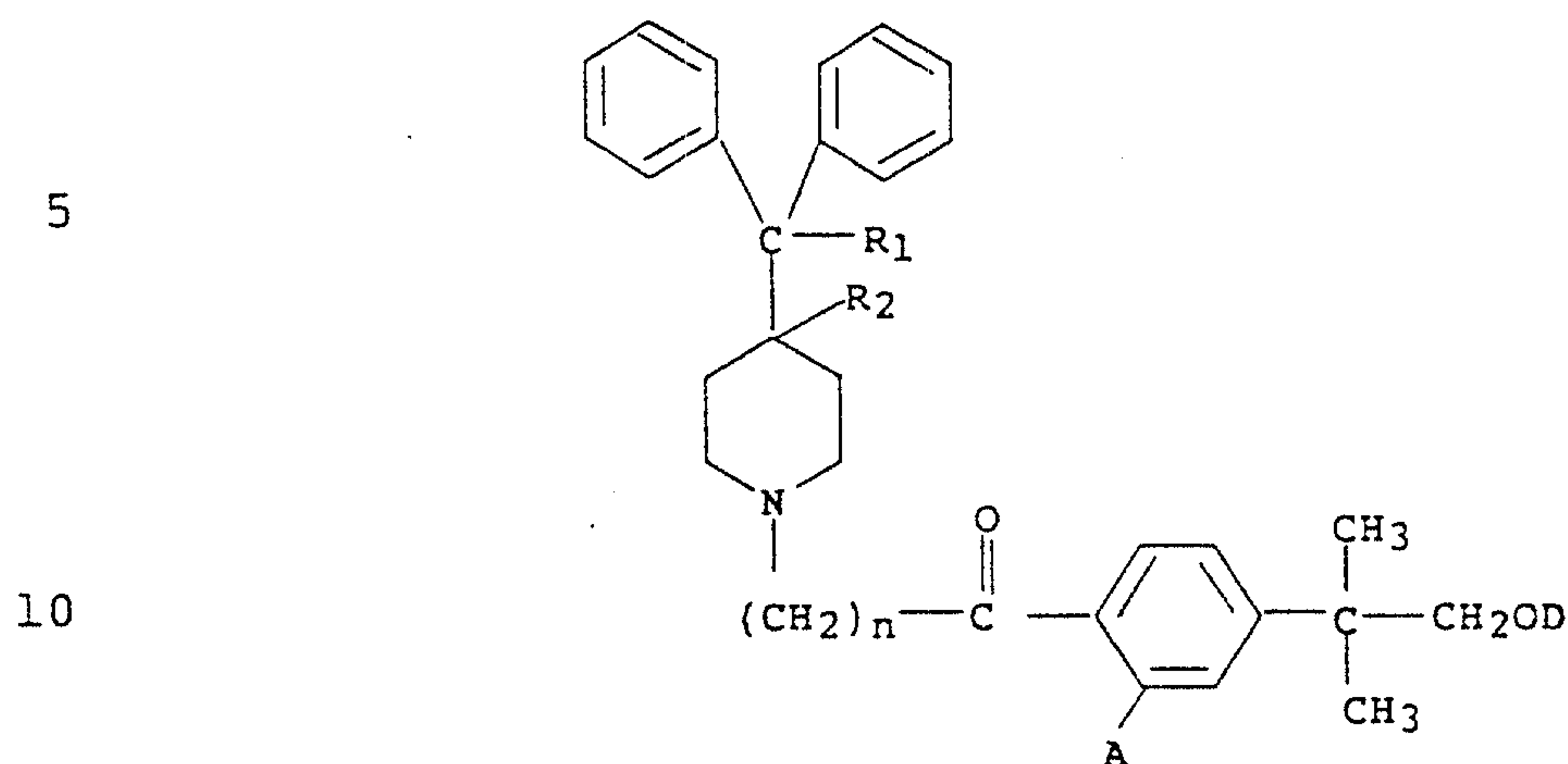
20



30 wherein R₁ and R₂ are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylketone of the formula

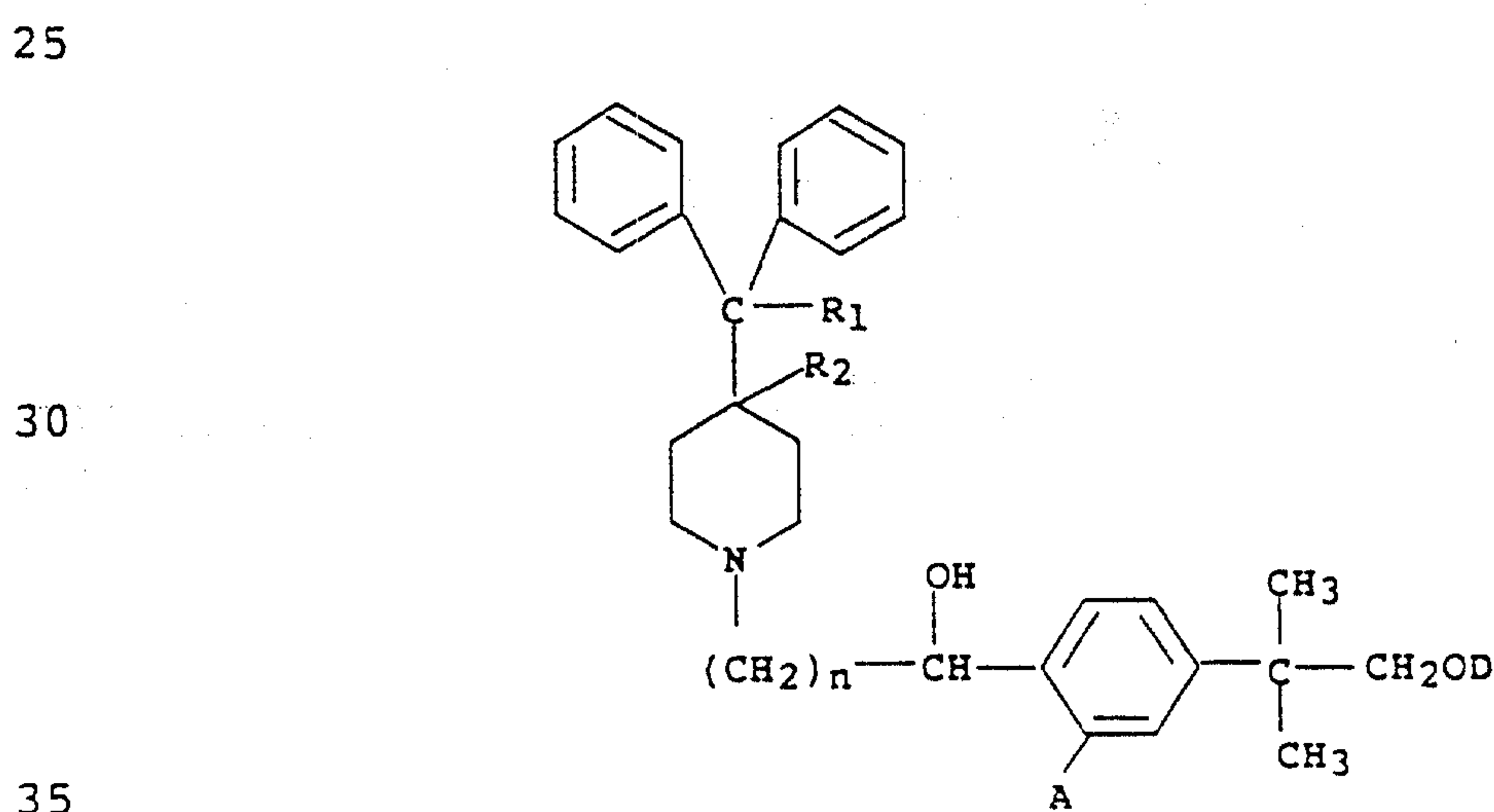
35

-183-



15 wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or deprotected;

(e) reacting the piperidine protected hydroxyethylphenylketone with sodium borohydride, potassium borohydride, sodium cyanoborohydride, tetramethylammonium borohydride, lithium tri-tert-butylaluminumhydride, diisobutylaluminum hydride or catalytic hydrogenation to produce a piperidine protected hydroxyethylphenylalcohol of the formula



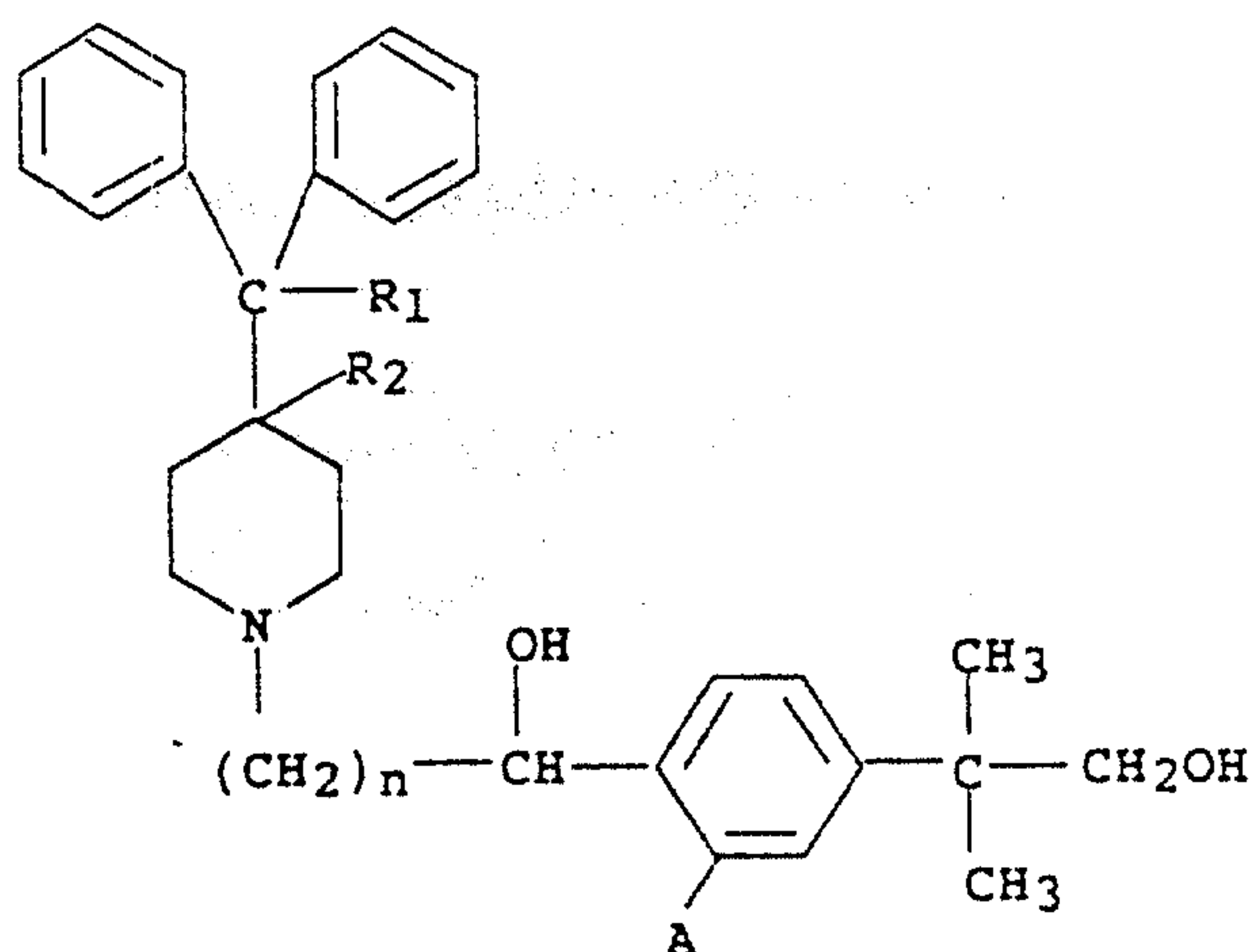
wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or deprotected;

5

(f) reacting the piperidine protected hydroxyethylphenylalcohol with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and
10 potassium cyanide in ethanol to produce the piperidine hydroxyethylphenylalcohol of the formula

15

20



wherein R_1 , R_2 and n are defined above and A is hydrogen or
25 hydroxy with the proviso that when A is hydroxy, A may be optionally protected or deprotected;

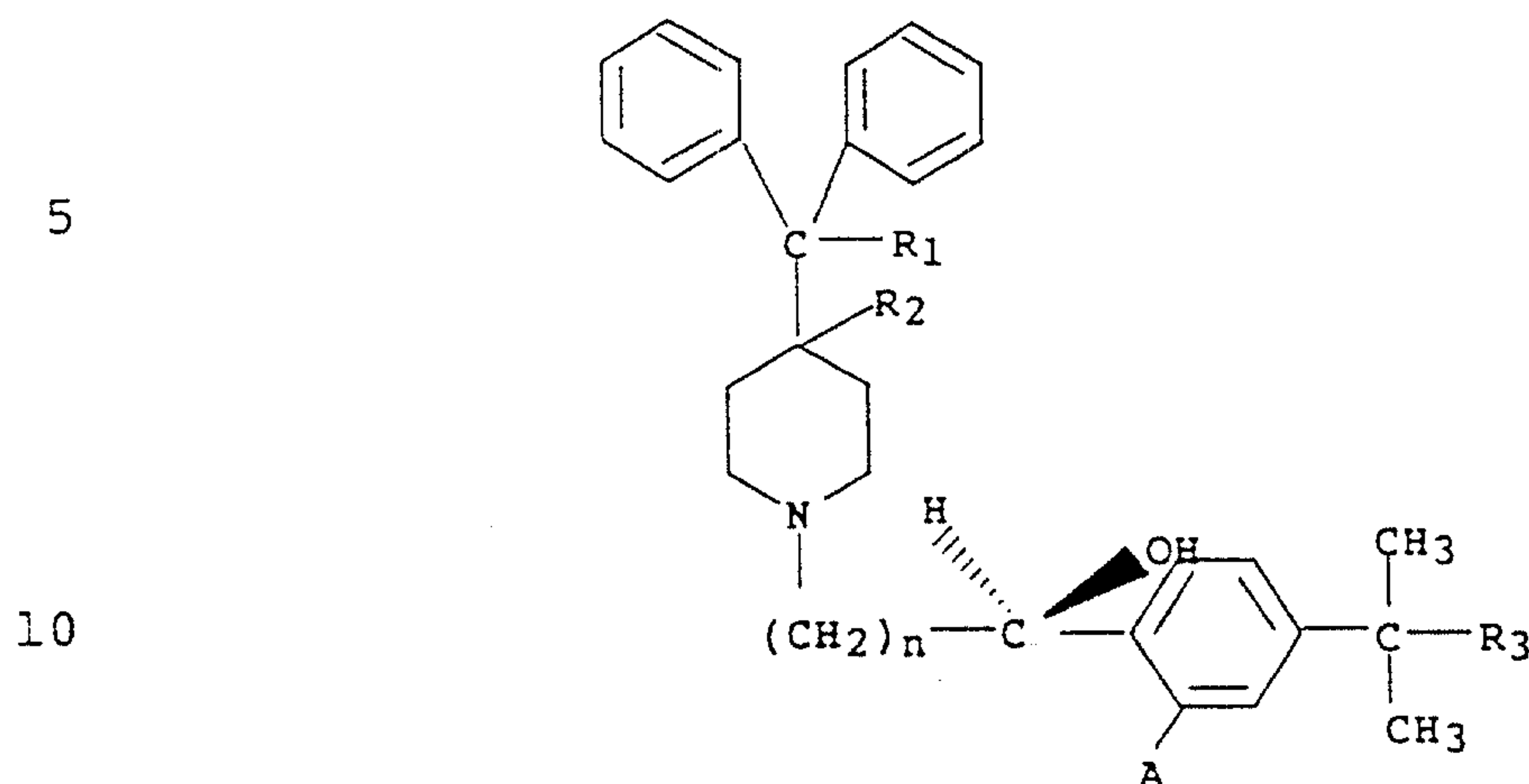
(g) optionally reacting the piperidine hydroxyethylphenylalcohols which bear hydroxy protecting
30 groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine hydroxyethylphenylalcohols.

35 34. A process for preparing a compound of the formula wherein

R_1 represents hydrogen or hydroxy;

R_2 represents hydrogen; or

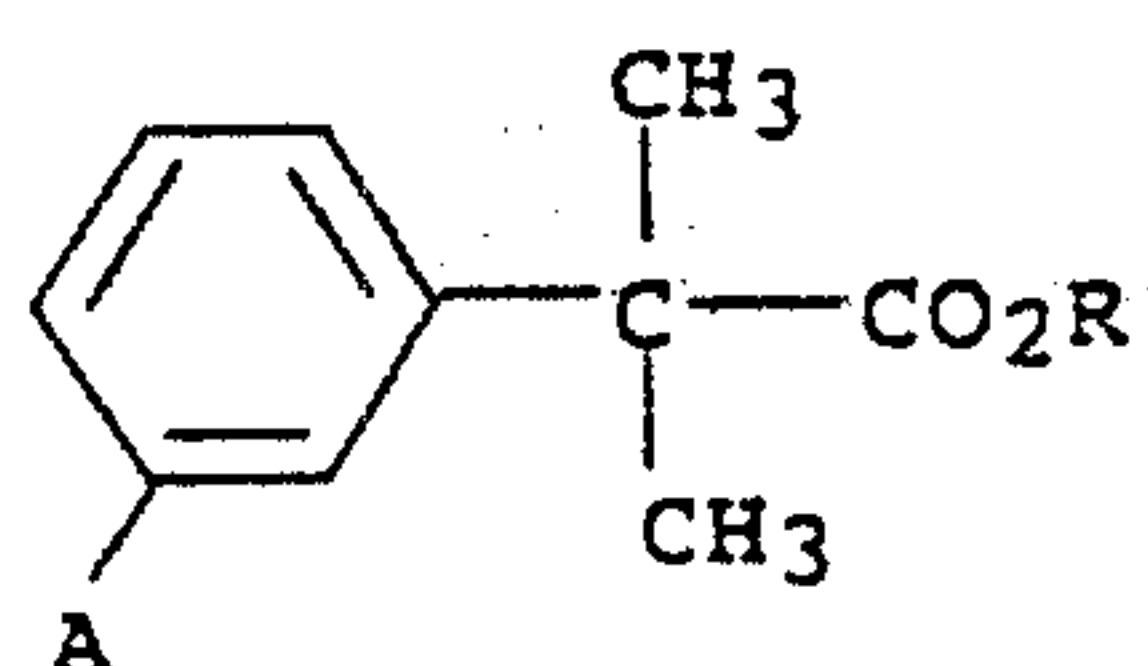
-185-



15 R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;
 R_3 is $-\text{COOH}$ or $-\text{COOalkyl}$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;
 A is hydrogen or hydroxy; and
 20 pharmaceutically acceptable salts thereof comprising the steps of:

(a) reacting a benzeneacetic acid compound of the formula

25



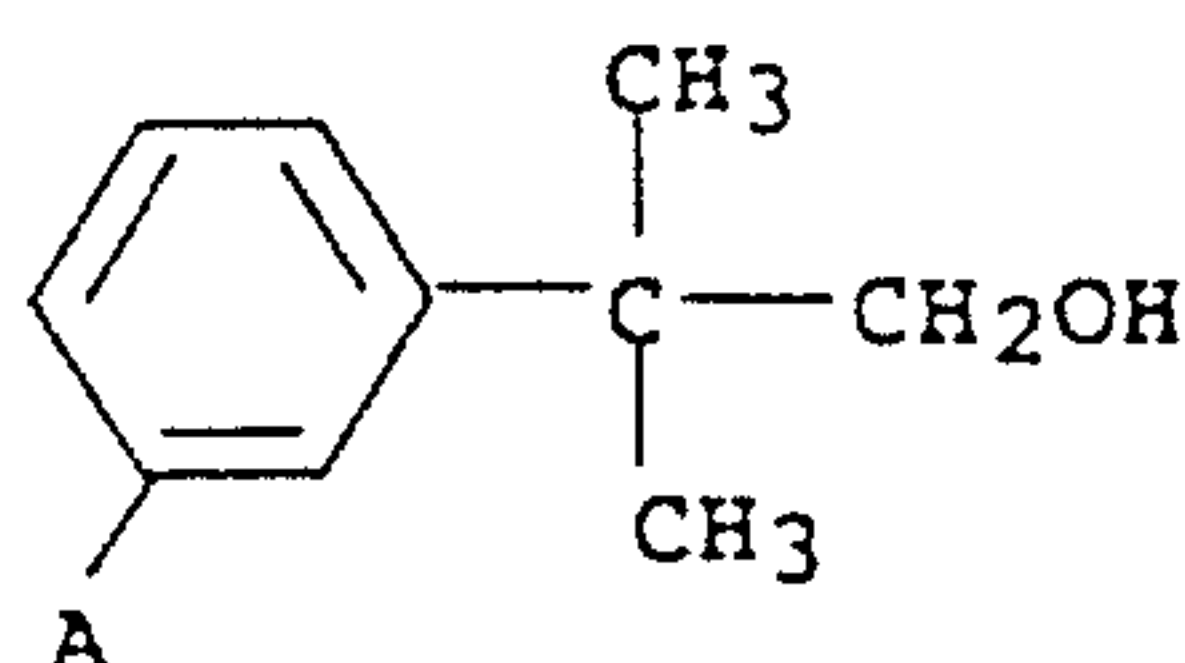
30

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and R is hydrogen or $\text{C}_1\text{-C}_6$ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride,
 35 diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

