Anal. Calcd. for $C_{14}H_{28}N_2$: C, 74.94; H, 12.58; N,[11] 12.59. Found: C, 74.71; H, 12.70; N,[11] 12.12.

Methobromide was formed in 90% yield when the camphidine derivative was treated with methyl bromide in hot acetone. It crystallized from ethanol-acetone as long needles, m.p. 246–247° dec.

Anal. Calcd. for $C_{15}H_{31}BrN_2$: Br, 25.03; N, 8.77. Found: Br, 25.2; N, 8.72.

1,6-Bis 1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-3-yl hexane. Camphidine (7.7 g., 0.05 mol.), 1,6-dibromohexane (6.1 g., 0.025 mol.), anhydrous potassium carbonate (5.8 g., 0.04 mol.) and toluene (80 cc.) were stirred and refluxed for 20 hr., more camphidine (1.5 g., 0.01 mol.) and potassium carbonate (2.0 g., 0.015 mol.) were added and refluxing was resumed for 20 hr. longer. It was filtered and the filtrates extracted well with 4*N* hydrochloric acid. The base was liberated from the extracts, extracted with ether, and fractionated. 1,6-Bis 1,8,8-trimethyl-3-azabicyclo[3.2.1]octan-3-yl hexane was obtained as a golden oil (7.1 g., 73% yield) which boiled at 155–160° (0.22 mm.); $n_D^{25} = 1.5010$.

Anal. Calcd. for $C_{26}H_{28}N_2$: C, 80.34; H, 12.45; N, 7.21. Found: C, 80.33; H, 12.35; N, 7.17.

The *dihydrochloride* was prepared in ether and separated from ethanol-ether as a chalky solid, m.p. >300°.

Anal. Calcd. for $C_{26}H_{48}N_2 \cdot 2HCl$: C, 67.65; H, 10.92; Cl, 15.36. Found: C, 67.77; H, 10.61; Cl, 14.99.

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Dithiol Diesters of Long-Chain Acids[1]

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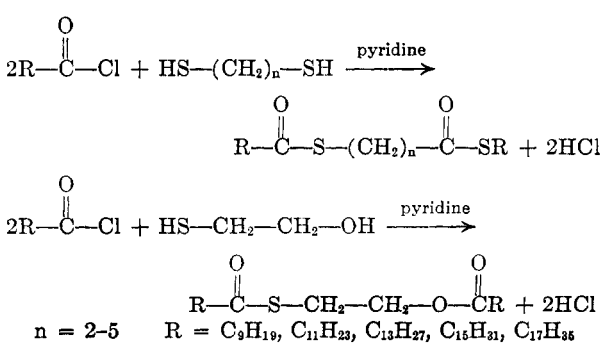
Glycol diesters of long-chain acids are well known and useful compounds. A literature search revealed that the corresponding dithiol diesters, however, apparently are not known.

Continuing our systematic study[2] of thiol esters, this paper describes the preparation and some of the properties of 1,2-ethanedithiol, 1,3-propanedithiol, 1,4-butanedithiol, and 1,5-pentanedithiol diesters of decanoic, dodecanoic tetradecanoic, hexadecanoic, and octadecanoic acids, as well as the 2-mercaptoethanol diesters of the above mentioned acids. Also prepared were 1,2-ethanedithiol and 1,4-butanedithiol dioctanoates.

The esters were prepared by the action of dithiols or 2-mercaptoethanol on acyl halides in the presence of pyridine.



The properties of the esters, yields obtained and analytical data are summarized in Tables I and II.

When the reaction was carried out in the absence of pyridine, impure products were obtained and repeated recrystallizations of these products failed to purify them. Traces of unreacted acids were removed from the crude esters by chromatography on Florisil.

The dithiol diesters prepared are white crystalline solids. The lower members are sparingly soluble in ethanol and very soluble in acetone. Their solubility decreases in these solvents with increasing molecular weight. The lower members have a distinct mercaptan-like odor while the higher members are odorless.

