METHOD OF MANUFACTURING THE INDIVIDUAL RACEMATES OF N-(P-HYDROXYPHENYL-ISOPROPYL) ARTERENOL AND PRODUCTS


No Drawing. Filed June 26, 1962, Ser. No. 205,203
Claims priority, application Netherlands, July 6, 1961, 2,660,787

15 Claims. (Cl. 260—501)

It is known from Dutch patent specification No. 86,359 that a compound according to Formula I

\[ \text{HO-CHOH-CH-NH-CHCH=CH-CH-OH} \]

has properties which are particularly interesting in pharmacological respect, so that this substance may be used in medicine notably as a bronchopasmodyl tic. As is well-known, the said compound is preferably manufactured by reducing a ketone of Formula II

\[ \text{HO-CH=CH-NH-CHCH=CH-CH-OH} \]

to the alcohol of Formula I.

However, a particular disadvantage of the product thus obtained results from the fact that two asymmetrical centres, indicated by \( a \) and \( b \) in Formula I, are present in the molecule. When starting in the usual way from the racemic ketone of Formula II, the asymmetrical centre \( a \) is introduced during reduction, so that the resulting product consists of a mixture of two pairs of optical antipodes. If the possible configurations of the centres \( a \) and \( b \) are indicated by \( l \) or \( d \) and \( 1' \) or \( d' \) respectively, the four stereoisomers \( l'd'd' \), \( l'd'd' \), \( d'1'd' \) and \( d'1'd' \) occur. When starting from the racemic ketone, the sums of the compounds having configurations \( l'd \) and \( 1'1 \) and those having configurations \( d'd \) and \( d'1 \) are then equal, it is true, but the two different racemates \( l'd+d'1' \) and \( d'1+l'1 \) may all the same be present in different amounts. As regards the stereospecificity of the reduction of the ketone according to Formula II it can only be predicted that certainly not only one of the two possible racemates will be formed, but on the other hand it may not be taken for certain that the two racemates necessarily occur in equal amounts, in other words, that stereospecificity may not occur at all in this reaction. Even if stereospecificity would not occur at all in this reaction, a mixture of racemates of variable composition could otherwise still be obtained, for example due to differences in solubility of the two racemates. For the use of a therapeutically active substance in medicine it is very important to have the security that the substance to be administered is always the same. For the manufacture of the bronchopasmodylic substance Formula I this means that either the mixture of racemates is separated into its two components, or use is made of a manufacturing method in which the two racemates are always obtained in the same mixing ratio. Now, in conventional manufacturing methods, the situation is such that a mixture of racemates is always obtained from the free base of which has a melting point of about 167° C., but this melting takes place with dissociation so that it must not be concluded therefrom that the composition of the mixture is constant. Thus, also if the mixture of racemates obtained by reduction of the ketone of Formula I is desired to be used as such, it is necessary first to manufacture the individual racemates and test the properties thereof, in order to be able to determine the composition of the remelting mixture with the aid of any differences found in the properties of the two pure racemates. As a matter of fact in such a test of the pure racemates, their pharmacological properties will also be examined thoroughly, not only to determine if one of the two racemates may have substantially the bronchopasmodylic activity known for the mixture, but also to find out how additional actions and any further actions present in the mixture in eventually masked form are divided over the two components of the mixture.

However, it has been found very difficult to separate the mixture of racemates of Formula I into the pure racemic components. None of the methods known for separating such a mixture of racemates yields the desired result. The mixture of racemic bases could be obtained in crystalline form only from the crystallization from water described in the aforementioned Dutch patent specification. It appeared impossible to isolate fractions of different properties by fractional crystallizations. Another point is that such catecholamines are very oxidizable so that dissociation readily occurs during prolonged crystallizations. Also salts of bases according to Formula I were found to be crystallizable very difficultly and unsuitable for separating the mixture of racemates by fractional crystallization.

According to the present invention, this problem which is specific for the manufacture of racemically pure compounds of Formula I, may be solved by first manufacturing in known manner a mixture of racemates of the tribenzyl ether of Formula III

\[ \text{CH-O-CHOH-CH-NH-CHCH=CH-CH-OH} \]

It was found that pure racemates could be obtained from a mixture of racemates of the said new compound by fractional crystallization either of the free bases, or of salts of the mixture. The racemically pure compounds of Formula I are obtained by subsequently splitting off the benzyl groups from the racemically pure tribenzyl ethers by a method known per se for this type of reactions, for example by catalytic hydrogenation.

