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IMIDAZOLIUM COMPOUNDS

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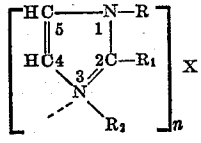
No Drawing. Application July 14, 1945, Serial No. 605,189

7 Claims. (Cl. 260—309)

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This invention relates to a group of new organic compounds and more particularly to new substituted imidazolium compounds.

By this invention we have provided new compositions of matter which may be represented by the following formula:



wherein R and R_1 are aliphatic hydrocarbon radicals, one of the radicals having from 1 to 7 carbon atoms and the other having from 7 to 18 carbon atoms, the total number of carbon atoms being from 10 to 25; R_2 is an aliphatic hydrocarbon radical having from 1 to 7 carbon atoms; X is an anion; and n is an integer from 1 to 3 inclusive.

The compositions of matter of our invention may be regarded as comprising positively charged imidazolium cations which are substituted by aliphatic hydrocarbon radicals and which are combined with negatively charged anions. The aliphatic hydrocarbon groups may be selected from straight chain saturated, branched chain saturated, and straight and branched chain unsaturated groups, such as, for example, the ethyl, isoamyl and allyl groups. The negatively charged anion associated with the imidazolium cation may be any one of a number of negative ions such as, for example, the chloride, bromide, sulfate, acetate, or phosphate ions. By way of example, and referring to the above structural formula, when R is a methyl group, R_1 is a decyl group, R_2 a methyl group, X a chloride ion and n is 1, the compound is 1,3-dimethyl-2-decylimidazolium chloride. Additionally, when R is a dodecyl group, R_1 an isoamyl group, R_2 an allyl group, X a sulfate ion, and n is 2, the compound is di-(1-dodecyl - 2 - isoamyl-3-allylimidazolium) sulfate.

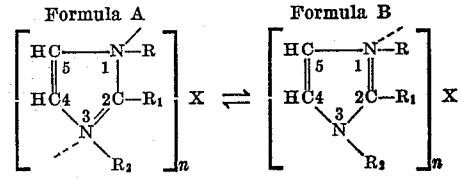
In compounds of this invention the number of carbon atoms contained in the two groups R and R_1 ranges from a total of 10 to 25 carbon atoms. The following examples illustrate this limitation: When R is a hydrocarbon group containing 1 carbon atom such as a methyl group, R_1 must be a hydrocarbon group containing at least 9 carbon atoms such as, for example, a nonyl group, but it may contain any number up to a total of 18 carbon atoms. Further by way of example, when R_1 is a hydrocarbon radical containing 2 carbon atoms such as the ethyl group, R must be a hydrocarbon group which contains at least 8 carbon atoms such as, for example, the

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octyl group, but it may contain any number up to a total of 18 carbon atoms.

It should be noted that two isomeric forms of our compounds exist simultaneously because of a dynamic equilibrium. Thus, compounds of our invention may be represented by either of the following formulas:

Formula A Formula B



wherein R, R_1, R_2, X and n have the same significance as before. In Formula A, the nitrogen at position 1 is a tertiary, and the nitrogen at position 3 is quaternary. In Formula B, the nitrogen at position 1 is quaternary, and the nitrogen in position 3 is tertiary. In the specification and claims, we employ for convenience Formula A where R is attached to the tertiary nitrogen at position 1, and R_2 is attached to the quaternary nitrogen at position 3. It will be understood that the two forms illustrated are to be regarded as equivalent, and that both forms are to be considered as within the scope of this invention.

The compounds we have invented have several fields of utility. For example, they are effective in reducing the surface tension of aqueous solutions. They have bacteriostatic properties. Additionally they are possessed of therapeutic qualties which make them suitable for application in the treatment of various bacterial invasions.

