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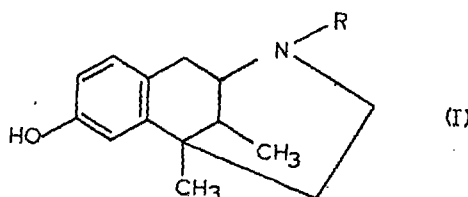
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(54) METHOD FOR PRODUCING 2,6-METHANO-3-BENZAZOCINE DERIVATIVES

(71) We, GRELAN SEIYAKU KABUSHIKI KAISHA (GRELAN PHARMACEUTICAL Co. LTD.) of 3-9, 3-chome, Nozawa, Setagaya-ku, Tokyo, Japan, a body corporate organised under the laws of Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

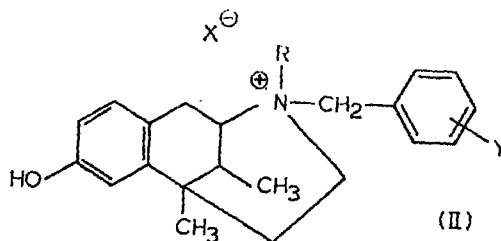
This invention relates to a new method of producing heterocyclic compounds, and is particularly concerned with an improved method for producing 3 - (alkyl or alkenyl)-1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocines represented by the formula (I):



wherein R represents an alkyl or alkenyl group having up to 10 carbon atoms.

It is well known that the compounds of the formula (I) have analgesic activity and some of them have been marketed as analgesics (e.g. pentazocine: $R = -CH_2CH=C(CH_3)_2$).

We have previously found that a 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methanol - 3 - benzazocine derivative of formula (I) can be produced by catalytic reduction of a quaternary ammonium salt of formula (II):



wherein X^- represents an anion; Y represents H or a halogen and R has the same meaning as defined above. Although this method certainly surpasses the other hitherto known methods as it requires fewer steps, there still remained room for improvement from the industrial point of view.

Thus:

- (1) The method requires an expensive catalyst such as palladium, nickel or platinum; and
 (2) In cases where the hydrocarbon residue (R) contains one or more un-

saturated bonds, there is produced at the same time a by-product saturated in the hydrocarbon residue which makes it difficult to purify the desired compound.

We have now found that a thiophenoxide anion is particularly effective in removing the benzyl group at the 3 position of the quaternary ammonium salt of formula (II) to afford the desired compounds of formula (I) in a simple reaction which results in easy purification as well as a high yield of the desired compound.

The present invention therefore provides a novel and industrially feasible method for producing the 3 - (alkyl or alkenyl) - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocines of formula (I) in a good yield and in a pure state at low cost.

The process comprises reacting the quaternary ammonium salt of formula (II) with a thiophenoxide anion.

As regards the compounds of Formulae (I) and (II), by the alkyl or alkenyl group represented by R is meant a straight, branched or cyclic group having up to 10 carbon atoms. The alkyl group is exemplified by methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, sec-butyl, tert-butyl, isobutyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, cyclobutyl, cyclopentyl, cyclohexyl or cyclopropylmethyl. The alkenyl group is exemplified by vinyl, 2,2-dimethylvinyl, 1-propenyl, allyl, cyclohexenyl, 3-methyl-2-butenyl, 1-pentenyl or 2-pentenyl. In formula (II), the anion represented by X⁻ is exemplified by Br⁻, Cl⁻, I⁻ or OH⁻, and the halogen represented by Y includes chlorine, bromine and iodine.

The quaternary ammonium salt to be employed as the starting material of the present invention is novel, and is easily prepared, for example, by reacting 3 - (benzyl or halobenzyl) - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6-methano - 3 - benzazocine (IV) with an alkylating or alkenylating agent RX(III) wherein each of R and X has the same meaning as defined above), the alkyl or alkenyl being introduced into the 3-position of the final product of formula (I). For this preparation, it is recommended to use a suitable solvent such as methanol, ethanol, chloroform, dioxane, tetrahydrofuran, benzene, xylene or toluene so far as it does not affect the reaction adversely. The reaction is carried out at from 20°C to 100°C. and is usually completed in from 1 to 48 hours.

