Patented June 16, 1953

2,642,451

UNITED STATES PATENT OFFICE

2,642,451

THIOLURETHANES AND PROCESSES FOR PREPARING THEM

John Weijlard, Maplewood, and Max Tishler, Westfield, N. J., assignors to Merck & Co., Inc., Rahway, N. J., a corporation of New Jersey

No Drawing. Original application December 13, 1949, Serial No. 132,793. Divided and this application June 25, 1952, Serial No. 295,113

8 Claims. (Cl. 260—455)

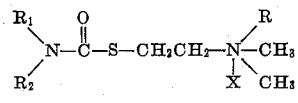
1

This invention is concerned generally with a new group of antispasmodics related to choline. More particularly, it relates to dimethyl-alkyl-β - (carbamylmercapto) ethyl - ammonium salts wherein both of the hydrogens attached to the nitrogen atom of the carbamyl grouping are replaced by saturated hydrocarbon radicals; to the process for preparing these novel quaternary ammonium salts and to the intermediate products thus obtained.

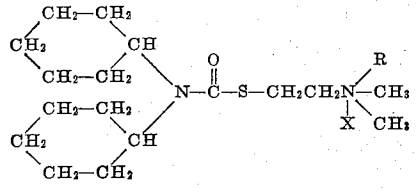
This application is a division of our co-pending application Serial No. 132,793, filed December 13, 1949.

Compounds, analogous to the quaternary ammonium salts herein described but wherein oxygen is substituted for sulfur, such as dibutoline sulfate (dimethylethyl - β-hydroxyethyl-ammonium sulfate dibutylurethane), have previously been found to be effective antispasmodics. The presently disclosed quaternary salts are, however, greatly superior in antispasmodic effectiveness to said oxygen analogs, and are at the same time much less toxic. Moreover, these novel quaternary salts have been found to be far superior to any other known antispasmodics, such as papaverine, Pavatrine and Syntropan. These new salts have also been found to have antitubercular activity.

These novel quaternary dimethyl-alkyl-β-(N, N-disubstituted - carbamylmercapto) ethyl - ammonium salts may be chemically represented as follows:



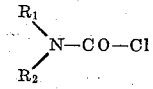
wherein R is an alkyl radical, R_1 and R_2 are saturated hydrocarbon radicals, and X is an anion. The preferred quaternary ammonium salts are those in which R_1 and R_2 are cyclohexyl radicals, i. e., dimethyl-alkyl-β-(dicyclohexylcarbamyl-mercapto)-ethyl-ammonium salts (which can also be referred to as dimethyl-alkyl-β-thiolethyl ammonium salt dicyclohexylurethanes), since salts of this class possess low toxicity and outstanding antispasmodic activity. These preferred quaternary ammonium salts may be represented chemically as follows:



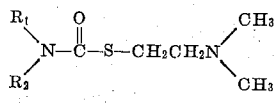
2

wherein R and X have the significance above defined.

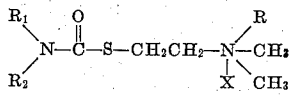
We have discovered that these dimethyl-alkyl-β-(N,N - disubstituted - carbamylmercapto) ethyl ammonium salts, wherein the substituents attached to the nitrogen atom of the carbamyl grouping are saturated hydrocarbon radicals, can be prepared by reacting dimethyl-aminoethyl-thiol with an N,N-disubstituted carbamyl chloride of the formula:



wherein R_1 and R_2 are saturated hydrocarbon radicals, for example, a dialkyl carbamyl chloride such as dibutyl carbamyl chloride, diamyl carbamyl chloride, and the like, or a dicycloalkyl carbamyl chloride, such as dicyclohexyl carbamyl chloride, to produce a thiolurethane of the formula:



wherein R_1 and R_2 are saturated hydrocarbon radicals, and reacting said thiolurethane with an alkyl ester of an inorganic acid, for example an alkyl iodide, such as ethyl iodide, propyl iodide, butyl iodide, amyl iodide, and the like, a dialkyl sulfate, such as diethyl sulfate, and the like, to produce a quaternary salt of the formula:

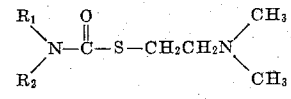


wherein R is an alkyl radical, R_1 and R_2 are saturated hydrocarbon radicals and X is an anion.

