United States Patent Office 3,557,148 Patented Jan. 19, 1971

3,557,148

1-AMINO-4-PHENYL-3-BUTEN-2-OLS AND SALTS THEREOF

Hendrik Durk Moed, Volkert Claassen, and Gerard Bernard Paerels, Van Houtenlaan, Weesp, Netherlands, assignors, by mesne assignments to U.S. Philips Corporation, New York, N.Y., a corporation of Delaware

No Drawing. Original application July 12, 1965, Ser. No. 471,434, now Patent No. 3,420,853, dated Jan. 7, 1969. Divided and this application Oct. 18, 1968, Ser. No. 768,925

Claims priority, application Netherlands, July 11, 1964, 6407943

Int. Cl. C07c *91/06, 149/24*

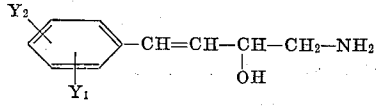
U.S. Cl. 260—343.7 17 Claims

ABSTRACT OF THE DISCLOSURE

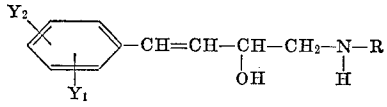
Styryl ethanol amines substituted in the benzene rings with alkyl, alkoxy and alkylthio radicals. Examples are 1-amino-4-(4-methoxy-phenyl)-3-butene-2-ol and 1-(2-p. ethoxyphenyl - 1 - methylethylamino)-4-phenyl-3-butene-2-ol. The compounds exhibit β-sympatholytic activities.

This application is a division of applicants' copending application Ser. No. 471,434, filed July 12, 1965, and now U.S. Pat No. 3,420,853.

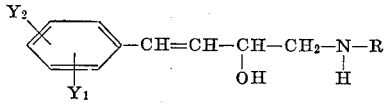
The invention relates to new compounds of Formula *Ia*:



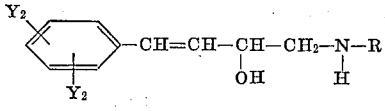
wherein Y_1 and Y_2 are each independently selected from the group consisting of hydrogen, alkyl of 1–4 carbon atoms, alkoxy of 1–4 carbon atoms and alkylthio of 1–4 carbon atoms and the pharmaceutically acceptable acid addition salts thereof and to new compounds of the Formula *Ib*:



wherein R is a member selected from the group consisting of alkyl and cycloalkyl, Y_1 and Y_2 are each independently selected from the group consisting of hydrogen, halogen, alkyl of 1–4 carbon atoms, alkoxy of 1–4 carbon atoms and alkylthio of 1–4 carbon atoms and the pharmaceutically acceptable acid addition salts thereof and to new compounds of the Formula *Ic*:



wherein R is a member selected from the group consisting of aralkyl and nuclear substituted derivatives thereof, Y_1 and Y_2 are each independently selected from the group consisting of hydrogen, halogen, alkyl of 1–4 carbon atoms, alkoxy of 1–4 carbon atoms and alkylthio of 1–4 carbon atoms and the pharmaceutically acceptable acid addition salts thereof and to new compounds of the Formula *Id*:



wherein R is phenoxyalkyl, Y_1 and Y_2 are each independently selected from the group consisting of hydrogen, halogen, alkyl of 1–4 carbon atoms, alkoxy of 1–4 carbon atoms and alkylthio of 1–4 carbon atoms and the pharmaceutically acceptable acid addition salts thereof.

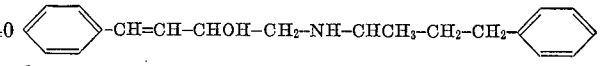
It was found that these compounds have interesting pharmacological activities. It was found inter alia that the compounds have a sympatholytic activity, in particular a favourable action on the heart and an action on the central nervous system, in particular an analgetic activity.

More in particular it was found that the compounds according to the invention have a very significant β-sympatholytic activity. In agreement herewith the compounds according to the invention, when brought in a suitable form of administration, may be used in drugs for the treatment of patients with arrhythmia and in tachycardia, both in the case that these disturbances of heart regulation are the result of the use of another drug, for example, a uterospasmolytic, and in diseases, for example, angina pectoris and in hypertension. The fall in blood pressure also, as a result of the use of a uterospasmolytic, can be prevented by administering previously one of the compounds according to the invention. The β-sympatholytic activity of the compounds according to the invention was found in experiments with a preparation of the isolated guinea pig atrium suspended in a Einger solution and connected to a frequency counter. By the addition of N-isopropylnoradrenaline to this solution a strong frequence increase is produced and the measure in which this effect can be checked was measured by previously administering compounds according to the invention.

It was found that in particular the secondary amines of Formulae *Ib*, *Ic* and *Id* have a strong activity.

In addition, in particular the compounds of Formulae *Ic* and *Id* possibly substituted in the phenyl group, have a very strong and prolonged β-sympatholytic activity.

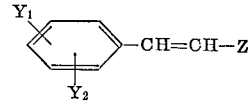
It was found, for example, that the compound of Formula II:



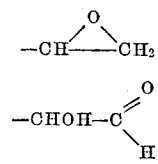
has an activity which lasts many hours longer than that of the known β-sympatholytic-α-(isopropylaminomethyl)-2 naphthalene methanol. For example, when in the above experiment, with a particular dose of β-naphthylethanolamine, an effect was reached which lasted 90 minutes, the same dose of the compound of Formula II gave an effect which was found to last over 6 hours.

The compounds according to the invention can be prepared according to methods which are known for the preparation of analogous compounds and according to methods analogous thereto.

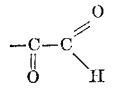
For example, the compounds according to the invention may be obtained by alkylating, in the reaction of a compound of Formula III, RNH_2, with a compound of Formula IV:



in which formulae R, Y_1 and Y_2 have the meanings indicated for Formulae *Ia*, *Ib*, *Ic* and *Id* and Z represents one of the groups —CHOH—CH_2Hlg wherein Hlg represents a halogen atom:



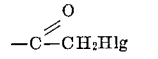
or



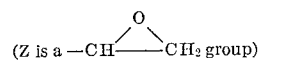
or a hydrate or alcoholate thereof.

When Z is a —CHOH—CH_2Hlg group, Hlg preferably is a Cl, Br or I atom. The reaction may be carried out in manners well known for alkylation reactions, preferably in the presence of an acid binder, for which an excess of the starting amine or, for example, a base, for example, triethylamine or calcium carbonate, may be added and preferably in an inert solvent, for example, an alcohol, for example, methanol or ethanol, a hydrocarbon, for example, benzene or toluene, or an ether, for example, diethyl ether or tetrahydrofurane.

The starting halide may be obtained, for example, by reduction of the corresponding keto halide, that is to say, the compound of Formula IV, in which Z represents a



group, which reduction may be carried out, for example, by means of a complex metal hydride, for example, $NaBH_4$. Starting from the alcohol halide of Formula IV (Z is a CHOH—CH_2Hlg group) the epoxide of Formula IV

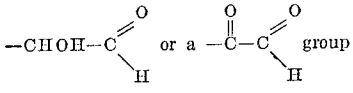


can be obtained by treatment with a base. It may consequently be assumed that on alkylation of the compound of Formula RNH_2 with the alcohol halide of Formula IV an epoxide of Formula IV is also formed intermediately.

However, the epoxide may also be used as the starting material which has been obtained, for example, by treating the alcohol halide of Formula IV with dilute alkali.

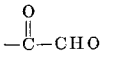
The reaction of the epoxide of Formula IV with the compound of Formula RNH_2 runs off particularly simply and may be carried out in the presence or in the absence of an inert solvent.

When the compound of Formula III is alkylated with a compound of Formula IV, in which Z is a:

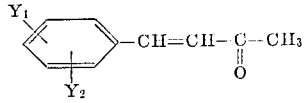


a Schiff base is intermediately formed which is reduced preferably during the alkylation reaction to the amine of Formula I. When Z is a keto aldehyde, also the keto group is reduced to a carbinol group. In this reductive alkylation a complex metal hydride, for example, $NaBH_4$, is preferably used as a reduction agent.

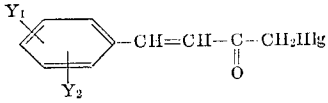
The starting substance of Formula IV, in which Z is a



group may be obtained, for example, by oxidation of a benzal acetone of Formula VI:



for example, with selenium dioxide, or of a keto halide of Formula VII:

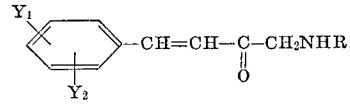


for example, with dimethylsulphoxide.

The compound of Formula IV in which Z is a —CHOH—CHO group, may be obtained, for example, by reduction of the nitrile of Formula IV, in which Z is a

CHOH—CN group, to the aldimine followed by hydrolysis.

Another example of a mode of preparing the compounds according to the invention is that in which in a keto compound of Formula VIII:

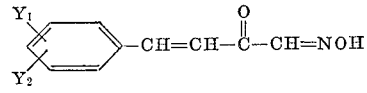


the keto group is reduced to a carbinol group. Of course, in this reduction only reduction agents are to be considered which do not reduce the alkene bond.

As examples of such reduction agents may be mentioned complex metal hydrides, for example $NaBH_4$. Alternatively, the reduction may be carried out, for example, according to the so-called Meerwein-Pondorf method by means of aluminium isopropylate in isopropanol.

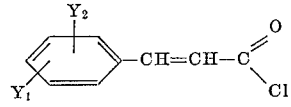
The amino ketones of Formula VIII may be obtained in different manners.

For example, a benzal acetone of Formula VI is reacted with isoamylnitrite after which the resulting oxime of Formula IX:

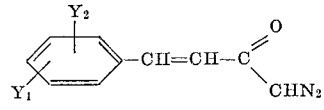


is converted, by reduction, for example, with stannic chloride, into the primary amino ketone of Formula VIII. If required, this primary amino ketone may be converted into a secondary amine of Formula VIII by alkylation.

Alternatively, the amino ketones of Formula VIII may be obtained by reaction of a compound of Formula III with a halogen ketone of Formula VII. Another example of a method of preparing amino ketones of Formula VIII is that in which an acid chloride of the Formula X:

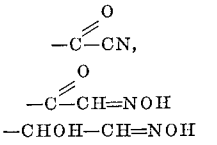


is converted with diazomethane into a diazoketone of Formula XI



followed by reaction of this diazo compound with a compound of Formula III.

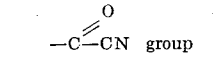
The primary amine of Formula I may be obtained also, in addition to any of the above methods, by reduction of a compound of Formula IV, in which Z represents one of the groups —CH(OH)—CN or a CHO—acyl—CN,



The compound of Formula IV, in which Z represents the group CH(OH)—CN, the cyanhydrin of a cinnamic aldehyde, may be obtained in a simple manner by the addition of HCN to the corresponding cinnamic aldehyde.