The thiophenoxide anion as the other reactant in the process of the present invention is usually employed in the form of an alkali metal thiophenate or of thiophenol in combination with an alkali metal hydroxide. Alkali metal thiophenate includes sodium thiophenate and potassium thiophenate, and the alkali metal hydroxide includes potassium hydroxide and sodium hydroxide.

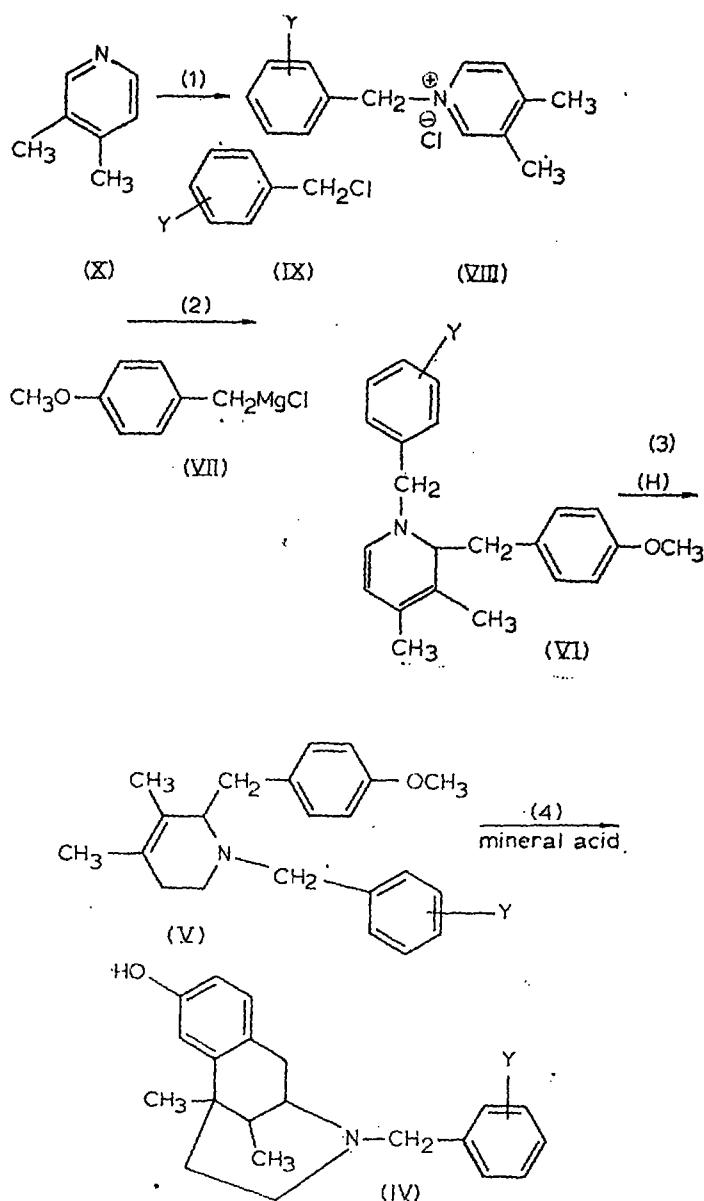
While the amount of the thiophenoxide anion relative to the quaternary ammonium salt should vary with the type of starting material, the reaction temperature and the solvent, it is generally recommended to employ from 1 to 20 gram ions, preferably 3 to 10 gram ions, per gram mole of the quaternary ammonium salt.