Broadly, we may prepare the compounds embodied in our invention by reacting a suitably substituted imidazole with a member of the class of alkylating agents such as, for example, the nitrates, sulfates or halides of aliphatic hydrocarbons. It is usually most convenient to employ the halides since they are readily available, and for therapeutic compounds we prefer to use a halide containing an anion commonly employed in therapeutic compounds, such as chlorine, bromine, or iodine. The reaction is effected by mixing the substituted imidazole with the halide of the aliphatic hydrocarbon, allowing any spontaneous reaction to subside and subsequently heating the mixture to complete the reaction. The product may be purified by recrystallization or precipitation from suitable solvents or mixtures thereof. The theoretical amount of the aliphatic hydrocarbon halide may be used but it is preferable to use an excess to assure completion of the reaction. The reaction is conveniently,

although not necessarily, carried out in a closed system thus eliminating any loss of the aliphatic hydrocarbon halide by volatilization. If desired, a suitable nonreactive solvent such as, for example, alcohol or ethyl acetate may be used as a vehicle during the reaction.

In preparing the compounds of our invention there may be used as starting material a mixture of similarly substituted imidazoles. Thus for example, referring to the above formulas, a group of imidazoles wherein R is a mixture of aliphatic hydrocarbon radicals having from 8–18 carbon atoms and R_1 is an aliphatic hydrocarbon group containing not more than 7 carbon atoms, may be reacted with a halide of an aliphatic hydrocarbon such as methyl bromide to yield a mixture of the correspondingly substituted imidazolium bromides. Likewise, by way of example, a group of imidazoles wherein R is an aliphatic hydrocarbon radical containing not more than 10 carbon atoms and R_1 is a mixture of aliphatic hydrocarbon radicals having 11–15 carbon atoms may be reacted with a halide of an aliphatic hydrocarbon such as methyl chloride to yield a mixture of the correspondingly substituted imidazolium chlorides.

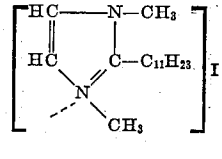
It should be noted that the compounds of our invention comprising both of two isomeric forms as mentioned heretofore may be prepared by either of two routes. An imidazole substituted by the groups R and R_1 may be alkylated with an R_2-containing alkylating agent. Likewise an imidazole substituted by the groups R_1 and R_2 may be alkylated by an R-containing alkylating agent. The same compound or mixture of compounds results when R, R_1, and R_2 are correspondingly identical in each alkylation reaction.

The compounds of our invention are salt-like and generally water-soluble, and consequently are subject to many of the ionic reactions which typify soluble inorganic salts. By anionic interchange reactions, one anion may be substituted for another. For example, by taking advantage of the lower solubilitiy of a substituted imidazolium sulfate as compared with the solubility of the corresponding imidazolium chloride, the sulfate may be crystallized preferentially from a solution containing the imidazolium, sulfate and chloride ions. Illustrating another method of effecting this conversion, an aqueous solution of substituted imidazolium halide may be shaken with substantially insoluble silver sulfate, whereby the halide ion is removed as insoluble silver halide leaving in solution the imidazolium sulfate. Additionally, ionic interchange may be effected through the hydroxyl ion as an intermediate. Upon shaking an aqueous solution of a substituted imidazolium halide with silver oxide, there is formed the corresponding soluble imidazolium hydroxide and insoluble silver halide. Treatment of the soluble imidazolium hydroxide solution with the appropriate acid forms the desired imidazolium compound.

The following examples illustrate methods by which we may prepare the new compositions of matter of our invention.