The reduction to the primary amine is preferably carried out by means of a complex metal hydride, in particular with $LiAlH_4$.

The compounds of Formula IV, in which Z represents a



may be obtained, for example, by replacing in the corresponding cinnamic acid chloride the chlorine atom by

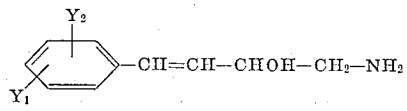
the cyano group by means of copper cyanide or silver cyanide or with HCN in pyridine.

The reduction of the keto cyano compound to the primary amine alcohol of Formula I*a* is preferably carried out also by means of a complex metal hydride as a reduction agent. Good results are obtained in particular with $LiAlH_4$.

The reduction of the keto oxime of Formula IX which, when $SnCl_2$ is used as a reduction agent, results in the keto amine, may result, by choice of a suitable reduction agent, in the corresponding amino alcohol, if required via an alcohol oxime (a compound of Formula IV) in which Z is a —CH(OH)—C=NOH group. As examples of such reduction agents may be mentioned complex metal hydrides, for example, $LiAlH_4$ and $NaBH_4$.

The compounds of Formula I*b*, I*c* and I*d* are preferably prepared by starting from the primary amine of Formula I*a* and introducing herein, in a manner known per se, the group R in an alkylation reaction which may be reductive.

These secondary amines according to the invention may be prepared, for example, by reacting the primary amine of Formula XII



with a halide R'Hlg, in which R' represents an alkyl group having 1 to 8 carbon atoms or an aralkyl group or phenoxy alkyl group possibly substituted in the phenyl group by one or two alkyl groups, alkoxy groups or hydroxy groups, and Hlg represents a halogen atoms, preferably a chlorine, bromine or iodine atom.

The substituent at the nitrogen atom of the compound of Formula III is preferably introduced by reaction of this primary amine with a carboryl compound of formula R'=O and reduction of the intermediately formed Schiff base according to methods know per se.

As salts of the compounds according to the invention are to be considered in particular acid addition salts, for example, those formed from the amine with hydrochloric acid, nitric acid, sulphuric acid, phospheric acid, sulphamic acid, acetic acid, tartaric acid, citric acid, asorbic acid, benzoic acid, p. amino benzoic acid, almond acid or salicylic acid.

According to the invention, the new compounds of Formula I*a*, I*b*, I*c*, I*d* and their salts are brought according to methods known per se, into a form of administration suitable for the therapy. For example, new pharmaceutical compositions are obtained which are characterized by a content of at least one of the new compounds according to the invention.

As examples of these pharmaceutical compositions may be mentioned injection liquids, draughts, powders, pills, suppositories, tablets and coated tablets.

The normally used pharmaceutical methods and materials may be used for the preparation of these compositions. For example, for the preparation of injection liquids solutions in water of salts of the new amines in a concentration of 1–50 mg./ml. are rendered isotonic with blood by means of kitchen salt. Alternatively, mixtures of water and alcohols, for example, glycerol or benzyl alcohol, may be used as liquid diluents.

Solid pharmaceutical dosage unit forms are prepared in the normal manner by taking up the active substance in solid pharmaceutical carrier materials, for example, lactose, powdered sugar, potato starch, talcum, magnesium stearate, gum arabic, gelatin, calcium phosphate and/or titanium dioxide and processing the mixture to tablets or coated tablets.

In order that the invention may readily be carried into effect, it will now be described in greater detail, by way of example, with reference to the ensuing specific examples.

EXAMPLE I

1-amino-4-phenyl-3-butene-2-ol

A solution of 40 g. (0.25 mol) of 2-hydroxy-4-phenyl-3-butenenitrile in 200 ml. of absolute ether was added dropwise with stirring to a solution of 24 g. (0.625 mol) of lithium aluminium hydride in 400 ml. of absolute ether. The mixture was then refluxed for 90 minutes and then decomposed with a mixture of 75 ml. of water and 150 ml. of tetrahydrofurane. After leaving to stand overnight the solid material was sucked off; it was stirred three times with warm chloroform and sucked off each time. The chloroform extracts were added to the filtrate and the whole was dried over sodium sulphate, filtered, and evaporated to dryness in vacuo. The residue (38 g.) was dissolved in 200 ml. of benzene to which 200 ml. of petroleum ether (boiling point 40–60°) were added. After leaving to stand overnight at +5° the crystallised substance was sucked off, washed with benzene-petroleum ether (1:2) and dried in air. Yield 12.2 g. (30%); the substance sintered at 75° and melted at 91–94.5°. After recrystallisation from 100 ml. of benzene 10.1 g. (25%) were obtained of melting point 95.5–97.5°.

A sample which was recrystallised from benzene two times had a melting point of 97–99°; an equivalent weight 166 (calculated 163); iodine addition number 155.8 (calc. 155.8); U.V. absorption maxima at 251, 282, and 291 mμ, ε 17,300, 1,270 and 890 respectively.

EXAMPLE II

1-isopropylamino-4-phenyl-3-butene-2-ol-HCl

To a solution of 3.26 g. (0.02 mol) of 1-amino-4-phenyl-3-butene-2-ol in 60 ml. of methanol were added successively 2 ml. of 2 N aqueous soduim hydroxide solution and 3 ml. (2.4 g.; 0.04 mol) of acetone and then carefully, while cooling with cold water, 3.04 g. (0.08 mol) of sodium borohydride. After the vehemence of the reaction had decreased somewhat, the mixture was boiled for 2 hours. The methanol was evaporated in vacuo and the residue shaken with 50 ml. of water and 50 ml. of benzene. The layers were separated and the aqueous layer shaken another two times with 25 ml. of benzene. The combined benzene extracts were extracted with 10 ml. of 2 N hydrochloric acid plus 20 ml. of water and then once again with 5 ml. of 2 N hydrochloric acid plus 10 ml. of water. The hydrochloric extracts were then made alkaline with aqueous alkali and extracted once with 50 ml. and twice with 25 ml. of benzene. These combined benzene layers were dried over $MgSO_4$ and evaporated to dryness in vacuo. The remaining oil (1.9 g.) was dissolved in a little absolute alcohol, the solution was filtered off and 3.5 ml. of 2.85 N alcoholic HCl were added to the filtrate. The solution was evaporated to dryness and the residue crystallised from a mixture of 3 ml. of alcohol and 30 ml. of acetone. Obtained were 1.3 g. (26.8%), melting point 160–163°.

1.84 g. of the resulting product were recrystallised from 4 ml. of absolute alcohol plus 35 ml. of acetone; this yielded 1.45 g. of substance with melting point 163–164°. Cl^1 found 15.1% (calc. 14.7%). Equivalent weight from bromo addition 267.5 (calc. 241.5) U.V. maxima: 251, 282 and 291 mμ, ε 19,500, 1,480 and 1,100 respectively.

EXAMPLE III

1-(1-methyl-3-phenylpropylamino)-4-phenyl-3-butene-2-ol-HCl

To a solution of 2.3 g. (0.0145 mol) of 1-amino-4-phenyl-3-butene-2-ol in 45 ml. of methanol were added 4.5 g. (0.03 mol) of benzylacetone, 5 ml. of 2 N aqueous sodium hydroxide and 2.3 g. of 91% (0.055 mol) of sodium borohydride respectively. The mixture was boiled for two hours, after which the methanol was evaporated in vacuo. 25 ml. of water were added to the residue and the whole was shaken three times with 25 ml. of ether.

The collected ether extracts were shaken with 20 ml. of water plus 10 ml. of 2 N hydrochloric acid. A solid immediately formed which was sucked off, washed with ether and dried; weight 1.13 g. (23%), melting point 164.5–172–174.5° (dec.), Cl[1] 11.4% (calc. 10.7%).

Recrystallisation from 20 ml. of water yielded 0.84 g. of substance with melting point 164–174–181° (dec.). This was recrystallised from 34 ml. of isopropyl alcohol and yielded 0.65 g. of substance with melting point 188–190°. Cl[1] 11.1% (calc. 10.7%). U.V. maxima: 251.5, 281 and 290.5 mμ, ε 20,000, 1,500 and 1,030 respectively.

EXAMPLE IV

1-amino-4-(4-methoxyphenyl)-4-butene-2-ol-HCl

(a) 2-hydroxy-4(4-methoxyphenyl)-3-butene-nitrile.—86 g. of the bisulphite addition of p.methoxy cinnamic aldehyde were suspended in a solution of 12 g. of sodium metabisulphite in 220 ml. of water. The mixture was cooled in an ice bath to 5–10° C. and 500 ml. of diethyl ether were added. An ice cold solution of 41 g. of NaCN in 100 ml. of water was added in one portion while stirring vigorously. After having stirred for 30 minutes (in the ice bath) 5 g. of sodium metabisulphite were added and then stirring was continued for another hour. The liquid layers were separated. The aqueous layer was extracted two times with 130 ml. of diethyl ether, after which the collected organic liquid was washed two times with 130 ml. of a 20% sodium metabisulphite solution in water and then with two times 130 ml. of water. The liquid was dried by means of Na_2SO_4. The solvent was removed under reduced pressure and the residue taken up in 100 ml. of benzene. The whole was evaporated to with 150 ml. of chloroform, filtered hot, once again this time in 200 ml. of benzene. After evaporating the benzene an oily residue (55 g.) was obtained which was crystallised from a mixture of 110 ml. of benzene and 45 ml. of petroleum ether (40–60°). The resulting cyanohydrin had a melting point of 73–78° C.

(b) 15.12 g. of the cyanohydrin obtained according to (a) were dissolved in 75 ml. of acetic anhydride. After leaving to stand at room temperature for 16 hours the mixture was heated on the steam bath for 30 minutes. After evaporating to dryness under reduced pressure an oily residue was obtained (19.0 g.). This oil was dissolved in 100 ml. of dry diethyl ether and this solution was then added dropwise in 45 minutes to a solution of 12 g. $LiAlH_4$ in 300 ml. of dry ether. Then the mixture was refluxed for three hours. The reaction mixture was then decomposed by the addition of 36 ml. of water. The hydroxide precipitate formed, to which the greater part of the desired reaction product, turned out to be absorbed, was sucked off. This precipitate was boiled with 150 ml. of chloroform, filtered hot, once again boiled with 150 ml. of chloroform, and then washed thoroughly with warm chloroform. Of the collected chloroform extracts the solvent was removed under reduced pressure after which a residue of 9.0 g. of solid was obtained. After crystallisation from 100 ml. of benzene and washing with 40 ml. of a benzene-petroleum ether mixture 1:1 and 40 ml. of petroleum ether, 7.65 g. of a white substance with melting point 114–116° C. were obtained.

