β-n-Dodecylmercaptopropionic acid was prepared in 81% over-all yield from *n*-dodecyl mercaptan. It melted at 59–60° as compared with 61–62° reported by Rapoport, Smith and Newman.[5]

β-n-Dodecylsulfonylpropionic acid, m.p. 132–133°. Rapoport and co-workers[5] reported 133–134°.

β-n-Octadecylmercaptopropionitrile,[9] recrystallized from acetone, m.p. 50–51°, was prepared in a yield of 70%.

Anal. Calcd. for $C_{21}H_{41}NS$: S, 9.45. Found: S, 9.35, 9.63.

β-n-Octadecylmercaptopropionic acid, m.p. 78–79°, was prepared in 98% yield by hydrolysis of the corresponding nitrile.

Anal. Calcd. for $C_{21}H_{42}O_2S$: neut. equiv., 358; S, 8.94. Found: neut. equiv., 364; S, 8.93.

β-n-Octadecylsulfonylpropionic acid, m.p. 136–136.5°, was prepared in 98% yield.

Anal. Calcd. for $C_{21}H_{42}O_4S$: neut. equiv., 390; S, 8.20. Found: neut. equiv., 398; S, 8.25.

(9) The octadecyl mercaptan used for the preparation of this compound was purchased from Medical Chemicals Corp. of Chicago, Ill.

RICHARDSON CHEMICAL LABORATORY
TULANE UNIVERSITY
NEW ORLEANS, LA. RECEIVED SEPTEMBER 28, 1950

Quaternary Ammonium Salts of Heterocyclic Bases

BY D. R. SMITH, M. MAIENTHAL AND R. L. EIFERT

In a previous communication from this Laboratory,[1] we reported the preparation of some N,N'-disubstituted piperazinium salts containing long aliphatic chains. It was hoped that they would have germicidal activity but they were found to be too insoluble. This paper has stemmed from the hope that the introduction of an ester linkage would increase the solubility. N. N. Mel'nikov[2] reported compounds of the type: (I) $\left[\begin{array}{c}|\\ -N-CH_2COOR\\ |\end{array}\right]^+ Cl^-$ which contained dimethylbenzylamine and pyridine as nuclei, but the decyl ester was the highest member of the series. Since the optimum length of a substituent on the quaternary nitrogen for germicidal activity seems to be from 14–16 carbon atoms, we prepared the lauryl, myristyl and cetyl esters of chloroacetic acid. The quaternary ammonium salts were then prepared by heating these alkyl chloroacetates (Table I) with N-methylmorpholine, N-N'-dimethylpiperazine, dimethylbenzylamine, N-morpholinoethyl benzyl ether, N-methyl-N'-carbethoxypiperazine and N-methylpiperidine. All of the quaternary salts were white crystalline solids, some of which, such as compounds 8, 9 and 10, crystallized out of solution as beautiful fine white needles. The salts are very stable toward heat and light and do not seem to decompose until the temperature approaches the melting point, and, even then, most of them melt with only slight decomposition.

From the data of Table II, it is apparent that for germicidal activity the optimum length of the group attached to the tertiary nitrogen is from 14–16 carbon atoms. This is in agreement with the data given by Shelton, *et al.*[3] In almost every case the compounds seem to be more active against *E. typhosa* than against *Staph. aureus*. Again Shelton, *et al.*,[3] found the opposite to be true for most of the compounds that they tested. The addition of the ester linkage in the side chain depressed the activity against *Staph. aureus* to less than half the value reported for the same compound in the straight chain series but had little effect on the activity against *E. typhosa*. The replacement of the methyl group by an ether linkage in the morpholine series had little effect on the activity toward *E. typhosa* but increased the activity toward *Staph. aureus*. The introduction of a carbethoxy group on one end of the piperazine molecule increased the solubility of that series to such an extent that it could be tested. The maximum activity is to be found in the piperidinium salts.

In addition to germicidal activity, definite detergent properties were noticed. A surface tension lowering of over 50% was exhibited by a 0.01% aqueous solution of the lauryl compound in the piperidine series.

Acknowledgments.—The authors wish to express their sincere appreciation to the Research Corporation of New York for a Frederick Gardner Cottrell Grant which made this work possible. We wish to express our thanks also to Dr. Clyde Dennis and R. D. Miller of the Department of Biology of James Millikin University for testing these compounds for germicidal activity.

TABLE I

ALKYL CHLOROACETATES—$ClCH_2COOR$

R	B.p., °C.	Mm.	$n^{20}D$	Formula	Chlorine, % Calcd.	Found
Lauryl	149–150	2.5	1.4480	$C_{14}H_{27}O_2Cl$	13.49	13.78
Myristyl	162–163	2.5	1.4500	$C_{16}H_{31}O_2Cl$	12.20	12.18
Cetyl	184–185	2.5	Solid	$C_{18}H_{35}O_2Cl$	11.13	11.33

Experimental[4,5]

N-Methylpiperidine, N,N'-dimethylpiperazine and N-methyl-N'-carbethoxypiperazine were prepared by methylating piperidine, piperazine, and carbethoxypiperazine according to the Eschweiler–Clarke[6] modification of the Leuckart reaction. **N-Carbethoxypiperazine** was prepared by treating piperazine with ethyl chlorocarbonate according to the procedure of Moore.[7] **N-Morpholinoethyl benzyl ether** was prepared according to the procedure described by Mason[8] which was essentially a Williamson synthesis.