In conformity therewith the present invention relates to a method of manufacturing racemically pure compounds of Formula I or salts thereof and is characterized in that a mixture of racemates of Formula III or of salts thereof is manufactured by methods known per se and the racemically pure compounds are isolated from this mixture by fractional crystallization, these racemically pure tribenzyl ethers subsequently being converted into the pure racemic compounds of Formula I or salts thereof by hydrolysis or hydrogenation.

The mixture of racemates of the tribenzyl ether according to Formula III is preferably manufactured by reduction of the corresponding ketone of Formula IV
which ketone may be obtained, for example, by condensation of the a-bromine ketone of Formula V

\[
\text{CH}_3\text{O} - \text{CH}_2\text{Br}
\]

with the amine of Formula VI

\[
\text{H}_2\text{N} - \text{CH}_2\text{CH}_2\text{O} - \text{CH}_2\text{CH}_3
\]

The reduction of the tribenzyl ketone to the corresponding alcohol must naturally be effected so that the benzyl groups are not preferably reduced to the alcohol with the aid of a metal hydride, such as LiAlH₄ or NaBH₄, or a dialkylaluminium hydride, such as diisobutylaluminium hydride or diisopropylaluminium hydride. Very satisfactory results are obtained, for example if the reduction of the ketone is effected with the aid of NaBH₄ in water, or in a lower aliphatic alcohol, for example methanol or ethanol or in mixtures of these alcohols and water.

According to the invention, the resulting racemic mixture of free bases or salts thereof is fractionated by fractional crystallization. Alternatively, various fractions of the mixture of free bases may first be crystallized and then converted into salts, whereafter the various salt fractions are purified further by fractional crystallization.

Suitable solvents for the crystallizations are aromatic or aliphatic hydrocarbons, for example benzene, toluene or petroleum ether, ethers, for example diethyl ether, diisopropyl ether, tetrahydrofuran or dioxane, lower aliphatic alcohols, for example methanol, ethanol, propanol or butanol, ketones, for example acetone, methyl ethyl ketone or methylisobutyl ketone or mixtures of these solvents.

Thus, for example, from the crystalline mixture of bases as obtained, in substantially theoretical yield, by reduction of the ketone with a melting range of about 55° to 75° C., two fractions were crystallized by fractional crystallization from ether, one having a melting range from 69° to 76° C., hereinafter referred to as the tribenzyl-α base, and a second fraction melting at 92.5° to 94.5° C., referred to as the tribenzyl-β base. The two fractions could be converted, by treatment with benzolic acid, into sharply-melting benzolic acid salts: the tribenzyl-α benzoate with melting point from 156° to 158° C. and the tribenzyl-β benzoate with melting point from 138° to 139° C.

A characteristic of the tribenzyl-α base is that it may occur in two modifications of different melting points. In fact, it has been found that, if the base melting at about 72° C. is converted to the corresponding benzoate with melting point from 156° to 158° C. and if this base was then isolated again by adding water to an aqueous solution of this salt, now a base with a melting point of 72° C., and now one with a melting point of 88° C. was obtained, without it being possible to indicate what circumstances are determinative of the formation of one modification or the other. The fact that the same pure base in two different modifications is concerned may be concluded from the following points:

(a) A base with the one melting point as well as one with the other melting point could be obtained from the same sharply-melting base via the benzoate.

(b) Mixing the base of the lower melting point with a small amount of the base of the higher melting point caused a rise in melting point of the mixture to about 85° C.

(c) Either base provides, in quantitative yield, the sharply-melting benzoate with melting point from 156° to 158° C.

(d) Upon heating above the melting point (about 80° C.) the base of the lower melting point resolidified. The resulting product melted at 84.5° to 89° C.

From both the pure tribenzyl-α base and the tribenzyl-β base, a plurality of pharmacologically acceptable acid addition crystalline salts could be obtained such as, for example: the p-nitrobenzoate with melting points from 133° to 134° C. and from 126° to 127° C., respectively; the nicotinate with melting points from 129° to 130° C. and from 135° to 136° C., respectively; the maleinate with melting points from 122° to 124° C. and from 137.5° to 138° C., respectively; the hydrochloride with melting points from 98° to 99° C. and from 95° to 97° C., respectively.