EXAMPLE V

1-isopropylamino-4-(4-methoxyphenyl)-3-butene-2-ol-hydrochloride

3.86 g. of the amine obtained according to Example IV and 3.0 ml. of acetone were dissolved in 60 ml. of methanol, after which 0.25 ml. of 2.3 N alcoholic HCl were added. After the mixture had been left to stand at room temperature for 30 minutes, 1.2 g. of approximately 90% $NaBH_4$ was added and the mixture was then boiled for one hour. After cooling 4 ml. of acetone were added and, after having been left to stand at room temperature again half an hour, 1.6 g. of 90% $NaBH_4$ were added and the mixture was boiled for another hour. After removing the solvent under reduced pressure the oily residue was dissolved in a mixture of 50 ml. of water and 50 ml. of diethylether. The liquid layers were separated. The aqueous layer was extracted two times with 25 ml. of diethylether. After drying by means of Na_2SO_4 the solvent of the combined ether extracts was removed under reduced pressure. The residue was taken up a few times in chloroform which then was removed again by evaporation. The resulting solid (4.6 g.) was dissolved in 25 ml. of absolute ethanol to which 8.7 ml. of 2.3 N alcoholic HCl were added. After the addition 75 ml. of dry diethylether a substance crystallised out which, after 30 minutes, was filtered and dried in air. Obtained were 4.2 g. of the above amino salt with melting point 153–154° C. (dec.).

EXAMPLE VI

1-amino-4-(2-methylphenyl)-3-butene-2-ol-oxalic acid

14 g. of o-methyl cinnamic aldehyde were shaken with a solution of 20 g. of $Na_2S_2O_5$ in 40 ml. of water. A precipitate was formed which, after sucking off, was washed with water and ether.

To 22.6 g. (0.09 mol) of this bisulphite addition product was aded a solution of 3.4 g. of $Na_2S_2O_5$ in 50 ml. of water and 150 ml. of ether. The mixture was cooled in ice. To the solution was rapidly added, while stirring thoroughly, an ice-cold solution of 11.9 g. (0.24 mol) of NaCN in 30 ml. of water. After stirring for 30 minutes 1.5 g. of $Na_2S_2O_5$ were added, after which stirring while cooling with ice was continued for another 90 minutes. The layers were separated, the water layer was shaken twice with 40 ml. of ether and the collected ether layers were twice washed with 40 ml. of 20% $Na_2S_2O_5$ solution and twice 40 ml. of water. The solution was dried on $MgSO_4$.

After filtration a mixture of 20 ml. of pyridine and 50 ml. of acetic acid anhydride was added to the ethereal solution while cooling with ice. After two hours the mixture was allowed to reach room temperature. After leaving to stand over night at room temperature the solution was evaporated to dryness. The residue was taken up in 100 ml. of dry ether.

The resulting solution was added dropwise, while stirring, at −10° C. in two hours to a solution of 15 g. (0.4 mol) of $LiALH_4$ in 650 ml. of dry ether. After the addition stirring was continued at −10° for one hour. Then, while cooling with ice, 80 ml. of ethyl acetate followed by 80 ml. of water were added. The ether was poured off; the residue was extracted 4 times with warm chloroform and sucked off. The chloroform and ether solutions were washed with water and saturated kitchen salt solution and dried on $MgSO_4$. After filtration the solvents were removed. The residue was taken up in ether and this solution was shaken with 2 N HCl. The HCl-solution was made alkaline and extracted with water. The ether solution was dried on $MgSO_4$. After filtration a solution of 4 g. of oxalic acid in 18 ml. of ethanol was added to the concentrated solution. A precipitate was formed which was washed with ether. Melting point 160° C. (decomposition).

EXAMPLE VII

4-(4-chlorophenyl)-1-isopropylamino-3-butene-2-ol hydrochloride

(a) 4-(4-chlorophenyl)-2-hydroxy-3-butenenitrile.—To a solution of 9:84 g. (0.059 mol) of p-chloro cinnamic aldehyde in 100 ml. of ether was added a solution of 7.70 g. (0.041 mol) of sodium metabisulphite in 30 ml. of water. After having stirred this mixture for one hour it was cooled in an ice bath to 5° and a solution of 7.3 g. (0.15 mol) of sodium cyanide in 20 ml. of water was added in one portion, while stirring. The mixture was then stirred at 0–5° for 30 minutes, 1.0 g. of sodium metabisulphite was added, and stirring was continued finally

for another 90 minutes at 0–5°. Then the layers were separated and the water layer was extracted twice with 25 ml. of benzene. The collected organic liquid was washed two times with 25 ml. of a 20% sodium metabisulphite solution, two times with 25 ml. of water, and finally dried on sodium sulphate. After filtration and evaporation of the solvents in vacuo the residue was evaporated to dryness in vacuo with 200 ml. of benzene and finally dissolved in 25 ml. of benzene. After dilution with 25 ml. of petroleum ether 40–60, 10.1 g. (88%) of substance crystallized with melting point 60–64° C.

(b) 1-amino-4-(4-chlorophenyl)-3-butene - 2 - ol.—A solution of 8.16 g. (0.042 mol) of the compound obtained sub 7*a* in 140 ml. of dry ether was added dropwise, while stirring, to a solution of 6 g. of lithium aluminium hydride in 200 ml. of dry ether. The temperature of the reaction mixture was kept at —5° by means of an ice-salt bath. Then stirring was continued at this temperature for another 5 hours after which the solution was decomposed with 18 ml. of water at such a rate that the temperature did not exceed 10°. Stirring was then continued at room temperature for 30 minutes after which the formed hydroxides, to which substantially all the reaction product was found to be absorbed, were sucked off. The hydroxides were then extracted three times with 200 ml. of warm chloroform and the resulting filtrates were collectively evaporated to dryness in vacuo. In this manner 5.5 g. of solid were obtained. They were dissolved in 55 ml. of benzene. After dilution with 28 ml. of petroleum-ether 40–60 4.37 g. (52%) crystallised with melting point 115–117° C.

(c) 4-(4-chlorophenyl) - 1 - isopropylamino-3-butene-2-ol.—To a solution of 3.95 g. (0.020 mol) of the substance obtained sub 7*b* in 60 ml. of methanol were added 0.16 ml. of 3.8 N alcoholic hydrochloric acid and then 3.0 ml. (2.37 g., 0.041 mol) of acetone. After 30 minutes 1.2 g. of sodium borohydride were added and the solution was boiled for one hour. The reaction mixture was then cooled to room temperature, after which 4.0 ml. (3.15 g., 0.055 mol) of acetone were added. After one hour finally 1.6 g. of sodium borohydride were added and boiling continued for another hour. The reaction mixture was evaporated to dryness in vacuo and the residue dissolved in a mixture of 50 ml. of ether and 50 ml. of water. After separating the layers, the water layer was extracted two times with 25 ml. of ether. The combined ethereal solutions were evaporated in vacuo after drying on sodium sulphate. The residue was once again evaporated to dryness in vacuo after 100 ml. of benzene had been added. The resulting residue (4.64 g.) crystallised. It was dissolved in 15 ml. of absolute alcohol, after which 8 ml. of 3 N alcoholic hydrochloric acid were added. The hydrochloride began to crystallise immediately. After dilution with 150 ml. of dry ether the white substance was sucked off and dried in air. This yielded 4.87 g. (88%) of substance with melting point 198–205° C. (dec.). The substance was finally recrystallised from 250 ml. of isopropyl alcohol. This yielded 4.34 g. with melting point 205–206° C. (dec.).

EXAMPLE VIII

1-isopropylamino-4-p-tolyl-3-butene-2-ol hydrochloride

(a) 1-amino - 4 - p-tolyl-3-butene-2-ol.—A solution of 49 g. (0.34 mol) of p-methyl cinnamic aldehyde in 50 ml. of ether was stirred for 30 minutes with a solution of 44 g. (0.23 mol) of sodium metabisulphite in 250 ml. of water. 450 ml. of ether were then added and the resulting reaction mixture was cooled while stirring in an ice bath. When the temperature was 5° an ice-cold solution of 41 g. (0.84 mol) of sodium cyanide in 100 ml. of water was added in one portion; the temperature increased to 15° but then rapidly decreased again to 5°. After stirring for 30 minutes 5 g. of sodium metabisulphite were added and stirring was continued for another 90 minutes, still in the ice bath. The layers were then separated, after which the water layer was extracted two times with 100 ml. of ether. The combined ether layers were washed with two times 100 ml. of 20% sodium metabisulphite solution followed by two times 100 ml. of water. After drying on sodium sulphate and evaporating the ether in vacuo an oil was obtained which was very carefully evaporated to dryness in vacuo with 100 ml. of benzene and two times 100 ml. of methylene chloride so as to remove the water present. The resulting oil (49 g.) was dissolved in 250 ml. of acetic acid anhydride. After 20 hours this reaction mixture was heated on the steam bath for 30 minutes and then evaporated to dryness in vacuo. The oily residue, dissolved in 250 ml. of dry ether, was then added dropwise while stirring and cooling so rapidly that the temperature of the reaction mixture did not exceed 10°, to a solution of 33 g. of lithium aluminium hydride in 1 l. of dry ether. Stirring was then continued at 5° for another 3½ hours. The reaction mixture was decomposed with 100 ml. of water at such a rate that the temperature did not exceed 15°. The hydroxides formed were then sucked off. After evaporating with ether in vacuo and evaporating to dryness once again in vacuo with 100 ml. of benzene, the filtrate yielded 22 g. of oil which were crystallised from a mixture of 70 ml. of benzene and 130 ml. of petroleum ether 40–60. This yielded 9.15 g. of substance with melting point 79–83°. The hydroxides sucked off were extracted three times with 300 ml. of chloroform. The combined extracts were evaporated to dryness in vacuo. This yielded 21.5 g. of oil which were crystallised from a mixture of 55 ml. of benzene and 100 ml. of petroleum-ether 40–60. This yielded 12.56 g. of substance with melting point 78–84°. Together with the 9.15 g. obtained above, this substance was recrystallised by dissolving in 57 ml. of benzene and diluting with 60 ml. of petroleum ether 40–60. After washing with a mixture of 20 ml. of benzene and 30 ml. of petroleum ether 40–60 and with 50 ml. of petroleum ether 40–60 the resulting product was dried in air. Yield 20.5 g. (35% overall) and the melting point was 79–83° C.

(b) 1-isopropylamino-4-p-tolyl-3-butane-2-ol hydrochloride.—To a solution of 5.31 g. (0.030 mol) of the substance prepared sub 8*a* in 90 ml. of methanol were added 4.5 ml. (3.56 g., 0.062 mol) of acetone and 0.25 ml. of 3.8 N alcoholic hydrochloric acid. After leaving to stand the solution at room temperature for 30 minutes 1.8 g. of sodium borohydride were added and the solution was then boiled for one hour. Then 6.0 ml. (4.74 g., 0.082 mol) of acetone were added. After 30 minutes finally 2.4 g. of sodium borohydride were added and the solution was boiled for one hour. The reaction mixture was evaporated to dryness in vacuo and the residue dissolved in a mixture of 75 ml. of water and 75 ml. of ether. The layers were separated and the water layer was then extracted two times with 30 ml. of ether. The combined ethereal layers were evaporated in vacuo, after drying on sodium sulphate, and the resulting residue was then evaporated to dryness in vacuo with 250 ml. of benzene. The resulting 6.38 g. of substance were dissolved in 20 ml. of absolute alcohol to which were added 15 ml. of 3 N alcoholic hydrochloric acid followed by 250 ml. of ether. The resulting crystalline substance was sucked off and dried in air. This yielded 6.63 g. (86%), melting point 158–162°. The substance was finally recrystallised from 40 ml. of isopropyl alcohol. This yielded 5.92 g. with melting point 158–162° C.