The dimethyl aminoethylthiol starting material can be prepared by reacting dimethyl-aminoethyl chloride and sodium hydrosulfide as described in Example 1 hereinbelow. The dialkyl or dicycloalkyl carbamyl chloride can be prepared by reacting the appropriate secondary amine with phosgene according to the procedure set forth in the illustrative examples and described in J. Chem. Soc. 1947, 313. The dimethyl aminoethylthiol and the disubstituted carbamyl chloride can be prepared in purified form, if desired, by fractional distillation in vacuo.

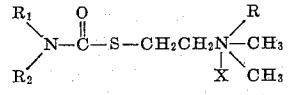
The reaction between the dimethyl aminoethylthiol and the carbamyl chloride having two saturated hydrocarbon substituents attached to the nitrogen atom of the carbamyl grouping, for

example a dialkyl carbamyl chloride such as dibutyl carbamyl chloride, diamyl carbamyl chloride, and the like, or a dicycloalkyl carbamyl chloride such as dicyclohexyl carbamyl chloride, and the like, is ordinarly conducted in the presence of a hydrogen chloride acceptor. The hydrogen chloride acceptor is preferably an organic base such as a compound containing a pyridine ring, such as pyridine, quinoline, picoline, and the like, and preferably an acceptor that also acts as a solvent for the reactants. The reaction is conveniently carried out by heating the reactants under reflux in the presence of pyridine under which conditions the reaction is ordinarily complete in approximately 3 hours. The thiolurethane thus produced is conveniently freed of non-basic impurities by evaporating the pyridine, dissolving the residual material in water, acidifying the aqueous solution and extracting the acidified solution with a water-immiscible organic solvent such as ether to remove impurities. The aqueous solution is then made alkaline and extracted with a water-immiscible solvent such as chloroform. Upon evaporation of the dried chloroform extracts there is obtained the desired thiolurethane of the formula:



wherein R_1 and R_2 are saturated hydrocarbon radicals.

This thiolurethane is then reacted with an alkyl ester of an inorganic acid as, for example, a dialkyl sulfate, such as diethyl sulfate, an alkyl iodide, such as ethyl iodide, n-propyl-iodide, n-butyl iodide, n-amyl iodide and the like, to produce the corresponding quaternary ammonium salt of the formula:

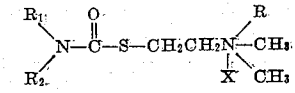


wherein R, R_1, R_2 and X have the significance defined hereinabove.

The reaction between the thiolurethane and the dialkyl sulfate (preferably diethyl sulfate) is conveniently conducted by bringing the reactants together in diethyl ether solution at substantially room temperature. Under these conditions the reaction is ordinarily substantially complete in about 15 hours and the quaternary dimethylalkyl-β-(N,N-disubstituted - carbamyl - mercapto)ethyl-ammonium ethyl sulfate which precipitates can be recovered by filtration.

When the thiolurethane is reacted with an alkyl iodide, the reaction is ordinarily carried out by mixing the reactants in the absence of a solvent and agitating the resulting mixture at a temperature of about 25–30° C. for a period of about 3 hours. The mixture is ordinarily allowed to stand overnight to insure completion of the reaction. The product, which is the corresponding dimethylalkyl-β - (N,N - disubstituted - carbamylmercapto) - ethyl - ammonium iodide is then converted to the corresponding sulfate by reaction with powdered silver sulfate in the presence of ethanol.

Examples of these quaternary salts having the formula:



wherein R is an alkyl radical, R_1 and R_2 are saturated hydrocarbon radicals and X is an anion, are the following:

(1) Dimethyl-ethyl-β-(N,N-dicyclohexyl - carbamylmercapto) ethyl-ammonium ethyl sulfate, also named dimethylethyl-β-thiolethyl ammonium ethyl sulfate dicyclohexylurethane;

(2) Dimethyl-n-propyl-β-(N,N - dicyclohexylcarbamylmercapto) ethyl - ammonium sulfate, also named dimethyl - n - propyl - β - thiolethyl ammonium sulfate dicyclohexylurethane;

(3) Dimethyl-n-butyl-β - (N,N - dicyclohexyl - carbamylmercapto) ethyl - ammonium sulfate, also named dimethyl-n-butyl - β - thiolethyl ammonium sulfate dicyclohexylurethane;