Each of the five series of the dithiol diesters shows an alternation in melting points. Figure 1 represents the plot of the melting points of dithiol diesters against the number of carbon atoms in thiols. As in most homologous series, the even members melt at a higher temperature than the odd members. The reverse is true for alkanethiol esters.[3]

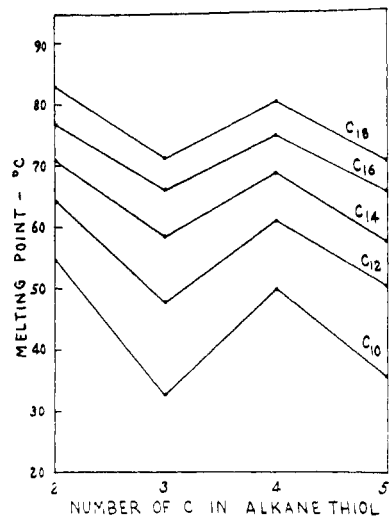


Fig. 1. Melting points of dithiol diesters

It is interesting to note that the 2-mercaptoethanol diesters melt at a lower temperature than either the corresponding 1,2-ethanedithiol or 1,2-ethane diesters.[4]

1,2-Ethanedithiol and 1,5-pentanedithiol dioctadecanoates reacted with methanol in the presence of a trace of sodium methoxide to form methyl octadecanoate by heating the reaction mixture on a steam bath for 12 hr.

(1) Taken in part from Senior Theses submitted by Paul A. Gwinner and Orestes T. Chortyk.

(2) Previous paper in this series is: *J. Org. Chem.*, **24**, 1143 (1959).

(3) R. Sasin, W. F. Ashley, J. W. Manning, Jr., A. Paolini, Jr., and G. S. Sasin, *J. Am. Oil Chem. Soc.*, **35**, 192 (1958).

(4) Ralston, A. W., *Fatty Acids and Their Derivatives*, John Wiley & Sons, New York, 1948, p. 528.

TABLE I

DITHIOL DIESTERS

	M.P.	Yield, %	Formula	% Sulfur Calcd.	% Sulfur Found
1,2-Ethanedithiols					
Dioctanoate	42.2–42.8	62.3	$C_{18}H_{34}O_2S_2$	18.5	18.5
Didecanoate	54.7–56.0	54.7	$C_{22}H_{42}O_2S_2$	15.9	15.9
Didodecanoate	64.4–65.4	60.5	$C_{26}H_{50}O_2S_2$	13.9	13.7
Ditetradecanoate	70.8–71.4	71.0	$C_{30}H_{58}O_2S_2$	12.4	12.3
Dihexadecanoate	76.4–77.4	76.9	$C_{34}H_{66}O_2S_2$	11.2	10.9
Dioctadecanoate	82.8–83.4	41.5	$C_{38}H_{74}O_2S_2$	10.2	10.3
1,3-Propanedithiols					
Didecanoate	34.2–35.0	42.0	$C_{23}H_{44}O_2S_2$	15.4	15.4
Didodecanoate	46.0–47.0	60.4	$C_{27}H_{52}O_2S_2$	13.6	13.4
Ditetradecanoate	57.0–58.0	63.1	$C_{31}H_{60}O_2S_2$	12.1	12.2
Dihexadecanoate	64.4–65.4	70.5	$C_{35}H_{68}O_2S_2$	10.9	10.9
Dioctadecanoate	70.8–71.4	40.0	$C_{39}H_{76}O_2S_2$	10.0	10.3
1,4-Butanedithiols					
Dioctanoate	36.5–37.5	52.1	$C_{20}H_{38}O_2S_2$	17.1	17.0
Didecanoate	49.8–50.4	44.2	$C_{24}H_{46}O_2S_2$	14.9	15.0
Didodecanoate	61.6–62.0	53.5	$C_{28}H_{54}O_2S_2$	13.2	13.4
Ditetradecanoate	67.4–68.6	81.3	$C_{32}H_{62}O_2S_2$	11.8	12.0
Dihexadecanoate	73.0–74.0	74.4	$C_{36}H_{70}O_2S_2$	10.7	10.8
Dioctadecanoate	80.0–80.9	41.3	$C_{40}H_{78}O_2S_2$	9.78	9.84
1,5-Pentanedithiols					
Didecanoate	35.0–36.0	50.2	$C_{25}H_{48}O_2S_2$	14.4	14.5
Didodecanoate	50.0–51.0	52.2	$C_{29}H_{56}O_2S_2$	12.8	13.0
Ditetradecanoate	57.1–58.1	63.3	$C_{33}H_{64}O_2S_2$	11.5	11.2
Dihexadecanoate	65.5–66.5	73.2	$C_{37}H_{72}O_2S_2$	10.5	10.8
Dioctadecanoate	69.6–71.2	43.2	$C_{41}H_{80}O_2S_2$	9.57	9.67

