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## SUBSTITUTED PYRIDINIUM SALTS

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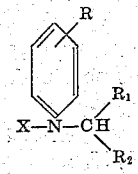
No Drawing. Application May 10, 1950, Serial No. 161,269

6 Claims. (Cl. 260—290)

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This invention relates to new substituted pyridinium salts which are useful in medicine for the treatment of certain disorders of the central nervous system such as schizophrenia. In addition, compounds of this class are valuable antibacterial and antifungal agents.

These compounds may be represented by the general formula:



wherein R represents a hydroxyalkyl group containing two to twenty carbon atoms, an alkyl group containing two to twenty carbon atoms, a carboalkoxy group or a halogen atom, X represents a non-toxic ion such as chloride, bromide, and iodide, $R_1$ and $R_2$ represent hydrogen, an aryl group such as phenyl and naphthyl or a substituted aryl group including alkylphenyl, halogenated phenyl, alkoxyphenyl and nitrophenyl, or $R_1$ and $R_2$ together represent a fused ring system such as the 9-fluorenyl radical.

The compounds of the invention are all characterized by a nuclear substituent in the pyridine ring. Bacteriological studies have revealed that the quaternary salts of the picolines are much less active as antibacterial agents than are the corresponding alkyl pyridinium salts containing at least two carbon atoms in the substituent group.

For example, compound A (1-benzohydryl-2-picolinium bromide) and compound B (1-benzohydryl-4-n-amylpyridinium bromide) have been found to completely inhibit the growth of the following representative microorganisms at the dilutions tabulated. These values, which indicate the minimum effective concentration for each compound, were obtained by the serial dilution method in broth, incubated at 37° C. for 18 hours and read by visual observation as negative or positive.

| Microorganism | Maximum Dilution Which Completely Inhibits Growth | |
|---|---|---|
| | A | B |
| *Klebsiella pneumonia* | 1:800 | 1:3200 |
| *Mucosus capsulatus* 3 | 1:800 | 1:3200 |
| *Esch. coli* | 1:800 | 1:1600 |
| *S. pullorum* | 1:800 | 1:6400 |
| *S. paratyphi* A | 1:1600 | 1:6400 |
| *Shigella paradysent*, Flex | 1:12800 | 1:102,400 |
| *B. subtilis* | 1:800 | 1:51,200 |
| *B. cereus* | 1:400 | 1:12,800 |
| *B. mesenterieus* | 1:1600 | 1:51,200 |
| *Staph. aureus*—Assay | 1:6400 | 1:25,600 |

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In general, the antibacterial activity increases as the size of the nuclear substituent is increased until the group consists of at least nine carbon atoms. On the other hand, substituents, comprising approximately five carbon atoms appear to exert an optimum therapeutic effect in the treatment of disorders of the central nervous system.

The new compounds are prepared by causing a substituted pyridine to react with an organic halide to form a pyridinium salt. Because of the slow rate at which most organic chlorides react with the pyridine compounds, we prefer to employ bromides or iodides in an inert solvent such as acetone to obtain the most favorable yields, but a solvent is not necessary. We prefer to use an excess of the halide and heat under reflux on the steam bath until the reaction has gone to completion. When the halide employed is particularly reactive, e. g. benzohydryl bromide, superior yields are obtained under anhydrous conditions. The compounds of the invention are white crystalline compounds, bitter to the taste. They are slightly soluble in water and quite soluble in ethyl alcohol.

The invention is more fully illustrated by the following specific examples, but it is not limited thereto.

### EXAMPLE 1

*1-p-chlorobenzohydryl-4-n-amylpyridinium bromide*

10.5 g. (0.07 mole) of 4-n-amyl pyridine was added to a solution of 21.6 g. (0.077 mole) of p-chlorobenzohydryl bromide in 50 ml. of reagent acetone. The light pink solution was refluxed for 15 hours, the solvent was removed under diminished pressure and the residual brown gum was caused to crystallize by prolonged scratching. The yield of crude material was 98.5% of theory. The compound was recrystallized twice from acetone to obtain 12.7 g. (42% yield) of fine white crystalline material, M. P. 140.5–143.5° C.