Alkyl chloroacetates were prepared by mixing together, in a water separator, chloroacetic acid (0.5 mole) and the alkyl alcohol (0.5 mole) with benzene as the solvent. 2-Naphthalenesulfonic acid (0.25 g.) was added as the condensing agent and the mixture refluxed until water no longer distilled with the benzene (about two hours). The mixture was then extracted with two 50-ml. portions of 25% sodium carbonate, the benzene layer dried over sodium sulfate, and the solvent distilled off. The esters were then obtained in yields of from 70–90% by vacuum distillation. The lauryl and myristyl esters were liquids while the cetyl ester was a solid melting at 28.8°.

(1) D. R. Smith, J. W. Curry and R. L. Eifert, THIS JOURNAL, **72**, 2969 (1950).

(2) N. N. Mel'nikov, N. D. Sukhareva and O. P. Arkhipov, *Zhur. Priklad. Khim.*, **20**, 642 (1947); see *C. A.*, **43**, 6976 (1949).

(3) R. S. Shelton, M. G. VanCampen, C. H. Tilford, H. C. Lang, L. Nisonger, F. J. Bandelin and H. L. Rubenkoenig, THIS JOURNAL, **68**, 753 (1946).

(4) Analyses by Clark Microanalytical Lab., Urbana, Illinois.

(5) Melting points are uncorrected.

(6) H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

(7) T. S. Moore, M. Boyle and V. M. Thorn, *J. Chem. Soc.*, 39 (1929).

(8) J. P. Mason and S. Malkiel, THIS JOURNAL, **62**, 1448 (1940).

TABLE II

PROPERTIES OF HETEROCYCLIC QUATERNARY AMMONIUM SALTS OF TYPE I

	R	C. K. D.[a] 1000 pts. H_2O *Staph. aureus*	*E. typhosa*	M.p., °C.[b]	Yield, %	Recrystn. solvent	Formula	Analyses, % Nitrogen Calcd.	Nitrogen Found	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
					Esters of N-carboxymethyl-N-methylmorpholinium chloride								
1	Lauryl	10–20	10–20	113–114 dec.	55	Me_2CO	$C_{19}H_{38}NO_4Cl$	3.85	3.71	62.70	62.90	10.52	10.25
2	Myristyl	1–10	10–20	118–119 dec.	67	Me_2CO	$C_{21}H_{42}NO_4Cl$	3.58	3.45	64.34	63.96	10.80	10.66
3	Cetyl	1	1–10	119–120 dec.	66	Me_2CO	$C_{23}H_{46}NO_4Cl$	3.34	3.38	65.76	65.74	11.04	10.74
					Esters of N,N′-dicarboxymethyl-N,N′-dimethylpiperazinium dichloride								
4	Lauryl	...	...	157–158	66	EtOH–Me_2CO	$C_{34}H_{68}N_2O_4Cl_2$	4.38	4.58	63.95	63.98	10.71	10.62
5	Myristyl	...	...	166–167	69	EtOH–Me_2CO	$C_{38}H_{76}N_2O_4Cl_2$	4.03	3.96	65.58	65.43	11.01	10.91
6	Cetyl	1.0	1–10	175–177 dec.	74	EtOH–Me_2CO	$C_{42}H_{84}N_2O_4Cl_2$	3.73	3.91	67.12	67.38	11.27	11.09
					Esters of carboxymethyldimethylbenzylammonium chloride								
7	Lauryl	1–10	20–30	120–121 dec.	89	Me_2CO	$C_{23}H_{40}NO_2Cl$	3.52	3.31	69.40	69.42	10.13	10.13
8	Myristyl	10–20	30	123–124	85	Me_2CO	$C_{25}H_{44}NO_2Cl$	3.29	3.30	70.47	70.73	10.41	10.17
9	Cetyl	1–10	1	121–122 dec.	79	Me_2CO	$C_{27}H_{48}NO_2Cl$	3.09	2.92	71.41	71.59	10.66	10.77
					Esters of N-carboxymethyl-N-(2-benzyloxy)-ethylmorpholinium chloride								
10	Myristyl	10–20	10–20	158–159	40	Me_2CO	$C_{29}H_{50}NO_4Cl$	2.74	2.76	68.00	68.25	9.84	9.93
					Esters of N-carboxymethyl-N-methyl-N′-carbethoxypiperazinium chloride								
11	Lauryl	24.0	20	125–127 dec.	40	Et_2O–Me_2CO	$C_{22}H_{43}N_2O_4Cl$	6.44	6.18	60.73	60.67	9.96	10.06
12	Myristyl	10–20	10–20	136–138 dec.	75	Et_2O–Me_2CO	$C_{24}H_{47}N_2O_4Cl$	6.06	5.79	62.27	61.80	10.16	10.22
					Esters of N-carboxymethyl-N-methylpiperidinium chloride								
13	Lauryl	20	40	156–157 dec.	87	Me_2CO	$C_{20}H_{40}NO_2Cl$	3.87	3.62	66.35	66.05	11.14	10.86
14	Myristyl	20	30	158–159 dec.	72	Me_2CO	$C_{22}H_{44}NO_2Cl$	3.60	3.42	67.74	67.62	11.37	11.41
15	Cetyl	1–10	10	160–161 dec.	74	Me_2CO	$C_{24}H_{48}NO_2Cl$	3.35	3.34	68.95	68.95	11.57	11.33