EXAMPLE IX

4-(2-butoxyphenyl)-1-isopropylamino-3-butene-2-ol hydrochloride

(a) 2-butoxybenzaldehyde diethylacetal.—A solution of 28.65 g. (0.152 mol) of 2-butoxybenzaldehyde in a mixture of 30.4 ml. of o-formic acid ethyl ester and 18.2 ml. of absolute supra ethanol to which 60 mg. of p-

toluenesulphonic acid had been added was stored at room temperature overnight. 1.5 ml. of 0.5 N alcoholic potassium hydroxide solution were then added after which the reaction mixture was evaporated to dryness in vacuo. Finally the resulting residue was distilled in vacuo. Fraction 80–82° C./0.09 mm. Yield 38.33 g. (=100%).

(b) 3-(2-butoxyphenyl) - 3 - ethoxypropionaldehyde diethylacetal.—To 1.5 ml. of a 10% solution of anhydrous zinc chloride in glacial acetic acid in 38.2 g. (0.151 mol) of the substance prepared sub 9*a* were added dropwise while stirring and at such a rate that the temperature of the reaction mixture did not exceed 50° 15.4 ml. (11.6 g., 0.161 mol) of ethylvinylether. The reaction mixture was then stirred for one hour at 50°. 30 ml. of ether and 30 ml. of 2 N sodium hydroxide solution were then added, the layers were separated and the water layer was extracted once with 15 ml. of ether. The combined ether layers were then dried on anhydrous potassium carbonate. After filtration and evaporation of the ether in vacuo a residue was obtained which was distilled in vacuo. Fraction 125–127° C./0.25 mm. Yield: 45.3 g. (=98%).

(c) 2-butoxy cinnamic aldehyde.—A solution of 45.3 g. (0.147 mol) of the substance prepared sub 9*b*, 2.5 ml. of water and 3.76 g. of anhydrous sodium acetate in 62 ml. of glacial acetic acid was boiled under nitrogen for three hours. After cooling a solution of 70 g. of anhydrous sodium carbonate in 250 ml. of water was added. The resulting oil crystallised practically immediately. After sucking off, washing six times with 50 ml. of water and drying in air, 26.74 g. of a pale yellow substance were obtained. This was recrystallised from 150 ml. of ligroin. Yield: 22.7 g. (=76%) with melting point 53.5–55° C.

(d) 4-(2-butoxyphenyl) - 2 - hydroxy - 3 - butenenitrile acetate.—A mixture of 20.4 g. (0.100 mol) of the substance prepared sub 9*c* in 50 ml. of ether and 26.6 g. (0.140 mol) of sodium metabisulphite in 100 ml. of water was evaporated in vacuo at room temperature while shaking vigorously until most of the ether was removed. A bright solution was obtained from which the bisulphite addition product began to crystallise, after a few moments. 200 ml. of ether were then added, after which the reaction mixture was cooled to 0° while stirring. A solution of 26.6 g. of sodium cyanide in 50 ml. of water was then added in portions while stirring at such a rate that the temperature of the reaction mixture did not exceed 10° C. Stirring was continued for another two hours at 0–5° C., after which the layers were separated. The water layer was extracted twice with 50 ml. of ether. The collected ethereal solutions were washed two times with 50 ml. of water and then dried on sodium sulphate at 0° C. After filtration, a solution of 10 ml. of dry pyridine in 25 ml. of acetic anhydride was added in one portion to the cold solution. The reaction mixture was stored at 0° for 20 hours and then the weekend over at room temperature. Finally it was evaporated to dryness in vacuo, 21.8 g. (80%) of pale brown bright oil being obtained which was used without further purification for the following reaction.

(e) 1-amino-4-(2-butoxyphenyl) - 3 - butene-2-ol hydrochloride.—A solution of 21.8 g. of the substance prepared sub 9*d* in 100 ml. of absolute ether was added dropwise while stirring and cooling at such a rate that the temperature of the reaction mixture did not exceed −5° to 12 g. of lithium aluminum hydride in 500 ml. of absolute ether. Stirring was continued at −5 to −10° for another 5 hours. The reaction mixture was then decomposed with 36 ml. of water, it being ensured that the temperature did not exceed 0°. After sucking off and washing with two times 50 ml. of ether the filtrate was evaporated to dryness in vacuo. The residue (13.5 g. of yellow oil) was dissolved in 80 ml. of benzene and this solution, after dilution with 200 ml. of petroleum ether 40–60, was extracted with 30 ml. of 2 N hydrochloric acid. This extract was washed with 20 ml. of ether, then rendered alkaline with 20 ml. of 50% potassium hydroxide solution and finally extracted three times with 20 ml. of ether. After drying on sodium sulphate and evaporating the ether in vacuo the resulting residue was evaporated to dryness in vacuo a few times with benzene until all the water was removed. This yielded 8.93 g. of oil. This oil was dissolved in 25 ml. of absolute supra ethanol, after which 3 N alcoholic hydrochloric acid was added until the solution was just acid. After dilution with 400 ml. of absolute ether 6.55 g. of hydrochloride crystallised with melting point 137–138°; λ_{max}=253 mμ, ϵ=14,000.

(f) 4-(2-butoxyphenyl)-1-isopropylamino-3-butene-2-ol hydrochloride.—To a solution of 0.475 g. (20.6 m. at) of sodium in 60 ml. of methanol were added 5.94 g. (21.8 m. mol) of the substance prepared sub 9*e* and then 3.0 ml. of acetone. After 30 minutes 1.2 g. of sodium borohydride were added after which the reaction mixture was boiled for 60 minutes. After cooling 4.0 ml. of acetone were added. 1.6 g. of sodium borohydride were added after 30 minutes after which the reaction mixture was boiled for another 60 minutes. The reaction mixture was evaporated to dryness in vacuo and the residue dissolved in 50 ml. of water and 25 ml. of ether. The layers were separated and the water layer was extracted with 30 ml. and 15 ml. of ether. The combined ethereal solutions were dried on sodium sulphate and then evaporated to dryness in vacuo. The residue was evaporated to dryness in vacuo with benzene until all the water was removed and then dissolved in 10 ml. of absolute supra ethanol. To this solution was added 3 N alcoholic hydrochloric acid until just acid reaction, after which it was diluted with 220 ml. of absolute ether. 5.01 g. of substance crystallised with melting point 129–131° C.

EXAMPLE X

4-(2,6-dimethoxyphenyl)-1-isopropylamino-3-butene-2-ol hydrochloride

(a) 2,6 - dimethoxybenzaldehyde diethylacetal.—This substance was prepared according to the same method as described sub 9*a*. Yield 92%, boiling point 103–104°/0.3 mm., melting point 42–44° C.

(b) 2-(2,6-dimethoxyphenyl)-3-ethoxypropionaldehyde diethylacetal.—This substance was prepared according to the method as described sub 9*b*. Yield 85%, boiling point 134–136°/0.5 mm.

(c) 2,6-dimethoxy cinnamic aldehyde.—This substance was prepared according to the method as described sub 9*c*. Recrystallised from benzene/petroleum ether 40–60 and tetra/petroleum ether 40–60. Yield 83%, melting point 77–80° C.

(d) 4-(2,6-dimethoxyphenyl)-2-hydroxy-3-butenenitrile acetate.—A mixture of 12.73 g. (0.070 mol) of the substance prepared sub 10*c* in 120 ml. of ether and 18.2 g. (0.096 mol) of sodium metabisulphite in 40 ml. of water was stirred vigorously until the bisulphite addition product began to crystallise. The reaction mixture was then cooled to 0° while stirring, after which a solution of 17.4 g. of sodium cyanide in 50 ml. of water was added in one portion followed by 50 ml. of chloroform. Then stirring was continued for two hours at 0–5° after which the layers were separated. After diluting the water layer with 50 ml. of water it was extracted two times with 50 ml. of benzene. The collected organic solutions were dried on sodium sulphate at 0°. After filtration and evaporation of the solvents at room temperature in vacuo a red oil was obtained which was dissolved immediately in 100 ml. of acetic anhydride. This solution was stored at room temperature for 20 hours and then heated on the steam bath for 60 minutes. After evaporating to dryness in vacuo finally 13.5 g. of oil were obtained which were used for the following reaction without further purification.

(e) 1-amino-4-(2,6-dimethoxyphenyl)-3-butene-2-ol hydrochloride.—A solution of 13.5 g. of the substance prepared sub 10*d* in 100 ml. of absolute ether was added dropwise to 5.0 g. of lithium aluminiumhydride in 200

ml. of absolute ether. The reaction mixture was then boiled for 90 minutes and then decomposed with 15 ml. of water. After sucking off the filtrate was evaporated to dryness in vacuo. The resulting residue was evaporated to dryness with benzene in vacuo until all the water was removed. This yielded 7.8 g. of oil. This oil was dissolved in 10 ml. of absolute alcohol and 6.5 ml. of 2.2 N alcoholic hydrochloric acid and 55 ml. of absolute ether were added to the solution. The white substance which crystallised was sucked off, washed three times with 25 ml. of absolute ether and dried in air. Yield 2.74 g. of substance with melting point 153–155° C. (dec.).

(f) 4-(2,6 - dimethoxyphenyl)-1-isopropylamino-3-butene-2-ol hydrochloride.—This substance was prepared according to the method described in Example 9(f). Yield 85%; melting point 149–155° C. (dec.).

EXAMPLE XI

4-(2,5-dimethoxyphenyl)-1-isopropylamino-3-butene-2-ol hydrochloride

(a) 2,5 - dimethoxybenzaldehyde diethylacetal.—To a solution of 20 g. (0.12 mol) of 2,5-dimethoxybenzaldehyde in 125 ml. of absolute supra ethanol were added 25 ml. of o-formic acid ethylester and 50 mg. of p-toluenesulphonic acid. After leaving to stand overnight at room temperature this reaction mixture was boiled for another 30 minutes. After cooling 1 ml. of 0.5 N alcoholic potassium hydroxide solution was added. The reaction mixture was then evaporated to dryness in vacuo after which the residue was distilled in vacuo. Fraction: 98–100° C./0.25 mm. Yield: 23.4 g. (81%).