Example 1

1,3-dimethyl-2-n-undecylimidazolium iodide represented by the following formula

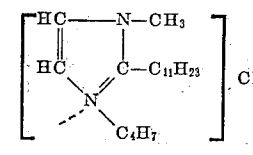


may be prepared by refluxing a mixture of 171 g. of ethyl laurate and 135 g. of anhydrous ethylene diamine at 110–112° C. for 12 hours. The alcohol and excess ethylene diamine were removed by distillation and 172 g. of crude N-lauroyl ethylene diamine was obtained. A mixture of 162 g. of the crude N-lauroyl ethylene diamine and 187 g. of powdered calcium oxide was heated with stirring at 225° C. for 36 hours. The reaction mixture was cooled to room temperature and extracted three times with about 350 cc. of alcohol. The extract was distilled in vacuo and the reaction product, 2-n-undecyl-4,5-dihydroimidazole, distilled at 180–189° C./10 mm. It melted at 81–83° C. To 56.5 g. of the 2-n-undecyl-4,5-dihydroimidazole was added 31.7 g. of dimethyl sulfate, the temperature of the reaction during the addition being maintained at about 85° C. About 150 cc. of water was added and the reaction mixture stirred until the solid material had dissolved. An aqueous solution of 20 g. of 50 percent sodium hydroxide and about 150 cc. of butyl alcohol was added to the reaction mixture with agitation, the mixture filtered and the butyl alcohol layer separated. The reaction product, 1-methyl-2-n-undecyldihydroimidazole, was obtained by evaporation of the butyl alcohol and distillation of the residue at 167–172° C./6 mm. A mixture of 30.9 g. of 1-methyl-2-n-undecyl-4,5-dihydroimidazole and 3.1 g. of nickel catalyst was heated at 226–246° C. until no more hydrogen was evolved. The desired reaction product, 1-methyl-2-n-undecylimidazole was isolated by distilling the reaction mixture at 166–203° C./5 mm.

A cold mixture of 1.8 g. of 1-methyl-2-n-undecylimidazole and 1.7 g. of methyl iodide was sealed in a tube. When the tube and its contents were warmed to about room temperature, a spontaneous reaction took place after which reaction the tube was heated for one hour at 100–110° C. The tube was then cooled to about room temperature and its contents dissolved in about 50 cc. of hot ethyl acetate. The hot solution was treated with decolorizing carbon, filtered and the filtrate cooled to about 0° C., whereupon crystals of 1,3-dimethyl-2-n-undecylimidazolium iodide separated. These were filtered off and redissolved in hot ethyl acetate from which solution, upon cooling to about 0° C., there separated substantially pure 1,3-dimethyl-2-n-undecylimidazolium iodide which melted at about 128–130° C.

Example 2

1-methyl- 2 -n-undecyl- 3 -methallylimidazolium chloride represented by the formula

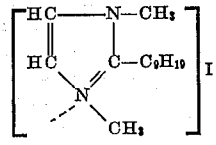


may be prepared by reacting 1-methyl-2-n-undecylimidazole with methallyl chloride as follows:

A cold mixture of 1.8 g. of 1-methyl-2-n-undecylimidazole and 2 g. of methallyl chloride was sealed in a glass tube and heated to 110–120° C. for two hours. The tube was cooled to room temperature, its contents dissolved in about 50 cc. of hot ethyl acetate and the hot solution treated with decolorizing carbon and filtered. Upon cooling the filtrate to about 0° C., there separated crystals of 1-methyl-2-n-undecyl-3-methallylimidazolium chloride which after recrystallization from ethyl acetate melted at about 133–134° C.

Example 3

1,3-dimethyl-2-n-nonylimidazolium iodide represented by formula



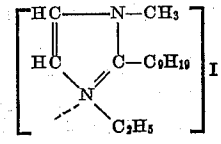
may be prepared by reacting 1-methyl-n-nonylimidazole with methyl iodide as follows:

1-methyl- 2 -n-nonylimidazole was prepared from anhydrous ethylene diamine and ethyl decanoate in substantially the same manner as was prepared 1-methyl- 2 -n-undecylimidazole described in Example 1.

A cold mixture of 1.5 g. of 1-methyl-2-n-nonylimidazole and 1.7 g. of methyl iodide was sealed in a tube. Upon warming to about room temperature the contents of the tube reacted spontaneously after which reaction the tube was heated to 110° C. for one hour. The tube was then cooled to about room temperature, its contents dissolved in about 50 cc. of a hot mixture of ethyl acetate and absolute ethyl alcohol, and the solution treated with decolorizing carbon and filtered. Upon cooling the filtrate to about 0° C., there separated a crystalline precipitate of 1,3-dimethyl-2-n-nonylimidazolium iodide which after recrystallization from a mixture of ethyl acetate and absolute ethyl alcohol melted at about 127–128° C.

