ethyl acetate and the solution was washed with 1*N* potassium bicarbonate (2 × 6 ml.). The ethyl acetate layer was dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue after crystallization from ethyl acetate–petroleum (30–60°) amounted to 90 mg. (49%); m.p. 114–116°; $[\alpha]_D^{26.0}$ −12.4°. The reported values[7] are 116–118° and $[\alpha]_D^{25}$ −12.0°.

Phthaloyl-L-phenylalanylglycine ethyl ester.[2] To 0.3 ml. of ethoxy acetylene cooled in a Dry Ice–acetone mixture bath was added 0.1 g. (0.34 mmole) of phthaloyl-L-phenylalanine. The suspension was slowly allowed to warm to 0° and held at this temperature until solution was effected. Dioxane was added at −20° and the resulting solution lyophilized. The residual oil was dissolved in 0.5 ml. of chloroform and to it was added 35 mg. (0.34 mmole) of ethyl glycinate. The solution was heated at reflux for 30 min. after which the solvent was distilled until 0.25 ml. was collected. An infrared curve of this distillate was identical with one of ethyl acetate in chloroform. The residue from the distillation was evaporated to dryness under reduced pressure and the resulting solid crystallized from ethanol, 75 mg. (60%); m.p. 160–161°; $[\alpha]_D^{26.0}$ −146° (ethanol).

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Synthesis from Thiolesters. II. Synthesis of Cyclic Sulfides[1]

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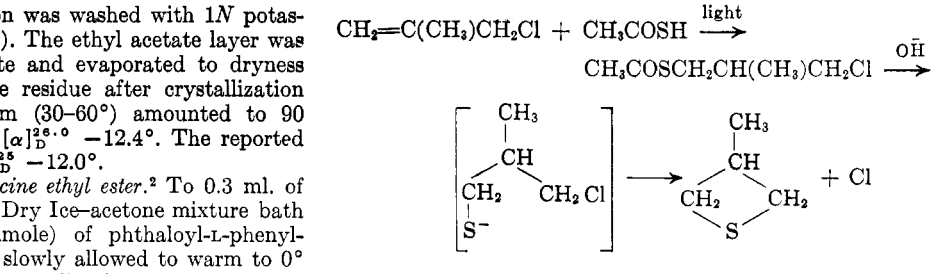
The high yields of thiolacetates obtained by the reaction of thiolacetic acid with most olefins makes these substances attractive as starting materials in the synthesis of a number of types of sulfur compounds including thiols[3] and alkanesulfonyl chlorides.[4] Applied to olefins containing a halogen or potential halogen grouping (*e.g.*, hydroxyl) the formation of thiolacetates by this route can serve as an approach to the synthesis of cyclic sulfides. For example, addition of thiolacetic acid to methallyl chloride gave an 88% yield of 2-methyl-3-chloropropyl thiolacetate. Hydrolysis of the latter by aqueous alkali together with concurrent steam distillation gave an 80% yield of redistilled 3-methylthiacyclobutane. The synthesis of this compound *via* 2-methyl-1,3-propanediol is much more tedious.



Over-all yields of 39% of thiacyclopropane (propylene sulfide) and 76% of thiacyclohexane were obtained by a similar route starting with 2-chloropropene and 5-chloro-1-pentene, respectively.

In the present paper this general method has been applied to the synthesis of simple 3-, 4-, and 6-membered ring cyclic sulfides. Its extension to other ring sulfides will be described later. The only previous use of this method that has come to our attention is the preparation of 3-hydroxythiacyclobutane by alkaline hydrolysis of mono- or diacetylated 2-hydroxy-3-chloropropanethiol.[5]

EXPERIMENTAL[6]

General procedure for the preparation of cyclic sulfides. The suspended haloalkyl thiolester was stirred and heated in an aqueous solution containing excess sodium hydroxide. The cyclic sulfide was isolated as it was formed by an internal steam distillation. It was separated mechanically and the aqueous portion of the steam distillate extracted three times with pentane. The sulfide and the pentane extracts were combined and dried over anhydrous magnesium sulfate. Distillation of the combined extracts yielded the product.

