The infrared spectrum (potassium bromide disk) showed strong absorption at 1025 and 1037 cm^{-1} (sulfoxide region) and at 967 cm^{-1}.

Cyclization of Propenylcysteine Sulfoxide to Cycloalliin.—A solution of 120 mg of the amino acid in 80 ml of 1 *N* ammonium hydroxide was allowed to stand 4 days when it was concentrated *in vacuo* to a crystalline solid. The solid was dissolved in 5 ml of water, 5 ml of 2 *N* hydrochloric acid was added, and the solution was concentrated *in vacuo* at <25° to *ca.* 2 ml. The resulting crystalline suspension, after storage at 0° for 4 hr, was filtered and the product was washed with 0.5 ml of ice water and 2 ml of acetone. A yield of 102 mg of prisms was obtained. An additional 36 mg was obtained from the mother liquor by precipitation with acetone. The cycloalliin hydrochloride hydrate melted at 204–206° dec.

Anal. Calcd for $C_6H_{11}NOS \cdot HCl \cdot H_2O$: C, 31.09; H, 6.09; N, 6.04; S, 13.84. Found: C, 31.2; H, 5.94; N, 6.04; S, 14.0.

It was shown to be identical by infrared (KBr disk) and by paper chromatography with a sample of cycloalliin isolated from fresh onions.

N-2,4-Dinitrophenyl-S-(1-propenyl)-L-cysteine S-Oxide.—A solution containing 137 mg of the amino acid, 0.3 ml of 1-fluoro-2,4-dinitrobenzene, and 600 mg of sodium bicarbonate in 25 ml of aqueous acetone (1:1) was stirred overnight in the dark at room temperature. The solution was concentrated *in vacuo* to remove acetone, 20 ml of water was added, and the mixture was extracted with ether to remove excess reagent. Acidification of the aqueous solution with cold 3 *N* hydrochloric acid yielded a crystalline precipitate, 259 mg. Two crystallizations from acetone yielded the pure derivative, 173 mg, dec pt 147–147.5°, $[\alpha]^{25}D$ −218° (*c* 0.6, acetic acid).

Anal. Calcd for $C_{12}H_{13}N_3O_7S$: C, 41.98; H, 3.82. Found: C, 42.2; H, 3.84.

N-2,4,6-Trinitrophenyl Derivative.—A solution of 255 mg of the amino acid and 524 mg of sodium 2,4,6-trinitrobenzenesulfonate was stirred for 1 hr at 25° and the pH maintained at 6.5–7.0 by the careful addition of 4% sodium carbonate solution. The deep red solution was allowed to stand at room temperature for 1 hr, cooled in an ice bath, and acidified with cold 3 *N* hydrochloric acid. The resulting yellow precipitate was filtered, washed with 20 ml of ice water, and dried *in vacuo*, yield 455 mg. Three recrystallizations from acetone yielded 373 mg of canary yellow prisms, dec pt 130–131.5°.

Anal. Calcd for $C_{12}H_{12}N_4O_9S$: C, 37.12; H, 3.11. Found: C, 37.40; H, 3.28.

Acknowledgment.—We thank L. M. White and G. E. Secor for elemental analysis, Lois Boggs for infrared determinations, and Nancy Henderson for assistance with pmr spectra.

A Synthetic Approach to Cephams

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A key intermediate in the total synthesis of penicillins, *t*-butyl-4-carboxy-5,5-dimethyl-α-phthalimido-2-thiazolidine acetate, was prepared by the condensation of *t*-butyl phthalimidomalonaldehydate (**1**) with penicillamine.[2] This success (Scheme I) led to the possibility that *t*-butyl-4-carboxy-α-phthalimido-2-thiazane acetate (**3**) could be prepared by condensing **1** with DL-homocysteine (**2**). Compound **3** might then be used to prepare saturated analogs of cephalosporin C (cephams[3]).