TABLE II

2-MERCAPTOETHANOL DIESTERS

	M.P.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Didecanoate	36.0–37.0	47.2	$C_{22}H_{42}O_3S$	68.4	69.0	10.9	10.6
Didodecanoate	49.6–50.4	60.4	$C_{26}H_{50}O_3S$	70.6	70.4	11.3	11.1
Ditetradecanoate	60.2–60.6	63.1	$C_{30}H_{58}O_3S$	72.3	72.2	11.7	11.7
Dihexadecanoate	67.8–68.0	70.5	$C_{34}H_{66}O_3S$	73.8	73.8	11.9	12.0
Dioctadecanoate	73.8–74.4	46.5	$C_{38}H_{74}O_3S$	74.7	74.4	12.1	12.3

$$C_{17}H_{35}\text{—}\overset{O}{\overset{\|}{C}}\text{—}S(CH_2)_n\text{—}S\text{—}\overset{O}{\overset{\|}{C}}\text{—}C_{17}H_{35} + CH_3OH \xrightarrow{CH_3ONa} 2C_{17}H_{35}\text{—}\overset{O}{\overset{\|}{C}}\text{—}OCH_3 + HS\text{—}(CH_2)_n\text{—}SH$$

n = 2,5

The above mentioned compounds, however, unlike alkanethiol esters[5] did not undergo ester interchange reactions with phenol and thiophenol even when the reaction mixtures consisting of the dithiol diester, phenol or thiophenol, sodium methoxide, and pyridine were heated on a steam bath for 24 hr.

EXPERIMENTAL

Starting materials. Decanoic acid and dodecanoyl, tetradecanoyl and hexadecanoyl chloride were obtained from Eastman. All of the thiols were obtained from the Aldrich Chemical Co. The Humko Chemical Co. supplied S-97, commercial stearic acid. This was crystallized once from methanol and once from acetone and melted at 69°. The properties, yields obtained and analyses of the dithiol and monothiol diesters are summarized in Tables I and II.

Decanoyl chloride. This compound was prepared from decanoic acid and PCl_3 according to the method of Bauer.[6]

1,2-Ethanedithiol, 1,3-propanedithiol, 1,4-butanedithiol didecanoates, didodecanoates, ditetradecanoates, and dihexadecanoates. 2-Mercaptoethanol didecanoates, didodecanoates, ditetradecanoates, and dihexadecanoates. To 0.04 mol. of the acid chloride and 0.04 mol. of pyridine in a 200-ml. round bottomed flask, fitted with a reflux condenser, was added 0.02 mol. of the appropriate mercaptan or 2-mercaptoethanol and the mixture was allowed to stand overnight. It was heated on a steam bath for 3 hr. and then washed with two 50-ml. portions of boiling water. The solid which formed on cooling was crystallized from acetone-alcohol or acetone-benzene until successive crystallizations showed no increase in melting point.

(5) G. S. Sasin, P. R. Schaeffer, and R. Sasin, *J. Org. Chem.*, **22**, 1183 (1957).

(6) S. T. Bauer, *Oil and Soap*, **23**, 1 (1946).

1,2-Ethanedithiol, 1,3-propanedithiol, 1,4-butanedithiol, and 1,5-pentanedithiol distearates. To 17 g. (0.06 mol.) of stearic acid and 100 ml. of petroleum ether in a 200-ml. round bottomed flask, fitted with a reflux condenser, was added 12 g. of PCl_5. The mixture was boiled under gentle reflux for 2 hr., cooled, and washed rapidly with four 25-ml. portions of ice water, and then dried over anhydrous Na_2SO_4.[7] To the dried solution of the acid chloride in petroleum ether was added a mixture of 0.03 mol. of the appropriate mercaptan and 0.06 mol. of pyridine in 100 ml. of petroleum ether. The rest of the procedure is identical to that used above.

2-Mercaptoethanol distearate. Stearoyl chloride was prepared by the method of Youngs *et al.* as described above. After the water wash and drying, the petroleum ether was removed by distillation and equivalent amounts of 2-mercaptoethanol and pyridine were added. The rest of the procedure is identical to that used above.

Chromatography. Analytical samples of the dithiol and monothiol diesters were chromatographed, using 20 g. of Florisil per gram of ester. The column was eluted with a total of 400 ml. of a solution containing 30% benzene–70% petroleum ether. The 1,2-ethanedithiol diesters were eluted with a total of 400 ml. of a solution containing 50% benzene–50% petroleum ether. After the solvent was removed by distillation, the product was crystallized from acetone-alcohol or acetone-benzene.