AMENDED SHEET

-186-

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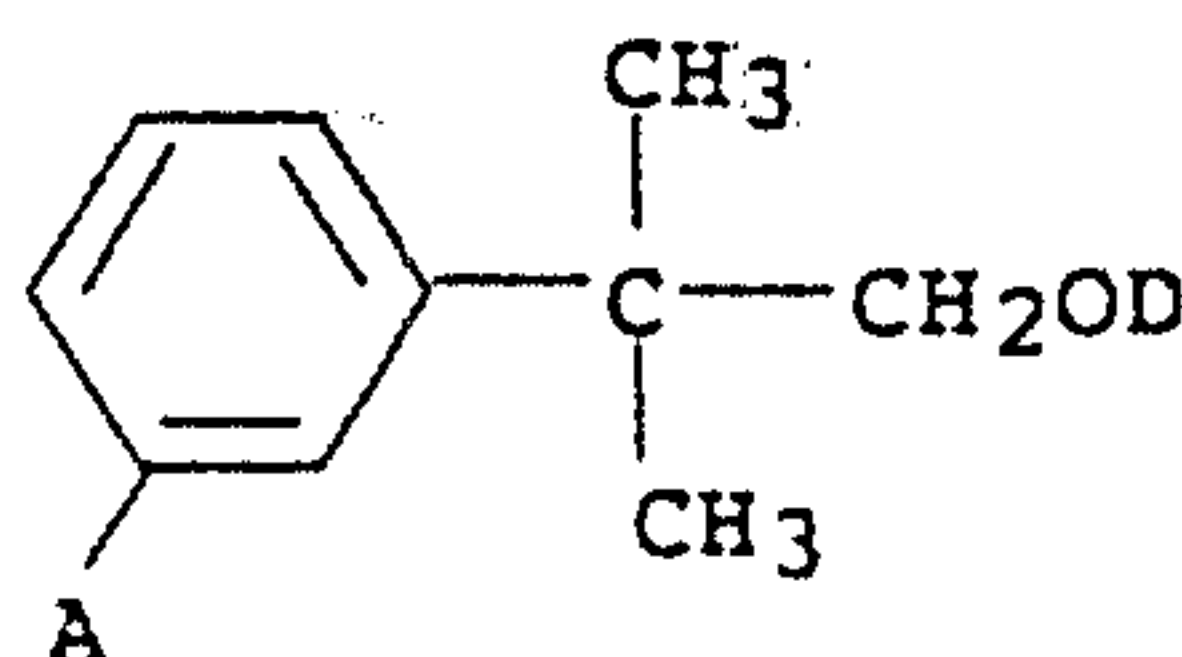
10

wherein A is hydrogen or hydroxy, with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

15

(b) reacting the phenethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

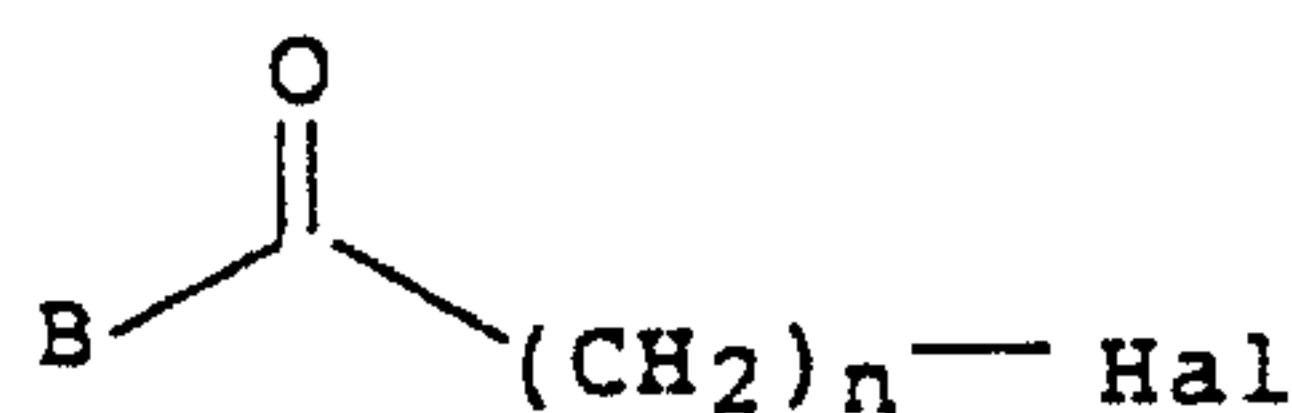
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25

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is C(=O)CH₃ or C(=O)C₆H₅;

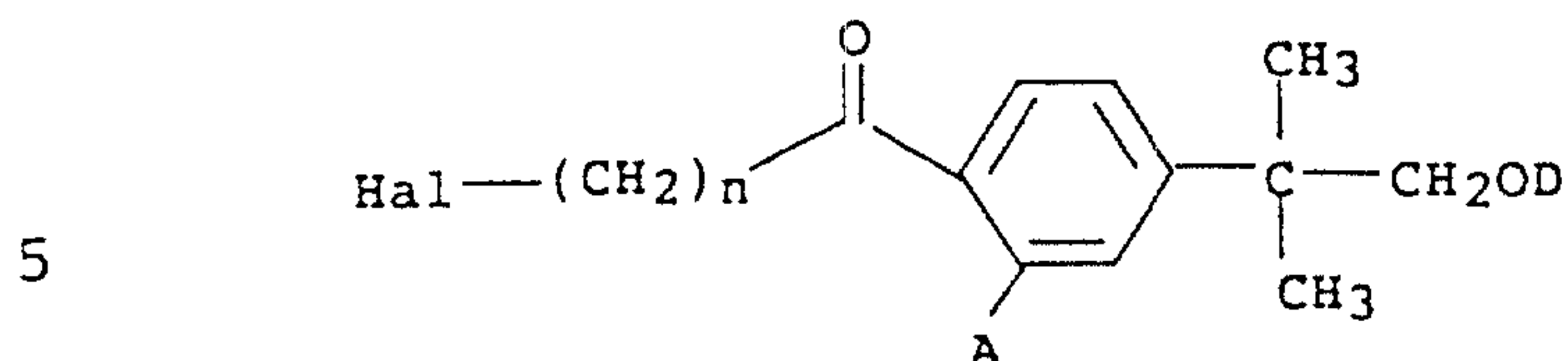
30



35

wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula

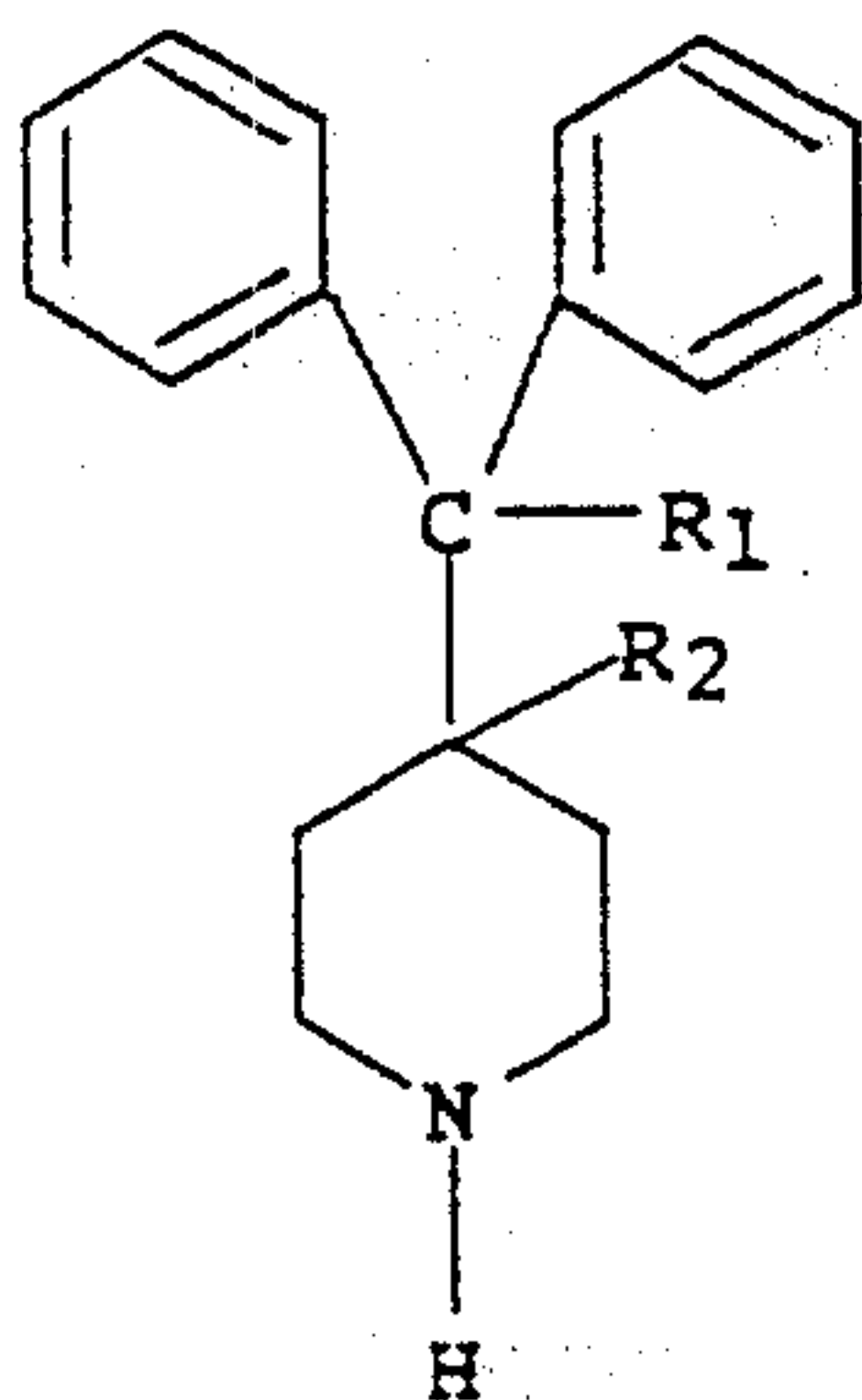
-187-



wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

15



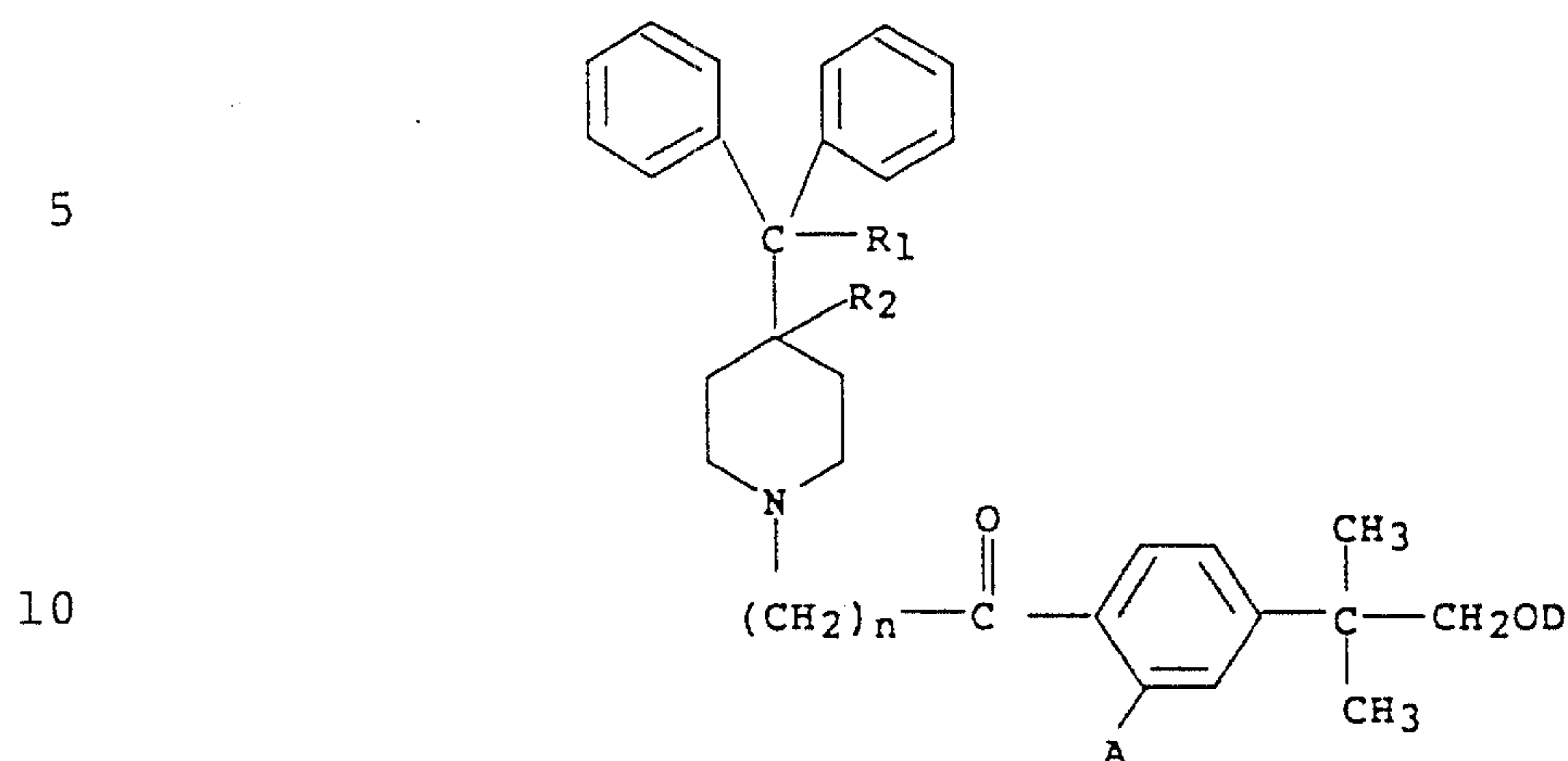
20

25 wherein R₁ and R₂ are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylketone of the formula

30

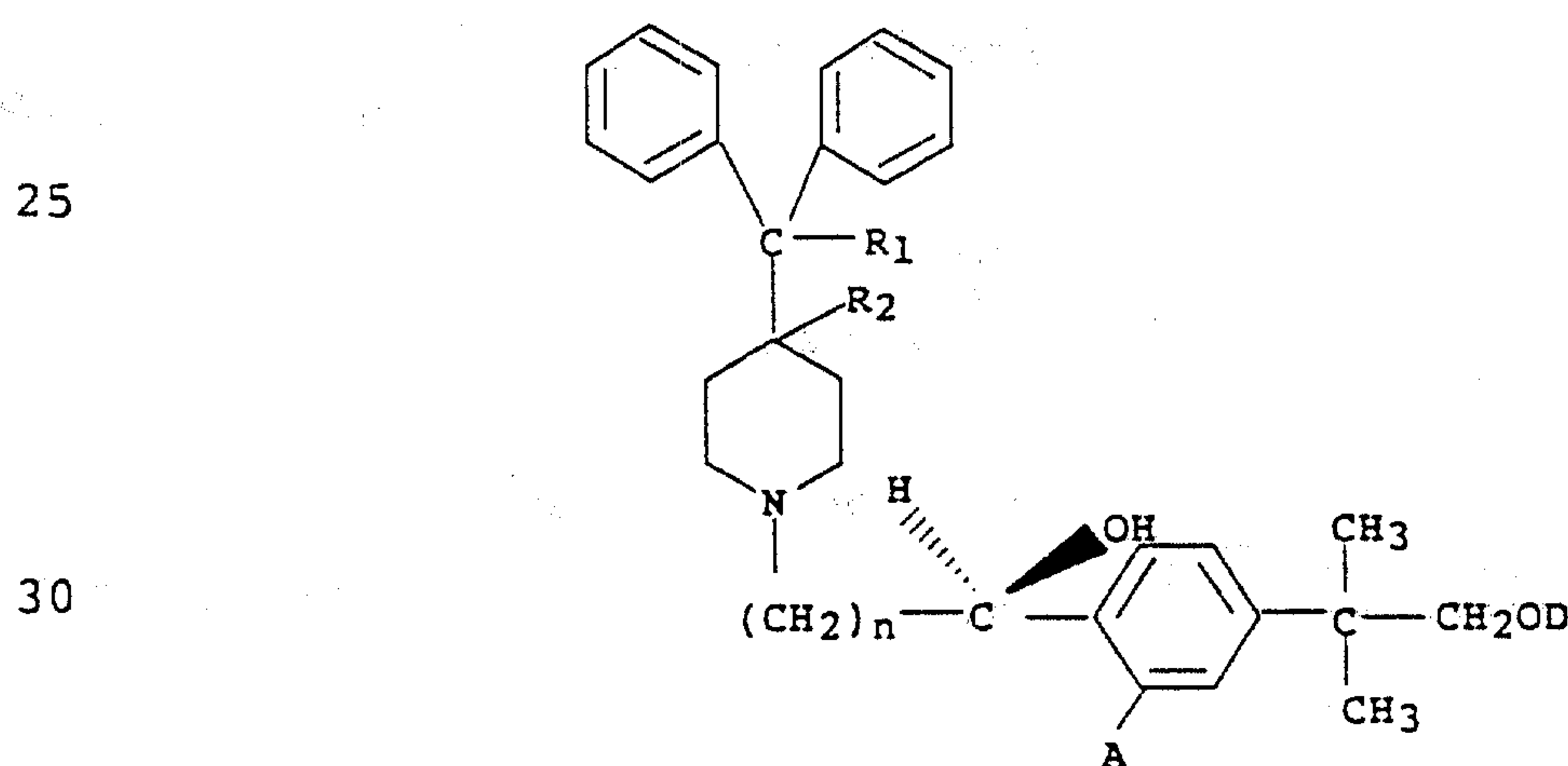
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-188-