Analysis for $C_{23}H_{25}NBrCl$:
Calculated: C, 64.1; H, 5.85
Found: C, 64.43; H, 5.79

### EXAMPLE 2

*1-(9-fluorenyl)-4-n-amylpyridinium bromide*

To a solution of 16.2 g. (0.066 mole) of 9-fluorenyl bromide (prepared in accordance with the procedure of Witting and Felletschin, Ann., 155, 138 (1944) in 75 cc. of acetone was added 9.0 g. (0.06 mole) of 4-n-amyl pyridine. After refluxing for 17 hours the solution was concentrated under diminished pressure; the residual oily material crystallized. It was recrystallized

once from isopropanol-ether. M. P. 204–204.5° C. Yield 20.0 g. (85%)

Analysis for $C_{23}H_{24}NBr$:
Calculated: C, 70.0; H, 6.13
Found: C, 69.81; H, 6.12

EXAMPLE 3

*1-benzohydryl-4-gamma-phenylpropyl-pyridinium bromide*

8.3 g. (0.042 mole) of 4-gamma-phenylpropyl-pyridine was dissolved in 20 cc. of acetone (reagent) and cooled. 10.4 g. (0.042 mole) of benzohydryl bromide dissolved in 10 cc. of reagent acetone was added with swirling to the pyridine solution. No immediate reaction was observed and the solution was allowed to stand overnight in the dark at room temperature.

The quaternary salt did not crystallize overnight but separated at once after cooling and scratching. It was recrystallized from absolute ethanol to a constant melting point of 175–177° C. (sintering at 136–138° C.) 4.7 g. (39.2%) of product was obtained.

Analysis for $C_{27}H_{26}NBr$:
Calculated: C, 73.0%; H, 5.90%
Found: C, 72.71%; H, 5.99%

EXAMPLE 4

*1-benzohydryl-4-(2'-methyloctyl) pyridinium bromide*

This was prepared in the same manner as Example 3 using acetone solutions of 9.4 g. (0.046 mole) of 4-(2-methyloctyl) pyridine and 11.4 g. (0.046 mole) of benzohydryl bromide. The quaternary did not separate overnight, but did immediately after cooling and scratching. Recrystallized to a constant melting point from reagent acetone. 2.7 g. (13.0%) of a product melting at 140–141° C. was obtained.

Analysis for $C_{27}H_{34}NBr$:
Calculated: C, 71.7; H, 7.58
Found: C, 71.52; H, 7.70

EXAMPLE 5

*1-benzohydryl-4-(5'-nonyl) pyridinium bromide*

Following the procedure of Example 3, 29.0 g. (0.15 mole) of 4-(5'nonyl) pyridine and 41.5 g. (0.165 mole) of benzohydryl bromide were mixed in acetone solution. The product crystallized out the next day and was recrystallized twice from isopropanol and once from methyl isobutyl ketone. 49.3 g. (65%) of a product melting at 167–168° C. was obtained.

Analysis for $C_{27}H_{34}NBr$:
Calculated: C, 71.6; H, 7.58
Found: C, 70.89; H, 7.95
70.8; 8.05

EXAMPLE 6

*1-benzyl-4-n-amylpyridinium bromide*

37.6 g. (0.22 mole) of benzyl bromide in 10 cc. of reagent acetone was added to a solution of 29.8 g. (0.2 mole) of 4-n-amyl pyridine in 75 cc. of reagent acetone. Within a few minutes the solution was very warm and when it was cooled, a white solid was precipitated. Recrystallized from acetone. 58.9 g. (91.8%) of material melting at 170–171.5° C. was obtained.

Analysis for $C_{17}H_{22}NBr$:
Calculated: C, 63.8; H, 6.90
Found: C, 63.89; H, 7.21

EXAMPLE 7

*1-benzohydryl-4-(4'-ethylcyclohexylmethyl)-pyridinium bromide*

Using the same procedure as for Example 3, 8.4 g. (0.041 mole) of 4-(4'-ethylcyclohexylmethyl) pyridine and 10.1 g. (0.041 mole) of benzohydryl bromide were mixed. After standing overnight, the quaternary was crystallized by cooling and scratching. It was recrystallized twice from methyl ethyl ketone, 1.6 g. (8.6%) of material of melting point 150.5–152.5° C. was obtained.

Analysis for $C_{27}H_{33}NBr$:
Calculated: C, 71.40; H, 7.37
Found: C, 71.70; H, 7.24

EXAMPLE 8

*1-benzohydryl-4-n-hexylpyridinium bromide*

Following the procedure of Example 3, 12.7 g. (0.077 mole) of 4-n-hexyl pyridine and 20.9 g. (0.085 mole) of benzohydryl bromide were mixed in acetone solution. The quaternary crystallized during the night. It was recrystallized from isopropanol. 20.0 g. (63%) of a product melting at 127.5–130° C. was obtained.