(4) Dimethyl-n-amyl-β - (N,N - dicyclohexyl - carbamylmercapto) ethyl - ammonium sulfate, also named dimethyl-n-amyl-β-thiolethyl ammonium sulfate dicyclohexylurethane;

(5) Dimethyl-ethyl-β-(N,N-diamyl - carbamylmercapto) ethyl - ammonium sulfate, also named dimethylethyl - β - thiolethyl ammonium sulfate diamylurethane;

(6) Dimethyl-ethyl-β-(N,N-diamyl - carbamylmercapto) ethyl - ammonium ethyl sulfate, also named dimethylethyl-β-thiolethyl ammonium ethyl sulfate diamylurethane;

(7) Dimethyl-ethyl-β-(N,N - dicyclohexyl-carbamylmercapto) ethyl - ammonium sulfate, also named dimethylethyl-β-thiolethyl ammonium sulfate dicyclohexylurethane;

(8) Dimethyl-ethyl-β - (N,N-dibutyl-carbamylmercapto) ethyl - ammonium iodide, also named dimethylethyl-β-thiolethyl ammonium iodide dibutylurethane;

(9) Dimethyl-ethyl-β-(N,N-dibutyl - carbamylmercapto) ethyl - ammonium sulfate, also named dimethylethyl-β-thiolethyl ammonium sulfate dibutylurethane;

(10) Dimethyl-ethyl-β-(N,N-dicyclohexyl - carbamylmercapto) ethyl - ammonium iodide, also named dimethylethyl - β - thiolurethyl ammonium iodide dicyclohexylurethane;

(11) Dimethyl-n-propyl-β-(N,N - dicyclohexyl - carbamylmercapto) ethyl - ammonium iodide, also named dimethyl - n - propyl - β-thiolethyl ammonium iodide dicyclohexylurethane;

(12) Dimethyl-n-butyl - β - (N,N-dicyclohexyl-carbamylmercapto) ethyl - ammonium iodide, also named dimethyl - n - butyl - β - thiolethyl ammonium iodide dicyclohexylurethane;

(13) Dimethyl-n-amyl - β - (N,N - dicyclohexyl-carbamylmercapto) ethyl - ammonium iodide, also named dimethyl - n - amyl - β-thiolethyl ammonium iodide dicyclohexylurethane;

(14) Dimethyl-ethyl-β - (N,N-diamyl-carbamylmercapto) ethyl - ammonium iodide, also named dimethylethyl-β-thiolethyl ammonium iodide diamylurethane.

Of particular interest are the first seven quaternary salts listed on the preceding page which have been found to possess outstanding antispasmodic activity.

These compounds were tested in comparison with Dibutoline sulfate (dimethylethyl-β-hydroxyethyl ammonium sulfate dibutylurethane) on isolated organs for antispasmodic activity as

follows: rabbit intestine, for inhibition of spontaneous activity; guinea pig uterus, for inhibition of spontaneous activity; guinea pig intestine, for inhibition of contraction produced by spasmogenic agents, urecholine, acetyl choline, and in some instances barium chloride.

The results obtained are summarized in the following table:

Compound	Inhibition of Spontaneous Activity of—		Inhibition of Contractions of G. P. Intestine Produced by Spasmogenic Agents	
	Rabbit Intestine	G. P. Uterus	Urecholine or Acetyl Choline	Barium Chloride
1	++++	++++	++++	++++
2	++++	++++	++	++++
3	++++	++++	+++	++++
4	++++	++++	++	++++
5	++	+	+	+
6	++	++	++	+++
7 (Dithioline Sulfate)	++++	++++	++++	+++
Dibutoline Sulfate	+	0	+++	++

As evident from the above table the novel quaternary salts described in this application, and especially the dimethylalkyl-β-thiolethyl ammonium (ethyl) - sulfate dicyclohexyl - urethanes, are more effective antispasmodics than Dibutoline. Of particular interest is the quaternary salt, dimethylethyl-β-thiolethyl-ammonium sulfate dicyclohexyl urethane (compound 7) which has been found to be two to three times as potent as Dibutoline in inhibiting the effect of spasmogenic agents on isolated guinea pig intestine.