2-Methyl-3-chloropropyl thiolacetate. Starting with 45.3 g. (0.5 mole) of 2-methyl-3-chloro-1-propene and 38.1 g. (0.5 mole) of freshly distilled thiolacetic acid, 73 g. (87.8%) of 2-methyl-3-chloropropyl thiolacetate, b.p. 89° (16 mm.), n_D^{25} 1.4575 was obtained by the general procedure previously described.[3,4]

Anal. Calcd. for $C_6H_{11}OSCl$: C, 43.24; H, 6.65. Found: C, 43.60; H, 6.55.

3-Methylthiacyclobutane. A 1-l. flask, fitted with a stirrer and condenser arranged for distillation was charged with 12 g. (0.3 mole) of sodium hydroxide dissolved in 400 ml. of water and 25 g. (0.15 mole) of 2-methyl-3-chloropropyl thiolacetate. Carrying out the general procedure, 10.6 g. (80%) of 3-methylthiacyclobutane, b.p. 108–109°, n_D^{25} 1.4840, was obtained.

Anal. Calcd. for C_4H_8S: C, 54.49; H, 9.15. Found: C, 54.21; H, 9.29.

The monomercuric chloride addition product of 3-methylthiacyclobutane was prepared according to the method of Mann and Purdie.[7] Immediately after formation, the complex was recrystallized from ethanol and then acetone. In a sealed tube softening of the derivative began at about 85° and at 153° decomposition to a purple substance was observed.

Anal. Calcd. for $C_4H_8S \cdot HgCl_2$: C, 13.36; H, 2.24. Found: C, 13.81; H, 2.25.

5-Chloro-1-pentyl thiolacetate. Starting with 29 g. (0.23 mole) of 5-chloro-1-pentene (Peninsular Chem. Research, Inc., Gainesville, Fla.) and 17.4 g. (0.3 mole) of freshly distilled thiolacetic acid, 36 g. (87%) of 5-chloro-1-pentyl thiol-

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acetate, b.p. 135–138° (25 mm.) was obtained by the general procedure previously described.[3]

Anal. Calcd. for $C_7H_{13}OSCl$: C, 46.52; H, 7.23. Found: C, 46.61, 46.54; H, 6.69, 6.87.

Thiacyclohexane. Starting with 34 g. (0.19 mole) of 5-chloropentyl thiolacetate, 16.52 g. (87%) of thiocyclohexane, b.p. 140–141° was obtained. Whitehead, Dean, and Fidler[8] reported the b.p. to be 141.6°.

2-Chloropropyl thiolacetate. Starting with 153 g. (2 moles) of 2-chloropropene (Shell Chemical Co.) and 114.2 g. (1.5 moles) of freshly distilled thiolacetic acid, 216 g. (94.2%) of 2-chloropropyl thiolacetate, b.p. 71° (10 mm.), was obtained by the general method previously described.[3,4] It was necessary to employ an ice water bath to control the exothermic reaction on a run of this size. Culvenor, Davies, and Heater[9] reported the b.p. to be 70–71° (9 mm.).

Thiacyclopropane (propylene sulfide). A. Starting with 68 g. (0.45 mole) of 2-chloropropyl thiolacetate, the above procedure was carried out with the exception that sodium carbonate was substituted for sodium hydroxide, which caused polymerization. Distillation of the combined extracts through a three-plate Vigreux column yielded 8.5 g. (25%) of thiacyclopropane, b.p. 72–75°, and 11 g. (16% recovery) of the starting material. The reaction flask continued a considerable amount of polymeric material.

B. Forty-five grams (0.29 mole) of 2-chloropropyl thiolacetate was stirred overnight with 500 ml. of methanol containing 5 ml. of concentrated hydrochloric acid. The reaction mixture was then neutralized to a *p*H of 7 (indicator paper) with a dilute sodium hydroxide solution. The reaction mixture was stirred at room temperature for an additional hour, and then extracted 4 times with 50-ml. portions of pentane. Distillation through a 3-plate Vigreux column yielded 7 g. (30.5%) of thiacyclopropane, b.p. 72–75°. Considerable polymeric material remained in the distillation flask.