The reaction of the present invention is generally carried out in a suitable solvent which does not disturb the reaction. Suitable solvents include water, alcohols (e.g. methanol, ethanol or propanol) ketones (e.g. acetone or methyl ethyl ketone), dioxane, acetic acid, ethyl acetate and chloroform. Of course, these solvents may be used in combination. While the reaction temperature should also vary with other reaction conditions, it usually falls in a range of from 30°C. to 120°C., preferably from 40° to 100°C.

After the reaction, the desired compound is recovered from the reaction mixture by means known in themselves, e.g. extraction, condensation, crystallization, recrystallization and chromatography.

As the 3 - (alkyl or alkenyl) - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8-hydroxy - 2,6 - methano - 3 - benzazocine is a base, it can be converted to the corresponding acid addition salts in a conventional manner, e.g. by reacting the base with a mineral acid such as hydrochloric acid, sulfuric acid or hydrobromic acid, or with an organic acid such as oxalic acid, fumaric acid, maleic acid, succinic acid, malonic acid, acetic acid, propionic acid or benzenesulfonic acid.

Further details are now given of the preparation of the starting material of the formula (IV) shown below. These compounds may of course be prepared by various means known per se but it is particularly recommended to use the following sequence of reaction steps:



(wherein Y has the same meaning as defined above).

Step (1) may be conducted by reacting 3,4-dimethyl-pyridine (X) with a benzyl chloride (IX), usually in a solvent such as methanol, ethanol, chloroform, dioxane, tetrahydrofuran, benzene, hexane or toluene, provided it does not adversely affect the reaction. The reaction temperature is ordinarily from 20°C. to 100°C. The reaction time depends on other reaction conditions, but it is usually enough to conduct the reaction for 1 to 48 hours for its completion. The reaction product, a 1-(benzyl or halobenzyl)-3,4-dimethylpyridinium salt (VIII), can be recovered from the reaction mixture by various procedures known *per se*, for example by collecting the precipitated crystals by filtration.

Step (2) may be conducted by reacting the above produced pyridinium salt (VIII) with a Grignard reagent (VII) in a solvent which dissolves at least one of the reactants and which does not affect the reaction adversely, most advantageously in an ether such as diethyl ether or dipropyl ether. The reaction is carried out at room temperature or with moderate heating, and anhydrous conditions give better results. The resulting 1 - (benzyl or halobenzyl) - 2 - (p - methoxy benzyl) - 3,4 - dimethyl-1,2 - dihydropyridine (VI) may be recovered from the reaction mixture, e.g. after

adjusting the pH of the reaction mixture to 7—10, by concentration and extraction, or may be subjected to the next step without being recovered.

Step (3) is conducted by reducing the 1,2-dihydro-pyridine (VI) to the corresponding 1,2,5,6-tetrahydro-pyridine (V). For the conversion, various conventional means for reducing a C—C double bond may be employed. Above all, such a specific reducing agent as sodium borohydride or so-called catalytic reduction in the presence of a metal catalyst such as palladium, platinum or nickel is satisfactorily employed. The reaction may be performed in a suitable solvent such as a lower alcohol (e.g. methanol, ethanol or propanol), an aqueous lower alcohol or a mineral acid (e.g. hydrochloric acid or sulfuric acid) at room temperature or with heating. The product i.e. 1 - (benzyl or halobenzyl) - 2 - (p - methoxybenzyl) - 3,4 - dimethyl - 1,2,5,6-tetrahydropyridine (V), may be recovered by a conventional procedure (e.g. concentration, adjustment of the pH of the resulting reaction mixture, extraction, crystallization, distillation or chromatography) or may be submitted to the next reaction step.