Thus, such salts of the pure racemic bases may also be isolated from the racemic mixture of bases obtained upon reduction of the tribenzyl ketone, by first converting this mixture of bases into a mixture of salts and then separating the mixture of salts by fractionated crystallization.

More particularly a conversion of the mixture of bases into the p-toluene sulphonate was found to give very satisfactory results. In fact, this salt of the tribenzyl-α compound crystallizes very difficulty, whereas that of the tribenzyl-β compound is readily obtained in crystalline form. For example the mixture of bases is dissolved in a mixture of from 50% to 95% of ethanol and from 50% to 5% of water, then an equivalent amount of p-toluene sulphonic acid is added thereto whereafter the solution is incubated with crystals of the p-toluene sulphonic acid salt of the tribenzyl-β-racemate. It has been found that only the salt of the tribenzyl-β base then crystallizes in pure form with a melting point from 137° to 138.5° C. From this salt, the pure tribenzyl-β base with melting point from 94° to 95° C. is obtained by hydrolysis.

The residue of the base is separated from the filtrate of the crystallized salt by adding caustic-soda lye and from this the pure tribenzyl-β-racemate may be formed after recrystallization.

Of the resulting pure racemates of Formula III or of salts thereof, the benzyl groups may be replaced, by methods known per se by hydrogen atoms for obtaining the racemically pure compounds of Formula I.

The compounds of Formula III are preferably converted into those of Formula II by hydrogenation in the presence of Raney nickel or a catalyst of rare metal. The compound of Formula I is obtained in good yield in a simple manner, more particularly by hydrogenation of a salt of the compound according to Formula III, for example of the benzoic-acid salt, with the aid of a palladium catalyst.

The differences in melting points (dissociation points) of both the salts and the free bases of the pure racemates of Formula I thus, obtained, were found to be particularly small. Also the dissociation points of the racemically pure bases differ but slightly from that of the mixture of racemic bases manufactured in accordance with Dutch patent specification No. 86,359.

The two benzoates show clear differences in crystal form, that of the a-base crystallizing from water into rosettes which do not weather in drying after having been dried over P₂O₅ in vacuo at 60° C. and the benzoate of the β-base crystallizing from water into thin plates containing about 11% of crystal water. This β-benzoate is hygroscopic after drying over P₂O₅.

In a provisional pharmacological test it could be ascertained that the β-racemate had a broncho spasmodic activity about thrice that of the α-racemate.

EXAMPLES

A. Manufacture of the mixture of racemates from the compound of Formula III

(a) 4-benziloxyl-β-methyl-β-nitrostyrene. — 153 g. (0.720 mol.) of p-benziloxylbenzaldehyde, 72.5 ml. (76.0 g. = 1.01 mol.) of nitro-ethane and 31.5 ml. of n-butyl amine, dissolved in 200 ml. of toluene, were boiled for 18.5 hours while the liberated water was distilled. Then the toluene was distilled at reduced pres-
sure, during which process the above-mentioned product crystallized spontaneously. After washing with petroleum ether, 0.43 mol. of crystalline product was obtained (this is 60%) with melting point from 144° to 146° C.