Example 4

1-methyl-2-n-nonyl-3-ethylimidazolium iodide represented by the formula

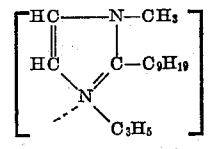


may be prepared from 1-methyl-2-n-nonylimidazole and ethyl iodide as follows:

A cold mixture of 1.8 g. of 1-methyl-2-n-nonylimidazole and 1.7 g. of ethyl iodide was sealed in a tube. The mixture upon warming to about room temperature reacted spontaneously after which reaction the tube was heated to 100–110° C. for one hour. The tube was then cooled to about room temperature, its contents dissolved in about 50 cc. of boiling ethyl acetate, and the solution treated with decolorizing carbon and filtered. Upon cooling the filtrate to about 0° C., there separated a crystalline precipitate of 1-methyl- 2 -n-nonyl- 3 -ethylimidazolium iodide which after recrystallization from ethyl acetate melted at about 82° C.

Example 5

1-methyl-2-n-nonyl-3-allylimidazolium bromide represented by the formula



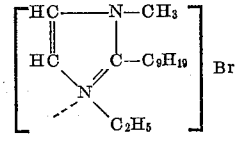
may be prepared from 1-methyl-2-n-nonylimidazole and allyl bromide as follows:

A cold mixture of 2 g. of 1-methyl-2-n-nonylimidazole and 1.9 g. of allyl bromide was sealed in a tube. Upon warming to about room temperature the mixture reacted spontaneously after

which reaction the tube was heated to 100–110° C. for two hours. The tube was then cooled to about room temperature, its contents dissolved in about 50 cc. of a hot mixture of ethyl acetate and dry ethyl alcohol, and the solution treated with decolorizing carbon and filtered. Upon cooling to about 0° C. a crystalline precipitate of 1-methyl-2-n-nonyl-3-allylimidazolium bromide separated. The precipitate after recrystallization from a mixture of ethyl acetate and absolute ethyl alcohol melted at about 97–98° C.

Example 6

In addition to the method given in Example 5, 1-methyl-2-n-nonyl-3-allylimidazolium bromide represented by the formula



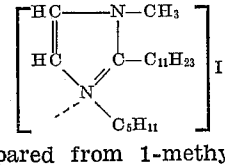
may also be prepared as follows:

1-allyl-2-n-nonylimidazole was prepared by ring closure of N-n-decanoyl ethylene diamine and subsequent allylation and dehydrogenation in substantially the same manner as was prepared 1-methyl-2-n-undecylimidazole described in Example 1.

By reacting 1-allyl-2-n-nonylimidazole with methyl bromide there results 1-methyl-2-n-nonyl-3-allylimidazolium bromide having a melting point of about 97–98° C. and causing no melting point depression with a sample of the 1-methyl-2-n-nonyl-3-allylimidazolium bromide obtained as described in Example 5.

Example 7

1-methyl-2-n-undecyl-3-amylimidazolium iodide represented by the formula

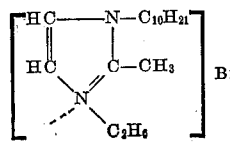


may be prepared from 1-methyl-2-n-undecylimidazole and amyl iodide as follows:

A cold mixture of 1.8 g. of 1-methyl-2-n-undecylimidazole and 2 g. of amyl iodide was sealed in a tube and the tube heated to 110–120° C. for two hours. The tube was then cooled to about room temperature, its contents dissolved in about 50 cc. of hot ethyl acetate, and the hot solution treated with decolorizing carbon and filtered. No precipitate was obtained upon cooling the filtrate to about 0° C. The filtrate was thereupon treated with an excess of petroleum ether which precipitated an oil, 1-methyl-2-n-undecyl-3-amylimidazolium iodide. The oil was purified by dissolving it in hot ethyl acetate, treating with decolorizing carbon, filtering and adding an excess of petroleum ether to reprecipitate 1-methyl-2-n-undecyl-3-amylimidazolium iodide as an oil which was dried in a vacuum desiccator over sulfuric acid.