(b) 3-(2,5-dimethoxyphenyl)-3-ethoxypropionaldehyde diethylacetal.—This substance was prepared according to the method as described in Example 9(b). Yield 80%, boiling point 122–123° C./0.25 mm.

(c) 2,5-dimethoxy cinnamic aldehyde.—Thus substance was prepared according to the method described in Example 9(c). Recrystallised from ligroin. Yield 92%; melting point 84.5–86.5° C.

(d) 4-(2,5-dimethoxyphenyl)-2-hydroxy-3-butenenitrile acetate.—13.96 g. (72.6 mmol) of the substance prepared sub 11*c* were shaken for 9 hours with a solution of 19.3 g. (102 mmol) of sodium metabisulphite in 60 ml. of water and 35 ml. of alcohol. The reaction mixture was left to stand overnight at 0° after which most of the alcohol was evaporated in vacuo at room temperature. Then 70 ml. of ether and 70 ml. of benzene were added after which the reaction mixture was cooled to 0° while stirring. Then, while stirring and at such a rate that the temperature of the reaction mixture did not exceed 10°, a solution of 19 g. of sodium cyanide in 35 ml. of water was added. Stirring was then continued at 0–5° for 4 hours. The layers were then separated and after the water layer had been diluted with 100 ml. of water it was extracted three times with a mixture of 20 ml. of benzene and 20 ml. of petroleum ether 40–60. The collected organic liquids were washed four times with 50 ml. of water and dried on sodium sulphate at 0°. After filtration a solution of 10 ml. of dry pyridine in 25 ml. of acetic anhydride was added to the cold solution in one portion. This mixture was stored for a few hours at 0° and then overnight at room temperature. Finally it was evaporated to dryness in vacuo. The remaining oil (15.0 g., 79%) was used for the following reaction without further purification.

(e) 1-amino-4-(2,5-dimethoxyphenyl) - 3 - butene - 2-ol.—15.0 g. (57.5 mmol) of the substance prepared sub 11*d* in 100 ml. of absolute ether were added dropwise while stirring and cooling at such a rate that the temperature of the reaction mixture did not exceed −5° to 8.6 g. of lithium aluminium hydride in 360 ml. of absolute ether. Stirring was continued for another 4 hours at a temperature between −5 and −10°. The reaction mixture was decomposed with 26 ml. of water, the temperature being kept below 10°. The hydroxides formed were sucked off and extracted three times with 150 ml. of warm chloroform. The combined filtrates were diluted with petroleum ether 40–60 until just cloudy and then left to stand overnight at 0°. 7.27 g. (57%) of white substance crystallised with melting point 109–111° C.

(f) 4 - (2,5-dimethoxyphenyl) - 1 - isopropylamino - 3-butene-2-ol hydrochloride.—This substance was prepared according to the method described in Example 8(b). Yield 87%. Melting point 156–158° C. (dec.).

EXAMPLE XII

4-(2-methoxyphenyl)-1-isopropylamino-3-butene-2-ol hydrochloride

(a) 4-(2-methoxyphenyl) - 2 - hydroxy - 3 - butenenitrile.—To a solution of 41.34 g. (0.25 mol) of o-methoxy cinnamic aldehyde in 400 ml. of ether was added a solution of 32.3 g. (0.17 mol) of sodium metabisulphite in 130 ml. of water. This mixture was stirred until the bisulphite compound was formed which was the case after approximately 10 minutes and then stirred for another hour. The mixture was then cooled in an ice bath to 5° and, while stirring, a solution of 31 g. of sodium cyanide in 75 ml. of water which was cooled in ice was added in one portion. The mixture was then stirred at 0–5° for 60 minutes, 3.6 g. of sodium metabisulphite were then added and stirring at 0–5° was continued for another 90 minutes. The layers were then separated and the water layer extracted two times with 100 ml. of ether. The collected ether extracts were washed twice with 100 ml. of a 20% sodium metabisulphite solution, twice with 100 ml. of water and finally dried on sodium sulphate. After filtration and evaporation of the solvents in vacuo the residue was evaporated to dryness in vacuo with 200 ml. of benzene. The residue, an orange-yellow oil, weight 41 g., would not crystallise and was used in the following reaction without further purification.

(b) 1-amino-4-(2-methoxyphenyl) - 3 - butene - 2 - ol hydrochloride.—A solution of 37.1 g. (0.196 mol) of the substance obtained sub 12*a* in 140 ml. of dry ether was added dropwise, while stirring, to a solution of 23 g. of lithium aluminium hydride in 700 ml. of dry ether. The temperature of the reaction mixture was kept between 0° and −5° by means of an ice-salt bath. The reaction mixture was then stirred for 4 hours, the temperature slowly increasing to room temperature, and then decomposed, while cooling, with 70 ml. of water at such a rate that the temperature did not exceed 15°. The mixture was then cooled at room temperature for 30 minutes after which the hydroxides formed were sucked off. The hydroxides were then extracted three times with 500 ml. of hot chloroform. The resulting filtrates were collectively evaporated to dryness in vacuo. A pale-yellow oil was obtained. To this oil the calculated quantity of alcoholic hydrochloric acid was added and then ether until the mixture just turned cloudy. The hydrochloric salt crystallised rather smoothly. This yielded 14.7 g. of substance with melting point 130.5–133° (dec.). It was recrystallised from a mixture of absolute alcohol and absolute ether; yield 11.6 g. with melting point 134.5–135.5° C.

(c) 4-(2-methoxyphenyl) - 1 - isopropylamino - 3 - butene-2-ol hydrochloride.—4.5 g. of the substance obtained sub 12*a* were dissolved in 50 ml. of water. To this solution were added 40 ml. of 2 N sodium hydroxide solution after which it was extracted three times with 100 ml. of ether. The ether extracts were dried on sodium sulphate. After filtering and evaporating to dryness in vacuo a white substance was formed which was dissolved in 60 ml. of methanol and 0.25 ml. of 2.22 N alcoholic hydrochloric acid and then 3 ml. of acetone (2.37 g.; 41 mmol) were added. After 30 minutes 1.2 g. of sodium borohydride were added and the mixture was boiled for one hour. The reaction mixture was then cooled to room temperature after which 4.0 ml. (3.16; 55 mmol) of acetone were added. Finally after 30 minutes 1.6 g. of

sodium borohydride were added and the whole was boiled for one hour. The reaction mixture was evaporated to dryness in vacuo and the residue dissolved in a mixture of 50 ml. of water and 50 ml. of ether. After separating the layers the water layer was extracted two times with 25 ml. of ether. The combined ether extract, after drying a sodium sulphate, were evaporated to dryness in vacuo. The residue was evaporated to dryness in vacuo once again after 100 ml. of chloroform had been added. The resulting residue (4.7 g.) crystallised. It was dissolved in 25 ml. of absolute alcohol, 9 ml. of 2.22 N alcoholic hydrochloric acid were then added and then 75 ml. of absolute ether. The hydrochloride began to crystallise practically immediately. It was then sucked off and dried in air. Yield 4.05 g. (74.6%) of substance with melting point 167.5–168.5° (dec.). The substance was finally recrystallised from isopropanol. Yield 3.21 g., melting point 169–170° C.

EXAMPLE XIII

1-n-octylamino-4-phenyl-3-butene-2-ol-oxalic acid

To a solution of 1.0 g. (6.1 mmol) of 1-amino-4-phenyl-3-butene-2-ol in 40 ml. of ethanol were successively added 1.8 g. (14 mmol) of n-octanal, a crystal of p-toluenesulphonic acid and 25 ml. of benzene. The solvents were distilled off as much as possible, the last traces in vacuo.

The residue was taken up in 25 ml. of methanol and 1.8 g. (47 mmol) of sodium tetrahydroborate were added in small portions while cooling with ice. The mixture was then boiled for an hour. The methanol was evaporated in vacuo and the residue shaken with 30 ml. of water and 60 ml. of ether. The layers were separated and the water layer extracted two times with 20 ml. of ether.

The combined ether extracts were washed with 25 ml. of water and dried on $MgSO_4$.

After filtration, a solution of 0.6 g. of oxalic acid in 8 ml. of ethanol was added to the concentrated solution.

A precipitate formed which, after sucking off, was washed with ether.

After recrystallisation from ethanol 1.4 g. of substance was obtained (62%) with melting point 170–172° C.

EXAMPLE XIV

1-phenoxyisopropylamino-4-phenyl-3-butene-2-ol

To a solution of 1.5 g. (0.009 mol) of 1-amino-4-phenyl-3-butene-2-ol in 60 ml. of ethanol were successively added 3.2 g. (0.02 mol) of phenoxyacetone, a crystal of p-toluenesulphonic acid and 40 ml. of benzene. The solvents were distilled off as much as possible, the last traces in vacuo.

The residue was taken up in 40 ml. of methanol and 2.5 g. (0.06 mol) of sodium tetrahydroborate were added in small portions while cooling with ice. The mixture was then boiled for 60 minutes. The methanol was evaporated in vacuo and the residue shaken with 40 ml. of water and 55 ml. of ether. The layers were separated and the water layer was shaken twice with 20 ml. of ether.

The combined ether extracts were washed with 25 ml. of water and dried on $MgSO_4$.

After filtration dry HCl was led into the ether. A precipitate was formed which was taken up in water.

The water layer was made alkaline with NaOH 2 N and extracted three times with ether (80 ml.). The ether extract was washed with 20 ml. of water and saturated NaCL-solution and dried on $MgSO_4$.

After filtration the ether was removed in vacuo. The residue was crystallised from a mixture of 20 ml. of benzene and 20 ml. of petroleum ether 40–60. Yield 1.69 g. (59%) melting point 77–78.5° C.

EXAMPLE XV

1-isopropylamino-4-(2-methylphenyl)-3-butene-2-ol-hydrochloride

From 2.5 g. (9.3 mmol) of 1-amino-4-(2-methylphenyl)-3-butene-2-ol-oxalic acid the isopropyl compound was prepared in a manner analogous to the synthesis of the 1-isopropylamino-4-(2,6-dimethoxy-phenyl)-3-butene-2-ol-hydrochloride. Melting point 175–177° C. (after recrystallisation from isopropanol).