A large number of experiments have been performed on isolated uteri of both pregnant and non-pregnant guinea pigs. Direct comparisons have been made of the activity on the isolated uterus between compound 7, Dibutoline, papaverine, Pavatrine, and Syntropan. In nearly every test compound 7 proved to be the most effective of all of these agents, sometimes being active on an organ which was relatively refractory to the other compounds. Moreover, compound 7 proved to be very effective in relaxing uterine contractions stimulated by urecholine, acetyl choline, histamine, pitocum, or ergotamine tartrate.

Compound 7 has been administered orally, subcutaneously, and intravenously to the dog with exteriorized intestinal loop. Good intestinal antispasmodic effects have been observed after administration by all three routes, though on some occasions oral administration failed. When Pavatrine was administtered orally for comparison in two experiments, it succeeded once and failed once. When Dibutoline iodide has been administered orally in comparable doses (up to 10 mg./kg.), no effect has been observed in five trials. In a single experiment, compound 7 (2 mg./kg. subcutaneously), relaxed the uterus of an intact anesthetized guinea pig.

Compound 7 produces mydriasis similar to that observed with Dibutoline when applied topically to the cat's eye, in 5% or 1% solution. Mydriasis was not produced by administration of oral doses up to 2 mg./kg.

The acute toxicity of compound 7 was tested and found to be approximately one-half as toxic as Dibutoline in mice treated with single doses subcutaneously. Determination of LD_{50} (the dosage that will kill one-half of the animals treated) of the two drugs simultaneously on two different strains of mice gave a figure of about 40 mg./kg. for Dibutoline, and about 80 mg./kg. for compound 7.

In order to determine the chronic toxicity, a group of young rats were given subcutaneous injections of compound 7 over a three-month period. Each injection was 2.5 mg./kg. twice daily on week days, with single injections of 5 mg./kg. on Saturdays and Sundays. A similar group was given the same dosage of Dibutoline, and a third group served as uninjected controls. At the end of three months, the growth rate of all groups was identical and there was no evidence of toxicity. Examination of the rats after administration for three months showed no divergence from normal in hemoglobin, red cell count, and white cell count (total and differential). No gross morphological changes were found at autopsy, except for a moderate degree of local tissue irritation at the site of injection (rats are particularly susceptible to local irritation). No local irritation was observed in dogs receiving repeated injections.

The antitubercular utility of the new quaternary salts is illustrated by the activities observed when compounds 1 and 9 were tested for in vitro activity against a human type strain of *M. tuberculosis* designated as H37Rv. These compounds were active at 10 micrograms per milliliter.

The following examples illustrate methods of carrying out the present invention, but it is to be understood that these examples are given for purposes of illustration and not of limitation.

Example 1

900 gms. (6.25 moles) of dimethylaminoethylchloride hydrochloride was dissolved in 850 ml. of water, and 850 ml. of 30% aqueous sodium hydroxide solution was added. The resulting solution was extracted successively with 1000 ml., 500 ml., and 500 ml. portions of diethyl ether. The extracts were combined and the ether was evaporated under reduced pressure to produce approximately 700 gms. of crude dimethylaminoethylchloride.

2700 gms. (11.2 moles) of sodium sulfide nonohydrate was melted in a five-liter flask provided with a mechanical stirrer, reflux condenser, thermometer and gas inlet tube. Hydrogen sulfide was passed into the molten mixture over a period of 6 to 7 hours, during which time the mixture was stirred rapidly and maintained at a temperature between about 50 and 60° C. The dimethylamino-ethylchloride (700 gms.) was added dropwise to the reaction mixture over a period of approximately 2 hours during which time the contents of the flask were stirred rapidly and maintained at a temperature of 50–60° C. The resulting mixture was then heated to 90–105° C., heated under reflux for 1 hour and cooled. The reaction mixture was extracted successively with

600 ml., 300 ml., and 300 ml. portions of diethyl ether, the extracts were combined and dried over anhydrous calcium sulfate (Drierite). The ether was then evaporated from the dry ether solution, and the residual material was fractionally distilled. The fraction distilling at 120–140° C. (temperature in distilling flask 140–190° C.) was collected to produce 199 gms. of crude dimethylaminoethylthiol (yield approximately 30% of theory).