In this laboratory **1** and **2** have been condensed under basic conditions to give a 30% yield of **3**. Only one isomer was obtained, mp 161–162°. The melting point indicates that it is identical with Eardley's isomer F,[4] mp 158–161°, which was stated to be formed together with isomer B under neutral conditions. Compound **3** is insoluble in dimethylformamide, acetone, ethanol, water, and pyridine. This insolubility is probably due to the dipolar ion structure.

Esterification of **3** with diazomethane generated the corresponding methyl ester **4** in 98% yield. The identity of this ester was determined by elemental analysis, infrared spectra, and nmr spectrum which confirmed the presence of an $-OCH_3$ at 3.8 ppm. By the action of hydrazine on **4**, the parent *t*-butyl-4-carbomethoxy-α-amino-2-thiazane acetate (**5**) was prepared in 25% yield.

The β-amino acid **6** is of special interest for the formation of the fused 1,3-thiazane β-lactam (**8**). A mixture of **6** and 2-phthalimidomethyl-4-carbomethoxythiazane hydrochloride (**7**) was obtained upon treatment of **4** with anhydrous hydrogen chloride at 0°. The major component of this mixture was **7**. Pure **6** was not isolated; attempted purification transformed the mixture into pure **7**. Treatment of **7** with pyridine gave a 95% yield of the free amine **9**. The acid **6** appears to be much more readily decarboxylated than the corresponding acid, 4-carbomethoxy-5,5-dimethyl-α-phthalimido-2-thiazolidineacetic acid hydrochloride, in the penicillin series. It has been reported that 2-phthalimido-4-carbomethoxy-5,5-dimethylthiazolidine hydrochloride is the principal product when *t*-butyl-4-carbomethoxy-α-phthalimido-5,5-dimethylthiazolidine is treated with anhydrous hydrogen chloride at temperatures above 90°; however, 2-phthalimido-4-carbomethoxy-5,5-dimethylthiazolidine hydrochloride is only a by-product at lower temperatures.[7]

Treatment of impure **6** with dicyclohexylcarbodiimide[8] afforded a complex mixture. An infrared spectrum of this mixture showed an absorption at 1760 cm^{-1}, which would be expected for a β-lactam. A tlc test for reactive β-lactams (using ammonia) was also positive. The complexity of the reaction mixture made it difficult to isolate the desired cepham **8** in pure form.

Wriston and Mackenzie have reported the synthesis of 1,3-thiazane-4-carboxylic acid (unreported yield) by condensing formaldehyde with homocysteine thiolactone hydrochloride (**10**) under basic conditions.[9] An attempted condensation of **1** with **10** at pH 8.0, however, produced a 63% yield of the Schiff base **11**.

(1) National Institutes of Health Predoctoral Fellow, 1963–1966.

(2) J. C. Sheehan and K. R. Henry-Logan, *J. Am. Chem. Soc.*, **81**, 3089 (1959).

(3) R. B. Morin, *et al.*, *ibid.*, **84**, 3400 (1962).

(4) After the completion of our work, a British patent came to our attention: S. Eardley, *et al.* (to Glaxo Group Ltd.), British Patent 985,966 (March 10, 1965), claim the preparation of *t*-butyl-4-carboxy-α-phthalimido-2-thiazane acetate (**3**) by condensing *t*-butyl phthalimidomalonaldehydate (**1**) with DL-homocysteine (**2**) under acidic or neutral conditions. By varying the conditions of the reaction they claimed to isolate four isomers, A, B, D, and F. It is surprising that the condensation can be run in neutral or acidic solutions since *t*-butyl esters are sensitive to hydrochloric acid[5] and homocysteine readily cyclizes to homocysteine thiolactone in neutral or acidic solutions.[6]

(5) J. C. Sheehan and G. D. Lauback, *J. Am. Chem. Soc.*, **73**, 4752 (1951).