EXAMPLE XVI

(a) 1-isopropylamino-4-(3-methoxyphenyl)-3-butene-2-ol hydrochloride.—10 ml. of 2 N NaOH were added to a solution of 4.25 g. (0.0186 mol) of 1-amino-4-(3-methoxyphenyl)-3-butene-2-ol hydrochloride in 15 ml. of water. The mixture was then shaken with chloroform: once with 50 ml. and once with 20 ml. After washing the chloroform extracts with water and drying on Na_2SO_4 the solvent was distilled off in vacuo. 3.33 g. (0.0173 mol=93%) of amine remained. The residue was dissolved in 55 ml. of methanol after which 2.6 ml. (2.0 g.=0.036 mol) of acetone and 0.25 ml. of 2.2 N alcoholic hydrochloric acid were added. After leaving to stand at room temperature for 30 minutes, 1.0 g. (0.026 mol) of $NaBH_4$ was carefully added. The mixture was boiled for one hour after which 3.5 ml. (2.8 g.=0.048 mol) of acetone were added. After leaving to stand for 30 minutes 1.4 g. (0.037 mol) of $NaBH_4$ were carefully added after which the mixture was boiled for another hour. The reaction mixture was evaporated to dryness in vacuo and 50 ml. of water and 50 ml. of ether were added to the residue. After all the solid had dissolved, the layers were separated and the water layer was washed two times with 25 ml. of ether. The ether extracts were dried on Na_2SO_4 and the ether was distilled off in vacuo. A residue of 3.89 g. remained which was dissolved in 10 ml. of absolute ethanol, after which 7 ml. of absolute alcoholic hydrochloric acid were added. After dilution with 100 ml. of absolute ether 3.74 g. (0.0138 mol) crystallised with melting point 124.5–126.5° C. UV spectrum E_{max}=13600 at λ=254 mμ.

(b) 1-amino - 4 - (3-methoxyphenyl)-3-butene-2-ol hydrochloride.—To a solution of 5.5 g. (0.144 mol) of $LiAlH_4$ in 150 ml. of absolute ether was added dropwise a solution of 9.17 g. (0.049 mol) of crude 2-hydroxy-4-(3-methoxyphenyl)-3-butenenitrile in 50 ml. of absolute ether. The temperature of the reaction mixture was maintained at approximately −10°. The mixture was then stirred at −15 to −10° for five hours. The mixture was then decomposed with 16.5 ml. of water, the temperature being kept below 10° by cooling with an ice/salt mixture. The hydroxides were sucked off and washed with some ether. The ethereal solutions were evaporated to dryness in vacuo, 4.09 g. of the residue having an equivalent weight of 224 remaining. The hydroxides were boiled four times with 50 ml. of chloroform. The chloroform was evaporated in which 3.58 g. of the residue remained with an equivalent weight of 248. The residue of 4.09 g. was dissolved in 50 ml. of absolute ethanol and acidified with 7 ml. of 2.2 N alcoholic hydrochloric acid. After the addition of 130 ml. of absolute ether 2.76 g. crystallised with a melting range of 133–162° C. The residue, 3.58 g., was converted into the hydrochloride in the same manner. 1.86 g. crystallised with a melting range of 138–160° C.

(c) 2-hydroxy-4-(3-methoxyphenyl)-3-butenenitrile.—A solution of 6.6 g. (0.035 mol) of sodium metabisulphite in 25 ml. of water was added to a solution of 8.21 g. (0.051 mol) of m-methoxy-cinnamic aldehyde in 80 ml. of ether. The mixture was stirred for 30 minutes and cooled in ice, after which a cold solution of 6.3 g. of NaCN in 15 ml. of water was added. The reaction mixture was then stirred for 2 hours while cooling with ice, 0.75 g. of $Na_2S_2O_5$ being added after 30 minutes. The

layers were separated, the water layer was washed two times with 15 ml. of ether and the collected ether layers were washed two times with 15 ml. of 20% sodium metabisulphite solution and two times wtih 15 ml. of water. The ethereal solution was dried on Na_2SO_4 and evaporated in vacuo. The residue was dried by azeotropic distillation of the water present with benzene in vacuo. A residue of 9.17 g. remained which would not crystallise and was further processed in the crude state.

EXAMPLE XVII

(a) 4 - (2-chlorophenyl)-1-isopropylamino-3-butene-2-ol hydrochloride.—3.66 g. (0.0156 mol) of 1-amino-4-(2-chlorophenyl)-3-butene-2-ol hydrochloride were added to a solution of 0.35 g. (0.015 mol) of sodium in 50 ml. of methanol, after which 2.35 ml. (1.85 g.=0.032 mol) of acetone were added. The mixture was left to stand at room temperature for 30 minutes after which 0.94 g. (0.025 mol) of $NaBH_4$ were carefully added. After refluxing on the steam bath for 60 minutes 3.0 ml. (2.4 g.=0.041 mol) of acetone were added. The mixture was again left to stand at room temperature for 30 minutes, after which 1.26 g. (0.033 mol) of $NaBH_4$ were added. The solution was again boiled for 60 minutes and then evaporated to dryness in vacuo. The residue was dissolved in 45 ml. of water and 45 ml. of ether, the layers were separated and the water layer was washed three times with 25 ml. of ether. The collected ether extracts were dried on Na_2SO_4 and the ether was evaporated in vacuo. The residue was dissolved in 10 ml. of absolute ethanol and acidified with 7.8 ml. of approximately 2 N alcoholic hydrochloric acid. The hydrochloride crystallised. Yield: 3.59 g. (0.013 mol=83%); melting point 182–185.5° C. UV spectrum: E_{max}=7180 at λ=249 mμ.

(b) 1-amino-4-(2-chlorophenyl)-3-butene-2-ol hydrochloride.—A solution of 7.39 g. (0.036 mol) of crude 4-(2-chlorophenyl)-2-hydroxy-3-butenenitrile in 100 ml. of absolute ether was added dropwise to a solution of 5.0 g. (0.13 mol) of $LiAlH_4$ in 150 ml. of absolute ether. The temperature of the reaction mixture was kept below —5°. The mixture was then stirred at —5° for five hours. The mixture was then decomposed with 15 ml. of water, the temperature being maintained below 5° by cooling with a mixture of ice/salt. 500 ml. of ether were added after which the reaction mixture was left to stand overnight at room temperature. The hydroxides were sucked off and washed with some ether. The ethereal solution was evaporated to dryness in vacuo, 5.3 g. of residue remaining. The hydroxides were boiled three times with 150 ml. of chloroform. The chloroform was evaporated, 1.5 g. of residue remaining. The residue, 5.3 g., was dissolved in 25 ml. of absolute ethanol and acidified with 10 ml. of approximately 2 N alcoholic hydrochloric acid. After dilution with absolute ether 3.86 g. (0.0165 mol=46%) crystallised with a melting range of 99–196° C. Recrystallisation from alcohol-ether did not change the melting point.

From the 1.5 g. of residue 0.51 g. of substance were obtained in the same manner as described above.

(c) 4-(2-chlorophenyl)-2-hydroxy-3-butenenitrile.—A solution of 4.7 g. (0.25 mol) of sodium metabisulphite in 20 ml. of water was added to a solution of 6.06 g. (0.036 mol) of o-chloro-cinnamic aldehyde in 60 ml. of ether. The mixture was stirred for one hour and cooled in ice, after which a cold solution of 4.4 g. of NaCN in 11 ml. of water was added. The reaction mixture was then stirred for two hours while cooling with ice, 0.5 g. of $Na_2S_2O_5$ being added after 30 minutes. The layers were separated, the water layer was washed two times with 10 ml. of ether and the collected ether layers were washed two times with 10 ml. of 20% sodium metabisulphite solution and two times with 10 ml. of water. The ethereal solution was dried over Na_2SO_4 and evaporated in vacuo. The residue was dried by azeotropic distillation of the water present with benzene in vacuo. A residue of 7.39 g. remained which would not crystallise and was further processed in the crude state.

EXAMPLE XVIII

(a) 1 - isopropylamino - 4 - (2 - propyloxyphenyl)-3-butene-2-ol hydrochloride.—4.00 g. (0.0181 mol) of 1-amino-4-(2-propoxyphenyl)-3-butene-2-ol were dissolved in 60 ml. of methanol, after which 2.7 ml. (2.14 g.=0.037 mol) of acetone and 0.25 ml. of approximately 2 N alcoholic hydrochloric acid were added. The reaction mixture was left to stand at room temperature for 30 minutes, after which 1.1 g. (0.029 mol) of $NaBH_4$ were carefully added. After refluxing on the steam bath for 60 minutes 3.7 ml. (2.94 g.=0.051 mol) of acetone were added and after 30 minutes at room temperature 1.5 g. (0.039 mol) of $NaBH_4$. The solution was boiled again for 60 minutes and then evaporated to dryness in vacuo. The residue was dissolved in 50 ml. of water and 50 ml. of ether, the layers were separated and the water layer was washed two times with 25 ml. of ether. The collected ether extracts were dried on Na_2SO_4 and the ether was evaporated in vacuo. The residue was dissolved in 20 ml. of absolute ethanol and carefully acidified with approximately 2 N alcoholic hydrochloric acid. After dilution of the alcoholic solution with 75 ml. of ether the hydrochloride crystallised. Yield 4.46 g. (0.015 mol=82%); melting point 170–172° C. UV spectrum E_{max}=15800 at λ=253 mμ.

(b) 1-amino-4-(2-propyloxyphenyl)-3-butene-2-ol.—A solution of 16.0 g. (0.060 mol) of crude 2-acetoxy-4-(2-propoxyphenyl)-3-butenenitrile in 200 ml. of ether was added dropwise to a solution of 15.0 g. (0.39 mol) of $LiAlH_4$ in 500 ml. of absolute ether. The temperature of the reaction mixture was kept below —6°. The mixture was then stirred at —10 to —5° for 4 hours. The mixture was then decomposed with 45 ml. of water, the temperature being kept below 10° by cooling with a mixture of ice salt. After leaving to stand overnight the hydroxides were sucked off and washed with some ether. The ethereal solution was evaporated to dryness in vacuo, 9.3 g. of residue having an equivalent weight of 411 remaining. The hydroxides were boiled three times with 100 ml. of chloroform. The chloroform was evaporated, 3.7 g. of residue having an equivalent weight of 412 remaining. The residues were joined and further processed. For that purpose the oil was dissolved in chloroform and shaken with 16 ml. of 2 N HCl and washed two times with water. The water layers were washed with ether and made alkaline with 16 ml. of 2 N NaOH. The alkaline water layer was then shaken out with ether and the ether dried on Na_2SO_4. After distilling the ether in vacuo 5.95 g. of residue remained. These were dissolved in 35 ml. of benzene and diluted with 70 ml. of petroleum ether. 4.51 g. (0.0205 mol=34%) crystallised with melting point 69–71° and an equivalent weight of 222.

(c) 2-acetoxy-4-(2-propyloxyphenyl)-3-butenenitrile.—A solution of 14.26 g. (0.075 mol) of 2-propoxy cinnamic aldehyde in 20 ml. of ether was added to a solution of 28.5 g. (0.150 mol) of sodium metabisulphite in 100 ml. of water. The ether was evaporated in vacuo without heating. The suspension formed of the aldehyde quickly reacted to the bisulphite compound. The mass was cooled to —10° and a solution of 19.5 g. (0.26 mol) of KCN in 35 ml. of water was added dropwise. The temperature was kept below —5°. After the addition of 50 ml. of ether the solution was stirred for three hours while cooling with ice until everything had dissolved. The ether and the water layer were separated. The water layer was washed three times with 60 ml. of ether and the ether layers two times with water. The ethereal solution was dried over Na_2SO_4 at 0° and filtered after which a mixture of 7.5 ml. of pyridine and 18.7 ml. of acetic acid anhydride was added dropwise while cooling with ice. After leaving to stand the weekend over the solution was evaporated to dryness in vacuo. 16.0 g. of residue remained which was further processed in the crude state.