(b) 2-(4'-benzoyloxyphenyl)-1-methyl ethyl amine.—
A hot solution (35° C.) of 78.5 gs. (0.292 mol.) of 4-benzoyloxy-phenyl-ethylyamine was added while stirring to a suspension of 50 gs. of LiAlH₄ in 850 mls. of tetrahydrofuran within a period of 3/4 of an hour. Boiling the mixture for another hour was followed by cooling below room temperature, whereupon 70 mls. of water were added under ice cooling. After several hours stay, the deposit was filtered off and washed with tetrahydrofuran. The filtrates and the washing liquid were dried together with Na₂SO₄ and then evaporated to dryness at reduced pressure. The crystalline residue (59 gs.) was again dissolved in 50 mls. of diethyl ether and this solution extracted with 150 mls. of 2 n HCl. The hydrochloric acid aqueous layer was subsequently washed with ether and then 35 mls. of 50% NaOH soln. were added. The alkaline solution was extracted with ether, the ethereal solution dried with Na₂SO₄ and then evaporated to dryness. The crystalline residue weighed 52 gs. (74% Eq. weight 244, calculated 241. (c) N-4-benzoyloxyphenylisopropyl-β-(3′,4′-dibenzoyloxyphenyl)-α-oxoethyl amine (Formula IV)—139.4 gs. (0.58 mol.) of 2-(4′-benzoyloxyphenyl)-1-methyl-ethyl amine were dissolved in 250 mls. of absolute ethanol and this solution had added to it at room temperature 95.5 gs. (0.232 mol.) of finely powdered 3′,4′-dibenzoyloxy-2-brom-acetophenone (Recueil 71 (1952), 933). After shaking for a few minutes, a clear solution was obtained, the temperature rising to about 35° C. The HBr-salt of the initial amine present in excess started crystallizing. After shaking the mixture for another 20 minutes, 1300 mls. of diethyl ether were added. The deposit was washed off and washed with ether, the washing water added to the filtrate and then 400 cc. of 2 n hydrochloric acid added to this liquid. A crystalline deposit then re-solved, which was filtered off and washed successively with 2 l. of water and 2 l. of ether. After drying, 83 gs. (0.137 mol.) of N-(4-benzoyloxyphenylisopropyl)-β-(3′,4′-dibenzoyloxyphenyl)-β-hydroxy-ethyl amine (Formula III) were obtained (0.11 mol.) dissolved in 50 mls. of water, and 200 mls. of tetrahydrofuran were added to a solution of 67.0 gs. (0.111 mol.) of the hydrochloride of the tribenzyl ketone, obtained as described sub c), in 1.7 litres of methanol. Immediately thereafter 13.0 gs. (0.245 mol.) of NaOH in 500 mls. of methanol and 5 mls. of 2 n NaOH were added to this solution. The mixture was heated to boiling point and then boiled for another 2 hours with reflux cooling. Subsequently 1.5 litres of solvent were removed by evaporation at reduced pressure, whereafter 2 litres of water were added and another 1.6 litres of liquid distilled again at reduced pressure. Next, an oil was separated in the remaining liquid. 500 mls. of benzene were added, in which the oil dissolved. The benzene and the aqueous layer were separated, the benzene phase dried with Na₂SO₄ and evaporated to dryness in vacuo to form a sticky residue. The residue was dissolved in 150 mls. of diethyl ether while heating. After a short stay at room temperature, the base crystallizes from this solution. The crystallisate was filtered off, washed with ether and dried. Yield 60 gs. this is 94%. The mixture of race- mates had a melting range about from 55° to 75° C.

B. Separation of the mixture of racemates of tribenzyl compounds

(1) By fractional crystallization of the free bases.—
30 gs. of the racemic mixture of the bases of Formula III obtained as described sub A were dissolved in 150 mls. of diethyl ether. After storage at room temperature for 16 hours there was a beginning of crystallization. After scratching and another hour's stay, 8.3 gs. of crystallize with melting point from 65.5° to 72° C. could be separated. After crystallization from a mixture of benzene and petroleum ether, 7 gs. of the tribenzyl-α base with melting point from 69° to 72° C. were obtained therefrom.

The ether filtrate of this first fraction was stored in a refrigerator (0 to 5° C.) for 1½ hours, whereafter a second crystallization of 7.5 gs. with melting range from 83° to 92° C. was sucked off. After crystallization to constant melting point from a mixture of benzene and petroleum ether, 4.5 gs. of the tribenzyl-β base with melting point from 92° to 94° C. could be obtained from this fraction.

Of the two racemates, for example the benzonic-acid salts were obtained in the following manner:
5.7 gs. of base and 1.7 gs. of benzoic acid were dissolved in 250 mls. of ethanol. Then 30 mls. of water were added, whereafter the base was filtered off and washed with ethanol and water (5:2), the pure salts were obtained, the α-benzate with melting point from 153.5° to 154° C. (after crystallization from benzene to benzene from 156° to 158° C.), the β-benzate with melting point from 138.5° to 139° C.

From these salts, the racemically pure bases were obtained again in substantially theoretical yield by taking up the salt in water, adding dilute caustic soda lye, extracting the solution with ether and allowing the base after partial evaporation to dryness to crystallize from the ether. In this process the α-base showed the remarkable phenomenon that now the modification with a melting point of about 72° C. and now that with a melting point of about 88° C. crystallized. (II) Separation of the mixture of racemates of tribenzyl by first converting the mixture of free bases into a mixture of salts.—61.4 gs. of (0.107 mol.) of a mixture of bases of tribenzyl obtained as described sub A, were taken up in 900 mls. of ethanol, whereafter a solution of 18.5 gs. (0.108 mol.) of p-toluene-sulfonic acid in 100 mls. of water and 75 mls. of diethyl ether were added.