Example 8

1-n-decyl-2-methyl-3-ethylimidazolium bromide represented by the formula



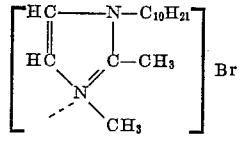
may be prepared from 1-n-decyl-2-methylimidazole and ethyl bromide.

1-n-decyl-2-methylimidazole was prepared by heating a mixture of 203 g. of N-acetyl ethylene diamine and 560 g. of finely powdered calcium oxide to 225–235° C. for 14 hours. After cooling to 90–100° C. the mixture was extracted with three 500 cc. portions of alcohol. The alcohol was evaporated and the residue upon distillation at 195–198° C. yielded 2-methyl-4,5-dihydroimidazole. A mixture of 50.4 g. of 2-methyl-4,5-dihydroimidazole, 52.8 g. of n-decyl chloride and 100 cc. of benzene was refluxed for seven hours and then cooled to 25° C. A solution of 24 g. of 50 percent sodium hydroxide solution in 150 cc. of water was added, the mixture filtered and the benzene layer separated from the filtrate. The benzene was removed in vacuo and the crude 1-n-decyl-2-methyl-4,5-dihydroimidazole distilled at 155–156° C./6 mm. A mixture of 3.2 g. of nickel catalyst and 6.7 g. of 1-n-decyl-2-methyl-4,5-dihydroimidazole was heated with agitation to 225–235° C. until hydrogen was no longer evolved. The reaction mixture was cooled to 125° C. and a further amount of ½ g. of nickel catalyst added. The heating was resumed and continued until hydrogen evolution ceased. The desired 1-n-decyl-2-methylimidazole thus obtained was purified by distilling at 153–160° C./5.5 mm.

A cold mixture of 1.8 g. of 1-n-decyl-2-methylimidazole and 1.7 g. of ethyl bromide was sealed in a tube and the tube was heated at 100–110° C. for two hours. The tube was then cooled to room temperature, its contents dissolved in about 40 cc. of boiling ethyl acetate, and the solution treated with decolorizing carbon and filtered. Upon cooling the filtrate to about 0° C., 1-n-decyl-2-methyl-3-ethylimidazolium bromide separated as an oil. The precipitation of the oil was completed by adding an excess of petroleum ether to the mixture. The oil was separated, redissolved in hot ethyl acetate, the solution treated with decolorizing carbon, filtered, and an excess of petroleum ether added to the filtrate. The 1-n-decyl-2-methyl-3-ethylimidazoliumbromide, which again separated as an oil, was dried in a vacuum desiccator over sulfuric acid.

Example 9

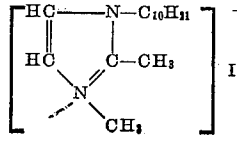
1-n-decyl - 2,3 - dimethylimidazolium bromide represented by the formula



may be prepared from 1-n-decyl-2-methylimidazole and methyl bromide by the sealed-tube reaction as used in the preceding examples. The 1-n - decyl - 2,3 - dimethylimidazolium bromide melted at about 83.5–85.5° C.

Example 10

1-n-decyl-2,3-dimethylimidazolium iodide represented by the formula

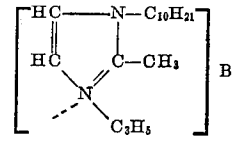


may be prepared by reacting 1-n-decyl-2-methylimidazole with methyl iodide as follows:

A mixture of 45 g. of 1-n-decyl-2-methylimidazole, 35 g. of methyl iodide and 150 cc. of ethyl acetate was allowed to stand in a pressure bottle until the spontaneous reaction had ceased and was then heated to 100° C. for one hour to ensure completion of the reaction. The contents of the bottle were dissolved in 250 cc. of boiling ethyl acetate, the solution treated with decolorizing carbon and filtered. Upon cooling the filtrate to about 0° C., there separated a precipitate of 1-n- decyl - 2,3 - dimethylimidazolium iodide which upon recrystallization from 400 cc. of ethyl acetate melted at about 108–109° C.