(d) 2-propyloxy cinnamic aldehyde.—30.91 g. (0.10 mol) of 3-ethoxy-3-(2-propoxyphenyl) propanal diethylacetal were dissolved in 42 ml. of acetic acid and 2.5 g. of anhydrous sodium acetate were then added. The mixture was refluxed for three hours in a heating mantle in a nitrogen atmosphere. After cooling the solution was neutralised with a solution of 44 g. of Na_2CO_3 (anhydrous) in 170 ml. of water. The precipitated aldehyde was taken up in ether and the water layer was shaken out two times with ether. The ether was dried over Na_2SO_4 and evaporated in vacuo. 18.90 g. of residue remained. This residue was dissolved by heating in 50 ml. of ligroin. After cooling the solution was stored in the refrigerator and after having been left to stand overnight it was sucked off. 15.41 g. (0.081 mol=81%) of substance crystallised with melting point 38–40° C.

(e) 3-ethoxy-3-(2-propyloxyphenyl)-propanol diethylacetal.—1.1 ml. of a 10% zinc chloride solution in acetic acid were added to 25.72 g. (0.108 mol) of 2-propoxybenzaldehyde diethylacetal after which, while stirring, 11.5 ml. (8.6 g.=0.120 mol) of vinylethylether were added at such a rate that the temperature of the reaction mixture remained 50°. The mixture was boiled at approximately 50° for 60 minutes and 50 ml. of ether and 9.5 ml. of 2 N NaOH were then added. After thoroughly shaking the mixture the layers were separated and the ether layer was washed two times with 15 ml. of water. The ethereal solution was dried over Na_2SO_4 and the ether was evaporated. The residue was distilled and the fraction with boiling $point_{0.35}$ 124–130° C. was caught. Yield 30.91 g. (0.10 mol=92%).

(f) 2-propyloxybenzaldehyde diethylacetal.—19.2 g. (0.117 mol) of 2-propoxybenzaldehyde were mixed with 23.5 ml. (21=0.14 mol) of orthoformic acid ethyl ester and 24 ml. of absolute ethanol supra. 0.05 g. of p-toluenesulphonic acid were then added after which the mixture was left to stand overnight. The acid was neutralised by the addition of 2 ml. of approximately 0.5 N alcoholic alkaline. The mixture was then evaporated in vacuo and the residue was distilled. The main fraction had a weight of 25.77 g. (0.108 mol=93%), boiling $point_{0.35}$=97–99°.

EXAMPLE XIX

(a) 4-(2-ethoxyphenyl)-1-isopropylamino-3-butene-2-ol hydrochloride.—8.66 g. (0.0355 mol) of 1-amino-4-(2-ethoxyphenyl)-3-butene-2-ol hydrochloride were added to a solution of 1.12 g. (0.0350 mol) of sodium in 120 ml. of methanol and 5.5 ml. (4.3 g.=0.075 mol) of acetone were then added, after 30 minutes 2.15 g. (0.057 mol) of $NaBH_4$ were carefully added after which the reaction mixture was refluxed on the steam bath for 60 minutes. 7 ml. (5.5 g.=0.095 mol) of acetone were then added and, after leaving to stand for 30 minutes, 3.0 g. (0.078 mol) of $NaBH_4$ were added. The mixture was then heated again on the steam bath for 60 minutes. The solution was then evaporated in vacuo, after which the residue was dissolved in 100 ml. of water and 100 ml. of ether. The layers were separated and the water layer was washed two times with 25 ml. of ether. The collected ether extracts were evaporated to dryness in vacuo, a residue of 7.4 g. remaining. The residue was dissolved in 30 ml. of absolute ethanol, acidified with 10.6 ml. of 2.8 N alcoholic hydrochloric acid and diluted with 50 ml. of ether. 8.69 g. (0.030 mol=85%) of hydrochloride crystallised with melting point 182–183° C. UV spectrum E_{max}=16000 at λ=253 mμ.

(b) 1 - amino-4-(2-ethoxyphenyl)-3-butene-2-ol hydrochloride.—A solution of 17.0 g. (0.07 mol) of crude 2-acetoxy-4-(2-ethoxy-phenyl)-3-butenenitrile in 200 ml. of absolute ether was added dropwise to a solution of 11.0 g. (0.29 mol) of $LiAlH_4$ in 350 ml. of absolute ether. The temperature of the reaction mixture was kept below —5°. The mixture was then stirred at —10 to —5° for 4 hours. The mixture was then decomposed with 33 ml. of water, the temperature being kept below 10° by cooling with a mixture of ice/salt. After leaving to stand overnight the hydroxides were sucked off and boiled five times with 100 ml. of chloroform. The ether and chloroform fractions were combined and the solvent distilled off in vacuo. 14.4 g. of residue remained with an equivalent weight of 301. The residue was dissolved in 50 ml. of 1 N hydrochloric acid and shaken two times with 50 ml. of ether. The ether extracts were washed with 25 ml. of water. The water layer and the wash water were rendered alcoholic with 25 ml. of 2 N NaOH and shaken with two portions of 50 ml. of $CHCl_3$. The chloroform extracts were washed with water and dried over Na_2SO_4. The solvent was then distilled off in vacuo, 10.7 g. of residue remaining. After acidifying a solution of this residue with 16 ml. of 2.8 N alcoholic hydrochloric acid, 8.66 g. (0.035 mol=50%) of hydrochloride could be isolated with melting-point 160–162° C.

(c) 2 - acetoxy-4-(2-ethoxyphenyl)-3-butenenitrile.—A solution of 17.60 g. (0.100 mol) of 2-ethoxy cinnamic aldehyde in 25 ml. of ether was added to a solution of 38.0 g. (0.200 mol) of sodium metabisulphite in 130 ml. of water. The ether was evaporated in vacuo in the cold. Initially a suspension of the aldehyde was formed, then by the formation of the bisulphite compound, a bright solution was formed from which the bisulphite compound crystallised. 50 ml. of ether were added. The mass was cooled to —5° after which a solution of 26.0 g. (0.35 mol) of KCN in 45 ml. of water was added dropwise. The temperature was kept at approximately 3°. After the addition of all the reagent the solution was stirred for 3.5 hours while cooling with ice. The ether and water layers were separated, the water layer was washed four times with 50 ml. of ether and the ether layers were washed two times with water. The ethereal solution was dried at 0° over Na_2SO_4 and filtered after which a mixture of 10 ml. of pyridine and 25 ml. of acetic acid anhydride was added dropwise, while cooling with ice. After leaving to stand overnight the ether and the excess of reagent were evaporated in vacuo. 17.0 g. (0.07 mol=70%) of an oily residue remained which was further processed in the crude state.

(d) 2-ethoxy cinnamic aldehyde.—36.5 g. (0.116 mol) of 3-ethoxy-3-(2-ethoxyphenyl) propanal diethylacetal were dissolved in 49 ml. of acetic acid after which 2.9 g. of anhydrous sodium acetate were added. The mixture was refluxed in a heating mantle in a nitrogen atmosphere for three hours. After cooling the solution was neutralised with a solution of 51 g. of Na_2CO_3 (anhydrous) in 200 ml. of water. The precipitated aldehyde was shaken up in some ether and the water layer was shaken two times with ether. The ether was dried over Na_2SO_4 and evaporated in vacuo. The resulting residue was dissolved in 50 ml. of ligroin and the solution was stored in the refrigerator. After leaving to stand the weekend over 17.79 g. (0.101 mol=87%) had crystallised with melting point 34–36° C.

(e) 3 - ethoxy-3-(2-ethoxyphenyl)-propanal diethylacetal.—2 ml. of 10% zinc chloride solution in acetic acid were added to 45.0 g. (0.20 mol) of 2-ethoxybenzaldehyde diethylacetal after which, while stirring, 23 ml. (17.5 g.=0.24 mol) of vinylethylether were added dropwise at such a rate that the temperature of the reaction mixture remained 50°. The mixture was stirred at approximately 50° for 60 minutes after which 50 ml. of ether and 40 ml. of 2 N KOH were added. After thoroughly shaking the mixture the layers were separated and the ether layer was dried over K_2CO_3. The ether was distilled off in vacuo and the residue (56.4 g.) was distilled in vacuo, a main fraction of 47.63 g. (0.170 mol=85%) being caught with boiling $point_{0.45}$ 118–122° C.

(f) 2 - ethoxybenzaldehyde diethylacetal.—116.44 g. (0.77 mol) of 2-ethoxybenzaldehyde were mixed with 154 ml. (136 g.=0.91 mol) of orthoformic ethyl ester and 160 ml. of absolute ethanol supra. 0.30 g. of p-toluene-

sulphonic acid were then added after which the mixture was left to stand overnight. After boiling the solution for 30 minutes 6.2 ml. of 0.5 N alcoholic alkali were added, after cooling. The mixture was then evaporated in vacuo and the residue was distilled in vacuo. The main fraction had a weight of 164.4 g. (0.73 mol=95%) boiling $point_{0.11}$=130–133° C.

EXAMPLE XX

(a) 1 - isopropylamino - 4 - (2-methylthiophenyl)-3-butene-2-ol hydrochloride.—0.37 ml. (0.28 g.=0.005 mol) of acetone were added to a solution of 0.48 g. (0.0023 mol) of 1-amino-4-(2-methylthiophenyl)-3-butene-2-ol in 10 ml. of methanol after the addition of one drop of 2 N alcoholic hydrochloric acid. After leaving to stand for 30 minutes 0.15 g. (0.0040 mol) of $NaBH_4$ were added after which the mixture was boiled for 60 minutes. 0.5 ml. of acetone were then added and after leaving to stand for 30 minutes 0.2 g. of $NaBH_4$ were added after which the mixture was boiled for another 60 minutes. The mixture was evaporated to dryness in vacuo and the residue was dissolved in 10 ml. of water and 10 ml. of ether. The layers were separated, the water layer was washed two times with 5 ml. of ether. The ether layers were dried over Na_2SO_4 after which the ether was evaporated. The residue (0.55 g.) was dissolved in 2 ml. of absolute ethanol and acidified with the calculated quantity of 2 N alcoholic hydrochloric acid. The solution was diluted with 10 ml. of absolute ether after which the salt crystallised. Yield 0.57 g. (0.00098 mol=86%). Melting point 170–174° C.