Analysis for $C_{24}H_{28}NBr$:
Calculated: C, 70.3; H, 6.82
Found: C, 70.47; H, 6.95

EXAMPLE 9

*1-methyl-4-n-amylpyridinium iodide*

17.0 g. (0.12 mole) of methyl iodide was added to a solution of 14.9 g. (0.1 mole) of 4-n-amyl pyridine in 65 cc. of methanol. The solution was allowed to stand in darkness overnight and was then refluxed for two hours and concentrated under reduced pressure. The residual dark red oil set up into an orange crystalline solid after the addition of dry ether, cooling and scratching. M. P. 73–76° C. Recrystallized from isopropanol ether: 24.2 g. (83%) of golden leaflets, M. P. 76–78° C.

Analysis for $C_{11}H_{18}NI$:
Calculated: C, 45.4; H, 6.23
Found: C, 45.77; H, 6.27

EXAMPLE 10

*1-benzohydryl-3-bromopyridinium bromide*

To a cooled acetone solution (100 ml.) of benzohydryl bromide (61 g.) (0.25 mole) was added 31.6 g. (0.2 mole) of 3-bromopyridine. After standing at room temperature for 15 hours, the mixture was refluxed for one hour, cooled in ice and filtered. The filtrate and washings were refluxed for a further 44 hours, yielding an additional 28.1 g. of material. Total yield—68.4 g. (84.3%) M. P. 165–174° C. The compound was recrystallized from Et OH twice, from Me OH once, M. P. 169–172° C.

Analysis for $C_{18}H_{15}NBr_2$:
Calculated: C, 53.4; H, 3.74
Found: C, 53.45; H, 3.73

EXAMPLE 11

*1-p-nitrobenzyl-4-4'-ethylcyclohexylmethyl)-pyridinium bromide*

4.8 g. (0.024 mole) of p-nitrobenzylbromide in 35 ml. of acetone was added to 4.1 g. (0.022 mole) of 4-(4'-ethylcyclohexylmethyl) pyridine in 15 cc. of acetone. The mixture was refluxed for 30 minutes, cooled and placed in the dark until the

next day. The solvent was removed under diminished pressure and the residual gum was set up by repeated scratching and washing with ether. 8.2 g. (89%) M. P. 140–161° C. The material was recrystallized from MIBK to a melting point of 177–180° C. 3.2 g. (35%).

Analysis for $C_{21}H_{27}O_2N_2Br$:
Calculated: C, 60.1; H, 6.49
Found: C, 60.06; H, 6.31

EXAMPLE 12

*1-α-naphthylmethyl-4-n-amylpyridinium chloride*

37.4 g. (0.25 mole) of 4-n-amylpyridine was added with cooling to a solution of 48.5 g. (0.27 mole) of α-chloromethylnaphthalene in 75 cc. of acetone. Standing for a week in darkness produced only a change in color of the solution. The solution was refluxed for four hours, cooled, and a large volume of dry ether added. The brown gum which precipitated set up after long scratching and cooling. Crude yield—78.0 g. (87%) M. P. 135–152° C. Recrystallized from n-propanol-ether and again from acetone to M. P. 159.5–160.5° C. Yield 34.7 g. (38.8%).

Analysis for $C_{21}H_{24}NCl$:
Calculated: C, 77.5; H, 7.42
Found: C, 76.88; H, 7.46

EXAMPLE 13

*1-benzohydryl-3-carbethoxypyridinium bromide hemihydrate*

30.2 g. (0.2 mole) of ethyl nicotinate, 54.4 g. (0.22 mole) of benzohydryl bromide and 100 cc. of acetone were mixed and refluxed for 15 hours. The acetone was removed under reduced pressure, leaving a red-brown gum which would not crystallize. The gum was washed several times with dry ether and the residual ether removed under diminished pressure on the steam bath. The gum finally crystallized from acetone on standing overnight at 5° C. Recrystallized three times from acetone to M. P. 113–114° C. Yield 13.2 g. (16.6%).