Reaction of methanol with 1,2-ethanedithiol and 1,5-pentanedithiol dioctadecanoate. To 0.005 mol. of 1,2-ethanedithiol or 1,5-pentanedithiol dioctadecanoate in a 200-ml. round bottomed flask, fitted with a reflux condenser, was added 0.05 g. of sodium methoxide and 70 ml. of methanol and the mixture was heated on a steam bath for 12 hr. At the end of the heating period, the methanol was removed by distillation and the product was dissolved in 100 ml. of ether. After the ether solution was washed with three 50-ml. portions of water, it was dried over anhydrous sodium sulfate. The ether then was removed by distillation and the methyl stearate was crystallized from methanol. The yield of product was 60–65% of the theoretical amount. Admixture of the products with an authentic sample of methyl stearate showed no depression of melting point.

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(7) C. G. Youngs, A. Epp, B. M. Craig, and H. R. Sallans, *J. Am. Oil Chem. Soc.*, **24**, 107 (1957).

Benzilates and Related Esters of Aminophenylethanols

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In continuation of our exploration of derivatives of the aminophenylethanols,[1] a series of basic esters (Table I) of the formula $R_1COOCH(C_6H_5)$-$CH_2NR_2R_3.R_4X$ (I) has been synthesized and examined for pharmacological activity.

Esters evaluated included benzilates[2] as well as variants of R_1CO— of lesser molecular bulk.[3] Structural relationships with proven active drugs suggested examination of the basic esters I as central nervous system depressants,[4] anti-tremorine agents,[5] and local anesthetics.[3d]

Treatment of the aminophenylethanol[1] with the acid chloride R_1COCl gave the basic ester I, either isolated directly as the hydrochloride, or converted to its free base which was distilled. The corresponding benzilates were prepared from the α-chloro-α,α-diphenylacetates by hydrolysis.[6]

Selected compounds showed activity as anesthetic agents,[7] reversed the neurotoxicity of tremorine,[8] depressed motor activity,[9] and were active as hypotensive agents.[10]

EXPERIMENTAL[11]

The acid chlorides were available commercially, or were processed as described in the literature in the instance of ω-cyclohexylbutyryl chloride,[12] and α-chloro-α,α-diphenylacetyl chloride.[13]

(1) S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 6060 (1958).

(2) (a) J. P. Long and A. M. Lands, *J. Pharmacol. Exp. Therap.*, **120**, 46 (1957); (b) F. Leonard and L. Simet, *J. Am. Chem. Soc.*, **77**, 2855 (1955); (c) R. B. Moffett, J. L. White, B. D. Aspergren, and F. E. Visscher, *J. Am. Chem. Soc.*, **77**, 1565 (1955); (d) F. F. Blicke and J. H. Biel, *J. Am. Chem. Soc.*, **76**, 3163 (1954); (e) A. P. Phillips, *J. Am. Chem. Soc.*, **76**, 1955 (1954); (f) H. A. Smith, C. A. Buehler, and K. V. Nayak, *J. Org. Chem.*, **21**, 1423 (1956); (g) A. W. Weston, R. W. DeNet, and R. J. Michaels, Jr., *J. Am. Chem. Soc.*, **75**, 4006 (1953); (h) G. R. Treves and F. C. Testa, *J. Am. Chem. Soc.*, **74**, 46 (1952).

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(7) Following the procedure outlined in ref. 3d, the data were reported in this order: compound no. of Table I/LD_{min} mg./kg./$ANED_{50}$ mg./ml.: 37/1000/7; 38/750/5.5; 39/100/6.7; 41/>1000/14; 43/1000/2.4; 46/1000/3.5; 50/750/1.5.

(8) Following the procedure outlined in ref. 3d, the compound No. of Table I/LD_{min} mg./kg./TED_{50} mg./kg. was noted: 34/750/75; 35/100/18; 36/450/89; 40/750/100; 49/250/56; 54/200/52.

(9) Following the procedure given by S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 1648 (1958), the compound No. of Table I/LD_{min} mg./kg./% depression of motor activity/test dose mg./kg. is given: 35/100/34/20; 40/750/30/100; 52/80/24/20.

(10) Following the procedure given by S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 2743 (1958), compound 47 had 3+ activity and compounds 35, 36, 42, 45, 49, and 52 had 2+ activity.

(11) Descriptive data shown in the table are not reproduced in the Experimental section. Typical examples of the synthesis are given.

(12) J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, **15**, 1082 (1950).

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