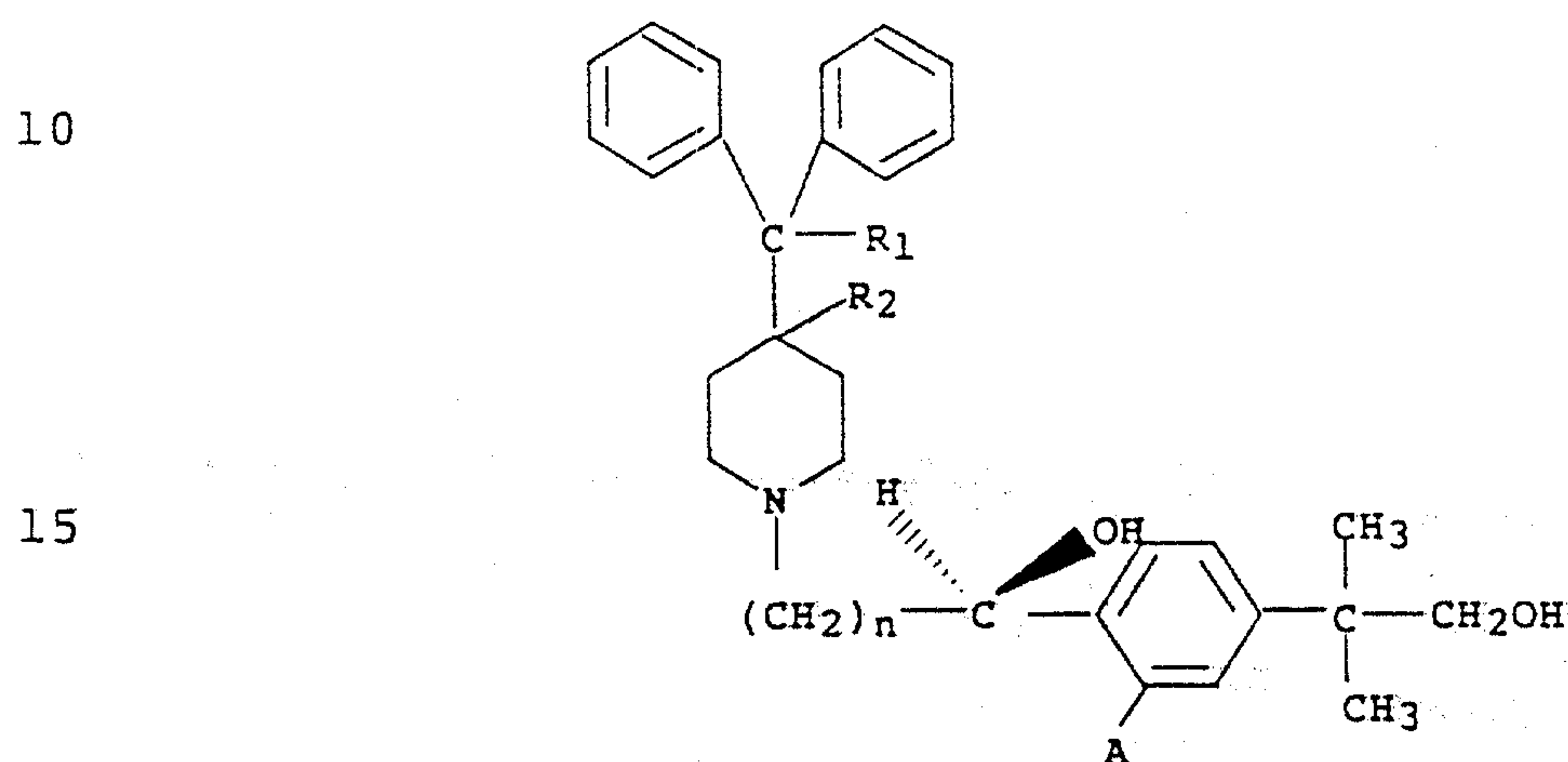
wherein R_1 , R_2 , n and D are defined above and A is hydrogen
 15 or hydroxy with the proviso that when A is hydroxy, A may
 be optionally protected or unprotected;

(e) reacting the piperidine protected
 hydroxyethylphenylketone with (+)-B-
 20 chlorodiisopinocampheylborane to produce a piperidine
 protected hydroxyethylphenylalcohol of the formula



wherein R_1 , R_2 , D and n are defined above and A is hydrogen
 35 or hydroxy with the proviso that when A is hydroxy, A may
 be optionally protected or unprotected;

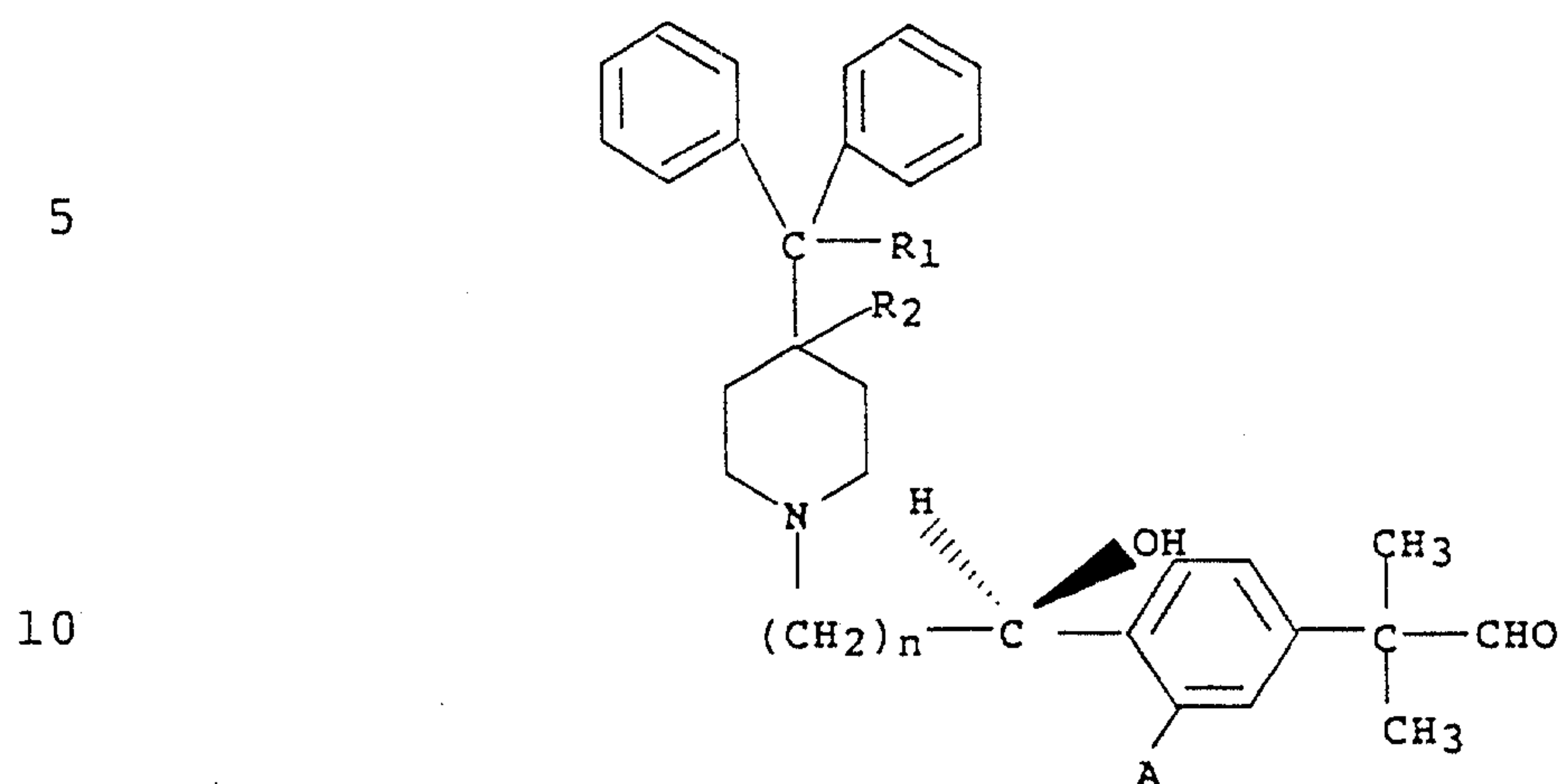
(f) reacting the piperidine protected hydroxyethylphenylalcohol with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylalcohol of the formula



20 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

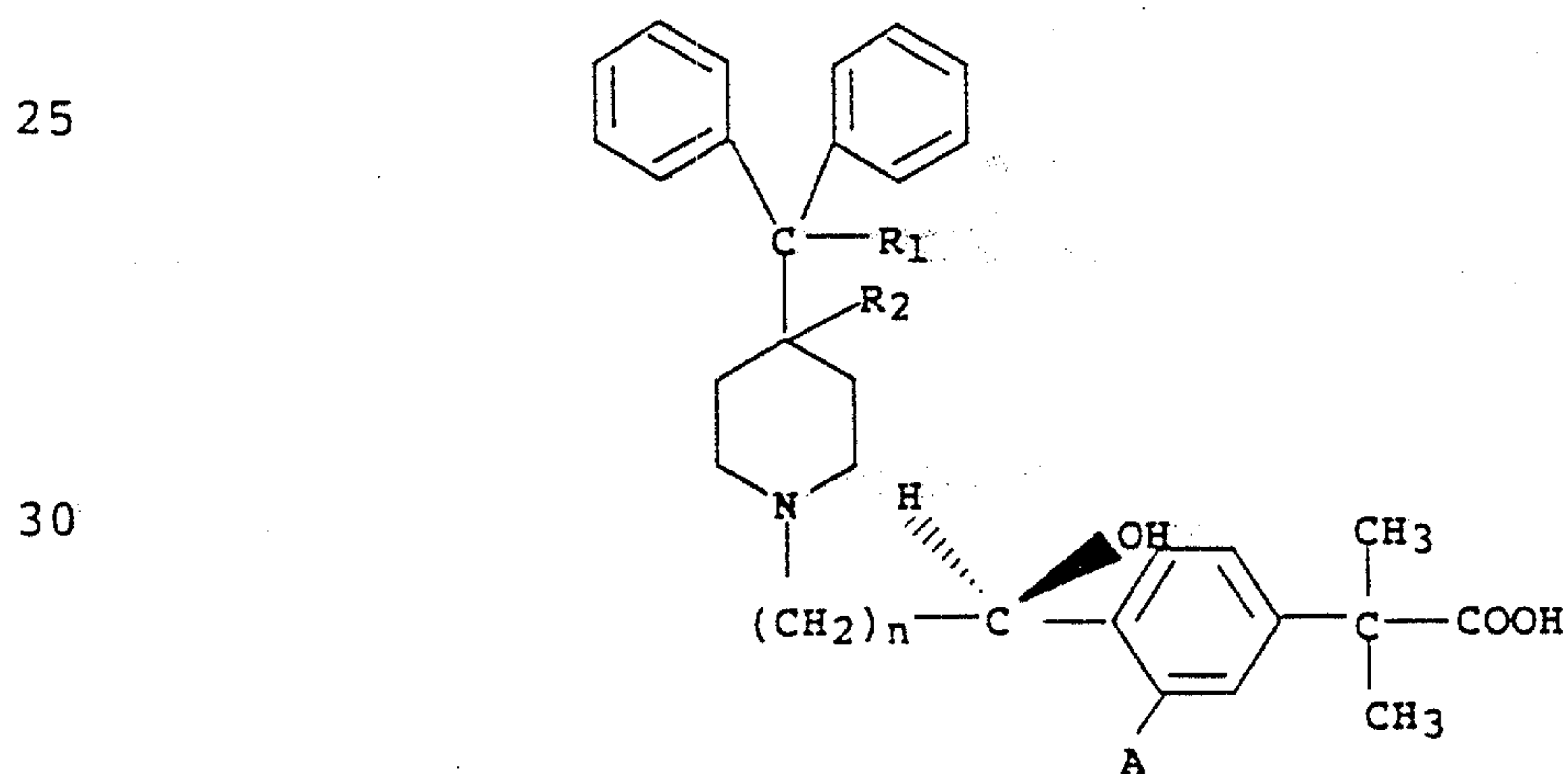
(g) reacting the piperidine hydroxyethylphenylalcohol with dimethyl sulfoxide, oxalyl chloride and triethylamine or with Dess-Martin reagent, chromium (IV) oxide, nickel peroxide, sodium dichromate, potassium dichromate, t-butyl chromate, silver oxide, argentic picolinate manganese dioxide lead tetraacetate, dicyclohexylcarbodiimide, 2,3-dichloro-5,6-dicyanoquinone, tetrachloro-1,2-benzoquinone, 2,2,6,6-tetramethylpiperidiny-1-oxyl (TEMPO) or quinolinium chlorochromate to produce a piperidine formylphenylalcohol of the formula

-190-



15 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

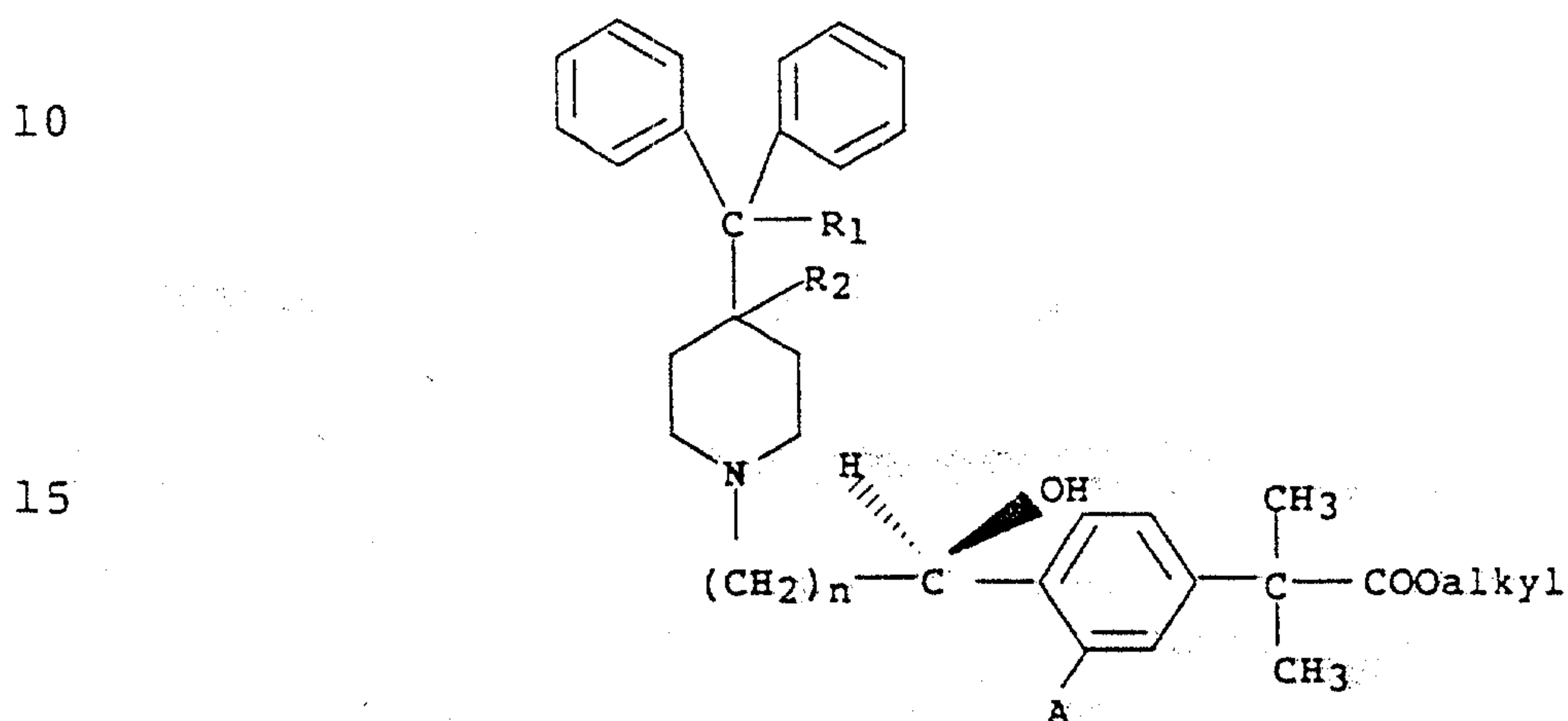
20 (h) reacting the piperidine formylphenylalcohol with potassium permanganate, chromium (IV) oxide, silver (I) oxide, silver oxide, argentic picolinate, peroxide, nitric acid, m-chloroperbenzoic acid and peracetic acid to produce a piperidine carboxyphenylalcohol of the formula



35 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

-191-

- (i) optionally reacting the piperidine carboxyphenylalcohol with diazomethane or 2,2-dimethoxypropane or with thionyl chloride followed by an alcohol of the formula HOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched to form a piperidine carboxyphenylalcohol ester of the formula



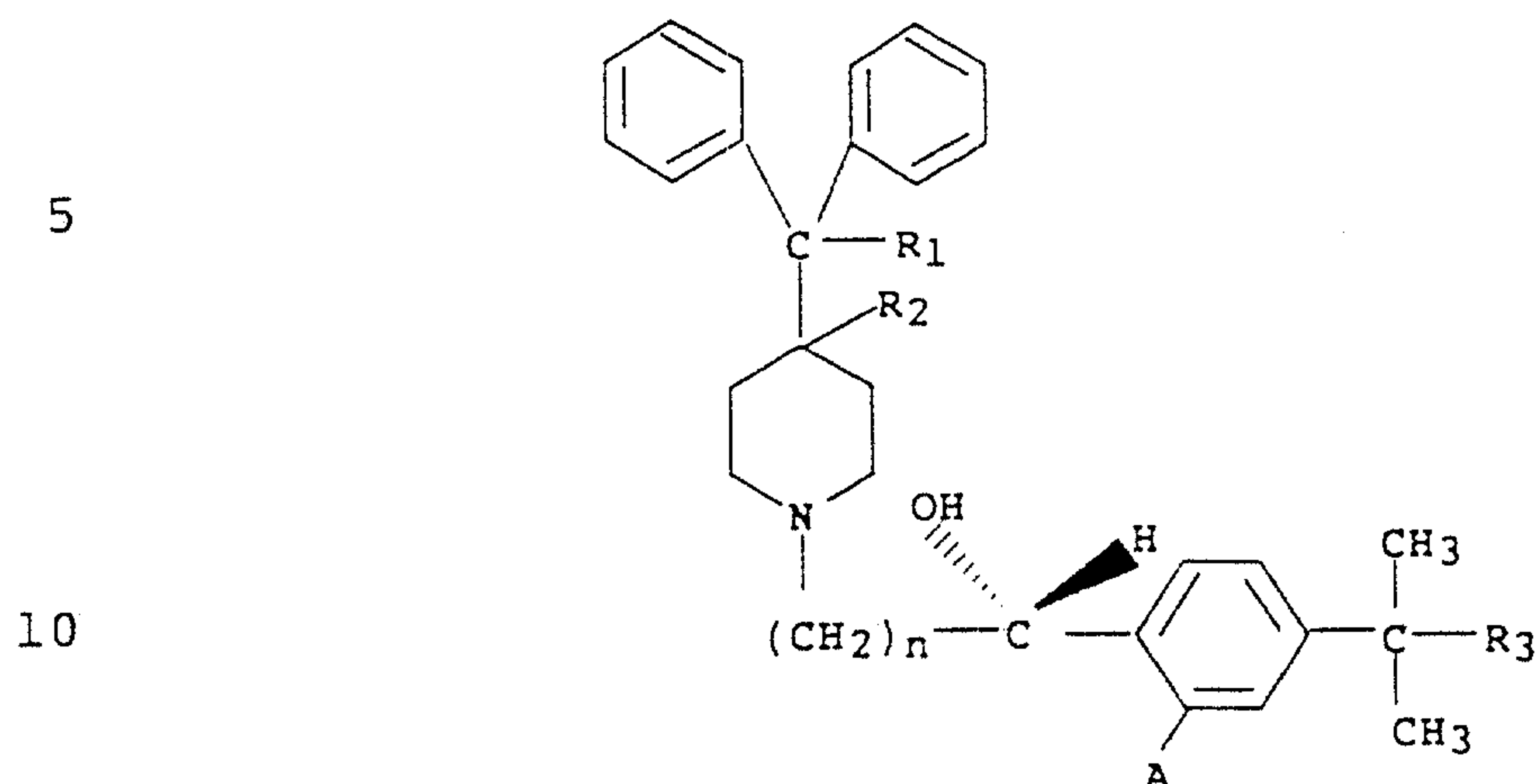
- 20 wherein R₁, R₂, n and alkyl are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected; and

- (j) optionally reacting the piperidine carboxyphenylalcohols or the piperidine carboxyphenylalcohol esters which bear hydroxy protecting groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine carboxyphenylalcohols or the piperidine carboxyphenylalcohol esters.