Analysis for $C_{21}H_{20}O_2NBr \cdot \frac{1}{2}H_2O$:
Calculated: C, 61.9; H, 5.16
Found: C, 62.28; H, 5.26
C, 62.10; H, 5.32

EXAMPLE 14

*1-benzohydryl-4-n-amylpyridinium bromide*

123.4 g. (0.5 mole) of benzohydryl bromide was added to a solution of 74.6 g. (0.5 mole) of 4-n-amylpyridine in 200 cc. of reagent acetone. After standing for 15 hours in the dark the flask was filled with yellowish crystals. Filtered, washed with ether and dried in vacuo. Wt.—113.8 g. (59%) M. P. 134–156° C. Two recrystallizations from acetone (using Darco) yielded 56.0 g. (28.4%) of pure white needles; M. P. 153–4° C. The compound is very light-sensitive, turning pink within a few minutes after exposure to sunlight.

Analysis for $C_{23}H_{26}NBr$:
Calculated: C, 69.8; H, 6.36
Found: C, 69.53; H, 6.54

EXAMPLE 15

*1-benzohydrylpyridinium bromide*

15.8 g (0.20 mole) of pyridine was dissolved in 20 ml. of reagent acetone and cooled. 49.4 g. (0.20 mole) of benzohydryl bromide was dissolved in 25 ml. of reagent acetone and while swirling was added to the pyridine solution. There was no immediate evidence of reaction, and the solution was placed in the dark and allowed to stand overnight at room temperature.

The quaternary salt crystallized during the night. It was filtered off and recrystallized from isopropanol to a constant melting point. 32.7 g. (50.2%) of a product with a melting point 209–213° C. was obtained.

Analysis for $C_{18}H_{16}BrN$:
Calculated: C, 66.3; H, 4.94
Found: C, 66.2; H, 5.03

EXAMPLE 16

*1-benzohydryl-4-ethylpyridinium bromide*

This was prepared in the same manner as Example 15 using acetone solutions of 15.3 g. (0.143 mole) of 4-ethylpyridine and 35.3 g. (0.143 mole) of benzohydryl bromide. The quaternary did not crystallize overnight but did after scratching and stirring with a glass rod. It was dissolved in hot isopropanol, treated with charcoal, and filtered. The filtrate was cooled and on gradually adding ether, the quaternary crystallized. It was also recrystallized from isopropanol-ether. 15.4 g. (30.4%) of a product with a melting point of 194–196° C. was obtained.

Analysis for $C_{20}H_{20}BrN$:
Calculated: C, 67.8; H, 5.68
Found: C, 67.5; H, 5.76

EXAMPLE 17

*1-benzohydryl-4-n-propylpyridinium bromide*

Using the same procedure as for Example 15, 18.1 g. (0.15 mole) of 4-n-propylpyridine and 37.0 g. (0.15 mole) of benzohydryl bromide were put together in acetone. The quaternary salt was crystallized the next morning by scratching with a glass rod. It was purified by two recrystallizations from isopropanol-ether solutions. 34.9 g. (63.3%) of material with melting point 177–178° C. was obtained.

Analysis for $C_{21}H_{22}BrN$:
Calculated: C, 68.6; H, 6.02
Found: C, 68.6; H, 6.34

EXAMPLE 18

*1-benzohydryl-4-n-butylpyridinium bromide*

Using the same procedure as for Example 15, 16.6 g. (0.123 mole) of 4-n-butylpyridine and 30.4 g. (0.123 mole) of benzohydryl bromide were put together in the acetone solution. The rest of the procedure is exactly like 664–25. 17.2 (36.6%) of material with a melting point 134–135° C. was obtained.

Analysis for $C_{22}H_{24}BrN$:
Calculated: C, 69.2; H, 6.33
Found: C, 69.4; H, 6.63

EXAMPLE 19

*1-benzohydryl-4-benzylpyridinium bromide*

In the same manner as in Example 15, 8.1 g. (0.048 mole) of 4-benzylpyridine and 11.8 g. (0.048 mole) of benzohydryl bromide were put together in acetone.

The quaternary crystallized after cooling and scratching. It was recrystallized twice from isopropanol after treating with charcoal in the isopropanol solution and filtering. 8.9 g. (44.7%) of

product with a melting point 169–170° C. was obtained.

Analysis for $C_{25}H_{22}BrN$:
Calculated: C, 72.3; H, 5.33
Found: C, 72.0; H, 5.68

EXAMPLE 20

*1-benzohydryl-4-n-octylpyridinium bromide*

With the same procedure as in Example 15, 8.0 g. (0.042 mole) of 4-n-octylpyridine and 10.3 g. (0.042 mole) of benzohydryl bromide were put together in acetone.

