United States Patent

Tanaka et al.

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[54] **CERTAIN HYOSCYAMINIUM COMPOUNDS**

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Related U.S. Application Data

[63] Continuation of Ser. No. 858,110, Sept. 15, 1969, abandoned.

[30] **Foreign Application Priority Data**

Feb. 18, 1969 Japan 44/11531

[52] **U.S. Cl.**.....**260/292, 424/265**

[51] **Int. Cl.**.....**C07d 43/06**

[58] **Field of Search**.....260/473 A, 292

[56] **References Cited**

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[57] **ABSTRACT**

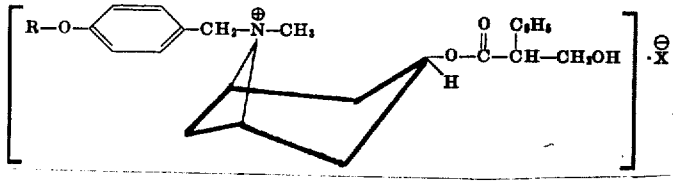
A class of new quaternary ammonium salts derived from atropine or its optical isomer called hyoscyamine base with p-alkoxy or alkenoxy-substituted benzyl halide. The new quaternary ammonium salts according to the present invention exhibit a strong parasympathetic blocking activity with low toxicity. They therefore are advantageously utilizable for chemotherapeutical treatment of patients suffering from diseases such as, for example, gastric cramp, gastric ulcer, duodenal ulcer and the like. Aqueous solutions of these salts are stable and are administrated to patients through venous and subcutaneous injections as well as oral administration.

5 Claims, No Drawings

CERTAIN HYOSCYAMINIUM COMPOUNDS

This is a continuation of U.S. application, Ser. No. 858,110; filed Sept. 15, 1969, now abandoned.

This invention relates to a process for synthesizing new quaternary salts of atropine or its optical isomer called hyoscyamine base and represented by the formula



wherein R is lower alkyl or alkenyl group and X is halogen atom.

Atropine and its optical isomer called hyoscyamine base are the essential components of the main alkaloids contained in belladonna and scopolia. These compounds exhibit a strong parasympathetic blocking activity and they therefore are utilized for the purpose of therapeutical treatment of diseases such as gastric cramp, gastric ulcer, duodenal ulcer and the like. Unfortunately it was found that they show undesirable side effects such as dryness of mouth, retention of urine, disturbance of heart rhythm and an injurious effect on central nervous system.

It was found as the result of several researches which had recently been conducted that the aforementioned drawbacks especially the undesired side effect on central nervous system caused by these researches which had recently been conducted that the afore-mentioned drawbacks especially the undesired side effect on central nervous system caused by these compounds can considerably be reduced, although their aimed original parasympathetic blocking activity is also somewhat reduced, when these compounds are administrated in a form of their conventional quaternary salts. The quaternary salts of atropine such as atropine methyl bromide and butyl scopolaminium bromide in commercial name "Buscopan", for example, are now available in market.

It cannot, however, be pronounced that difficulty of the side effect on central nervous system presented by these quaternary salts was satisfactorily eliminated.

It has now been found according to our extensive researches in this field that the aforementioned drawbacks or difficulty can satisfactorily be removed by providing the new quaternary salts of atropine or hyoscyamine base with p-alkoxy or p-alkenoxy-substituted benzyl halide.

The followings are comparative data with respect to the pharmacological effects and toxicities (as acute toxicity LD_{50}) of p-butoxybenzyl hyoscyaminium bromide as one of the typical quaternary salts according to the present invention and the hitherto known butyl scopolaminium bromide.

I Experiment on Isolated Stomac of Rat According to Magnus' Method

1. Direct Effect:

a. With 1×10^{-4} g/ml of p-butoxybenzyl hyoscyaminium bromide, 74.7 percent control and with 1×10^{-5} g/ml of the compound, 42.5 percent control of spontaneous motility were respectively observed.

b. With 1×10^{-4} g/ml of butyl scopolaminium bromide, no appreciable control was observed.