35. A process for preparing a compound of the formula

35

-192-



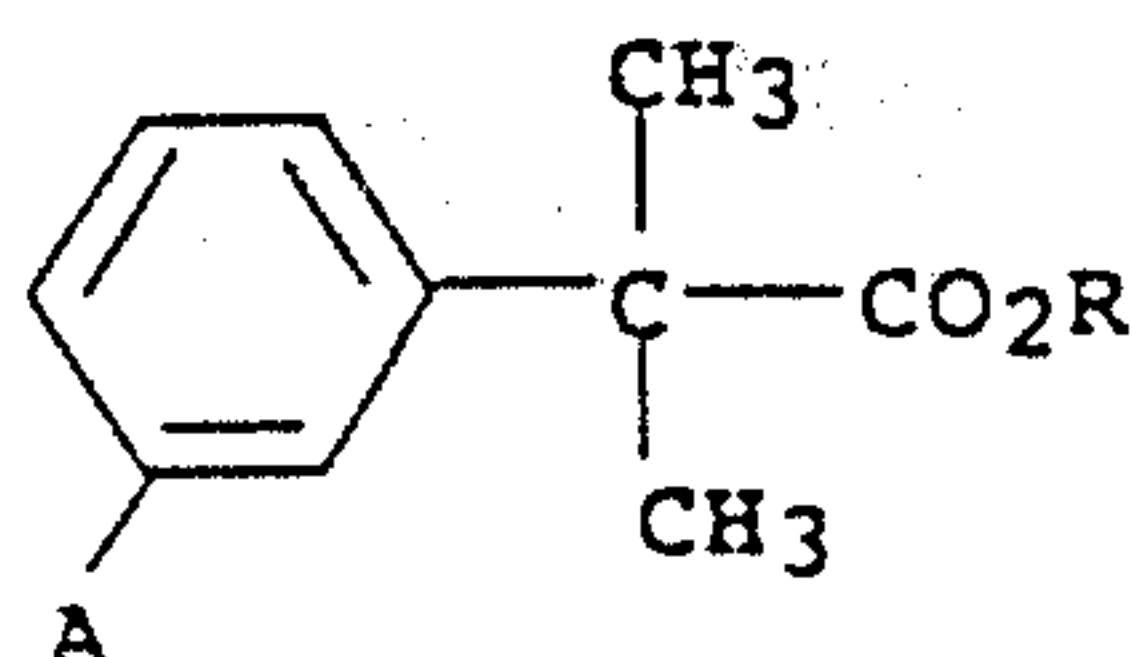
wherein

- 15 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the
carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;
20 R_3 is $-\text{COOH}$ or $-\text{COOalkyl}$ wherein the alkyl moiety has
from 1 to 6 carbon atoms and is straight or branched;
 A is hydrogen or hydroxy; and
pharmaceutically acceptable salts thereof comprising
the steps of:

25

- (a) reacting a benzeneacetic acid compound of the
formula

30



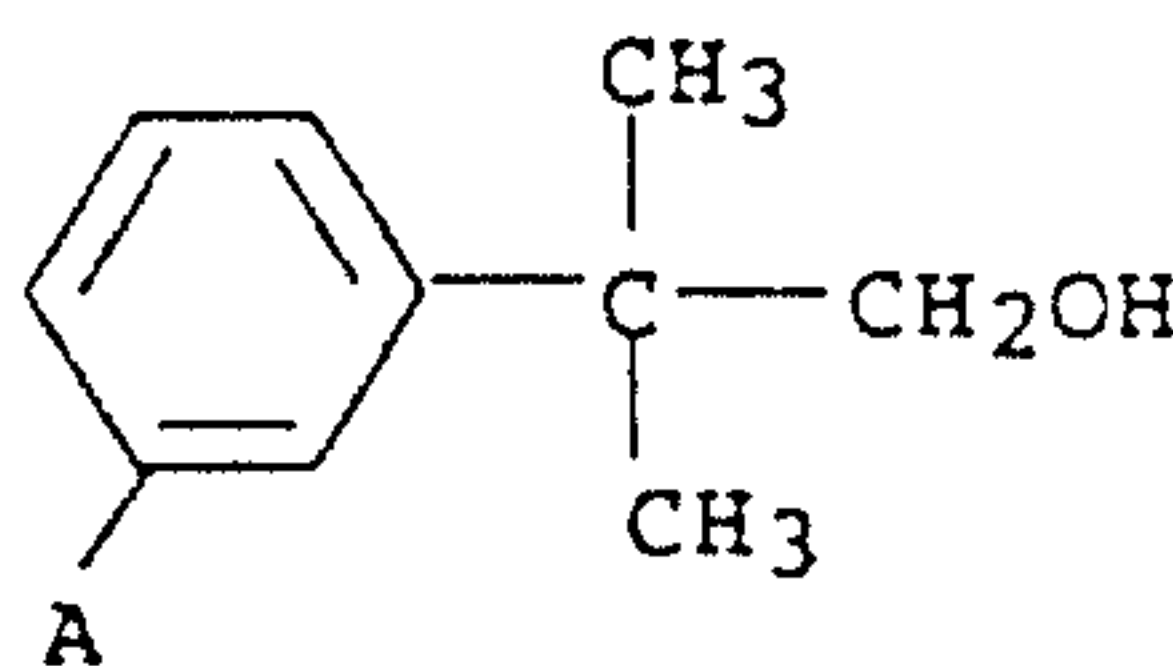
35

wherein A is hydrogen or hydroxy with the proviso that when
 A is hydroxy, A may be optionally protected or unprotected
and R is hydrogen or $\text{C}_1\text{-C}_6$ alkyl with sodium bis(2-
methoxyethoxy)aluminum hydride, lithium aluminum hydride,
diborane, lithium borohydride, lithium triethylborohydride

-193-

and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula

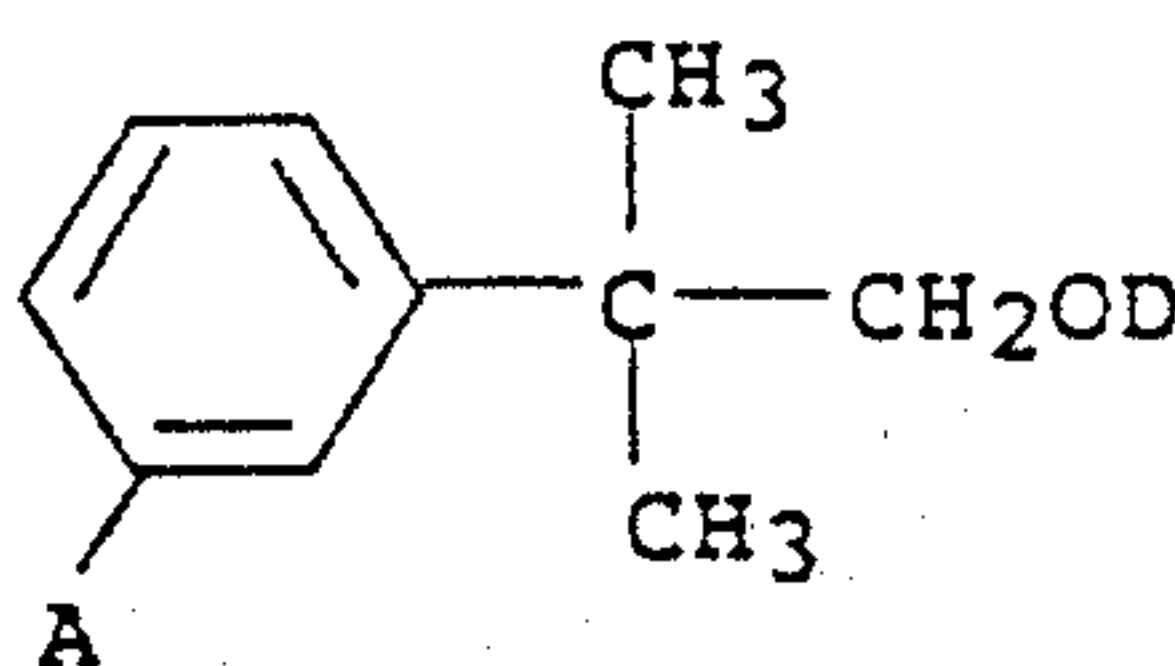
5



10 wherein A is hydrogen or hydroxy, with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

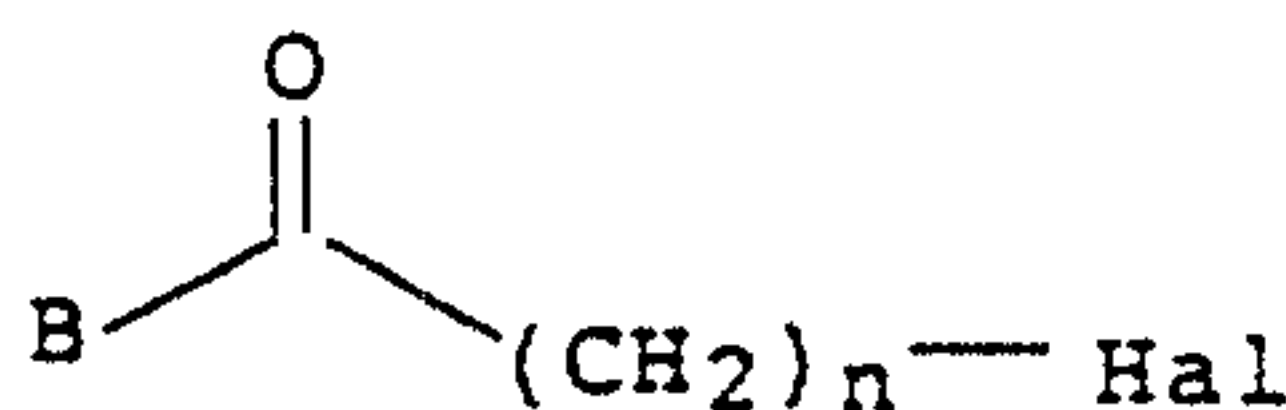
15 (b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

20



25 wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected and D is C(=O)CH₃ or C(=O)C₆H₅;

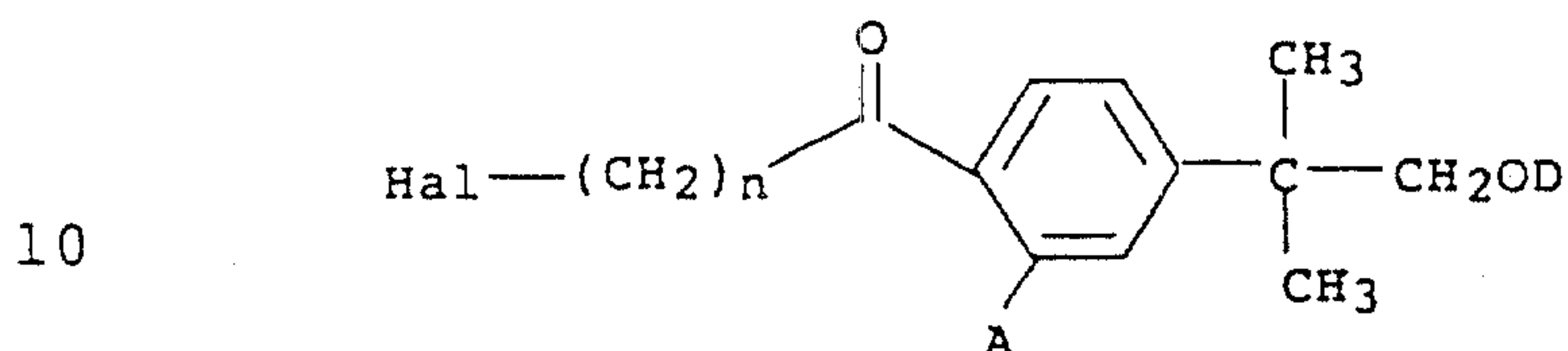
30 (c) reacting the protected phenethyl alcohol with a ω-halo compound of the formula



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-194-

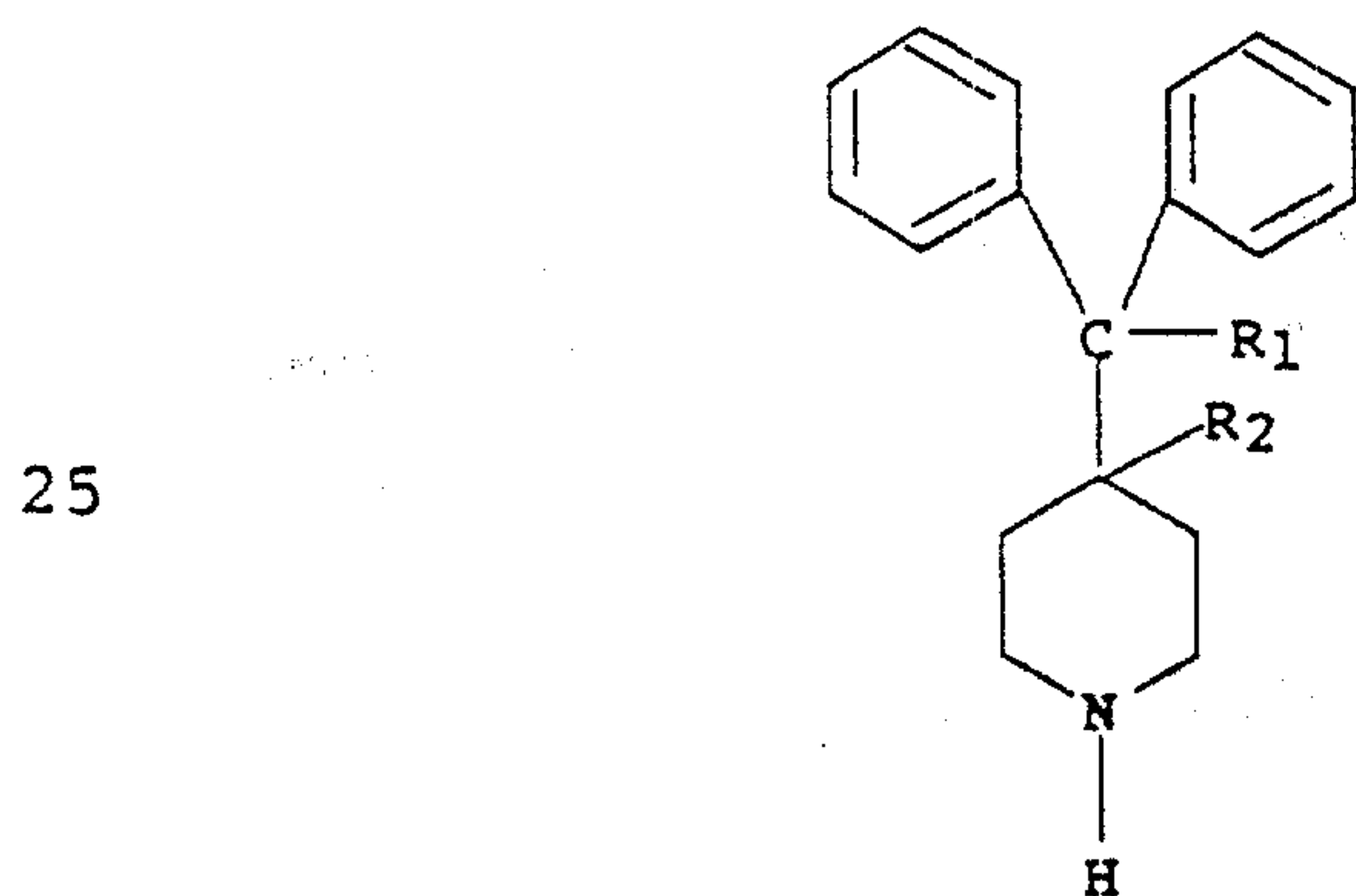
wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula



15 wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula

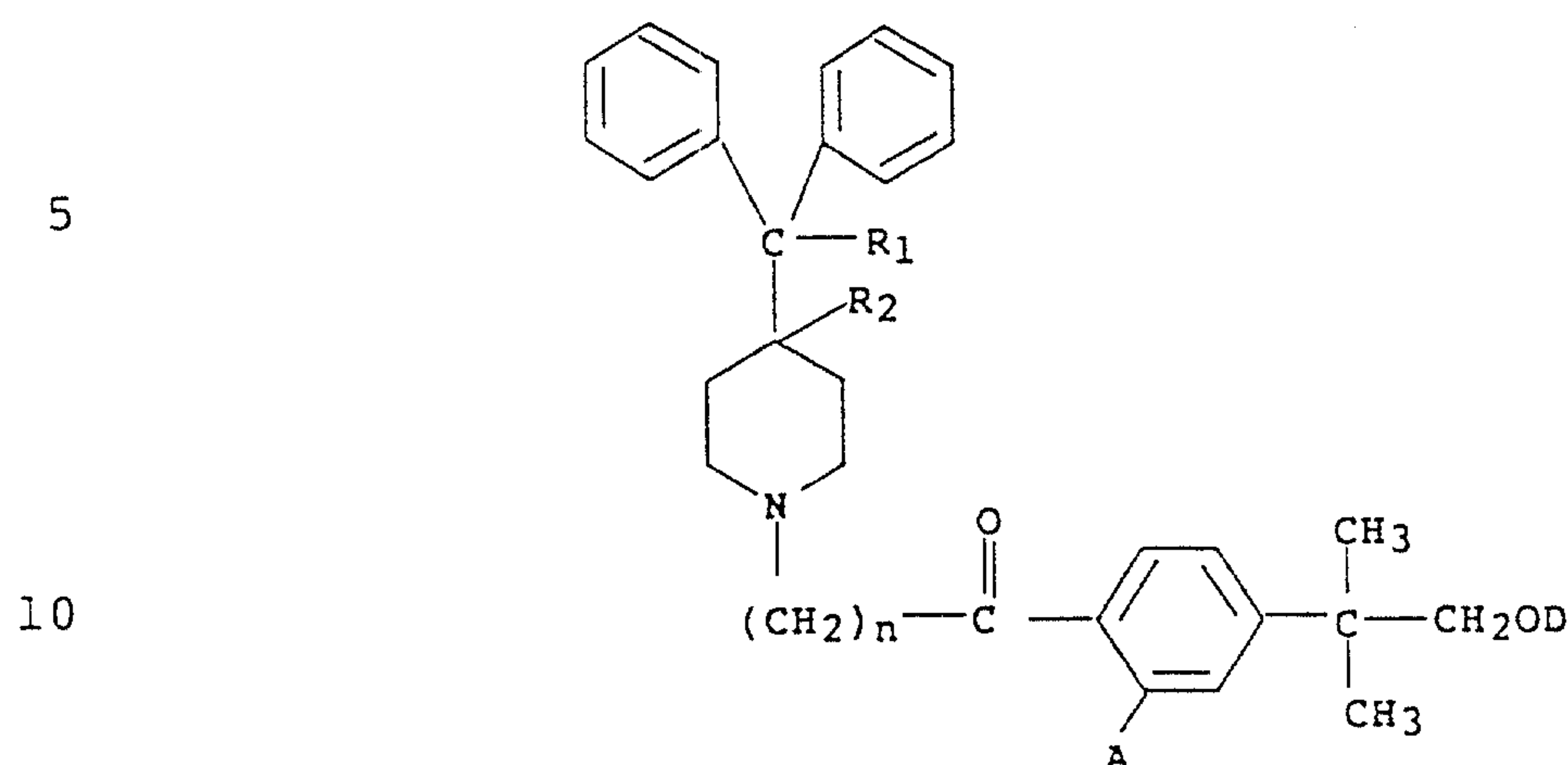
20



30 wherein R₁ and R₂ are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine protected hydroxyethylphenylketone of the formula