Step (4) is conducted by reacting the compound (V) with a mineral acid (e.g. hydrogen bromide, hydrogen chloride, phosphoric acid or polyphosphoric acid) or its salt with a weak base such as an organic base (e.g. pyridine, N,N-dimethylaniline, triethylamine or trimethylamine). The reaction does not necessarily need a solvent, but is preferably conducted in a suitable solvent exemplified by a lower alcohol (e.g. ethanol or methanol) or an aqueous lower alcohol. The amount of the mineral acid to be employed is preferably more than 3 mols per mol of the compound (V). The reaction is generally performed by heating, preferably at 80°C. to 200°C., under atmospheric pressure or in a pressure vessel, and is completed in 3 to 24 hours. The product is recovered from the reaction mixture by a *per se* known procedure (e.g. by adjusting the pH of the reaction mixture, extraction, crystallization, recrystallization and filtration).

The above procedures for the preparation of the starting compounds are further explained below by way of example. Hereinafter, the parts by weight bear the same relationship to parts by volume as do grams to milliliters.

1-Benzyl-3,4-dimethylpyridinium chloride:
10 parts by weight of 3,4-dimethylpyridine and 11.8 parts by weight of benzyl chloride are dissolved in 15 parts by volume of dry benzene. The solution is refluxed for 3 hours to precipitate crystals, which are filtered and recrystallized from a mixture of acetone and ether to give 18.4 parts by weight (83.6%) of the product as needles melting at 156°C. to 158°C.

In the same manner as described above, 1-(p-chlorobenzyl)-3,4-dimethylpyridinium chloride, melting at 178 to 181°C., is obtained (yield 85%).

1-Benzyl-3,4-dimethyl-2-(p-methoxybenzyl)-1,2-dihydropyridine:
To 40 parts by volume of an ethereal solution of p-methoxybenzylmagnesium chloride (prepared from 4.0 parts by weight of p-methoxybenzyl chloride), there are added 1.8 parts by weight of 1-benzyl-3,4-dimethylpyridinium chloride. The resulting solution is refluxed for 1.5 hours, and poured into 20 parts by weight of an aqueous solution containing 1.5 parts by weight of ammonium chloride. The mixture is made alkaline with a 10% aqueous ammonia solution and extracted with ether. The ether layer is extracted with a 10% aqueous hydrogen chloride solution. The extract is made alkaline with a 10% aqueous ammonium hydrogen solution and extracted with ether. The ether layer is dried over potassium carbonate and then ether is evaporated to leave 1.9 parts by weight of oily 1-benzyl-3,4-dimethyl-2-(p-methoxybenzyl)-1,2-dihydropyridine. This compound is so unstable that it should preferably immediately be subjected to the next reaction.

In the same manner as described above 1 - (p - chlorobenzyl) - 3,4 - dimethyl-2 - (p - methoxybenzyl) - 1,2 - dihydropyridine is produced (yield 92%).

1-Benzyl-3,4-dimethyl-2-(p-methoxybenzyl)-1,2,5,6-tetrahydropyridine:
0.1 part by weight of sodium hydroxide and 0.1 part by volume of water are dissolved in 50 parts by volume of methanol. 1.9 parts by weight of 1-benzyl-3,4-dimethyl-2-(p-methoxybenzyl)-1,2-dihydropyridine are added to the solution, followed by the addition of 0.2 part by weight of sodium borohydride. The resulting solution is refluxed for 30 minutes, and the methanol is distilled off to leave a residue, which is then extracted with ether. The ether extract is dehydrated over potassium carbonate and subjected to distillation to remove the ether. The residue is further distilled *in vacuo* to yield 1.1 parts by weight of 1 - benzyl - 3,4 - dimethyl - 2 - (p - methoxybenzyl) - 1,2,5,6 - tetrahydropyridine as a pale yellow oil boiling at 175°C. to 178°C. under 0.2 mmHg.

The compound is converted to the picrate, which is recrystallized from a mixture of ethanol and ether to give granular yellow crystals melting at 115°C. to 118°C.

By the same manner as described above, 1 - (*p* - chlorobenzyl) - 3,4 - dimethyl-2 - (*p* - methoxybenzyl) - 1,2,5,6 - tetrahydropyridine, melting at 183°C. to 185°C., is obtained (yield 97%).