850 gms. of crude dimethylaminoethylthiol (from several preparations) was distilled in vacuo using a 6–8 inch Vigreux column to produce 748 gms. of substantially pure dimethylaminoethylthiol; B. P. 37–43° C./20 mm.; recovery yield approximately 88%. Analysis.—Calc'd for $C_4H_{11}NS$; C, 45.66; H, 10.54; N, 13.32. Found: C, 45.44; H, 10.56; N, 13.06.

Example 2

1800 ml. of xylene were placed in a five-liter, three-necked flask provided with a mechanical stirrer and thermometer. The xylene was cooled to −10° C. and 297 gms. (3 moles) of phosgene was added. A solution containing 516 gms. (4 moles) of n-dibutylamine dissolved in 1030 ml. of xylene was added to the phosgene solution over a period of approximately 5 hours, said addition being carried out while rapidly stirring the flask contents and maintaining the reaction temperature at approximately 5–10° C. The reaction mixture was stirred at room temperature for an additional period of about 18 hours, the dibutylamine hydrochloride which precipitated was removed by filtration and the precipitate was washed with seven 100 ml. portions of xylene. The filtrate and washings were combined and the xylene evaporated therefrom by distillation in vacuo. The residue material was fractionally distilled using a 12 inch Vigreux column to produce approximately 361 g. of substantially pure dibutyl carbamylchloride; B. P. 89–90° C./2 mm., yield approximately 94.2% of theory.

Example 3

35 gms. (0.33 mole) of pure dimethylaminoethylthiol (B. P. 37–43° C./20 mm.), prepared as described in Example 1, was dissolved in 250 ml. of pyridine contained in a one-liter, three-necked flask equipped with a mechanical stirrer and reflux condenser. 57.5 g. (0.0 mole) of n-dibutylcarbamylchloride, prepared as described in Example 2, was added to the flask contents. The resulting mixture was heated under reflux for approximately 3 hours and was then evaporated to dryness in vacuo. The residual material was dissolved in 200 ml. of water and the pH was adjusted to 3 by adding 30 ml. of concentrated aqueous hydrochloric acid solution. The resulting solution was extracted with four 100 ml. portions of diethyl ether and the ether extracts were discarded. The aqueous solution was made alkaline by adding thereto an excess of sodium carbonate, and the resulting solution was extracted with the three 100 ml. portions of chloroform. The chloroform extracts were combined, dried over anhydrous calcium sulfate (Drierite) and the chloroform evaporated. The residual material was heated at 100–110° C. at a pressure of 1 mm. to remove all traces of solvent, thereby producing approximately 76 gms. of dimethylamineothylthioldibutylurethane; yield approximately 97% of theory.

Example 4

75 gms. (0.29 mole) of dimethylaminoethylthioldibutylurethane, prepared as described in Example 3, was mixed with 235 g. (1.5 moles) of ethyl iodide. The mixture was stirred until solution was effected and the resulting solution was maintained at 25–30° C. for approximately 3 hours. 750 ml. of diethyl ether was then added and the mixture was allowed to stand overnight. The supernatant liquid was decanted, the reaction product was filtered and repeatedly washed by decantation with ether and then dried in vacuo to produce 116 gms. of dimethylethyl-β-thiolethylammonium iodide dibutylurethane; M. P. 56° C.; yield aproximately 96.6% of theory.

Example 5

116 gms. (0.278 mole) of dimethylethyl-β-thiolethylammonium iodide dibutylurethane, prepared as described in Example 4, was dissolved in 1100 ml. of 90% aqueous ethanol, and 60 gms. (0.19 mole) of powdered silver sulfate was added to the solution. The resulting mixture was stirred rapidly for 2 hours, the silver iodide was removed by filtration and washed with three 50 ml. portions of ethanol. The combined filtrate and washings were evaporated in vacuo to a syrup. The syrup was dissloved in 400 ml. of water, the solution was extracted with two 200 ml. portions of diethyl ether, and the extracts were discarded. The pH of the aqueous solution was adjusted to 6.7 by the addition of aqueous barium hydroxide solution, hydrogen sulfide was passed into the solution to precipitate residual silver, 5 gm. of activated charcoal was added, and the mixture was filtered. The filtrate was avaporated in vacuo to a syrup and the residual material was subjected to benzene distillation using three 150 ml. portions of benzene. The residual material was dried over sulfuric acid at a pressure of 1 mm. to produce 83.8 gms. of dimethylethyl-β-thiolethyl ammonium sulfate dibutylurethane; yield approximately 89.3% of theory. Analysis.—Calc'd for $C_{30}H_{66}O_6N_4S_3.H_2O$; C, 51.99; H, 9.89; N, 8.08. Found: C, 51.78; H, 10.09; N, 7.80.