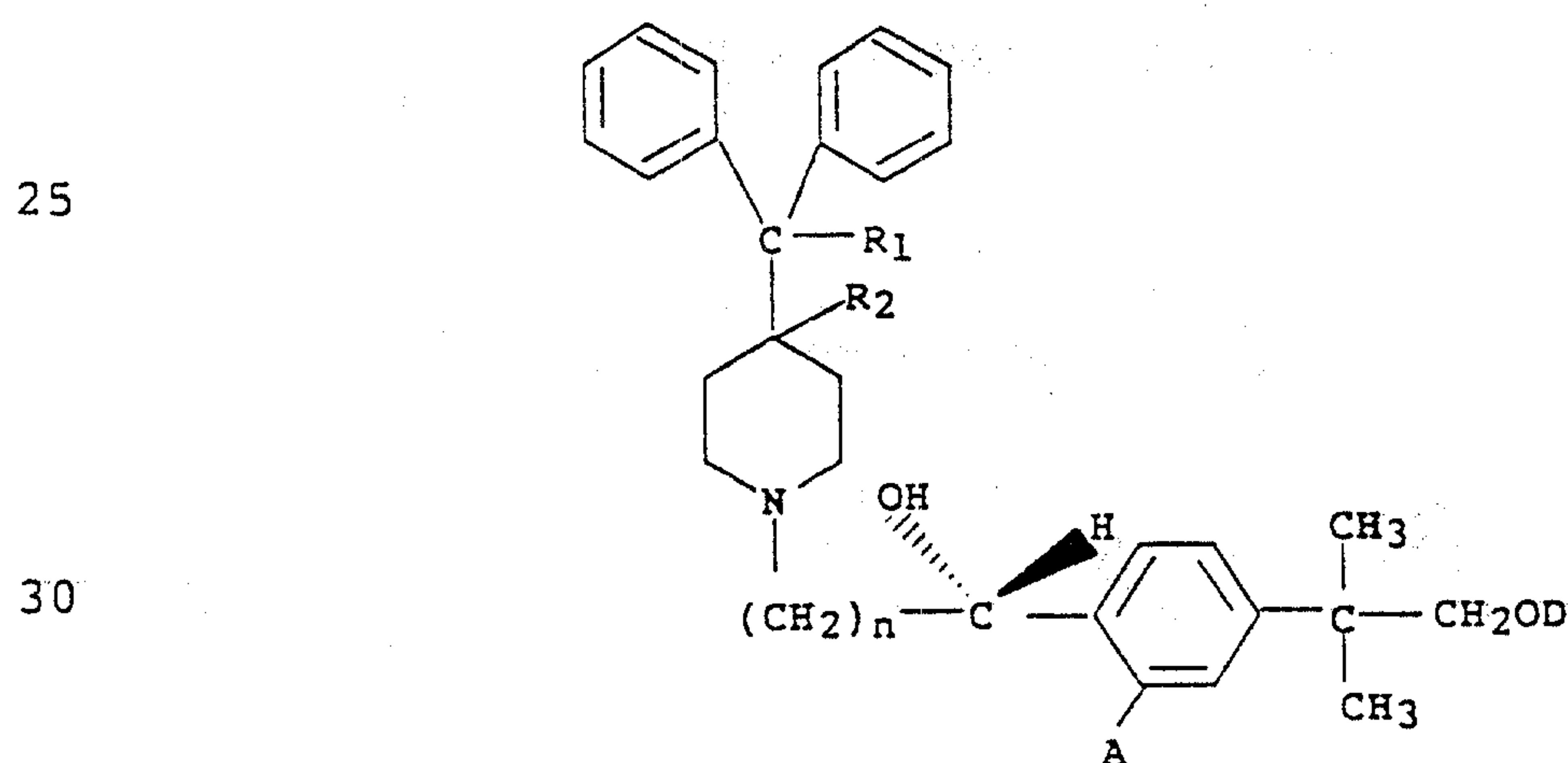
35

-195-



15 wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

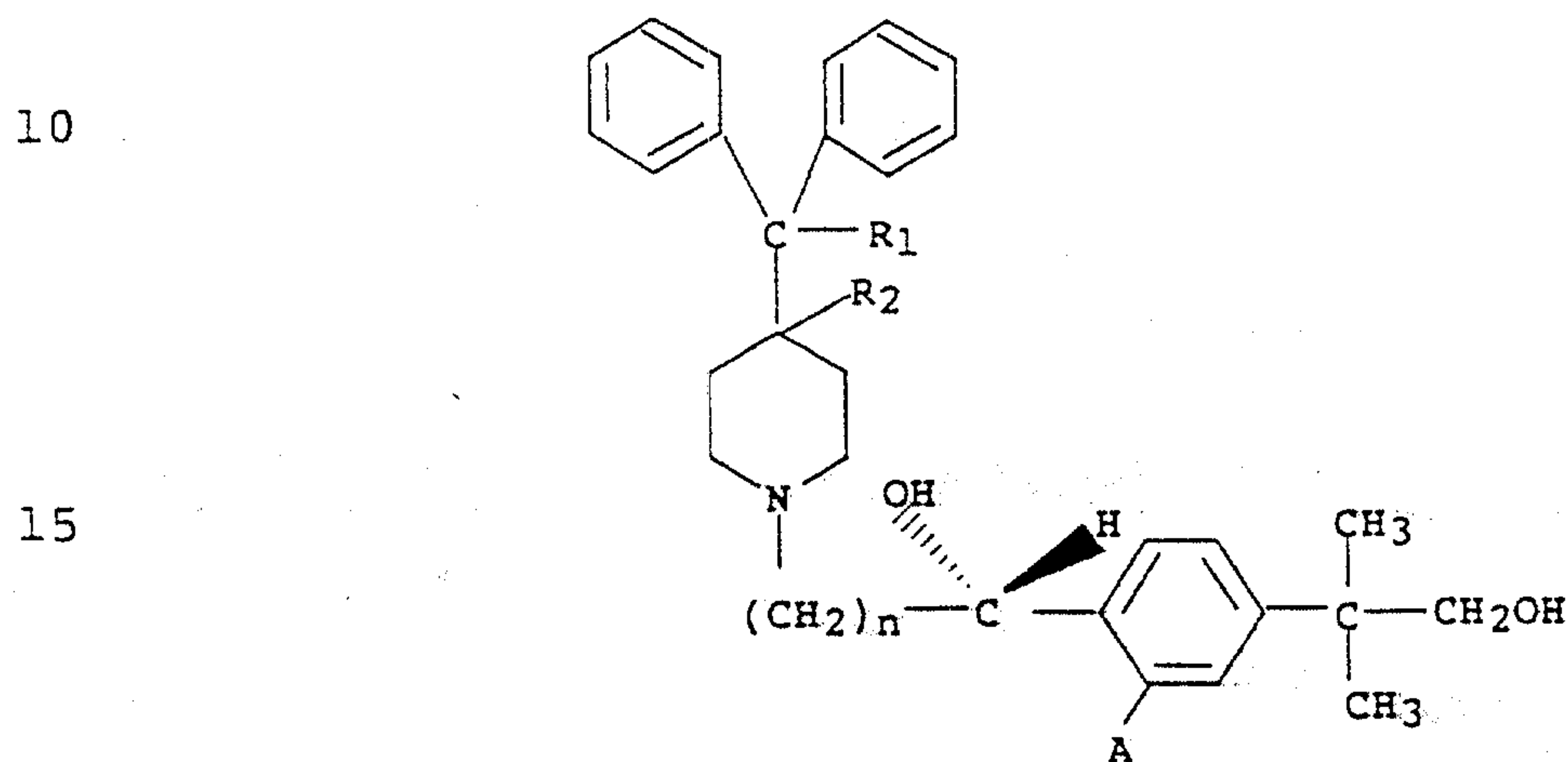
(e) reacting the piperidine protected hydroxyethylphenylketone with $(-)-B-$ chlorodiisopinocampheylborane to produce a piperidine protected hydroxyethylphenylalcohol of the formula



35 wherein R_1 , R_2 , D and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

-196-

(f) reacting the piperidine protected hydroxyethylphenylalcohol with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce a piperidine hydroxyethylphenylalcohol of the formula

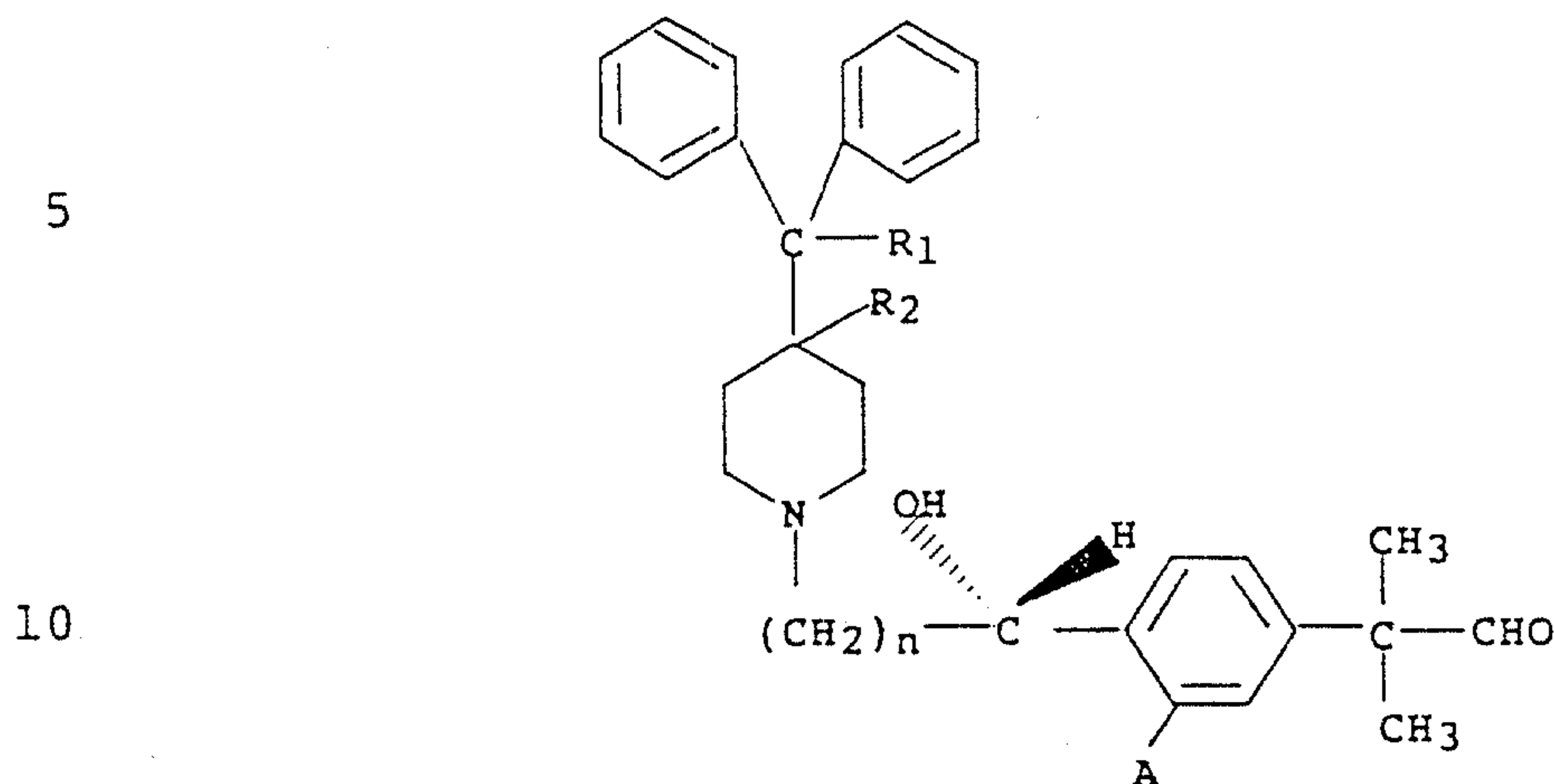


20 wherein R₁, R₂ and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

(g) reacting the piperidine hydroxyethylphenylalcohol with dimethyl sulfoxide, oxyalyl chloride and triethylamine or with Dess-Martin reagent, chromium (IV) oxide, nickel peroxide, sodium dichromate, potassium dichromate, t-butyl chromate, silver oxide, argentic picolinate manganese dioxide lead tetraacetate, dicyclohexylcarbodiimide, 2,3-dichloro-5,6-dicyanoquinone, tetrachloro-1,2-benzoquinone, 2,2,6,6-tetramethylpiperidiny-1-oxy (TEMPO) or quinolinium chlorochromate to produce a piperidine formylphenylalcohol of the formula

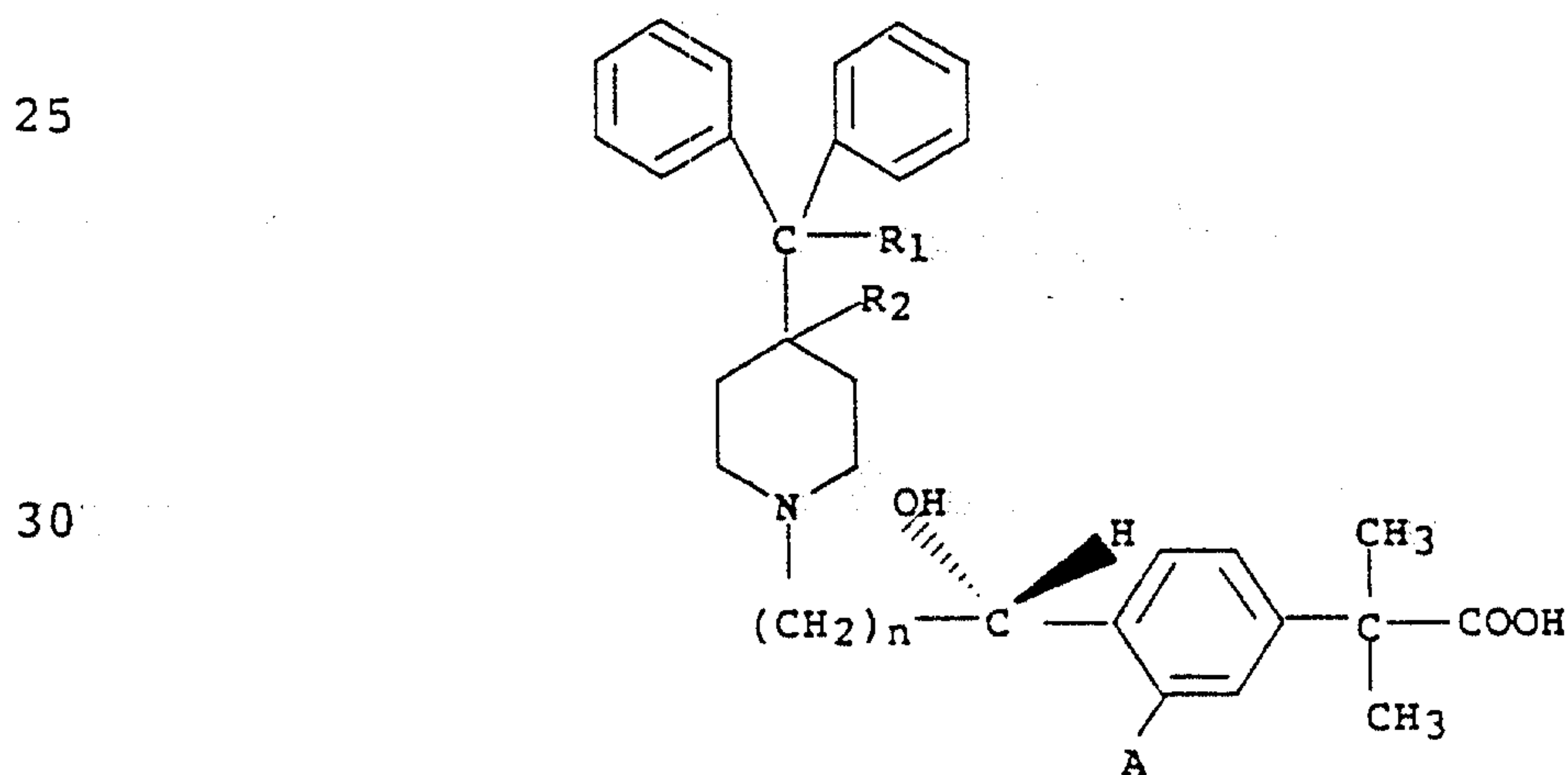
35

-197-



15 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

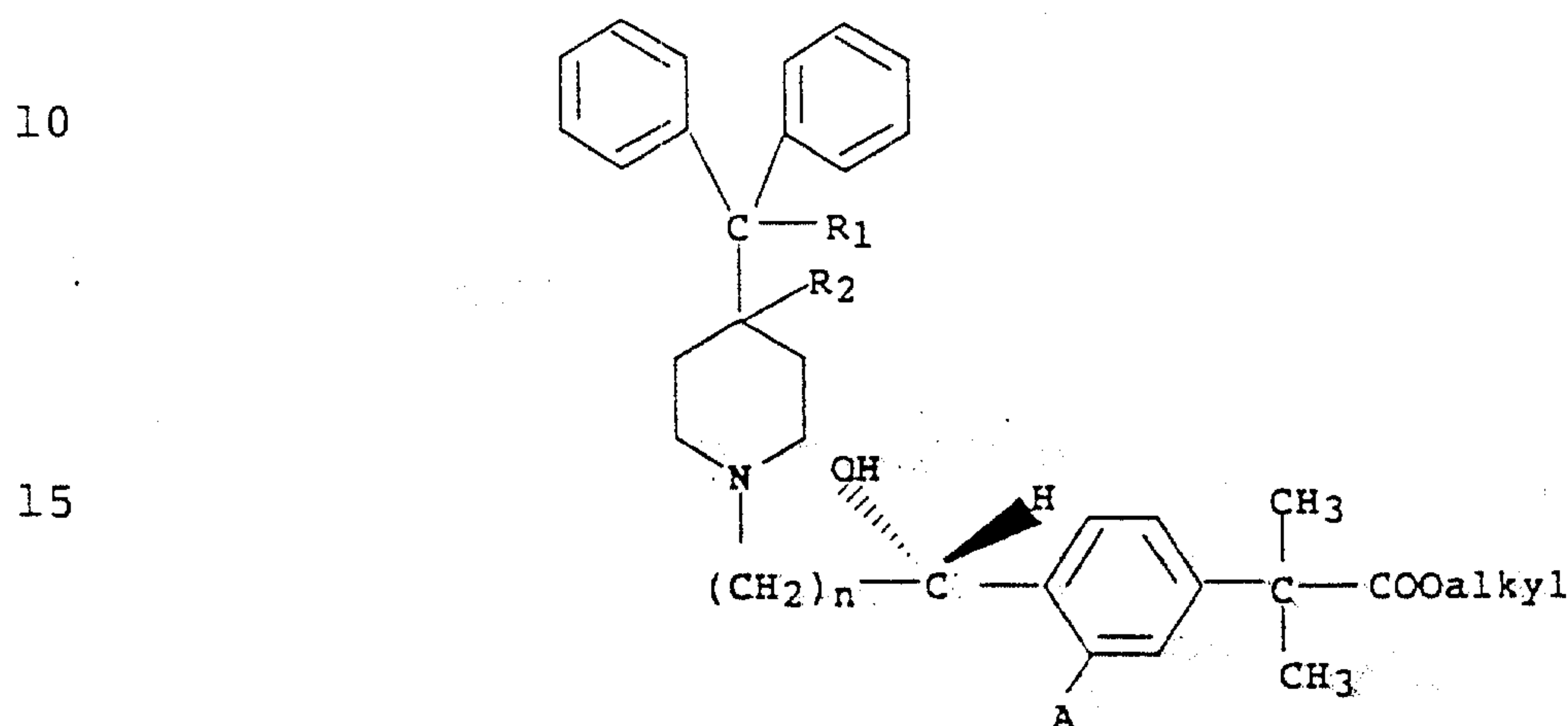
(h) reacting the piperidine formylphenylalcohol with potassium permanganate, chromium (IV) oxide, silver (I) oxide, silver oxide, argentic picolinate, peroxide, nitric acid, m-chloroperbenzoic acid and peracetic acid to produce a piperidine carboxyphenylalcohol of the formula



35 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or unprotected;

-198-

- (i) optionally reacting the piperidine carboxyphenylalcohol with diazomethane or 2,2-dimethoxypropane or with thionyl chloride followed by an alcohol of the formula HOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched to form a piperidine carboxyphenylalcohol ester of the formula

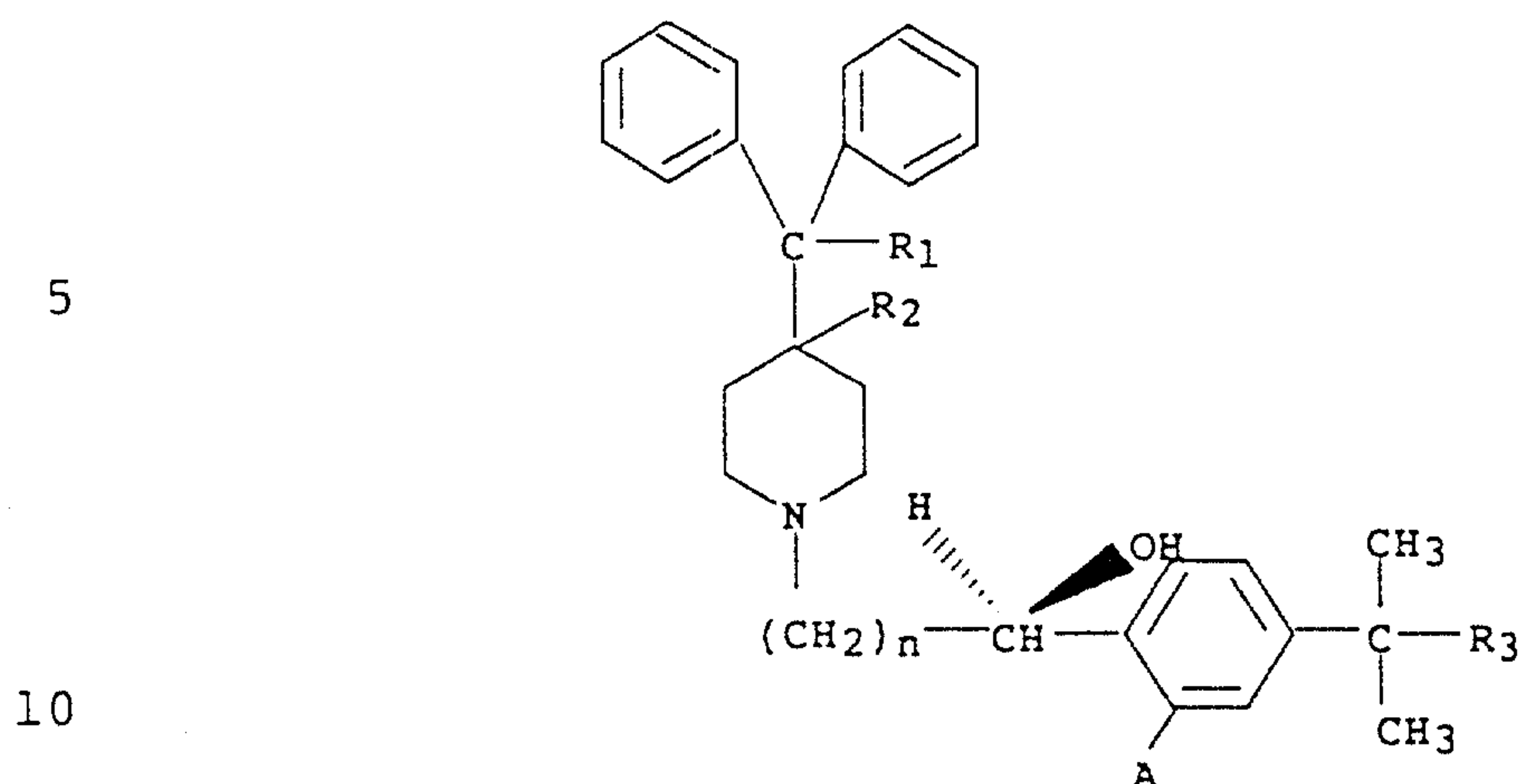


- (j) optionally reacting the piperidine carboxyphenylalcohols or the piperidine carboxyphenylalcohol esters which bear hydroxy protecting groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine carboxyphenylalcohols or the piperidine carboxyphenylalcohol esters.