3-Benzyl-1,2,3,4,5,6-hexahydro-6,11-dimethyl-8-hydroxy-2,6-methano-3-benzazocine:

1.1 parts by weight of 1 - benzyl - 3,4 - dimethyl - 2 - (*p* - methoxybenzyl)-1,2,5,6 - tetrahydropyridine are dissolved in 30 parts by volume of a 48% aqueous hydrobromic acid solution. The solution is refluxed for 19 hours. The reaction mixture is then made alkaline with a concentrated aqueous sodium hydroxide solution, and extracted with ether. The ether layer is dried over potassium carbonate, and the ether is evaporated to leave a solid material. The solid material is submitted to column chromatography, using 11 parts by weight of silicic acid. The column is eluted with 180 parts by volume of chloroform, and then with 80 parts by volume of a mixture of chloroform and methanol (95:5) to obtain the eluate, which is concentrated to dryness to give 0.55 part by weight of the solid product.

The product can be converted in a conventional manner to the corresponding hydrochloride melting at 268°C. to 270°C.

In the same manner as described above, 3 - (*p* - chlorobenzyl) - 1,2,3,4,5,6-hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine is obtained (Yield: 72.7%).

The following examples illustrate the method of the present invention without limiting it thereto.

EXAMPLE 1

3.52 parts by weight of 3 - benzyl - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl-8 - hydroxy - 2,6 - methano - 3 - benzazocine hydrochloride are treated with 10 parts by volume of 28% aqueous ammonium hydroxide solution, followed by extraction with ether to give 3.07 parts by weight of the corresponding free base. The base is dissolved in 50 parts by volume of methanol together with 7.1 parts by weight of methyl iodide, and the solution is refluxed for 2 hours. The solvent is distilled off, and the residue is washed with ether, whereupon 4.2 parts by weight of a solid precipitate are obtained. The precipitate is recrystallized from isopropanol to give 3.9 parts by weight of 3 - benzyl - 1,2,3,4,5,6 - hexahydro - 3,6,11 - trimethyl - 8-hydroxy - 2,6 - methano - 3 - benzazocinium iodide as a colourless powder melting at 217°C. to 218°C. (with decomposition).

Elementary Analysis: $C_{22}H_{24}ONI$ (Molecular weight 449.394)

Calculated: C, 58.80; H, 6.28; N, 3.12

Found: C, 58.82; H, 6.68; N, 3.01

Infrared Absorption Spectrum ν_{max} KBr cm^{-1} :

3270 (OH); 1602 (benzene ring), 1590 (benzene ring), 765, 710 (5 hydrogen atoms on the benzene ring).

4.5 parts by weight of the quaternary ammonium iodide prepared above are suspended in a mixture of 11.0 parts by weight of thiophenol and 80 parts by volume of a 5% aqueous solution of sodium hydroxide, and the whole is heated on a water bath at 40°C. to 50°C. for 5 hours with constant stirring. After cooling, 50 parts by volume of ether are added to the reaction mixture, which is extracted with 100 parts by volume of 10% aqueous hydrochloric acid. The acid extract is made alkaline with 28% aqueous ammonium hydroxide solution and then extracted with a few portions of chloroform, while salting out. The extracts are washed with water and dried over anhydrous sodium sulfate. The chloroform is distilled off to yield 2.3 parts by volume of a colourless powder, which is then recrystallized from ethanol. The procedure yields 2.0 parts by weight of 1,2,3,4,5,6 - hexahydro - 3,6,11 - trimethyl-8 - hydroxy - 2,6 - methanol - 3 - benzazocine as colourless needles melting at 229°C to 232°C.