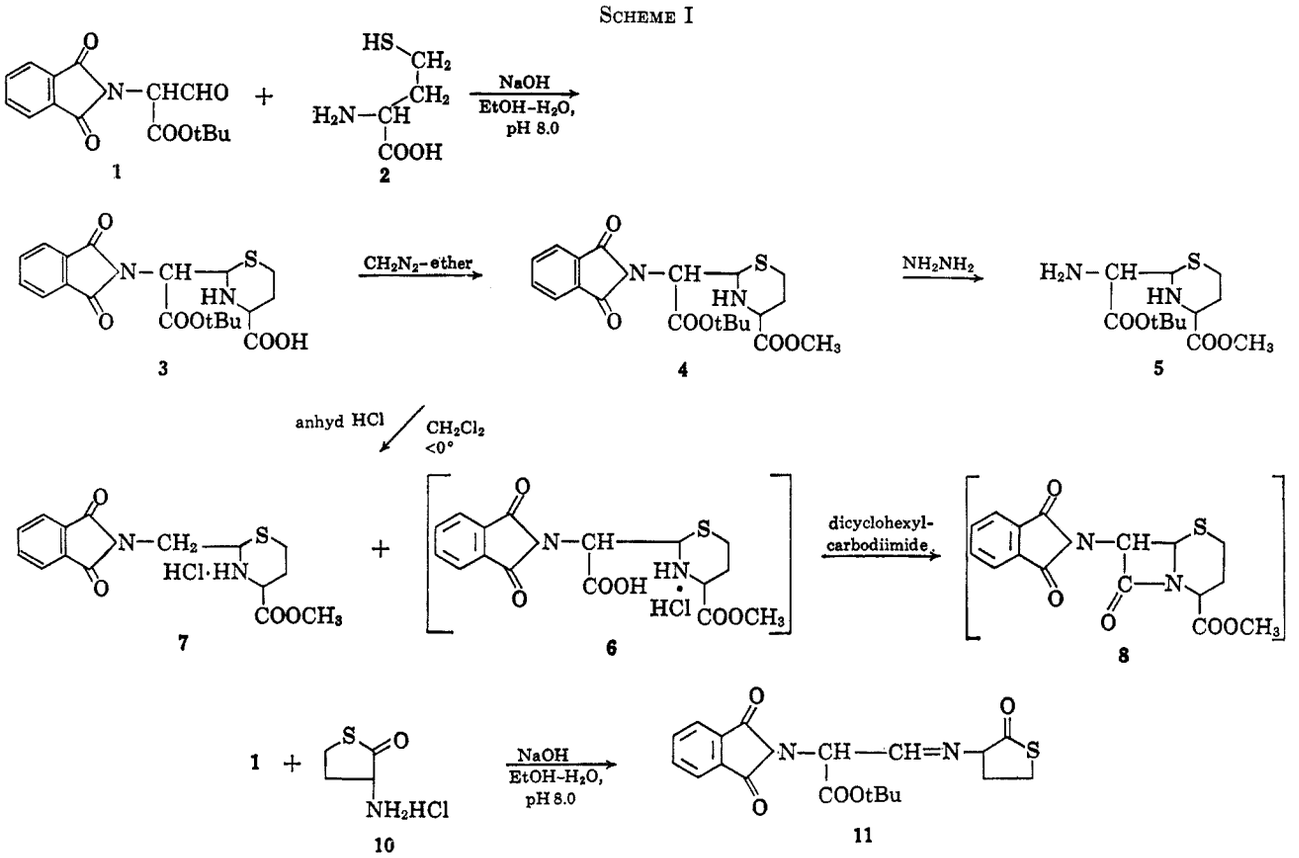
(6) E. H. Rodd, Ed., "Chemistry of Carbon Compounds," Vol. 1, Elsevier Publishing Co., New York, N. Y., 1952, p 1076.

(7) J. C. Sheehan and P. A. Cruickshank, *J. Am. Chem. Soc.*, **78**, 3677 (1956).

(8) J. C. Sheehan and G. P. Hess, *ibid.*, **77**, 1067 (1955).

(9) J. C. Wriston, Jr., and C. G. Mackenzie, *J. Biol. Chem.*, **225**, 607 (1957).