After 5 days stay at room temperature, 26 gs. of crystallize with a melting range (dissociation) from 132° to 137° were filtered off. Half a litre of solvent was removed from the filtrate by evaporation, whereupon after another 4 days stay another 3.5 gs. of crystallize, melting from 133° to 137° C., were collected. The crystallizes were dissolved together while shaking, in a mixture of 150 mls. of petroleum ether consisting of 150 mls. of petroleum ether, 25 mls. of 2 n NaOH and 200 mls. of benzene. The aqueous layer was separated and washed twice with 100 mls. of benzene and once with 100 mls. of ether. The layers of benzene-ether were then washed thrice with 100 mls. of water and dried with Na₂SO₄, followed by evaporation to about 100 mls. After adding 125 mls. of petroleum ether to this residue 21 gs. of the tribenzyl-β base with melting point from 86° to 95° C. was crystallized after crystallizing twice from a mixture of benzene and petroleum ether, 17.5 gs. of the pure tribenzyl-β base with melting point from 94° to 95° C. were obtained therefrom.

50 mls. of 2 n NaOH, 600 mls. of benzene and 1 litre of water were added to the filtrate of the 29.5 gs. of salt crystallize. After shaking, the layers were separated. The aqueous layers was washed thrice with 250 mls. of benzene, whereafter the organic liquid layers were added together and washed four times with 500 mls. of water. After washing with Na₂SO₄, the organic liquid was evaporated at reduced pressure to about 150 mls. After adding 170 mls. of petroleum ether, 32.5 gs. of substance with melting point from 70° to 74° C. crystallized within 15 hours (at room temperature). After crystallization from a mixture of benzene and petroleum ether, 24 gs. of the tribenzyl-α base with melting point from 71° to 72° C.
C. Separation of the three benzyl groups from the racemically pure tribenzyl compounds of Formula III for obtaining the racemically pure N-(p-hydroxyphenylisopropyl)arterenols of Formula I

15 mls. of a 1% solution of PdCl₂ in water, to which 1.5 gs. of norite had been added, and 75 mls. of water were hydrated, sucked off and washed with water. This pre-hydrated catalyst was then added to a suspension of 9.05 gs. (9.013 mol.) of the α-tribenzyl benzoate with melting point from 156° to 158° C., obtained as described sub B, in 600 mls. of ethanol. The mixture was then shaken with hydrogen at 1.1 atm. at room temperature. After the calculated amount of hydrogen had been taken up, the catalyst was filtered off and the filtrate evaporated to reduced pressure to about 100 mls. Subsequently, 50 mls. of water were added and the liquid was again evaporated at reduced pressure until it became turbid. After 15 hours stay at about 5° C. 4.8 gs. of crystallize could be filtered off. This benzoate of the α-racemate of Formula I crystallised into rosettes. In determining the melting point at a heating rate of 2°/min., vitrification was found at 102° to 106° C., liquefaction at 105° to 110° C., and dissociation at 130° to 133° with formation of gas.

1 g. of this α-benzoate was dissolved in 15 mls. of water while heating, thereafter 1.1 mls. of 2.5 n NH₄OH were added at 60° C. 0.64 g. of the free α-base of Formula I crystallized, which base melted with dissociation at about 171° to 173° C. From this base, for example the phenoxyacetate with melting point (with dissociation) from 175° to 176° C. and the phenyl acetate with melting point (with dissociation) from 156° to 158° C., could be obtained.

In quite a similar manner the tribenzyl-β-benzoate was converted into the β-benzoate of the base of Formula I which crystallizes into thin plates containing about 11% of crystal water. Upon drying in vacuo over P₂O₅ while heating to about 60° C., the crystal water is extracted. The salt thus dried is hydroscopic.

In determining the melting point of this benzoate at a heating rate of 2°/min., vitrification was found at 111° to 112° C., liquefaction at 112° C. and dissociation at 145° C. to 146° C., with evaluation of gas.

The free β-base of Formula I melts with dissociation between 163° and 168° C. The phenoxy acetate obtained therefrom melts at 175° to 176.5° and the phenyl acetate at 151° to 154.5° C.

What is claimed is:

1. A member selected from the group consisting of N-p-benzyloxyphenylisopropyl-β-(3’4’-dibenzylxoxophenyl)-β-hydroxyethyl amine and pharmacologically acceptable acid addition crystalline salts thereof.