EXAMPLE 2

A suspension of 4.5 parts by weight of 3 - benzyl - 1,2,3,4,5,6 - hexahydro-3,6,11 - trimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocinium iodide in a mixture of 11.0 parts by weight of thiophenol and 110 parts by volume of a 5%

- aqueous solution of potassium hydroxide is heated on a water bath at 80°C. to 90°C. for 10 hours, with constant stirring. After cooling, 50 parts by weight of ether are added to the reaction mixture, which is then treated in the same manner as Example 1, whereupon 2.5 parts by weight of a colourless powder are obtained. The powder is recrystallized from ethanol to yield 2.2 parts by weight of 1,2,3,4,5,6 - hexahydro-3,6,11 - trimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine as colourless needles melting at 229°C—232°C.

EXAMPLE 3

- A solution of 2.5 parts by weight of 3 - benzyl - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine and 0.11 part by weight of 3-methyl-2-butenyl bromide in 10 parts by volume of benzene is refluxed for 1 hour to give precipitates which are filtered and recrystallized from a mixture of ethanol and ether to yield 1.7 parts by weight of 3 - benzyl - 3 - (3 - methyl - 2 - butenyl)-1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocinium bromide as a colourless powder melting at 159°C to 161°C. (with decomposition).

Elementary Analysis: $C_{27}H_{34}ONBr \cdot H_2O$

Calculated: C, 65.81; H, 7.64; N, 2.95

Found: C, 66.07; H, 7.51; N, 2.91

- Infrared Absorptions $KBr_{max} \text{ cm}^{-1}$:
3200 (OH), 3450 (H_2O), 1670 ($C=C$), 1615 (phenyl), 760 (5 hydrogen atoms on benzene ring), 720 (5 hydrogen atoms on benzene ring).

- A suspension of 4.5 parts by weight of 3 - benzyl - 3 - (3 - methyl - 2 - butenyl)-1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocinium bromide in a mixture of 11.0 parts by weight of thiophenol and 80 parts by volume of 5% aqueous sodium hydroxide solution is heated on a water bath at 40°C. to 50°C. for 5 hours with constant stirring. After cooling, 50 parts by volume of ether are added to the reaction mixture, which is then extracted with 100 parts by volume of 10% aqueous hydrochloric acid. The acid extract is made alkaline with a 28% aqueous ammonium hydroxide solution, followed by extraction with chloroform. The extract is washed with water and dried over anhydrous sodium sulfate. The chloroform is distilled off, and the white powdery residue is chromatographed on a column of 80 parts by weight of silicic acid. The column is eluted with 200 parts by volume of ether and then with 800 parts by volume of a mixture of ether and chloroform (95:5). The second eluate is concentrated to recover 2.25 parts by weight of 3 - (3 - methyl - 2 - butenyl) - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine as a colourless powder melting at 146°C. The infrared absorption spectrum, thin-layer chromatogram, nuclear magnetic resonance spectrum and ultraviolet absorption spectrum of the above product are in good agreement with those of an authentic sample.

EXAMPLE 4

- After the manner described in Example 1, 0.27 part by weight of cyclopropylmethyl chloride is allowed to react with 0.31 part by weight of 3 - benzyl - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine to give 0.52 part by weight of 3 - benzyl - 3 - cyclopropylmethyl - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocinium chloride. The quaternary ammonium chloride prepared above is submitted to the same procedures as in Example 1 to give 3 - cyclopropylmethyl - 1,2,3,4,5,6 - hexahydro-6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine as crystals melting at 201°C. The product is in accord with an authentic sample on the infrared absorption spectrum thin-layer chromatogram and nuclear magnetic resonance spectrum.

EXAMPLE 5

- A suspension of 2.5 parts by weight of 3 - benzyl - 3 - (3 - methyl - 2 - butenyl)-1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocinium bromide (which has been prepared in the same manner as described in Example 3) in a mixture of 11.0 parts by weight of thiophenol and 110 parts by volume of 5% aqueous potassium hydroxide solution is heated on a water bath at 60°C. to 70°C. for 7 hours with constant stirring. After cooling, 50 parts by volume

of ether are added to the reaction mixture, which is then extracted with 100 parts by volume of 10% aqueous hydrochloric acid. Thereafter, the procedure of Example 1 is followed to yield 2.2 parts by weight of 3 - (3 - methyl - 2 - butenyl) - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine as a colourless powder melting at 146°C.