[a] Critical Killing Dilution—that concentration of the substance which will kill organisms of standard phenolic resistance in ten minutes but not in five minutes, at 37°, determined by the method described in Circular 198 of the U. S. Department of Agriculture. [b] Determined on a Fisher–Johns melting point apparatus.

Quaternary ammonium salts were prepared by adding the equivalent quantity of the alkyl chloroacetate to 0.05 mole of the tertiary amine in 20 ml. of acetone. This mixture was refluxed for from two to 30 hours on a steam-bath. The cooled mixture was then filtered and the solid recrystallized. Compounds 11 and 12 in Table II were best recrystallized from a mixture of acetone and ether containing a trace of alcohol. If the melting points of compounds 11 and 12 were taken in a capillary tube, they appeared to melt at 88 and 78°, respectively. If a Fisher–Johns melting point apparatus was used, much higher melting points were obtained; however, a change in crystalline structure was observed at the lower temperatures which seem to be the transition points for the compounds. Most yields were very good, but the primary objective was to obtain pure compounds rather than to determine the maximum yield attainable.

DEPARTMENT OF CHEMISTRY
JAMES MILLIKIN UNIVERSITY
DECATUR, ILLINOIS

RECEIVED OCTOBER 19, 1950

Quaternary Carbon Compounds. V. Trisubstituted Carbinylcarbamates

BY NATHAN SPERBER, ROSEMARIE FRICANO, ERWIN SCHWENK AND DOMENICK PAPA

Although the majority of compounds synthesized as antispasmodics are basic esters of alicyclic and/or aromatic acids,[1] a limited number of diversified structures have also shown this interesting pharmacological action. Of the latter group, carbamic acid derivatives may be viewed as intermediate in structure between the basic esters and the non-ester type of antispasmodic compounds. Only one series of carbamic acid esters has been reported to exhibit antispasmodic activity.[2] Of a number of derivatives of carbamylcholine, the dibutylcarbamate of dimethylethyl-β-hydroxyethylammonium sulfate, the most active member of this series, exhibited a quick-acting atropine-like action. Two other series of carbamates, the alkamine esters of disubstituted methylcarbamic acids, $R_1R_2CHNHCOO(CH_2)_nNR_2$ where R_1 and R_2 are either aliphatic or aromatic radicals[3] and the dialkylaminoalkyl esters of α-naphthylphenylcarbamic acid[4] have been reported to possess local anesthetic activity.

In continuation of studies on quaternary carbon compounds,[5] it appeared of interest to investigate the pharmacological action of carbamic acid derivatives of the general formula $RR'R''CNHCOO(CH_2)_nR'''$ (I)[6] where R is an alkyl, diethylaminomethyl or a N-piperidinomethyl group, R′ and R″ are alkyl groups containing two to five carbon atoms, R‴ is a dialkylamino group, and *n* is two or three (Table I). In addition, the tributylcarbinylcarbamates from β-(2-pyridyl)-ethanol and β-(N-piperidino)-ethanol were prepared as examples of cyclic amino alcohols. The carbamates were prepared by refluxing the trisubstituted carbinylisocyanate and the amino alcohol in xylene. Upon removal of the solvent, and fractionation of the residual oil *in vacuo*, the carbamates were obtained as viscous, yellow liquids.

The *in vitro* antispasmodic activity of the carbamates was determined on isolated rabbit intestinal muscle by measuring the relaxation produced by the test compound against Doryl and barium chloride-induced spasms using atropine and papaverine as standards. The most active compounds were those in which R, R′ and R″ were butyl or amyl, R‴ was dimethylamino, diethylamino or

(1) F. F. Blicke, *Ann. Rev. Biochem.*, **13**, 549 (1944).

(2) K. C. Swan and N. G. White, *Proc. Soc. Exptl. Biol. Med.*, **53**, 164 (1943); *Arch. Opthalmol.*, **33**, 16 (1945); R. M. Featherstone and N. G. White, *J. Pharmacol. Exptl. Therap.*, **84**, 105 (1945).

(3) J. J. Donleavy and J. English, Jr., THIS JOURNAL, **62**, 218 (1940).

(4) A. B. Boese, Jr., and R. T. Major, *ibid.*, **57**, 175 (1935).

(5) For paper IV in this series, see N. Sperber, D. Papa and E. Schwenk, *ibid.*, **72**, 2012 (1950).

(6) U. S. Patent 2,536,079, Jan. 2, 1951.