36. A process for preparing a compound of the formula

35

-199-



wherein

R₁ represents hydrogen or hydroxy;

R₂ represents hydrogen; or

15 R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;

n is an integer of from 1 to 5;

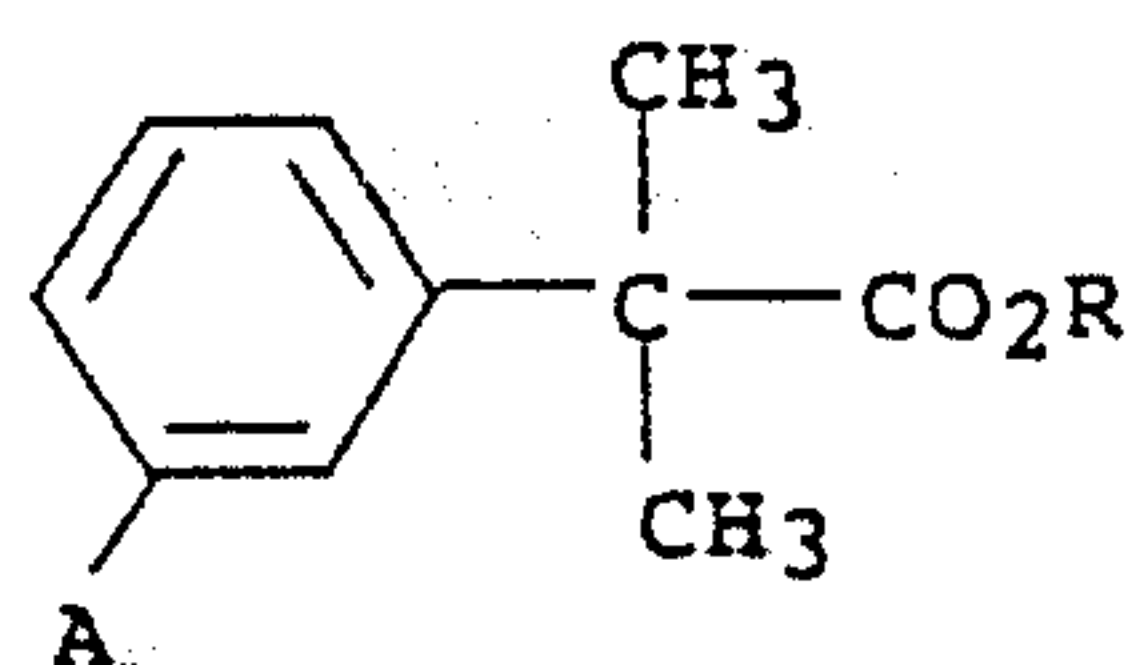
A is hydrogen or hydroxy;

R₃ is -CH₂OH; and

20 pharmaceutically acceptable salts thereof comprising the steps of:

(a) reacting a benzeneacetic acid compound of the formula

25

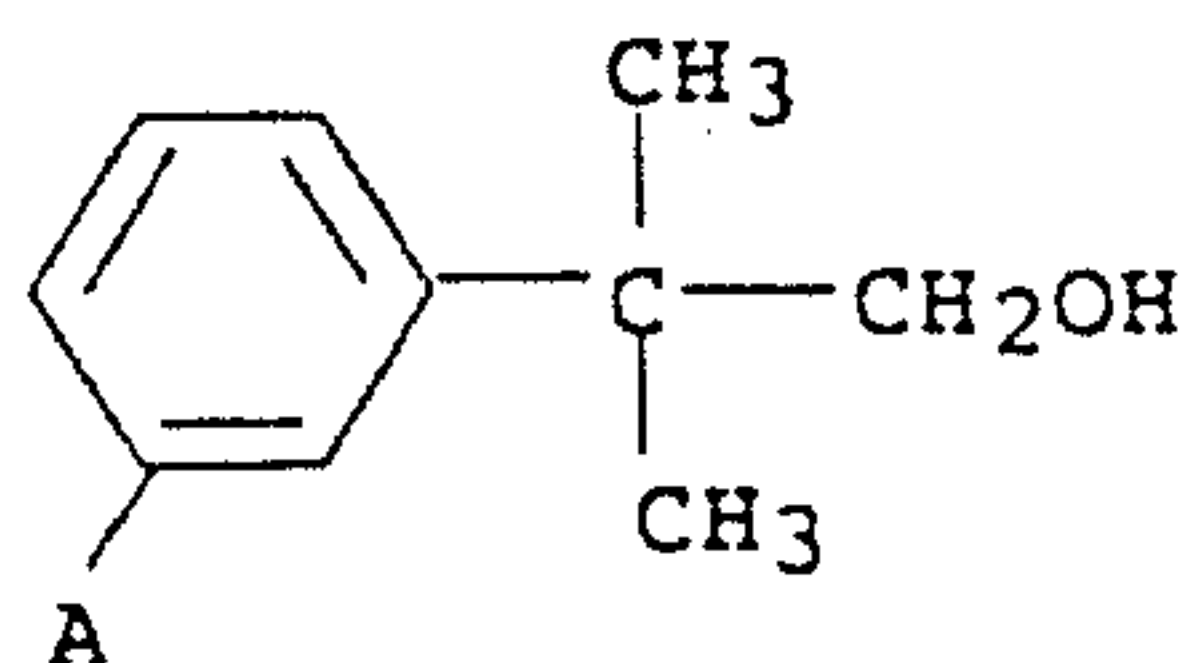


wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or deprotected and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, 35 diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula;

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-200-

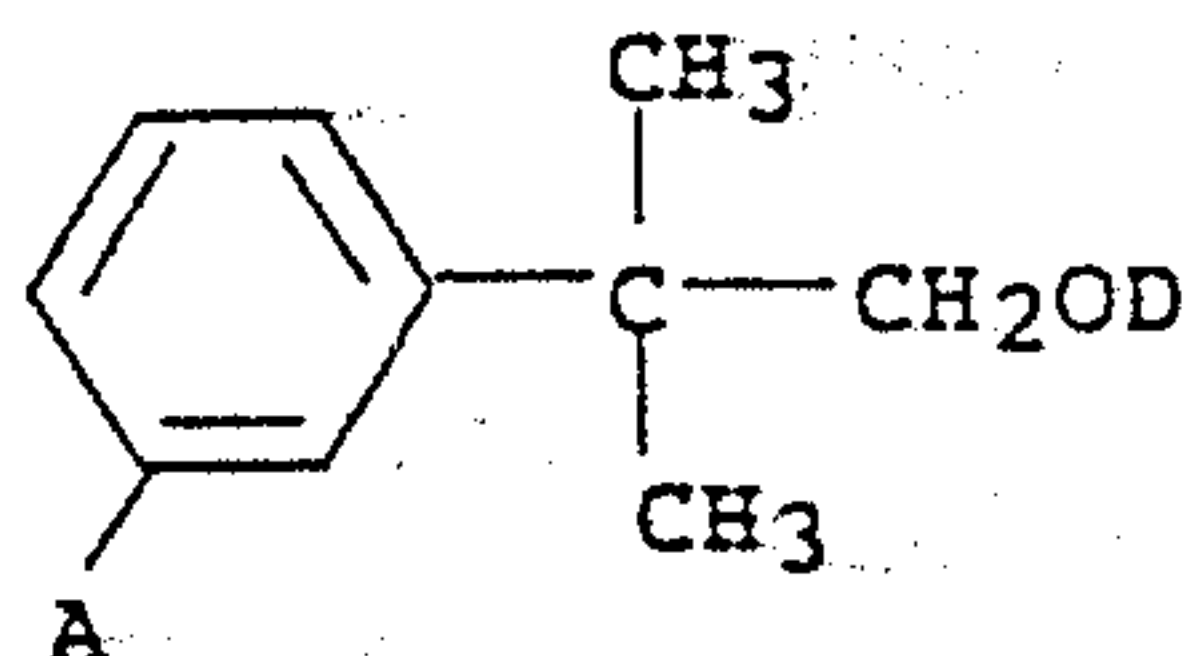
5



10

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

15

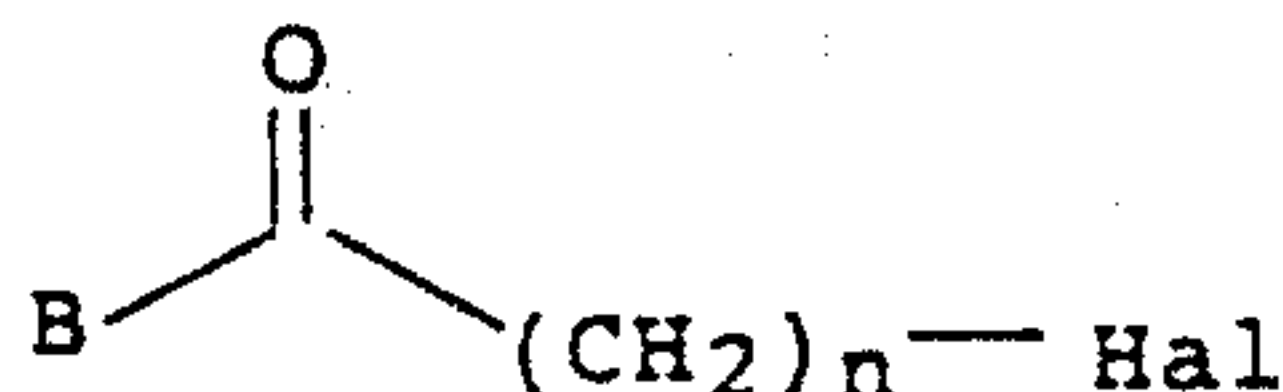


20

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or deprotected and D is C(=O)CH₃ or C(=O)C₆H₅;

25

(c) reacting the protected phenethyl alcohol with a ω-halo compound of the formula

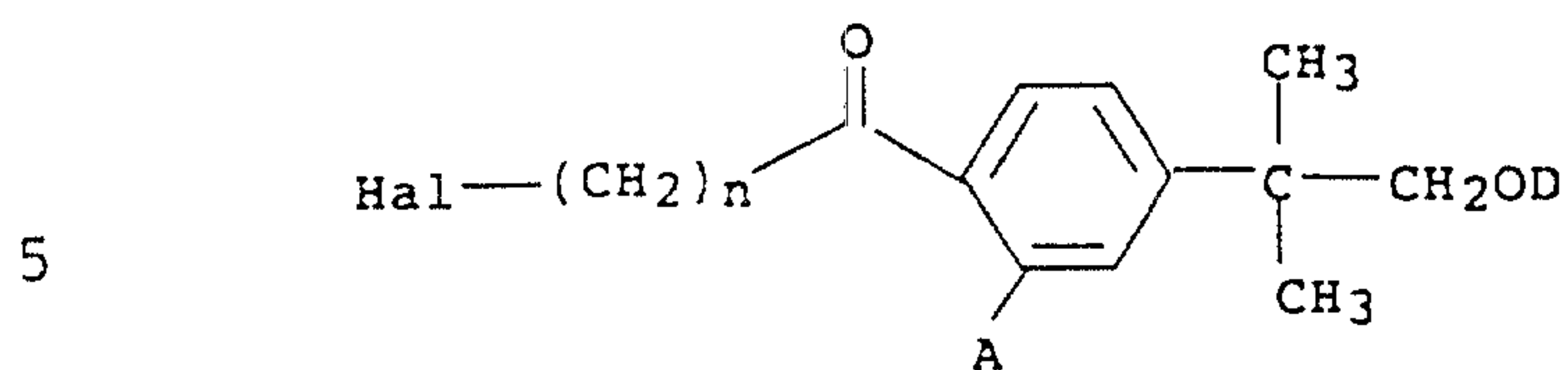


30

wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω-halo protected hydroxyethylphenylketone of the formula

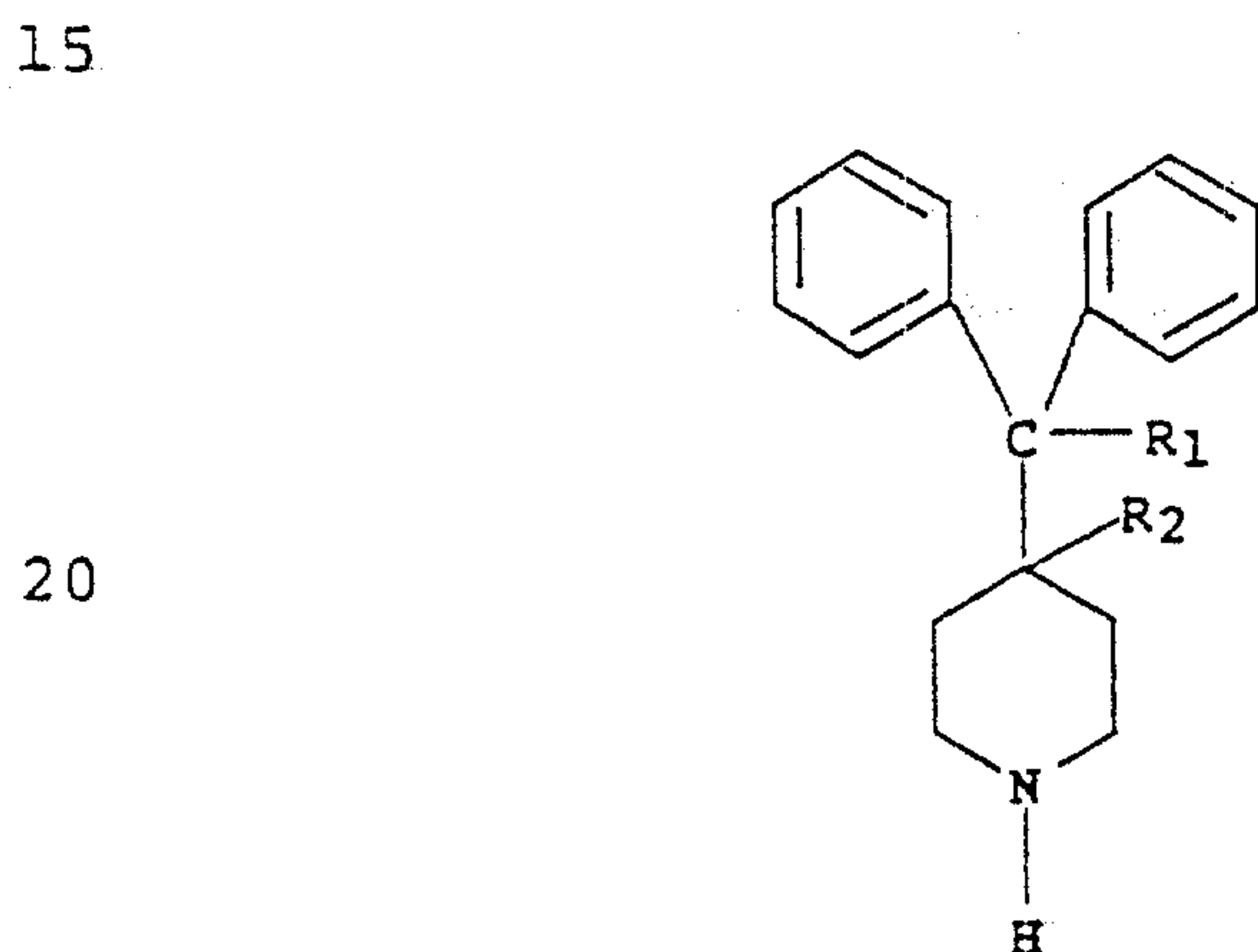
35

-201-



10 wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or deprotected;

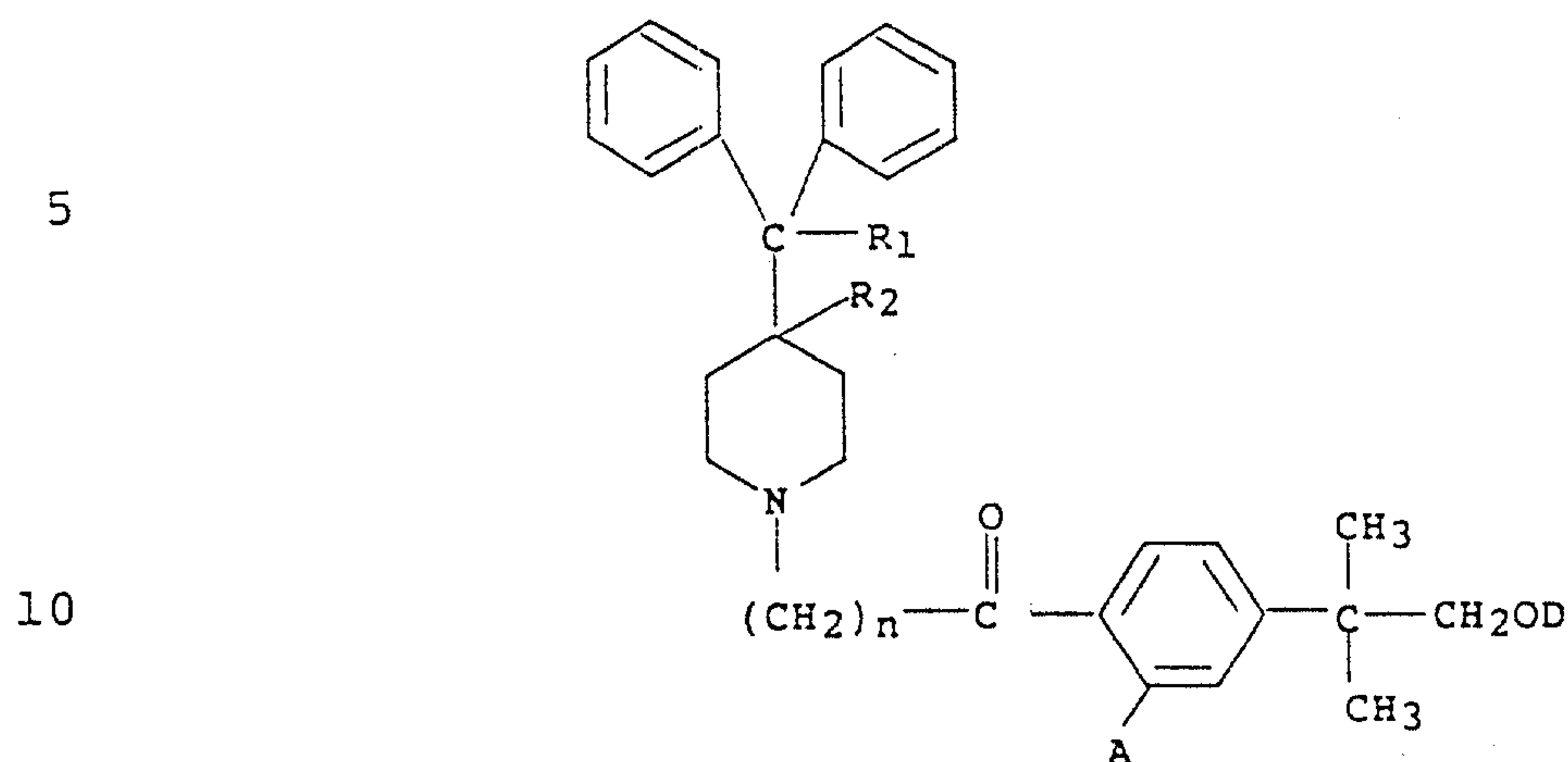
15 (d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula



25 wherein R₁ and R₂ are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine
30 protected hydroxyethylphenylketone of the formula