EXAMPLE 6

A suspension of 2.2 parts by weight of 3 - benzyl - 3 - (3 - methyl - 2 - butenyl) - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocinium bromide in a mixture of 6.0 parts by weight of thiophenol and 3.5 parts by volume of 10% aqueous potassium hydroxide solution is heated on a water bath at 80°C. $\pm$ 5°C. for 5 hours with constant stirring. After cooling, 50 parts by volume of ether are added to the reaction mixture, which is then extracted with 10% aqueous hydrochloric acid. Thereafter the procedure of Example 1 is followed to yield 1.05 parts by weight of 3 - (3 - methyl - 2 - butenyl) - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine as a colourless powder melting at 146°C.

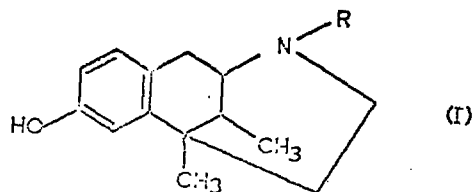
EXAMPLE 7

A mixture of 1.3 parts by weight of 3 - (p - chlorobenzyl) - 3 - (3 - methyl - 2 - butenyl) - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocinium bromide, 2.9 parts by weight of thiophenol and 10.6 parts by volume of 5% aqueous sodium hydroxide solution is warmed on a water bath with stirring for 5 hours. After cooling, 100 parts by volume of 10% hydrochloric acid are added to the reaction mixture. 100 parts by volume of ether were then added to the reaction mixture. After shaking the mixture vigorously, the aqueous layer is separated and made alkaline by adding 28% aqueous ammonium hydroxide. The resulting solution is extracted with chloroform. The chloroform layer is washed with water and dried with anhydrous sodium sulphate. Chloroform is distilled off to give 0.85 part by weight of a pale brown syrup. The compound is subjected to column chromatography on 16 parts by weight of silicic acid using firstly 240 parts by volume of ether and then 300 parts by volume of ether-chloroform (95:5) as eluant. The ether-chloroform eluate is collected and concentrated to give 5 parts by volume of 3 - (3 - methyl - 2 - butenyl) - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine as a colourless powder.

The infrared absorption spectrum, thin layer chromatogram, nuclear magnetic resonance spectrum and ultraviolet absorption spectrum of the compound are in perfect agreement with those of 3 - (3 - methyl - 2 - butenyl) - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine obtained by the method disclosed in Japanese Patent Publication No. 21622/1965.

WHAT WE CLAIM IS:—

1. A method of producing a heterocyclic compound represented by the general formula:



(wherein R is an alkyl or alkenyl group, each having up to 1 carbon atoms), which comprises reacting a quaternary ammonium salt represented by the general formula:



* C L M S *

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of ether are added to the reaction mixture, which is then extracted with 100 parts by volume of 10% aqueous hydrochloric acid. Thereafter, the procedure of Example 1 is followed to yield 2.2 parts by weight of 3 - (3 - methyl - 2 - butenyl) - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine as a colourless powder melting at 146°C.

EXAMPLE 6

A suspension of 2.2 parts by weight of 3 - benzyl - 3 - (3 - methyl - 2 - butenyl) - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocinium bromide in a mixture of 6.0 parts by weight of thiophenol and 3.5 parts by volume of 10% aqueous potassium hydroxide solution is heated on a water bath at 80°C. $\pm 5^\circ\text{C}$. for 5 hours with constant stirring. After cooling, 50 parts by volume of ether are added to the reaction mixture, which is then extracted with 10% aqueous hydrochloric acid. Thereafter the procedure of Example 1 is followed to yield 1.05 parts by weight of 3 - (3 - methyl - 2 - butenyl) - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine as a colourless powder melting at 146°C.

