tillation gave 36.8 g. of crude glyoxal tetramethyl acetal (72% yield, b.p. 68–71° (25 mm.), $n^{25}D$ 1.4010). The crude product containing traces of hydrogen chloride was neutralized with sodium methoxide and redistilled at atmospheric pressure. The pure acetal boiled at 159–160°, $n^{28}D$ 1.4399.

Anal. Calcd. for $C_6H_{14}O_4$: C, 48.00; H, 9.33; O, 42.67. Found: C, 48.28; H, 9.56; O, 42.86.[5]

(5) C. C. Harris, D. M. Smith and J. Mitchell, Jr., *Anal. Chem.*, **22**, 1297 (1950).

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Some Long Chain β-Alkylmercaptopropionitriles and their Derivatives

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As a part of a study of modified long chain aliphatic carboxylic acids as potential antitubercular chemotherapeutic agents, we have undertaken to prepare for biological evaluation some of these types containing sulfide and sulfone groups. Compounds of this type have previously been of interest because of their bactericidal properties.[1,2]

In the present work the route chosen for preparation of some sulfur containing aliphatic acids was the well-known cyanoethylation reaction[3] involving the condensation of long chain mercaptans with acrylonitrile in the presence of basic catalysts to give β-alkylmercaptopropionitriles (I).

$$RSH + CH_2{=}CHCN \longrightarrow \underset{I}{RSCH_2CH_2CN}$$

The corresponding carboxylic acid, β-alkylmercaptopropionic acid (II), was obtained by alkaline hydrolysis of the nitrile, which in turn was oxidized to the β-alkylsulfonylpropionic acid (III) using potassium permanganate.

$$\underset{I}{RSCH_2CH_2CN} \xrightarrow[NaOH]{H_2O} \underset{II}{RSCH_2CH_2COOH}$$

$$\underset{II}{RSCH_2CH_2COOH} \xrightarrow[KMnO_4]{} \underset{III}{RS(=O)_2CH_2CH_2COOH}$$

Cyanoethylation of mercaptans has been shown to proceed in high yield by Gershbein and Hurd[4] and Rapoport, Smith and Newman[5] have previously carried through the sequence of reactions listed above using octyl, nonyl and dodecyl mercaptans as the starting material. We have repeated the sequence using dodecyl mercaptan and in addition have prepared the series of compounds in which R = decyl and octadecyl. The procedure used was similar to that of Rapoport, Smith and Newman[5] except that strong alkali was used for hydrolysis of the nitrile instead of an acidic medium. The alkaline hydrolysis (I → II) gave near quantitative yields of the alkylmercaptopropionic acid.

Rapoport, Smith and Newman[5] do not report a yield for the hydrolysis of β-dodecylmercaptopropionitrile to the corresponding acid but an over-all yield from dodecyl mercaptan to the acid is reported as 62%. Using the basic hydrolysis, we have obtained an over-all yield of β-dodecylmercaptopropionic acid of 81% based on the starting mercaptan.

All of the compounds reported in this paper are being tested *in vitro* for antitubercular chemotherapeutic activity by the Eli Lilly Co. of Indianapolis, Indiana. We are grateful to Dr. Reuben G. Jones for arranging the tests.

We would also like to acknowledge the aid of the Research Corporation of New York for a Frederick G. Cottrell grant which supported a portion of this work.

Experimental

β-*n*-Decylmercaptopropionitrile.—A mixture of 87 g. (0.5 mole) of *n*-decyl mercaptan[6] and 20 drops of a saturated solution of sodium ethoxide in ethanol was stirred while 53 g. (1.0 mole) of acrylonitrile was added in dropwise fashion over a period of 30 minutes. The reaction mixture was cooled during the addition of the acrylonitrile in order to maintain its temperature in the range of 40–50°. After standing for one hour the mixture was distilled. After removal of the excess acrylonitrile, 78.2 g. of β-*n*-decylmercaptopropionitrile was collected at 154–156° at 3 mm. pressure. This represented a yield of 69%. The index of refraction of the colorless liquid product was $n^{24}D$ 1.4714.

Anal. Calcd. for $C_{13}H_{25}NS$: S, 14.1; N, 6.16. Found: S, 13.9; N, 5.91.

β-*n*-Decylmercaptopropionic Acid.—A mixture of 22.7 g. (0.1 mole) of β-*n*-decylmercaptopropionitrile and a solution of 75 g. of sodium hydroxide in 175 ml. of water was stirred and refluxed until the evolution of ammonia became very slow (eight hours). The resulting solution was acidified with concentrated hydrochloric acid and cooled. The precipitated acid was filtered off and dried. It weighed 23.9 g. corresponding to a 98% yield. The solid acid could not be recrystallized from common solvents. Six grams of the acid was distilled at a pressure of 35 mm. and 4.2 g. of product was collected boiling at 210°. There was considerable decomposition during the distillation. The product was a white solid melting at 42–43°.

Anal. Calcd. for $C_{13}H_{26}O_2S$: neut. equiv., 246; S, 13.0. Found: neut. equiv., 246; S, 13.1.

β-*n*-Decylsulfonylpropionic Acid.—A solution of 10 g. (0.0405 mole) of β-*n*-decylmercaptopropionic acid in a minimum amount of glacial acetic acid was treated with a 50% excess of a saturated aqueous solution of potassium permanganate in accordance with the method of Bost and Conn.[7] The reaction mixture was shaken thoroughly and allowed to stand overnight. Saturated aqueous sodium bisulfite solution was added until the mixture was decolorized. The resulting white solid was filtered off, washed thoroughly with water and recrystallized from acetone to yield 11 g. (97%) of β-*n*-decylsulfonylpropionic acid melting at 127–128°.

Anal. Calcd. for $C_{13}H_{26}O_4S$: neut. equiv., 278; S, 11.5. Found: neut. equiv., 286; S, 11.5.

The compounds listed below were prepared in general accordance with the procedures described above.

β-*n*-Dodecylmercaptopropionitrile, b.p. 197–198° at 4 mm. pressure, m.p. 21°, $n^{24}D$ 1.4709. This compound was prepared by Rapoport, Smith and Newman[5] but no physical constants reported. Harman[8] also reported this compound and a boiling point of 160–185° at 5 mm. was indicated.

(1) Hill and Fager, THIS JOURNAL, **65**, 2300 (1943).

(2) (a) Barry, O'Rourke and Twomey, *Proc. Roy. Irish Acad.*, **51B**, 223 (1947); (b) **51B**, 229 (1947).

(3) Bruson, "Organic Reactions," Vol. V, Roger Adams, ed., John Wiley and Sons, Inc., New York, N. Y., 1949, p. 95.

(4) Gershbein and Hurd, THIS JOURNAL, **69**, 241 (1947).

(5) Rapoport, Smith and Newman, *ibid.*, **69**, 693 (1947).

(6) The *n*-decyl mercaptan was obtained from the Humphrey-Wilkinson Co. of New Haven, Conn.

(7) Bost and Conn, THIS JOURNAL, **62**, 1753 (1940).

(8) Harman, U. S. Patent 2,413,917 (to E. I. du Pont de Nemours and Co.), [*C. A.*, **41**, 2447 (1947)].

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.

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Quaternary Ammonium Salts of Heterocyclic Bases

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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.

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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).