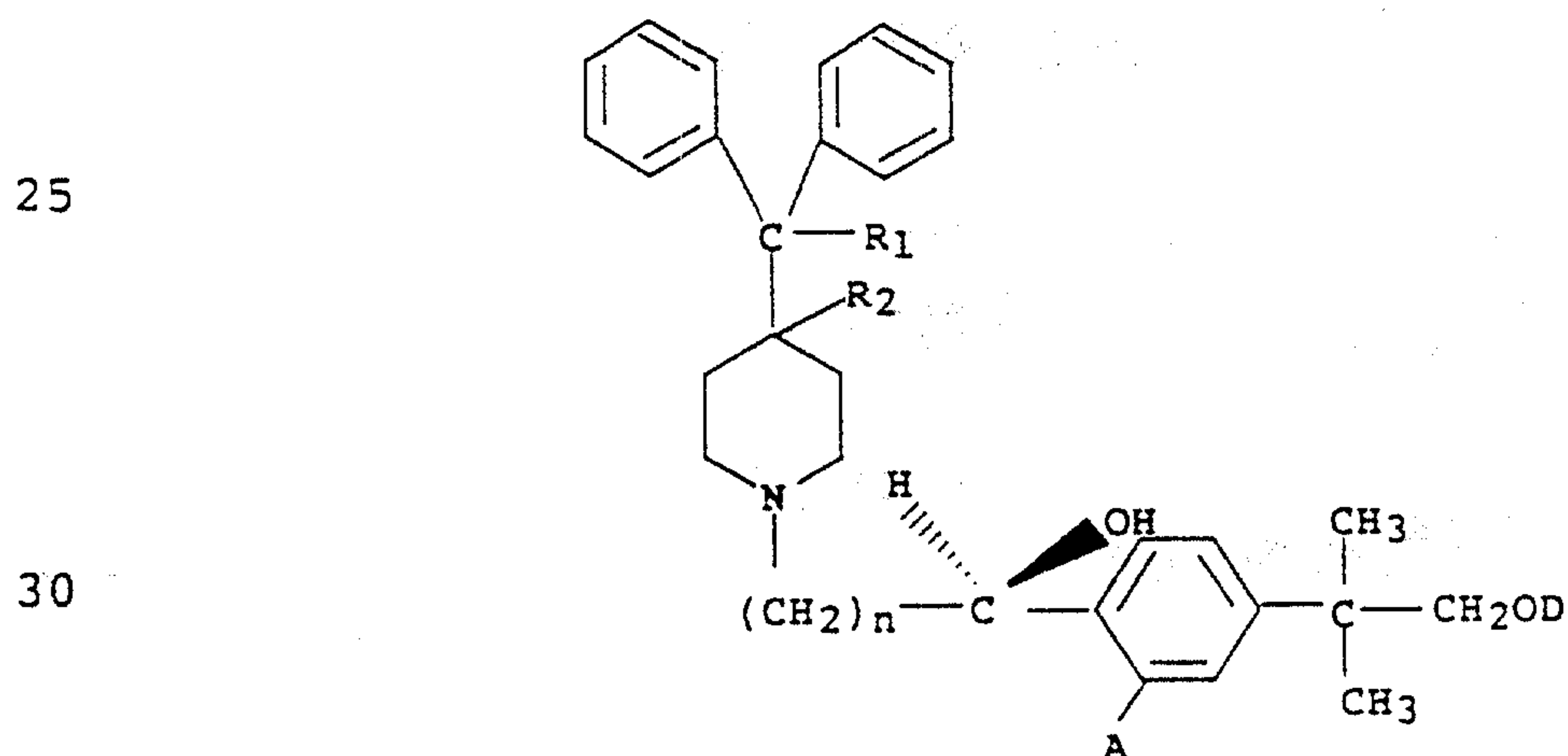
35

-202-



wherein R_1 , R_2 , n and D are defined above and A is hydrogen
 15 or hydroxy with the proviso that when A is hydroxy, A may
 be optionally protected or deprotected;

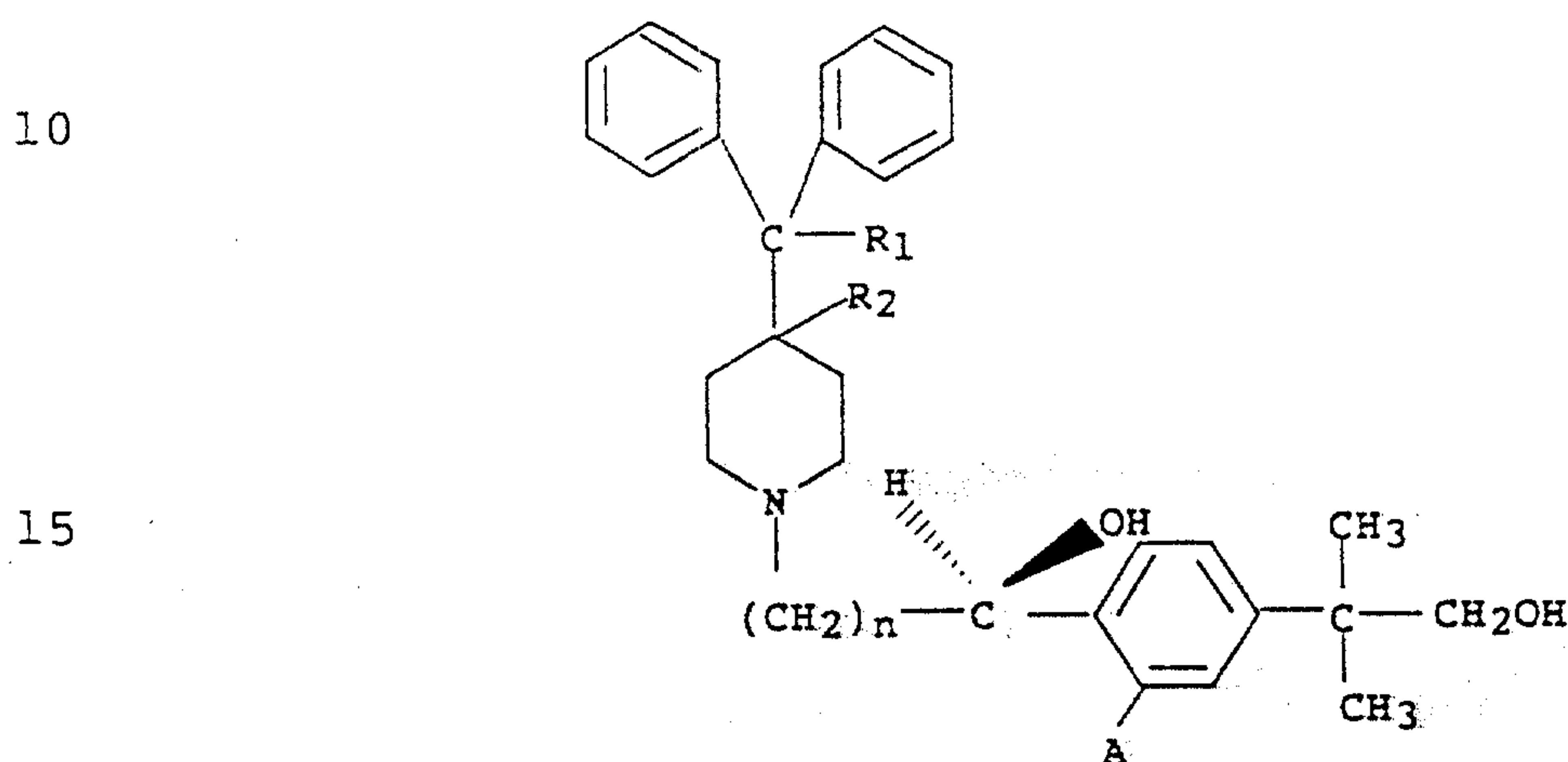
(e) reacting the piperidine protected
 hydroxyethylphenylketone with (+)-B-
 20 chlorodiisopinocampheylborane to produce a piperidine
 protected hydroxyethylphenylalcohol of the formula



wherein R_1 , R_2 , n and D are defined above and A is hydrogen
 35 or hydroxy with the proviso that when A is hydroxy, A may
 be optionally protected or deprotected;

-203-

(f) reacting the piperidine protected hydroxyethylphenylalcohol with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and potassium cyanide in ethanol to produce the piperidine hydroxyethylphenylalcohol of the formula



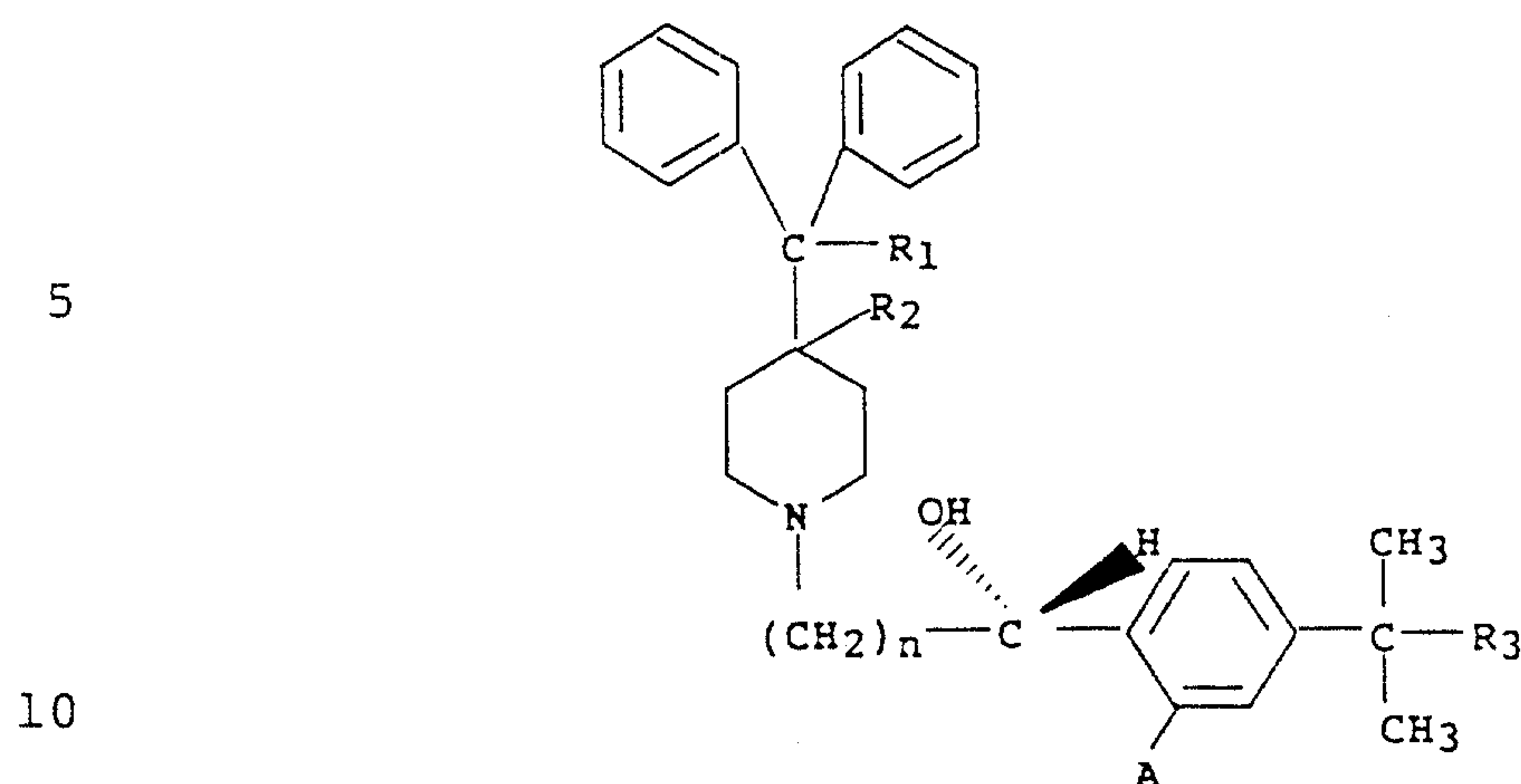
20 wherein R_1 , R_2 and n are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or deprotected;

(g) optionally reacting the piperidine hydroxyethylphenylalcohols which bear hydroxy protecting groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine hydroxyethylphenylalcohols.

30

37. A process for preparing a compound of the formula

35



wherein

R₁ represents hydrogen or hydroxy;

R₂ represents hydrogen; or

15 R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;

n is an integer of from 1 to 5;

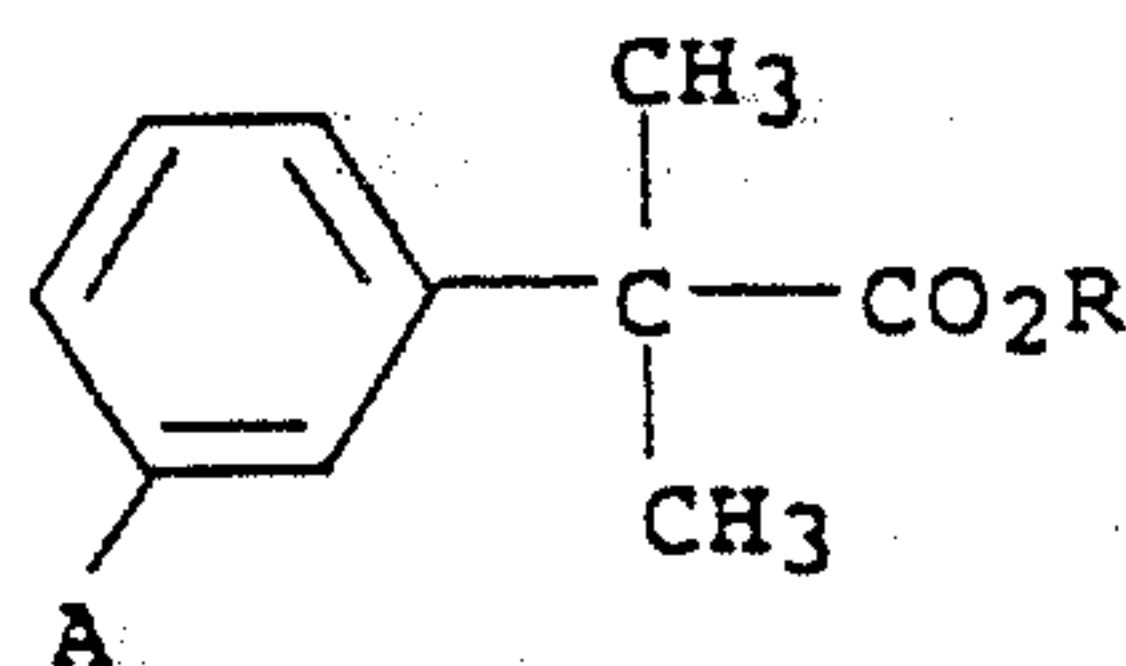
A is hydrogen or hydroxy;

R₃ is -CH₂OH; and

20 pharmaceutically acceptable salts thereof comprising the steps of:

(a) reacting a benzeneacetic acid compound of the formula

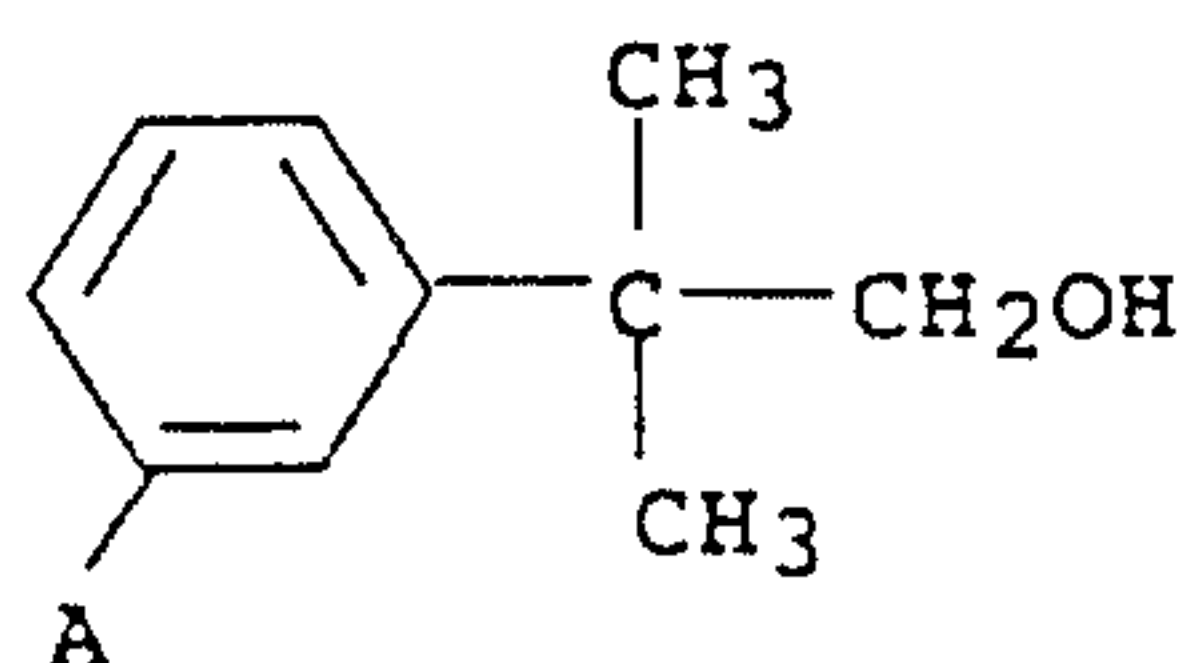
25



wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or deprotected and R is hydrogen or C₁-C₆ alkyl with sodium bis(2-methoxyethoxy)aluminum hydride, lithium aluminum hydride, 35 diborane, lithium borohydride, lithium triethylborohydride and lithium tri-sec-butylborohydride or aluminum hydride to give a phenethyl alcohol of the formula;

-205-

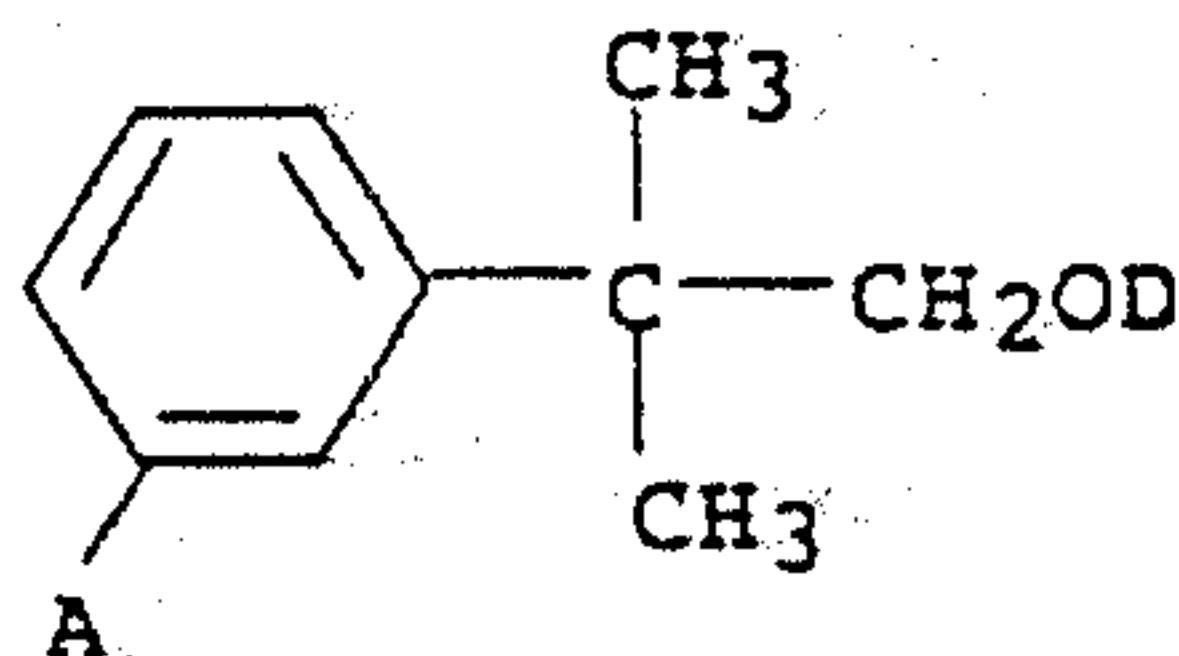
5



10

(b) reacting the phenylethyl alcohol with acetyl chloride, acetic anhydride, benzoyl chloride or benzoic anhydride in the presence of sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine or pyridine to give a protected phenethyl alcohol of the formula