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Synthesis of DL-Norleucine-2-C^{14}

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Since DL-norleucine-2-C^{14} was desired for metabolic studies but had not previously been synthesized, the following synthesis was undertaken:[2–7]

$$R = CH_3CH_2CH_2CH_2$$

$$RBr \xrightarrow[\text{Ether}]{Mg^\circ} RMgBr \xrightarrow[H_2SO_4]{C^{14}O_2} R{-}C^{14}OOH \xrightarrow[\text{Ether}]{LiAlH_4}$$

$$RC^{14}H_2OH \xrightarrow{PBr_3} RC^{14}H_2Br \xrightarrow[\text{Ether}]{Mg^\circ} RC^{14}H_2MgBr \xrightarrow[H_2SO_4]{CO_2}$$

$$RC^{14}H_2COOH \xrightarrow[PCl_3]{Br_2} R{-}C^{14}HCOOH \xrightarrow{\text{concd. } NH_3}$$

(Br)

$$R{-}C^{14}H{-}COOH$$

(NH_2)

EXPERIMENTAL

Valeric acid-1-C^{14}. *n*-Butylmagnesium bromide (0.203 mole) was prepared according to standard procedures and carbonated with $C^{14}O_2$ in a vacuum manifold at 2-mm. pressure.[3] The acid was recovered from the reaction flask by steam distillation over silver sulfate. The product was separated, washed with ether, dried several hours over anhydrous magnesium sulfate, and redistilled to yield 7.1–9.1 ml. (77–83%), b.p. 170–190°.

n-Amyl alcohol-1-C^{14}. Valeric-acid-1-C^{14} was reduced to *n*-amyl alcohol-1-C^{14} with $LiAlH_4$ using anhydrous ether as a solvent.[4] The product was recovered by separation of the ether phase, removal of the ether and distillation of the fraction boiling between 128–140°. The yield was 76–78% (6.4–7.0 ml.).

Caproic-acid-2-C^{14}. *n*-Amyl bromide-1-C^{14} was prepared by the bromination of *n*-amyl-alcohol-1-C^{14} with PBr_3.[5] The reaction mixture was allowed to stand for 2 hr. The product was recovered by distillation and washed successively with water, concd. H_2SO_4 and 10% Na_2CO_3. The product was dried over anhydrous Na_2SO_4 and redistilled, collecting the fraction boiling between 125–128°. The yield was 70–72% (5.5–5.1 ml.). *n*-Amylmagnesium bromide-1-C^{14} was then prepared and carbonated at −20° by passing inactive CO_2 gas through the solution. Caproic-acid-2-C^{14} was recovered by the method used for valeric acid-1-C^{14} and yielded 55–66% (5.5–7.3 ml.).

DL-*norleucine-2-C^{14}.* α-Bromocaproic acid-2-C^{14} was prepared by brominating caproic acid-2-C^{14} with Br_2 and PCl.[6] The product was recovered by fractional distillation at 10-mm. Hg pressure collecting the product boiling at 128–131°. Yield: 45–67% (5.14–5.91 g.). α-Bromocaproic acid-2-C^{14} was then added to a flask containing concentrated NH_3, tightly stoppered and heated in a 50–55° water bath for 24 hr. The flask was then cooled to and kept at 4° for 24 hr. The shiny white flakes which crystallized were recovered by filtration, washed with cold methanol, and dried at 105°.[7] The yield was 59–62% (2.16–2.24 g.). The over all yield was 8.2–8.3% based on $BaC^{14}O_3$, and the over all isotopic yield based on the specific activity of $BaC^{14}O_3$, was 6.7–7.2% (3.67–3.97 mc.). The specific activities of the final products were 1.64 μc./mg. and 1.85 μc./mg. for 2 successive syntheses. These specific activities were determined by the oxidation of the product to $C^{14}O_2$ with $K_2S_2O_8$.[8] The $C^{14}O_2$ was then precipitated as $BaC^{14}O_3$ and counted at infinite thickness in a Tracerlab windowless Geiger flow gas counter and autoscaler. The total isotopic yield was increased by 0.2 mc. by the addition of inactive norleucine to the filtrate and subsequent recrystallization. Paper chromatograms developed with butanol–acetic acid–H_2O and phenol-H_2O systems in one and/or two dimensions and sprayed with ninhydrin showed a single spot which coincided with known samples of norleucine. Mixed chromatograms also showed a single spot. Autoradiograms of these papers showed only a single radioactive spot matching the ninhydrin spot showing the radioactive purity of the norleucine.

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