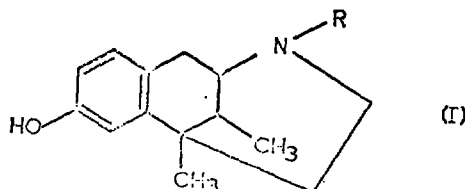
EXAMPLE 7

A mixture of 1.3 parts by weight of 3 - (*p* - chlorobenzyl) - 3 - (3 - methyl - 2 - butenyl) - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocinium bromide, 2.9 parts by weight of thiophenol and 10.6 parts by volume of 5% aqueous sodium hydroxide solution is warmed on a water bath with stirring for 5 hours. After cooling, 100 parts by volume of 10% hydrochloric acid are added to the reaction mixture. 100 parts by volume of ether were then added to the reaction mixture. After shaking the mixture vigorously, the aqueous layer is separated and made alkaline by adding 28% aqueous ammonium hydroxide. The resulting solution is extracted with chloroform. The chloroform layer is washed with water and dried with anhydrous sodium sulphate. Chloroform is distilled off to give 0.85 part by weight of a pale brown syrup. The compound is subjected to column chromatography on 16 parts by weight of silicic acid using firstly 240 parts by volume of ether and then 300 parts by volume of ether-chloroform (95:5) as eluant. The ether-chloroform eluate is collected and concentrated to give 5 parts by volume of 3 - (3 - methyl - 2 - butenyl) - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine as a colourless powder.

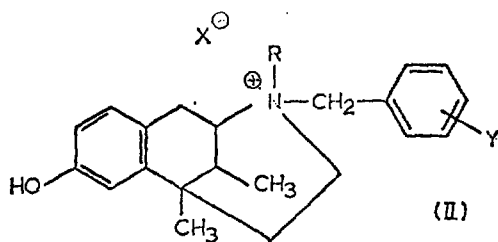
The infrared absorption spectrum, thin layer chromatogram, nuclear magnetic resonance spectrum and ultraviolet absorption spectrum of the compound are in perfect agreement with those of 3 - (3 - methyl - 2 - butenyl) - 1,2,3,4,5,6 - hexahydro - 6,11 - dimethyl - 8 - hydroxy - 2,6 - methano - 3 - benzazocine obtained by the method disclosed in Japanese Patent Publication No. 21622/1965.

WHAT WE CLAIM IS:—

1. A method of producing a heterocyclic compound represented by the general formula:



(wherein R is an alkyl or alkenyl group, each having up to 1 carbon atoms), which comprises reacting a quaternary ammonium salt represented by the general formula:



(wherein R has the same meaning as defined above, Y is hydrogen or a halogen and $X^{\ominus}$ is an anion) with thiophenoxide anion.

2. A method as claimed in claim 1, wherein R is 3-methyl-2-butenyl.
3. A method as claimed in claim 1, wherein R is cyclopropylmethyl.
4. A method as claimed in claim 1, wherein R is methyl.
5. A method as claimed in any of claims 1 to 3, wherein Y is hydrogen.
6. A method as claimed in any of claims 1 to 3 wherein Y is Cl at position 4 on the phenyl group.
7. A method as claimed in any of claims 1 to 6, wherein X is chlorine.
8. A method as claimed in any of claims 1 to 6 wherein X is bromine.
9. A method as claimed in any of claims 1 to 6 wherein X is iodine.
10. A method as claimed in any of claims 1 to 9 wherein the amount of thiophenoxide anion is 1 to 20 gram ions per gram mole of the quaternary ammonium salt.
11. A method according to claim 1 substantially as herein described with reference to any of the specific examples.
12. Heterocyclic compounds of formula (I) as defined in claim 1 when made by a method as claimed in any of claims 1 to 11.

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