Example 6

Dicyclohexylamine was reacted with phosgene according to the procedure described for reacting phosgene with n-dibutylamine in Example 2. After evaporation of the xylene solvent, the residual material was dissolved in petroleum ether, and the crystalline material which separated from the petroleum ether solution was recovered and dried to produce substantially pure dicyclohexylcarbamylchloride; M. P. 85–86° C.

781 gms. (3.2 moles) of powdered dicyclohexylcarbamylchloride was added to a solution containing 350 gms. (3.3 moles) of dimethylaminoethylthiol (prepared as described in Example 1) dissolved in 2000 ml. of pyridine. The mixture was stirred and heated under reflux at a temperature of 100–105° C. for a period of 3 hours, and the mixture was then cooled to room temperature. The nearly-solid mass was dissolved in 1000 ml. of water and the aqueous solution was evaporated in vacuo at a temperature below 50° C. until a mush resulted. This residual material was treated in the manner described in Example 3 to produce 948 gms. of dimethylaminoethylthioldicyclohexylurethane; M. P. 48–50° C.; yield approximately 95% of theory.

Example 7

948 gms. of dimethylaminoethylthioldicyclo-

hexylurethane, prepared as described in Example 6, was reacted with ethyl iodide, according to the procedure described in Example 4, to produce 1465 gms. of dimethylethyl-β-thiolethyl ammonium iodide dicyclohexylurethane; M. P. 190–191° C.; yield approximately 98% of theory. Analysis.—Calc'd for $C_{19}H_{37}ON_2SI.\frac{1}{2}H_2O$; C, 47.79; H, 8.02; N, 5.87. Found: C, 47.90; H, 7.78; N, 5.63.

Example 8

2715 gms. of dimethylethyl-β-thiolethyl ammonium iodide dicyclohexylurethane, prepared as described in Example 7, was reacted with silver sulfate according to the procedure described in Example 5 to produce 2188 gms. of dimethylethyl-β-thiolethyl ammonium sulfate dicyclohexylurethane; M. P. 143–144° C.; yield approximately 97% of theory. Analysis.—Calc'd for $C_{38}H_{74}O_6N_4S_3.5.5\ H_2O$; C, 51.96; H, 9.75; N, 6.37; H_2O, 11.27. Found: C, 51.73; H, 9.60; N, 6.41; H_2O, 11.17.

Example 9

31 gms. of dimethylaminoethylthioldicyclohexylurethane, prepared as described in Example 6, was reacted with 85 gms. of n-propyl iodide, utilizing substantially the same procedure as that described in Example 4 for reacting dimethylaminoethylthioldibutylurethane with ethyl iodide, to produce 20 gms. of dimethyl-n-propyl-β-thiolethyl ammonium iodide dicyclohexylurethane; M. P. 149–151° C.; yield approximately 41.7% of theory. Analysis.—Calc'd for

$C_{20}H_{39}ON_2SI$

C, 49.78; H, 8.15; N, 5.80. Found: C, 49.63; H, 7.99; N, 5.82.

Example 10

20 gms. of dimethyl-n-propyl-β-thiolethyl ammonium iodide dicyclohexylurethane was reacted with silver sulfate, according to the procedure described in Example 5, to produce 16.4 gms. of dimethyl-n-propyl-β-thiolethyl ammonium sulfate dicyclohexylurethane; M. P. 137–139° C.; yield approximately 85% of theory. Analysis.—Calc'd for $C_{40}H_{78}O_6N_4S_3.6H_2O$; C, 52.48; H, 9.91; N, 6.12; H_2O, 11.80. Found: C, 52.61; H, 9.60; N, 6.37; H_2O, 11.44.