2. A member selected from the group consisting of a racemate of the compound N-p-benzyloxyphenylisopropyl-β-(3’4’-dibenzylxoxophenyl)-β-hydroxyethyl amine with melting point from 92° to 94° C. and pharmacologically acceptable acid addition crystalline salts thereof.

3. A member selected from the group consisting of a racemate of the compound N-p-benzyloxyphenylisopropyl-β-(3’4’-dibenzylxoxophenyl)-β-hydroxyethyl amine with melting point from 70° to 72° C. and pharmacologically acceptable acid addition crystalline salts thereof.

4. A member selected from the group consisting of a racemate of the compound N-p-benzyloxyphenylisopropyl-β-(3’4’-dibenzylxoxophenyl)-β-hydroxyethyl amine with melting point from 85° to 88° C. and pharmacologically acceptable acid addition crystalline salts thereof.

5. The benzoate of N-p-benzyloxyphenylisopropyl-β-(3’4’-dibenzylxoxophenyl)-β-hydroxyethyl amine with melting point from 156° to 158° C.

6. The benzoate of N-p-benzyloxyphenylisopropyl-β-(3’4’-dibenzylxoxophenyl)-β-hydroxyethyl amine with melting point from 138° to 139° C.

7. The p-toluene sulphonate of N-p-benzyloxyphenylisopropyl-β-(3’4’-dibenzylxoxophenyl)-β-hydroxyethyl amine with melting point from 137.5° to 138° C.

8. A method of producing the individual racemates of a compound selected from the group consisting of the base

\[
\begin{align*}
&\text{HO} \\
&\text{CH₂CH₃} \\
&\text{CH₂CH₃} \\
&\text{CH₂CH₃}
\end{align*}
\]

and the pharmacologically acceptable acid addition crystalline salts thereof from a mixture of racemates of a member selected from the group consisting of

\[
\begin{align*}
&\text{CHOH-CH₂-NH-CH₂CH₂-CH₂-OCH₃} \\
&\text{CH₂-CH₂} \\
&\text{CH₂}\text{-CH₂-CH₂} \\
&\text{-OCH₃}
\end{align*}
\]

and the pharmacologically acceptable acid addition crystalline salts thereof comprising the steps of isolating a pure racemate from said mixture of racemates by fractional crystallization and then converting said pure racemate into a pure racemate of said compound.

9. A method of producing the mixture of racemates of claim 8 comprising reducing a member selected from the group consisting of a racemic ketone of the formula

\[
\begin{align*}
&\text{HO} \\
&\text{CH₂CH₃} \\
&\text{CH₂CH₃} \\
&\text{CH₂CH₃}
\end{align*}
\]

and the pharmacologically acceptable acid addition crystalline salt thereof.

10. The method of claim 8 wherein the conversion is carried out by catalytic hydrogenation.

11. The method of claim 10 wherein a mixture of racemates of the benzoate of

\[
\begin{align*}
&\text{CHOH-NH-CH₂CH₂-CH₂-OCH₃} \\
&\text{CH₂-CH₂} \\
&\text{CH₂-CH₂} \\
&\text{-OCH₃}
\end{align*}
\]

and the pharmacologically acceptable acid addition crystalline salt thereof.

12. The method of claim 8 wherein the base, the benzoate of which melts at 138° C.-139.5° C. and the base the benzoate of which melts at 156° C.-158° C. are isolated by fractional crystallization from a racemic mixture thereof.

13. The method of claim 12 wherein the fractional crystallization takes place from ether.

14. The method of claim 8 wherein p-toluene-sul-
fonic acid is added to a solution of a mixture of the racemates of the formula

and the p-toluene sulfonate of one of said racemates is separated therefrom in crystalline form.

The method of claim 14 wherein the crystallization takes place from a mixture of ethanol and water.

References Cited by the Examiner

<table>
<thead>
<tr>
<th>Patent Number</th>
<th>Date</th>
<th>Inventor(s)</th>
<th>Class</th>
<th>Year</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,068,283</td>
<td>12/1962</td>
<td>Kaiser et al.</td>
<td>260—570.5</td>
<td>1962</td>
<td>United States</td>
</tr>
<tr>
<td>3,078,307</td>
<td>2/1963</td>
<td>Craig et al.</td>
<td>260—570.8</td>
<td>1963</td>
<td>United States</td>
</tr>
</tbody>
</table>


OTHER REFERENCES

CHARLES B. PARKER, Primary Examiner.