The product crystallized on cooling and scratching. It was recrystallized from acetone-ether. 6.2 g. (33.9%) of material with a melting point of 150–151° C. was obtained.

Analysis for $C_{32}H_{32}BrN$:
Calculated: C, 71.3; H, 7.34
Found: C, 71.6; H, 7.34

EXAMPLE 21

*1-benzohydryl-4-n-nonylpyridinium bromide*

8.3 g. (0.040 mole) of 4-n-nonylpyridine and 10.0 g. (0.040 mole) of benzohydryl bromide were treated in exactly the same manner as in 730–46. 6.0 g. (32.9%) of material melting at 158–159° C. was obtained.

Analysis for $C_{27}H_{34}BrN$:
Calculated: C, 71.8; H, 7.58
Found: C, 71.8; H, 7.54

EXAMPLE 22

*1-benzohydryl - 2 - β - hydroxyethyl - pyridinium bromide*

A mixture of 12.4 g. (0.1 mole) of 2-β-hydroxyethylpyridine and 24.7 g. (0.1 mole) of benzohydryl bromide was allowed to stand at room temperature in a stoppered flask for two days. The yellow-white crystalline mass which had formed was crystallized from isopropanol to obtain 14.3 g. (38.8% yield) of white crystals, M. P. 150–151° C. Recrystallization from absolute alcohol raised the melting point to 151° C. The compound was dried in vacuo over phosphorus pentoxide before analysis.

Analysis for $C_{20}H_{20}BrNO$:
Calculated: C, 64.9; H, 5.41
Found: C, 64.8; H, 5.38

EXAMPLE 23

*1 - benzohydryl - 4 - β - hydroxypropylpyridinium bromide monohydrate*

To 24.7 g. (0.1 mole) of benzohydryl bromide was added 13.7 g. (0.1 mole) of 4-β-hydroxypyridine and the mixture was allowed to stand for ten days at 5–10° C. The resulting semi-solid was crystallized from isopropanol to obtain 13.4 g. of white crystals, M. P. 108–115° C. Successive recrystallizations from absolute alcohol-ether and isopropanol yielded 8.7 g. of colorless crystals, M. P. 119–122° C.

Analysis for $C_{21}H_{22}BrNO \cdot H_2O$:
Calculated: C, 62.8; H, 6.00
Found: C, 62.9; H, 6.06

EXAMPLE 24

*1-benzohydryl-4-n-amylpyridinium bromide*

A mixture of 14.9 g. (0.1 mole) of 4-n-amylpyridine and 24.7 g. (0.1 mole) of benzohydryl bromide was placed in a tightly stoppered flask and allowed to stand at 5–10° C. for two weeks. The resulting white crystalline solid was then stirred with ethyl acetate and collected by suction; weight 28.0 g. (71% yield). Recrystallization from acetone afforded 17.9 g. of white crystals, M. P. 133–135° C.

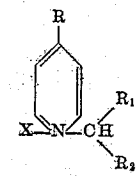
Analysis for $C_{23}H_{26}BrN$:
Calculated: C, 69.8; H, 6.36
Found: C, 69.2; H, 6.78

On long standing the compound changed to its higher melting from M. P. 153–154° C.

We do not limit ourselves to the specifically-mentioned times, temperatures, quantities, chemicals or steps of procedures, since these are given simply to clearly describe the invention and they may be varied without going beyond the scope of the invention.

I claim:

1. A new class of compounds having the general formula




wherein R represents a member of the group consisting of alkyl containing two to twenty carbon atoms, hydroxyalkyl containing two to twenty carbon atoms, carboalkoxy and halogen, X represents a member of the group consisting of chloride, bromide and iodide, $R_1$ and $R_2$ represent a member of the group containing phenyl, napthyl, alkylphenyl, halogenated phenyl, alkoxyphenyl and nitrophenyl and $R_1$ and $R_2$ when taken together with the adjacent —CH— group represent 9-fluorenyl.

2. The compound 1-benzohydryl-4-n-amylpyridinium bromide.

3. The compound 1-benzohydryl-4-n-hexylpyridinium bromide.

4. The compound 1 - benzohydryl - 4-n-butylpyridinium bromide.

5. The compound 1-benzohydryl-4-ethylpyridinium bromide.

6. The compound 1-benzohydryl-4-n-propylpyridinium bromide.

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