Example 11

31 gms. of dimethylaminoethylthioldicyclohexylurethane, prepared as described in Example 6, was reacted with 92 gms. of n-butyl-iodide, utilizing substantially the same procedure described in Example 4, to produce 28.5 gms. of dimethyl-n-butyl-β-ethiolethyl ammonium iodide dicyclohexylurethane; M. P. 161.5–162.5° C.; yield approximately 57.5% of theory. Analysis.—Calc'd for $C_{21}H_{41}ON_2SI$; C, 50.80; H, 8.32; N, 5.64. Found: C, 51.10; H, 8.15; N, 5.63.

Example 12

28.5 gms. of dimethyl-n-butyl-β-thiolethyl ammonium iodide dicyclohexylurethane was reacted with silver sulfate, according to the procedure described in Example 5, to produce 23.7 gms. of dimethyl-n-butyl-β-thiolethyl ammonium sulfate dicyclohexylurethane; M. P. 99–99.5° C.; yield approximately 87% of theory. Analysis.—Calc'd for $C_{42}H_{82}O_6N_4S_3.6H_2O$; C, 53.47; H, 10.04; N, 5.94; H_2O, 11.45. Found: C, 53.47; H, 9.90; N, 5.94; H_2O, 11.12.

Example 13

31 gms. of dimethylaminoethylthioldicyclohexylurethane, prepared as described in Example 6, was reacted with n-amyl iodide, utilizing the substantially same procedure as that described in Example 4, to produce 36 gms. of dimethyl-n-amyl-β-thiolethyl ammonium iodide dicyclohexylurethane; M. P. 179–180° C.; yield approximately 71% of theory. Analysis.—Calc'd for $C_{22}H_{43}ON_2SI$; C, 51.75; H, 8.49; N, 5.48. Found: C, 51.96; H, 8.38; N, 5.64.

Example 14

36 gms. of dimethyl-n-amyl-β-thiolethyl ammonium iodide dicyclohexylurethane, prepared as described in Example 13, was reacted with silver sulfate, utilizing substantially the same procedure as that described in Example 5, to produce 29.4 gms. of dimethyl-n-amyl-β-thiolethyl ammonium sulfate dicyclohexylurethane; M. P. 99–105° C.; yield approximately 92% of theory. Analysis.—Calc'd for $C_{44}H_{86}O_6N_4S_3.3H_2O$; N, 6.10; H_2O, 5.88. Found: N, 6.03; H_2O, 5.50.

Example 15

31 gms. (0.1 mole) of dimethylaminoethylthioldicyclohexylurethane, prepared as described in Example 6, was dissolved in 200 ml. of diethyl ether, 31 gms. (0.2 mole) of diethyl sulfate was added, and the mixture was allowed to stand at room temperature overnight. The crystals that formed were recovered by filtration, washed with ether and dried in vacuo to produce 29 gms. of dimethylethyl-β-thiolethyl ammonium ethyl sulfate dicyclohexylurethane; M. P. 178–179° C.; yield approximately 62.4% of theory. Analysis.—Calc'd for $C_{21}H_{42}O_5N_2S_2$; C, 54.04; H, 9.07; N, 6.00. Found: C, 53.88; H, 8.87; N, 5.93.

Example 16

n-Diamylamine was reacted with phosgene in the presence of xylene, utilizing substantially the same procedure described for reacting n-dibutylamine with phosgene in Example 2, and the residual material obtained after evaporation of the xylene was fractionally distilled in vacuo using a Vigreux column to produce diamylcarbamylchloride; B. P. 112–114° C./1 mm.

62.6 gms. of diamylcarbamylchloride, prepared as described on the preceding page, was reacted with 33 gms. of dimethylaminoethylthiol, prepared as described in Example 1, and the reaction product was treated in substantially the same manner as described in Example 6, to produce 75.6 gms. of dimethylaminoethylthioldiamylurethane, which was obtained as a liquid; yield approximately 94% of theory.

Example 17

60.6 gms. of dimethylaminoethylthioldiamylurethane, prepared as described in Example 16, was reacted with ethyl iodide, utilizing substantially the same procedure as that described in Example 4, to produce 90 gms. of dimethylethyl-β-thiolethyl ammonium iodide diamylurethane which was obtained as an amorphous mass; yield approximately 97% of theory. Analysis.—Calc'd for $C_{17}H_{37}ON_2SI$; C, 45.94; H, 8.39; N, 6.30. Found: C, 45.89; H, 8.02; N, 6.38.