15

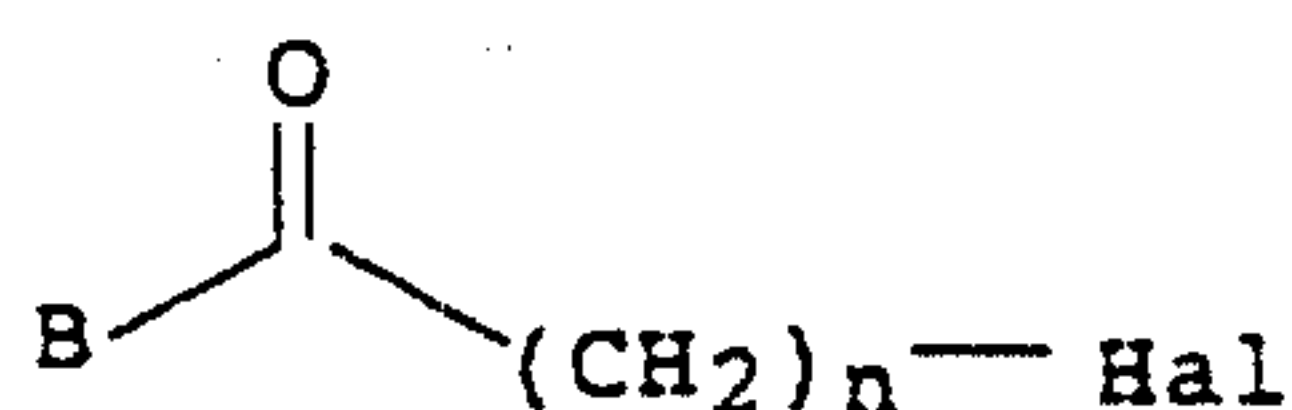


20

wherein A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or deprotected and D is $C(=O)CH_3$ or $C(=O)C_6H_5$;

25

(c) reacting the protected phenethyl alcohol with a ω -halo compound of the formula

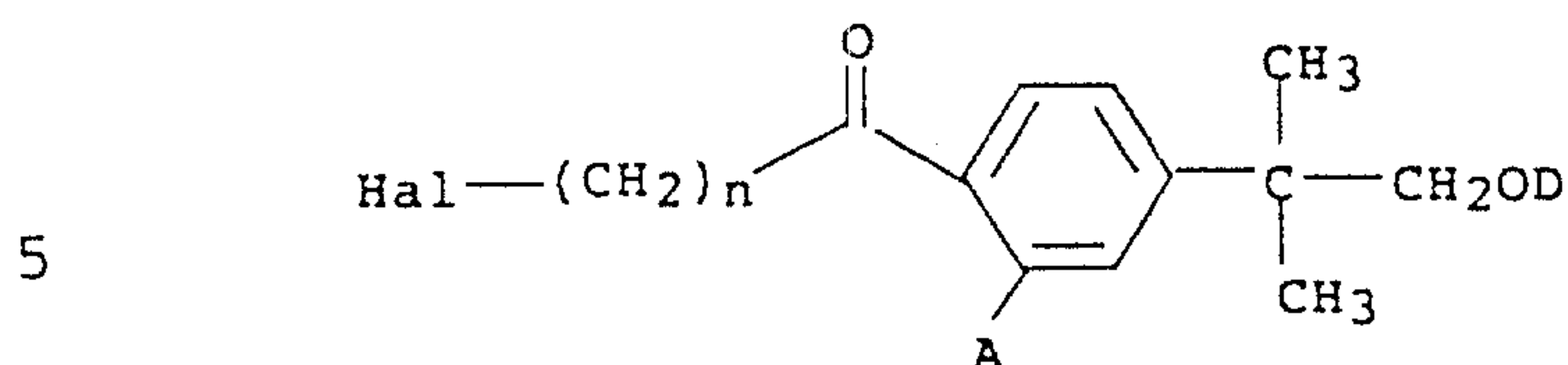


30

wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride to produce a ω -halo protected hydroxyethylphenylketone of the formula

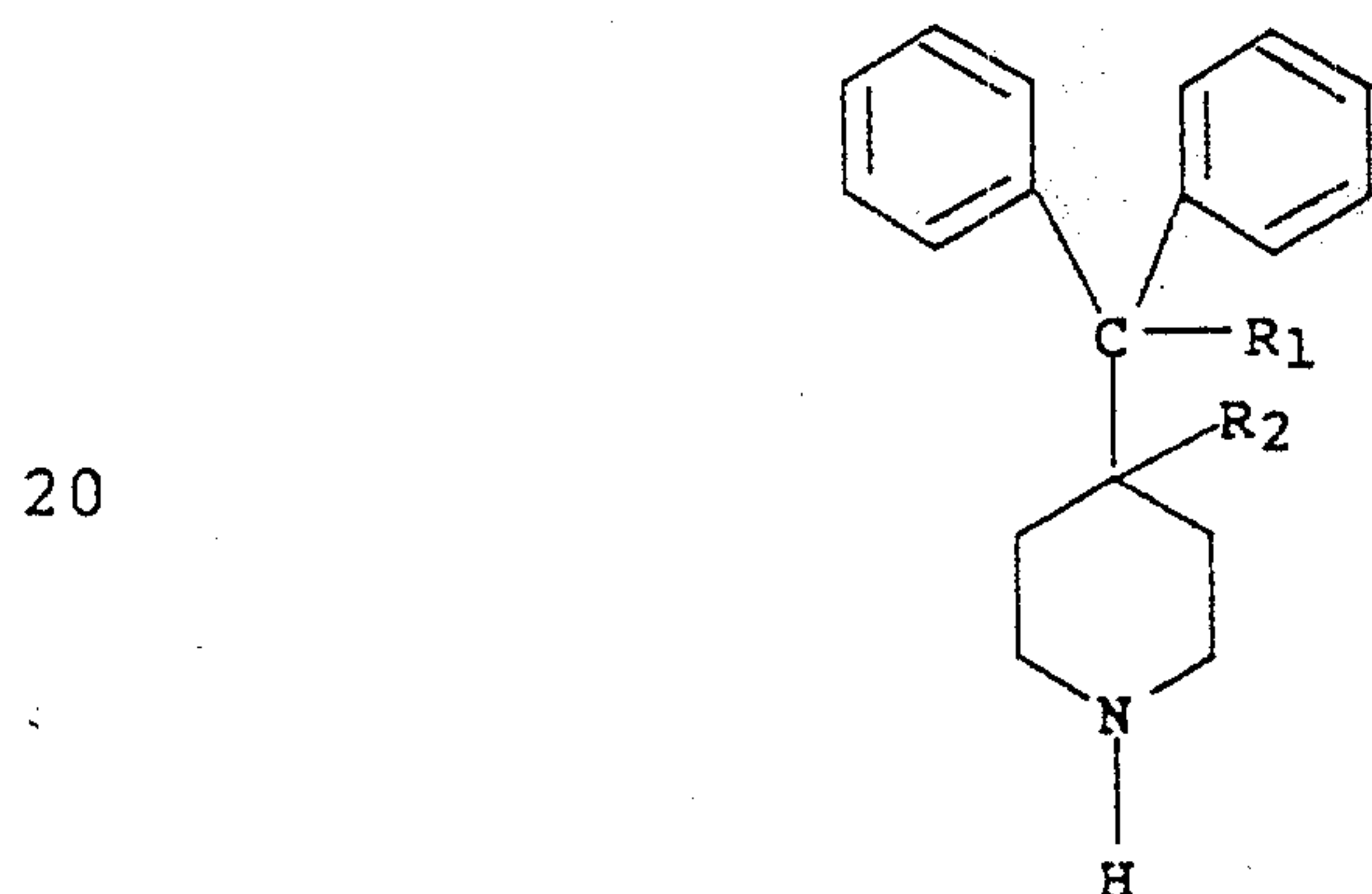
35

-206-



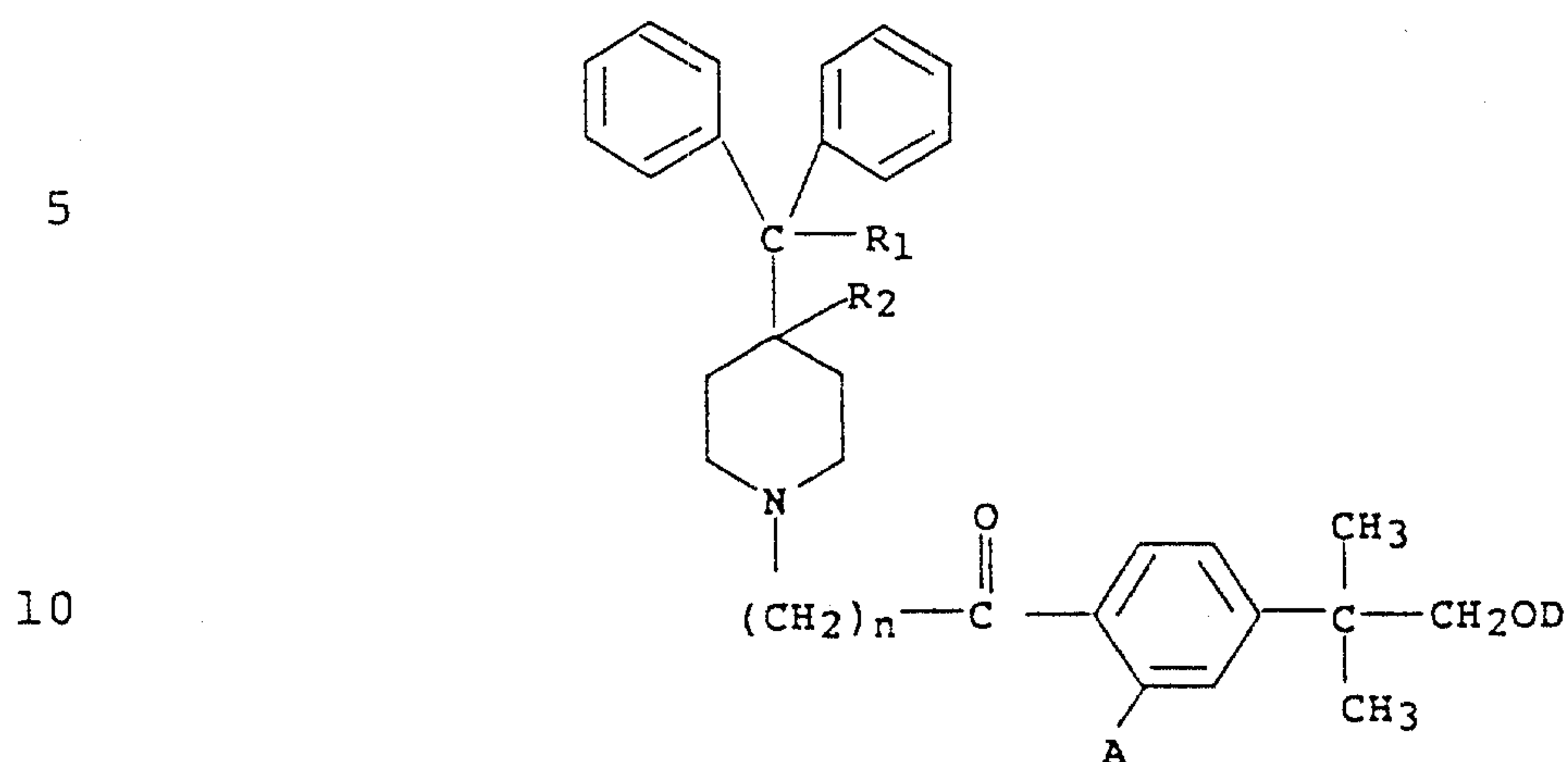
10 wherein Hal, n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or deprotected;

15 (d) reacting the ω -halo protected hydroxyethylphenylketone with a piperidine compound of the formula



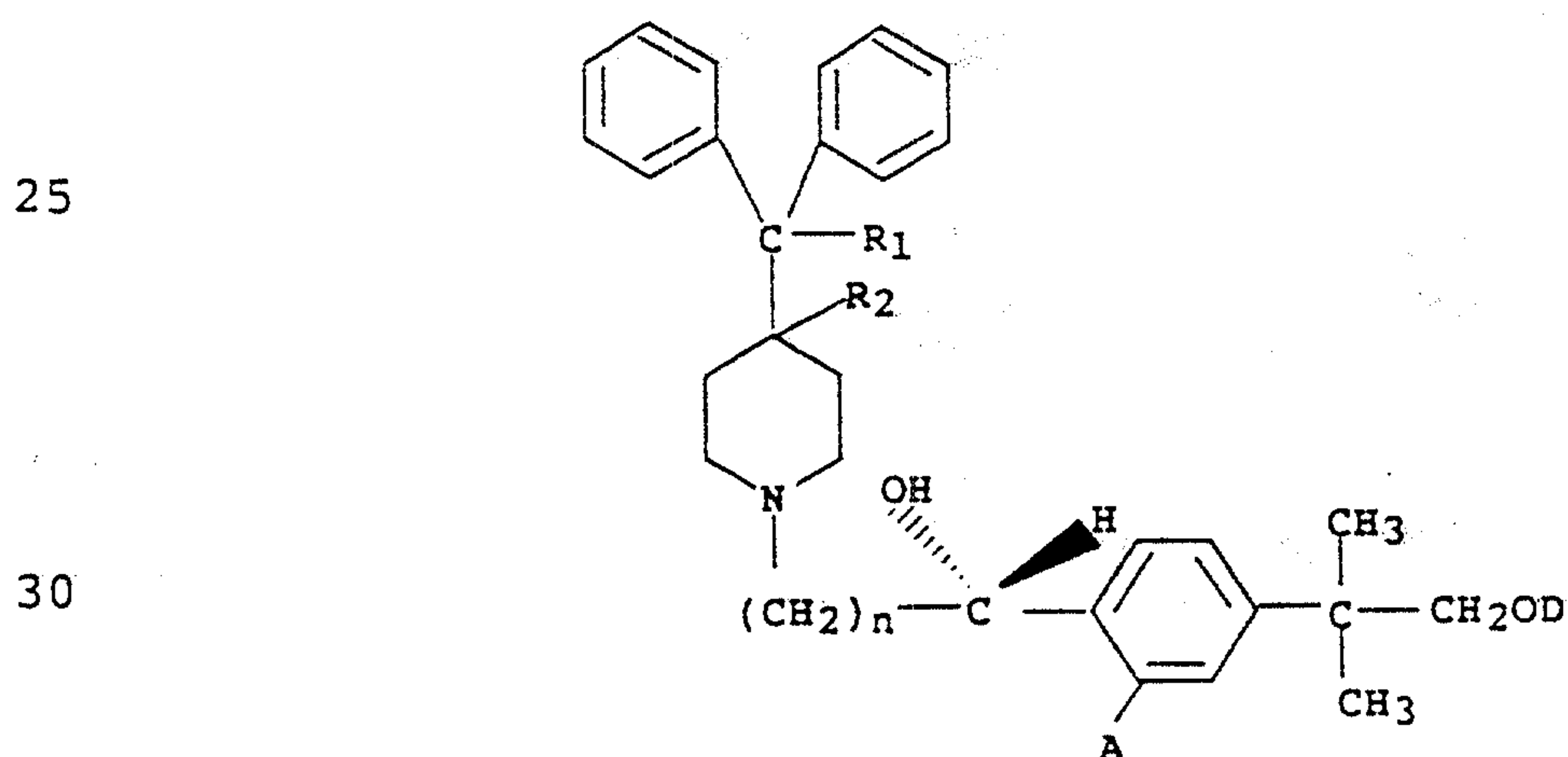
25 wherein R₁ and R₂ are as defined above in the presence of a sodium bicarbonate, potassium carbonate, potassium bicarbonate, triethylamine, pyridine, or an excess of the piperidine compound may be used to produce a piperidine
30 protected hydroxyethylphenylketone of the formula

35



15 wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or deprotected;

(e) reacting the piperidine protected hydroxyethylphenylketone with $(-)-B-$
 20 chlorodiisopinocampheylborane to produce a piperidine protected hydroxyethylphenylalcohol of the formula

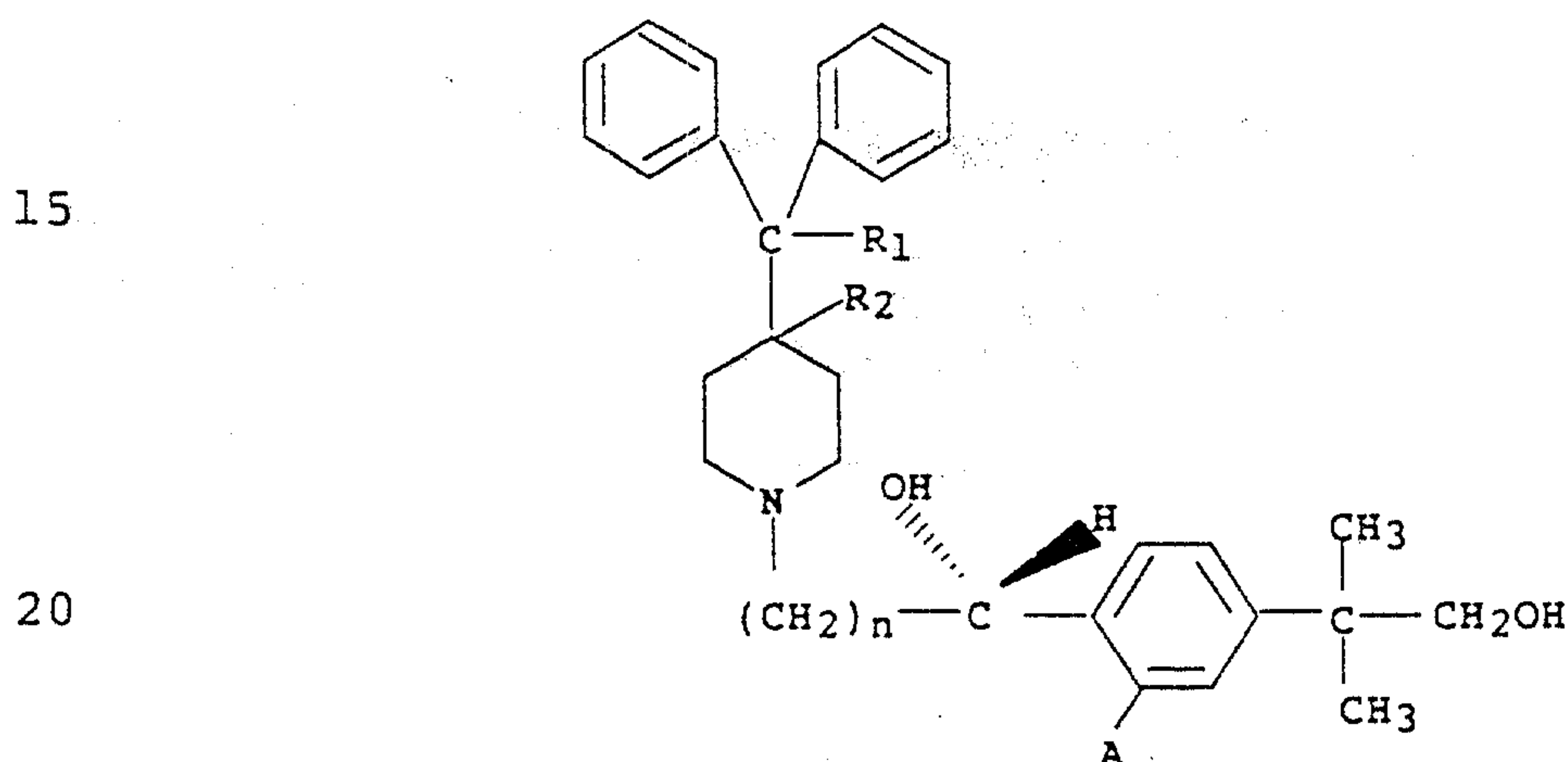


-208-

wherein R_1 , R_2 , n and D are defined above and A is hydrogen or hydroxy with the proviso that when A is hydroxy, A may be optionally protected or deprotected;

5

(f) reacting the piperidine protected hydroxyethylphenylalcohol with sodium methoxide in methanol, potassium carbonate in methanol, methanolic ammonia, sodium hydroxide/pyridine in methanol and
10 potassium cyanide in ethanol to produce the piperidine hydroxyethylphenylalcohol of the formula



wherein R_1 , R_2 and n are defined above and A is hydrogen or
25 hydroxy with the proviso that when A is hydroxy, A may be optionally protected or deprotected;

(g) optionally reacting the piperidine hydroxyethylphenylalcohols which bear hydroxy protecting
30 groups with mineral acids, strong organic acids, Lewis acids, aqueous mineral bases or catalytic hydrogenation to produce the unprotected piperidine hydroxyethylphenylalcohols.

35