Example 11

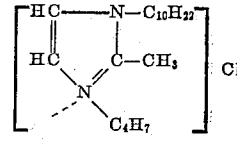
1-n-decyl-2-methyl- 3 - allylimidazolium bromide represented by the formula



may be prepared by reaction of 1-n-decyl-2-methylimidazole with allyl bromide in a sealed tube substantially as described in the preceding examples. 1-n-decyl-2-methyl-3 - allylimidazolium bromide melted at about 70–71° C.

Example 12

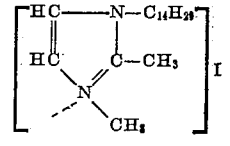
1-n-decyl-2- methyl - 3 - methallylimidazolium chloride represented by the formula



melting at 110–111° C. may be prepared by reaction of 1-n-decyl-2-methylimidazole with methallyl chloride substantially as described in the preceding examples.

Example 13

1-n-tetradecyl-2,3-dimethylimidazolium iodide represented by the formula

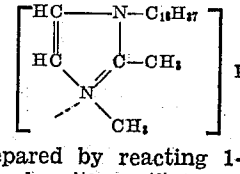


melting at about 108–110° C. may be prepared by reacting 1-n-tetradecyl-2 - methylimidazole with methyl iodide.

The 1-n-tetradecyl-2-methylimidazole used in the preparation was prepared by methods analogous to those used in Example 8 for the preparation of 1-n-decyl-2-methylimidazole.

Example 14

1. 1-n-octadecyl - 2,3 - dimethylimidazolium iodide represented by the formula

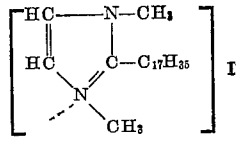


may be prepared by reacting 1-n-octadecyl-2-methylimidazole with methyl iodide in a sealed tube substantially as described in the preceding examples.

The 1-n-octadecyl-2-methylimidazole used in the reaction is prepared by a method similar to that used in Example 3 for the preparation of 1-n-decyl-2-methylimidazole.

Example 15

1,3-dimethyl-2-n-heptadecylimidazolium iodide represented by the formula



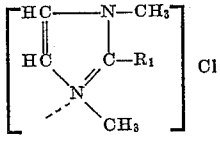
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may be prepared by reacting 1-methyl-2-n-heptadecylimidazole with methyl iodide in a sealed tube substantially as described in the preceding examples.

The 1-methyl-2-n-heptadecylimidazole used in the preparation is obtained from ethyl n-octadecanoate and ethylene diamine by a method similar to that used for the preparation of 1-methyl-2-n-undecylimidazole described in Example 1.

Example 16

A mixture of substituted imidazolium chlorides represented by the following formula:

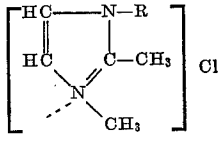


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wherein R_1 represents a mixture of aliphatic hydrocarbon radicals derived from commercial ethyl laurate may be prepared by the method of Example 1 except that in place of pure ethyl laurate as used in Example 1 there is used ethyl laurate obtained from commercial lauric acid, and in place of methyl iodide there is used methyl chloride.

Example 17

A mixture of substituted imidazolium chlorides represented by the following formula:

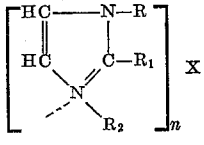


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wherein R represents a mixture of aliphatic hydrocarbon radicals derived from a commercial mixture of monohydric alcohols such as Lorol alcohol may be prepared by the method of Example 8 except that in place of pure N-decyl chloride there are used chlorides derived from a commercial mixture of monohydric alcohols such as Lorol alcohol, and in place of ethyl bromide there is used methyl chloride.