Example 18

90 gms. of dimethylethyl-β-thiolethyl ammonium iodide diamylurethane, prepared as described in Example 17, was reacted with silver sulfate, utilizing substantially the same procedure as that described in Example 5, to produce 69 gms. of dimethylethyl-β-thiolethyl ammonium sulfate diamylurethane; M. P. 124–125° C.;

yield approximately 91% of theory. Analysis.—Calc'd for $C_{34}H_{74}O_6N_4S_3.1.5H_2O$; H_2O, 3.56. Found: H_2O, 3.85. Sample dried to constant weight at 80° C./1 mm. Analysis.—Calc'd for $C_{34}H_{74}O_6N_4S_3$; N, 7.67. Found: N, 8.18.

Example 19

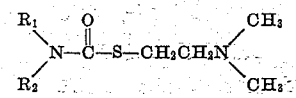
15 gms. of dimethylaminoethylthioldiamylurethane, prepared as described in Example 16, was dissolved in 100 ml. of diethyl ether, 15.4 gms. of diethyl sulfate was added to the solution and the resulting mixture was allowed to stand overnight. No crystallization took place. The mixture was then heated under reflux for an additional 24 hours, without any formation of crystals.

The ethereal mixture was extracted with two 25 ml. portions of water, the combined aqueous extracts were washed with ether and the other layers were discarded. The pH of the aqueous solution was adjusted to 6.4 by the addition of 10% aqueous barium hydroxide solution, a small amount of activated charcoal was added, and the mixture was filtered. The traces of barium ion were removed from the filtrate by adding a minute amount of ammonium sulfate and a slight turbidity was removed by adding activated charcoal and filtering. The solution was evaporated in vacuo to a syrup and the syrup was air-dried to constant weight. During the drying period, the syrup crystallized slowly, and the crystalline masses were broken up during the drying period. There was thus obtained 12 gms. of dimethylethyl-β-thiolethyl ammonium ethyl sulfate-diamylurethane; M. P. 55–56° C.; yield approximately 55% of theory. Analysis.—Calc'd for $C_{19}H_{42}O_5N_2S_2.\frac{1}{2}H_2O$; C, 50.51; H, 9.59; N, 6.19; H_2O, 1.99. Found: C, 50.20; H, 9.08; H, 6.36; H_2O, 1.85.

Modifications may be made in carrying out the present invention without departing from the spirit and scope thereof. Insofar as these changes and modifications are within the purview of the annexed claims, they are to be considered part of our invention.

We claim:

1. The process which comprises reacting dimethylamino-ethylthiol with a carbamyl chloride having two saturated hydrocarbon substituents attached to the nitrogen atom of the carbamyl grouping to produce a thiolurethane of the formula:



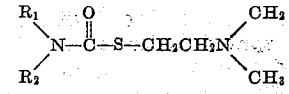
wherein R_1 and R_2 are saturated hydrocarbon radicals.

2. The process which comprises reacting dimethylamino-ethylthiol with a dialkyl carbamyl chloride to produce the corresponding dimethylaminoethylthiol-dialkylurethane.

3. The process which comprises reacting dimethylamino-ethylthiol with a dicycloalkyl carbamyl chloride to produce the corresponding dimethylaminoethylthioldicycloalkylurethane.

4. The process which comprises reacting dimethylamino-ethylthiol with dicyclohexyl carbamyl chloride to produce dimethylaminoethylthioldicyclohexylurethane.

5. Thiolurethanes having the formula:



wherein R_1 and R_2 are saturated hydrocarbon radicals.

6. Dimethylaminoethylthiol-dialkylurethanes.

7. Dimethylaminoethylthiol - dicycloalkylurethanes.

8. Dimethylaminoethylthiol - dicyclohexylurethane.

JOHN WEIJLARD.
MAX TISHLER.

References Cited in the file of this patent

UNITED STATES PATENTS

Number	Name	Date
2,356,163	Jones et al.	Aug. 22, 1944
2,387,873	Boon	Oct. 30, 1945

FOREIGN PATENTS

Number	Country	Date
587,105	Great Britain	Apr. 14, 1947
609,545	Great Britain	Sept. 30, 1948