(b) 1 - amino-4-(2-methylthiophenyl)-3-butene-2-ol.—A solution of 4.57 g. (0.019 mol) of crude 2-acetoxy-4-(2-methyl-thiophenyl)-3-butenenitrile in 50 ml. of absolute ether was added dropwise to a solution of 3.0 g. (0.078 mol) of $LiAlH_4$ in 100 ml. of absolute ether. The temperature of the reaction mixture was kept at −10 to −5°. The mixture was then stirred for 4 hours at −10 to −5°. The mitxure was then decomposed with 9 ml. of water while cooling with ice. The hydroxides were sucked off and washed three times with 20 ml. of ether. The amine crystallised in the filtrate. The filtrate was diluted with petroleum ether until just cloudy. 0.48 g. of amine crystallised with melting point 78–83° C. A second portion of amine can be isolated by washing the hydroxides with chloroform succeded by drying and evaporating the extracts.

(c) 2 - acetoxy - 4 - (2 - methylthiophenyl)-3-butenenitrile.—A solution of 5.48 g. (0.031 mol) of 2-methylthiocinnamic aldehyde in 30 ml. of ether was added to a solution of 12 g. of sodium metabisulphite in 40 ml. of water. The ether was evaporated in vacuo without heating. The bisulphite compound crystallised. 30 ml. of ether were added to the suspension of the bisulphite compound. The mixture was cooled to 0° and a solution of 8.0 g. (0.108 mol) of KCN in 14 ml. of water was added dropwise. The temperature was kept below 5°. The mixture was stirred for another three hours while cooling with ice after which the layers were separated. The water layer was shaken four times with 15 ml. of ether. The ether layers were washed two times with water and then dried over Na_2SO_4 at 0°. The solution was filtered after which, while cooling with ice, a mixture of 3 ml. of pyridine and 8 ml. of acetic acid anhydride was added dropwise. After leaving to stand the weekend over at room temperature the solution was evaporated to dryness in vacuo. 4.57 g. of residue were obtained which were further processed without further purification.

(d) 2-methylthiocinnamic aldehyde.—11.55 g. (0.0387 mol) of 3-ethoxy-3-(2-methylthiophenyl)- propanol diethylacetal were dissolved in 16 ml. of acetic acid, after which 0.97 g. of anhydrous sodium acetate were added. The mixture was refluxed in a heating mantle in a nitrogen atmosphere for three hours. After cooling the solution was neutralised with a solution of 17 g. of Na_2CO_3 (anhydrous) in 65 ml. of water. The aldehyde was taken up in 100 ml. of ether and the water layer was washed with 50 ml. of ether. The ether was dried over Na_2SO_4 and evaporated in vacuo. 6.94 g. of residue were obtained which were recrystallised from 50 ml. of ligroin. 5.48 g. (0.031 mol=80%) crystallised with melting point 73–76° C.

(e) 3 - ethoxy - 3-(2-methylthiophenyl)-propanol diethylacetal.—0.3 ml. of a 10% $ZnCl_2$ solution in glacial acetic acid were added to 8.87 g. (0.039 mol) of 2-methylthiobenzaldehyde diethylacetal and then, while stirring, 4.2 ml. (3.2 g.=0.044 mol) of vinylethylether were added at such a rate that the temperature of the reaction mixture remained 50°. The mixture was stirred at 50° for 60 minutes and then 20 ml. of ether and 3.5 ml. of 2 N NaOH were added. After thoroughly shaking the mixture the layers were separated and the ether layer was washed two times with 5 ml. of water. The ether was dried and evaporated, 11.55 g. (0.038 mol=99%) of coupling product remaining.

(f) 2 - methylthiobenzaldehyde diethylacetal.—7.0 g. (0.046 mol) of 2-methylthiobenzaldehyde were mixed with 9 ml. (8 g.=0.05 mol) of orthoformic acid ethyl ester, 9.5 ml. of absolute ethanol supra and 0.02 g. of p-toluenesulphonic acid after which the mixture was left to stand overnight at room temperature. After adding 0.2 ml. of 0.5 N alcoholic alkaline the excess of ethanol and orthoformic acid ethyl ester was evaporated in vacuo. The residue was distilled. The main fraction with boiling point 88–91° C. at 0.15 mm. had a weight of 9.07 g. (0.040 mol=87%).

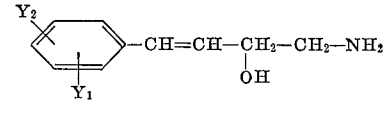
Other examples of compounds according to the invention are:

1-cyclopentylamino-4-phenyl-3-butene-2-ol;
1-octylamino-4-phenyl-3-butene-2-ol;
1-tert.butylamino-4-phenyl-3-butene-2-ol;
1-sec. butylamino-4-phenyl-3-butene-2-ol;
1-(2-p-hydroxyphenyl-1-methylethylamino)-4-phenyl-3-butene-2-ol;
1-(2-p-methoxyphenyl-1-methylethylamino)-4-phenyl-3-butene-2-ol;
1-(3-p-methylphenylpropylamino)-4-phenyl-3-butene-2-ol;
1-[3-(3,4-dimethoxy phenyl)-1-methylpropylamino]-4-phenyl-3-butene-2-ol;
1-[3-(3,4-dimethylphenyl)-1-methylpropylamino]-4-phenyl-3-butene-2-ol;
1-(2-phenoxyethylamino)-4-phenyl-3-butene-2-ol;
1-(1-methyl-2-phenoxyethylamino)-4-phenyl-3-butene-2-ol;
1-(2-p-ethoxyphenoxy-1-methylethylamino)-4-phenyl-3-butene-2-ol;
1-(2-p-methylphenoxyethylamino)-4-phenyl-3-butene-2-ol;
1-isopropylamino-4-p-methylphenyl-3-butene-2-ol;
4-p-chlorophenyl-1-isopropylamino-3-butene-2-ol;
1-isopropylamino-4-o-methoxyphenyl-3-butene-2-ol;
1-isopropylamino-4-o-methylphenyl-3-butene-2-ol;
4-(3,4-dichlorophenyl)-1-isopropylamino-3-butene-2-ol;
4-p-bromophenyl-1-isopropylamino-3-butene-2-ol;
4-p-chlorophenyl-1-(1-methyl-3-phenylpropylamine)-3-butene-2-ol;
4-p-methylphenyl-1-(1-methyl-2-phenoxyethylamino)-3-butene-2-ol;

and pharmaceutical acceptable said addition salts thereof.

What is claimed is:

1. A member selected from the group consisting of the styrylethanol amines of the formula:

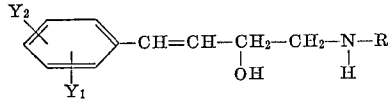


wherein Y_1 and Y_2 are each independently selected from the group consisting of hydrogen, alkyl of 1–4 carbon atoms, alkoxy of 1–4 carbon atoms and alkylthio of 1–4 carbon atoms and the pharmaceutically acceptable acid addition salts thereof.

2. As styrylethanol amines of claim 1, 1-amino-4-phenyl-3-butene-2-ol and pharmaceutical acceptable acid addition salts thereof.

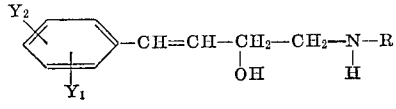
3. As styrylethanol amines of claim 1, 1-amino-4-(4-methoxyphenyl)-3-butene-2-ol and pharmaceutical acceptable acid addition salts thereof.

4. A member selected from the group consisting of the styrylethanol amines of the formula:



wherein R is a member selected from the group consisting of aralkyl of 7 to 10 carbon atoms and nuclear substituted derivatives wherein the substituent is lower alkyl, lower alkoxy, halogen or hydroxyl thereof Y_1 and Y_2 are each independently selected from the group consisting of hydrogen, halogen, alkyl of 1–4 carbon atoms, alkoxy of 1–4 carbon atoms and alkylthio of 1–4 carbon atoms and the pharmaceutically acceptable acid addition salts thereof.

5. As styrylethanol amines of claim 4, a member selected from the group consisting of the styrylethanol amines of the formula:



wherein R is phenoxyalkyl of 8 to 9 carbon atoms, Y_1 and Y_2 are each independently selected from the group consisting of hydrogen, halogen, alkyl of 1–4 carbon atoms, alkoxy of 1–4 carbon atoms and alkylthio of 1–4 carbon atoms and the pharmaceutically acceptable acid addition salts thereof.

6. As styrylethanol amines of claim 4, 1-(1-methyl-3-phenylpropylamino)-4-phenyl-3-butene-2-ol and pharmaceutical acceptable acid addition salts thereof.

7. As styrylethanol amines of claim 4, 1-(2-p.phdroxyphenyl-1-methylethylamino) - 4-phenyl-3-butene-2-ol and pharmaceutical acceptable acid addition salts thereof.

8. As styrylethanol amines of claim 4, 1-(2-p.methoxyphenyl-1-methylethylamino) - 4 - phenyl - 3 - butene-2-ol and pharmaceutical acceptable acid addition salts thereof.

9. As styrylethanol amines of claim 4, 1-(3-p. methylphenylpropylamino)-4-phenyl-3-butene-2-ol and pharmaceutical acceptable acid addition salts thereof.

10. As styrylethanol amines of claim 4, 1-[3-(3,4-dimethyloxyphenyl)-1-methylpropylamino] - 4 - phenyl-3-butene-2-ol and pharmaceutical acceptable acid addition salts thereof.

11. As styrylethanol amines of claim 4, 1-[3-(4-dimethylphenyl)-1-methylpropylamino] - 4 - phenyl-3-butene-2-ol and pharmaceutical acceptable acid addition salts thereof.

12. As styrylethanol amines of claim 4, 1-(2-phenoxyethylamino)-4-phenyl-3-butene-2-ol and pharmaceutical acceptable acid addition salts thereof.

13. As styrylethanol amines of claim 4, 1-(1-methyl-2-phenoxyethylamino)-4-phenyl-3-butene-2-ol and pharmaceutical acceptable acid addition salts thereof.

14. As styrylethanol amines of claim 4, 1-(2-p.ethoxyphenyl-1-methylethylamino)-4-phenyl - 3 - butene - 2 - ol and pharmaceutical acceptable acid addition salts thereof.

15. As styrylethanol amines of claim 4, 1-(2-p.methylphenoxyethylamino)-4-phenyl-3-butene-2-ol and pharmaceutical acceptable acid addition salts thereof.

16. As styrylethanol amines of claim 4, 4-p.chlorophenyl-1-(1-methyl-3-phenylpropylamino) - 3 - butene-2-ol and pharmaceutical acceptable acid addition salts thereof.

17. As styrylethanol amines of claim 4, 4-p.methylphenyl-1-(1-methyl-2-phenoxyethylamino) - 3 - butene-2-ol and pharmaceutical acceptable acid addition salts thereof.

References Cited

UNITED STATES PATENTS

3,395,143 7/1968 Thiele et al. ------ 260—570.5X

ROBERT V. HINES, Primary Examiner

U.S. Cl. X.R.

260—141, 348, 348.6, 456, 465, 501.11, 501.12, 501.17, 501.18, 544, 546, 566, 570.5, 570.6, 590, 592, 599, 600, 613, 618; 424—330