We claim as our invention:

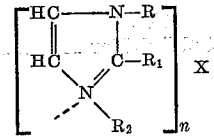
1. A composition of matter represented by the formula:



X

wherein R and R_1 are aliphatic hydrocarbon radicals, one of the radicals having from 1 to 7 carbon atoms and the other having from 7 to 18 carbon atoms, the total number of carbon atoms being from 10 to 25; R_2 is an aliphatic hydrocarbon radical having from 1 to 7 carbon atoms; X is an anion; and n is an integer from 1 to 3 inclusive.

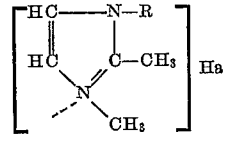
2. A composition of matter represented by the formula:



X

wherein R and R_1 are aliphatic hydrocarbon radicals, one radical having from 1 to 7 carbon atoms and the other having from 7 to 18 carbon atoms, the total number of carbon atoms being from 10 to 25; R_2 is a saturated aliphatic hydrocarbon radical having from 1 to 7 carbon atoms; X is an anion; and n is an integer from 1 to 3 inclusive.

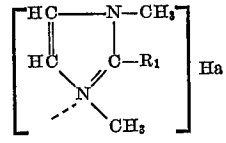
3. A composition of matter comprising a mixture of compounds, and represented by the formula



Ha

wherein R is a mixture of aliphatic hydrocarbon radicals having from 8–18 carbon atoms, said radicals being derived from a commercial lauryl alcohol, and Ha is a halogen ion other than fluorine.

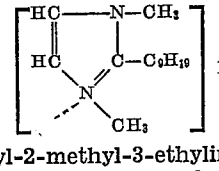
4. A composition of matter comprising a mixture of compounds, and represented by the formula



Ha

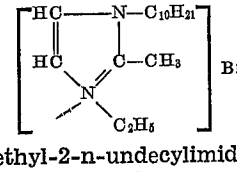
wherein R_1 is a mixture of aliphatic hydrocarbon radicals having from 11–15 carbon atoms, said radicals being derived from a commercial lauric acid, and Ha represents a halogen ion other than fluorine.

5. 1,3-dimethyl-2-n-nonylimidazolium iodide represented by the formula:



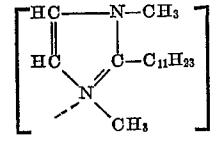
I

6. 1-n-decyl-2-methyl-3-ethylimidazolium bromide represented by the formula:



Br

7. 1,3-dimethyl-2-n-undecylimidazolium iodide represented by the formula:



I

HORACE A. SHONLE.
EDWIN R. SHEPARD.

(References on following page)

REFERENCES CITED

The following references are of record in the file of this patent:

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Number	Name	Date
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2,404,299	Kyrides	July 16, 1946
2,404,300	Kyrides	July 16, 1946

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Number	Country	Date
501,727	Great Britain	Feb. 28, 1939

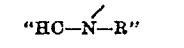
Certificate of Correction

Patent No. 2,493,318 **January 3, 1950**

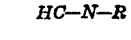
HORACE A. SHONLE ET AL.

It is hereby certified that errors appear in the printed specification of the above numbered patent requiring correction as follows:

Column 2, lines 9 and 10, for that portion of Formula A reading



read



column 3, line 22, after the word "having" insert *from*; column 6, line 22, for "C_2H_5" read C_3H_5; line 75, for "C_2H_5" read C_2H_5; column 8, line 35, for "$C_{10}H_{22}$" read $C_{10}H_{21}$; line 64, before "1–n–" strike out the numeral and period "1."; column 9, line 55, for "Lorol" read *'Lorol'*;

and that the said Letters Patent should be read with these corrections therein that the same may conform to the record of the case in the Patent Office.

Signed and sealed this 25th day of April, A. D. 1950.

[SEAL]

THOMAS F. MURPHY,
Assistant Commissioner of Patents.