2. Blocking Effect on the Contraction caused by 1×10^{-4} g/ml of Barium Chloride:

a. With 1×10^{-4} g/ml of p-butoxybenzyl hyoscyaminium bromide, 74.7 percent control and with 1×10^{-5} g/ml of the compound, 5 percent control of the contraction respectively observed.

b. With 1×10^{-4} g/ml of butyl scopolaminium bromide, only 15.0 percent control of the contraction were observed.

3. Anti-acetylcholine effect against the contraction caused by 1×10^{-6} g/ml of acetylcholine:

a. With 1×10^{-7} g/ml of p-butoxybenzyl hyoscyaminium bromide, 72.5 percent control of the contraction were observed.

b. With 1×10^{-7} g/ml of butyl scopolaminium bromide, only 15.0 percent control of the contraction were observed.

II. Experiment on the Isolated Small Intestin of Mouse According to Magnus' Method

1. Blocking Effect on the Contraction caused by 5×10^{-4} g/ml of Barium Chloride:

a. With 1×10^{-5} g/ml of p-butoxybenzyl hyoscyaminium bromide, 40.0 percent control of contraction, and with 1×10^{-5} g/ml of butyl scopolaminium bromide, only 27.1 percent control of the contraction were respectively observed.

2. Anti-acetylcholine Effect on the Contraction caused by 1×10^{-7} g/ml of Acetylcholine:

a. With 1×10^{-6} g/ml of butyl scopolaminium bromide, 22.6 percent control of the contraction were observed.

III. Acute Toxicity on Male Mouse Weighing ca 20 Grams

Intravenous injection (LD_{50}): 12.0 mg/kg (11.0–13.1 mg/kg)

Subcutaneous injection (LD_{50}): 660 mg/kg (545.5–798.6 mg/kg)

Oral administration (LD_{50}): 1,500 mg/kg (2,362–952 mg/kg)

As is seen from the above, it is apparent that the novel compounds according to the instant invention show a marked parasympathetic blocking activity with low toxicity.

A class of the novel quaternary ammonium salts according to the present invention can conveniently be prepared by reacting atropine base or its optical isomer, i.e., hyoscyamine base, in the presence of a solvent with p-alkoxy or alkenoxy benzyl halide represented by the formula

wherein R and X have the same meanings as previously defined.

Typical solvents which have been found preferable to carry out the above reaction include lower alcohol, acetone, ether and the like. The reaction takes place readily at room temperature. In order to prevent from racemisation of the reacting materials, it is advisable to carry out the reaction at low temperature.

Since p-alkoxy or alkenoxy benzyl halide is generally unstable in some extent and is liable to be con-

taminated with resinous matters thus formed, it is desirable to use it soon after purification by distillation.

In practice, however, no appreciable lowering in yield of the contemplated quaternary salts was observed even though the reaction was conducted with crude substance.

Because no report or reports are found in the literatures so far as our knowledge is concerned with respect to the particular p-alkoxy or alkenoxy benzyl hyoscyaminium halides according to the present invention, the compounds are regarded as new substances.

They are tolerably water-soluble. The aqueous solutions thus obtained are relatively stable to heat. In aqueous solutions, the compounds have no tendency to cause racemisation. The fact offers one of the serious advantages in the production of pharmaceutical preparations.

The following examples illustrate the invention.

EXAMPLE 1

Preparation of p-Methoxybenzyl Hyoscyaminium Bromide

To 40 milliliters of ice-cooled ethanol solution containing 6 grams of hyoscyamine base were added drop by drop with stirring under ice-cooling 10 milliliters of an ethanol solution containing 5 grams of p-methoxybenzyl bromide. After stirring for two hours, separation of white crystals appeared. The stirring was continued for additional 5 hours at room temperature. The crystals separated out were then recovered by filtration. The crude crystals were dissolved in 40 milliliters of methanol and 200 milliliters of ethyl ether were then added to the solution. There was recovered 7.5 grams of the white needles having the melting point at 190°~200° C.

