fractional acidification;[10] it was identified by melting point and mixed melting point. Small amounts of unidentified acidic material remained behind. The results in runs in nitrobenzene were similar, except that no di- or tribromonaphthalenes were obtained.

2-Bromonaphthalene (10 g.) was succinoylated in nitrobenzene solution. The crude acid weighed 4.4 g. Repeated recrystallizations from methanol afforded eventually 0.35 g. (2.4%) of yellow crystals of β-(6-bromo-2-naphthoyl)-propionic acid, which started to change color at 198° and decomposed at 207°.

Anal. Calcd. for $C_{14}H_{11}O_3Br$: C, 54.74; H, 3.61. Found: C, 54.82; H, 3.70.

Small amounts of β-(2-naphthoyl)propionic acid were obtained from the mother liquor. In tetrachloroethane the yields of pure acid were even smaller.

Hypohalite oxidation of the above acid afforded 6-bromo-2-naphthoic acid, which after two crystallizations from ethanol melted with decomposition at 279–286° (lit.[11] 280° dec.). The methyl and ethyl esters, after crystallizations from methanol and ethanol, respectively, melted at 122.0–123.5° and at 66.5–68.0° (lit.[11] 123–124.5° and 67–68°).

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A Reactive Peptide Intermediate Derived from Ethoxyacetylene

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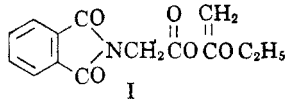
Our studies[2,3] of peptide synthesis in aqueous solution prompted us to investigate the possible utility of ethoxyacetylene[4] under these conditions. An aqueous solution of ethoxyacetylene, phthaloylglycine, and glycine ethyl ester deposited a solid, which was composed of the expected phthaloylglycylglycine ethyl ester[5] and a neutral product in an approximate ratio of 1:8.

The analytical data for the major product supported a structure arising from a 1/1 addition of acid and ethoxyacetylene.

The reaction of the adduct and ethyl glycinate at 60° and at room temperature in anhydrous solvents gave 80% and 75% respectively of phthaloylglycylglycine ethyl ester. These results rule out the symmetrical anhydride of phthaloylglycine, a plausible structure since ethoxyacetylene is known to convert acids to anhydrides,[6]

An infrared spectrum of a chloroform distillate om the reaction of the adduct and ethyl glycinate was identical to that of an ethyl acetate in chloroform solution. The isolation of ethyl acetate is convincing evidence for structure I. Similar results were obtained with phthaloyl-L-phenylalanine.



I

In the examples of peptide synthesis using alkoxyacetylenes published by Arens and coworkers[4] no case was reported in which the possibility of racemization by an azlactonization mechanism existed. We have prepared carbobenzyloxyglycyl-L-phenylalanylglycine ethyl ester[7] from carbobenzyloxyglycyl-L-phenylalanine and glycine ethyl ester with no sign of racemization.

EXPERIMENTAL[8]

1-Ethoxyvinyl phthaloylglycinate (I). A solution of 0.6 g. (2.93 mmoles) of phthaloylglycine[9] and 0.302 g. (2.93 mmoles) of glycine ethyl ester in 6 ml. of water and 0.6 ml. of ethoxyacetylene[10] was stirred at room temperature for 2 hr. The solid, which separated slowly, amounted to 300 mg.; m.p. 102–107°. Recrystallization from benzene and petroleum ether (30–60°) gave as a first crop (yield, 36 mg.) a crystalline product which proved to be identical with phthaloylglycylglycine ethyl ester.[5] The filtrate was evaporated to dryness under reduced pressure and the residue was crystallized from ether, 200 mg., m.p. 108–110°.

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.36; H, 4.91; N, 5.15.

Phthaloylglycylglycine ethyl ester.[5] *A.* A solution of 50 mg. (0.182 mmole) of the adduct I and 19 mg. (0.182 mmole) of glycine ethyl ester in 1 ml. of dioxane was heated at 50° for 30 min. The dioxane solution was freeze dried and the residue crystallized from ethanol; yield, 42 mg. (80%); m.p. 191–193°. The melting point of a mixture with authentic phthaloylglycylglycine ethyl ester did not show a depression.

B. A solution of 19 mg. (0.182 mmole) of ethyl glycinate and 50 mg. (0.182 mmole) of I in 3 ml. of methylene chloride was stored at room temperature for 4 hr. Removal of the solvent and crystallization from ethanol afforded a product (40 mg.; 75%) which was identical to the product obtained in Run A.

Isolation of ethyl acetate from I. A solution of 400 mg. (1.5 mmole) of I and 152 mg. (1.5 mmole) of glycine ethyl ester in 0.5 ml. of chloroform was heated at reflux for 30 min. The solvent was then distilled until 0.25 ml. was collected. An infrared spectrum of this distillate was identical to one of ethyl acetate in chloroform. The residue yielded 480 mg. of phthaloylglycylglycine ethyl ester; m.p. 191–192°.

Carbobenzyloxyglycyl-L-phenylalanylglycine ethyl ester.[7] A mixture of 0.15 g. (0.42 mmole) of carbobenzoxyglycyl-L-phenylalanine, 43 mg. (0.42 mmole) of glycine ethyl ester, and 0.5 ml. of ethoxyacetylene was heated under reflux for 30 min. The excess ethoxyacetylene was distilled under reduced pressure. The oily residue was dissolved in 6 ml. of

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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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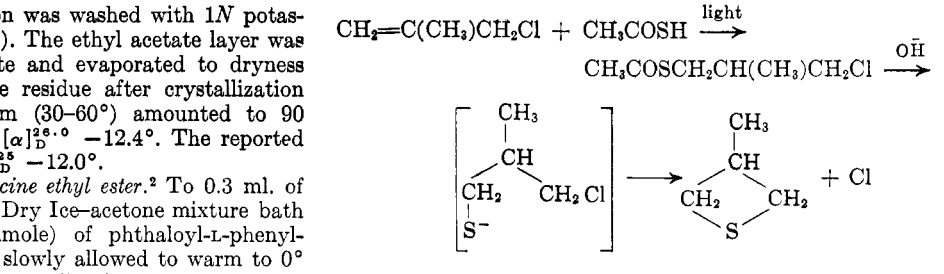
The high yields of thiolacetates obtained by the reaction of thiolacetic acid with most olefins makes these substances attractive as starting materials in the synthesis of a number of types of sulfur compounds including thiols[3] and alkanesulfonyl chlorides.[4] Applied to olefins containing a halogen 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-

(1) Presented in part at the 126th meeting of the American Chemical Society, New York, September 1954 (p. 6-O of Abstracts).

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