Upon elementary analysis, the product gave the following results:

For $C_{25}H_{32}NO_4Br$; molecular weight 490.45;	C	H	N
Calculated (%):	61.22	6.58	2.86
Found (%):	61.27	6.33	3.02

Rotatory polarization of the product was $[\alpha]_D^{22} = -21.5°$ (c = 0.5 in water)

From the above, the product was regarded as p-methoxybenzyl hyoxcyaminium bromide.

EXAMPLE 2

Preparation of p-Ethoxybenzyl Hyoscyaminium Bromide

To 50 milliliters of an acetone solution containing 8.4 grams of hyoscyamine base were added drop by drop 10 millimeters of an acetone solution containing 7.4 grams of p-ethoxybenzyl bromide while ice-cooling. After stirring for a while, white crystals separated out. The reaction mixture was stirred at room temperature for additional 5 hours. The crystalline substance was recovered by filtration, which was then recrystallized from isopropanol. 10.4 Grams of the purified product were obtained in a form of white needles which had the melting point of 164°~166° C.

Analysis of the product gave the following results:

For $C_{26}H_{34}NO_4Br$; molecular weight: 504.47;	C	H	N
Calculated (%):	61.89	6.80	2.78
Found (%):	61.62	7.17	2.84

EXAMPLE 3

Preparation of Allyloxybenzyl Hyoscyaminium Bromide

To 50 milliliters of an etheral solution containing 5.8 grams of hyoscyamine base were added drop by drop with stirring 10 milliliters of an etheral solution containing 5.5 grams of p-allyloxybenzyl bromide. The reaction mixture was stirred at room temperature for 10 hours, when white crystals gradually separated out. The crystals were recovered by filtration which were then recrystallized from a mixture of methanol and ethyl ether. There was thus obtained 9.3 grams of white crystals having the melting point of 165°~166° C.

Analysis of the product gave the following data:

For $C_{27}H_{34}NO_4Br$; molecular weight: 516.48;	C	H	N
Calculated (%):	62.78	6.64	2.71
Found (%):	62.30	6.73	2.73

EXAMPLE 4

Preparation of p-Butoxybenzyl Hyoscyaminium Bromide

To 100 milliliters of an isopropanol solution containing 11.8 grams of hyoscyamine base were added drop by drop with stirring 10 milliliters of an isopropanol solution containing 11 grams of p-n-butoxybenzyl bromide.

After a while, the reaction mixture had a turbid appearance followed by separation of white crystals.

After stirring for 5 hours at room temperature, the crystals were recovered by filtration, which were then recrystallized from 120 milliliters of isopropanol. There was obtained 15.8 grams of white needles having the melting point of 158°~160° C.

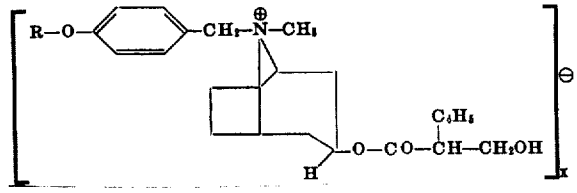
Analysis of the product gave the following properties:

For $C_{28}H_{38}NO_4Br$; molecular weight: 532.50;	C	H	N
Calculated (%):	63.10	7.20	2.63
Found (%):	63.34	7.31	2.69

Rotatory polarization: $[\alpha]_D^{22} = -21.7°$ (c = 0.5 in water)

What is claimed is:

1. Atropinium and hyoscyaminium quaternary salts represented by the formula:



wherein R is lower alkyl or alkenyl group and X is halogen atom.

2. A compound according to claim 1, which is, p-methoxybenzyl hyoscyaminium bromide.

3. A compound according to claim 1, which is, p-ethoxybenzyl hyoscyaminium bromide.

4. A compound according to claim 1, which is, allyloxybenzyl hyoscyaminium bromide.

5. A compound according to claim 1, which is, p-butoxybenzyl hyoscyaminium bromide.

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