SCHEME I



Experimental Section[10]

t-Butyl-4-carboxy-α-phthalimido-2-thiazane Acetate (3).—To a solution of 2.68 g (0.02 mole) of DL-homocysteine[11] (2) in 54 ml of hot water (70°) was added 30 drops of 0.5 *N* sodium hydroxide, pH 8.0. To this solution was added 5.64 g (0.02 mole) of *t*-butyl phthalimidomalonaldehydate (1)[12] in 66 ml of hot (70°) absolute ethanol. The reaction mixture was aerated with nitrogen and sealed. After storage for 96 hr at room temperature, 2.45 g (30%) of **3** was collected by filtration. Successive washings with acetone, ethanol, and pyridine gave pure **3**; mp 161–162°. The infrared spectrum showed absorption at 1775, 1735, 1720, 1625, and 1390 cm^{-1}.

Anal. Calcd for $C_{19}H_{22}N_2O_6S$: C, 56.16; H, 5.42; N, 6.90. Found: C, 56.22; H, 5.16; N, 6.76.

t-Butyl-4-carbomethoxy-α-phthalimido-2-thiazane Acetate (4).—A suspension of 2.41 g (0.0059 mole) of **3** in 15 ml of dioxane was treated with an excess of ethereal diazomethane. After all of **3** went into solution, the ether and dioxane were evaporated under reduced pressure leaving 2.44 g (98%) of **4**. The ester was recrystallized from 95% ethanol; mp 131–134°. The infrared spectrum showed absorption at 1775, 1740, and 1725 cm^{-1}.

Anal. Calcd for $C_{20}H_{24}N_2O_6S$: C, 57.14; H, 5.71; N, 6.67. Found: C, 56.97; H, 5.77; N, 6.88.

t-Butyl-4-carbomethoxy-α-amino-2-thiazane Acetate (5).—To a solution of 0.420 g (0.001 mole) of **4** in 10 ml of methylene chloride was added 0.032 g (0.001 mole) of 95% hydrazine. After storage for 96 hr at room temperature, the solution was evaporated to produce a solid. Diethyl ether was added and 0.104 g of a solid was removed by filtration; mp >300°. The ethereal solution was evaporated and the residue triturated with petroleum ether (bp 40–60°) to yield 0.102 g (35%) of impure **5**. Recrystallization from petroleum ether–diethyl ether produced prisms; mp 91–95°. The infrared spectrum showed absorption at 3300, 1750, and 1740 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}N_2O_4S$: C, 49.65; H, 7.59; N, 9.66. Found: C, 49.76; H, 7.62; N, 9.75.

4-Carbomethoxy-α-phthalimido-2-thiazane Acetate (6).—Hydrogen chloride was bubbled through a solution of 0.200 g (0.0048 mole) in 5 ml of methylene chloride, which was maintained below 0° by a Dry Ice–acetone bath, for 7 min. Addition of 5 ml of ligroin produced 0.114 g of a solid which was shown to contain two components by tlc on silica gel G (7.5 cm) with benzene–methanol (10:1). The infrared spectrum showed absorption at 1710, 1720, 1750, 1770, and 3200–2800 cm^{-1}.

2-Phthalimidomethyl-4-carbomethoxythiazane (9).—A suspension of the mixture of **6** and **7** in 10 ml of methanol was heated for 10 min. All the solid went into solution with vigorous bubbling; evaporation produced pure **7**. To a suspension of 0.200 g (0.00056 mole) of **7** in 2 ml of water and 0.2 ml of acetone was added 0.04 ml of pyridine. After stirring for 2 hr at room temperature, 0.17 g (95%) of **9** was obtained by filtration; mp 143–146°. The nmr spectrum showed the presence of 17 protons, but no protons were found at lower field than 8.0 ppm. The infrared spectrum showed absorption at 1770, 1735, and 1720 cm^{-1}.

Anal. Calcd for $C_{18}H_{20}N_2O_6S$: C, 55.10; H, 5.10; N, 7.14. Found: C, 54.96; H, 5.21; N, 7.35.

Attempted Preparation of 4-Carbomethoxy-7-phthalimidocepham (8).—A suspension of 0.108 g of impure **6** and 0.03 g of triethylamine in 7 ml of dioxane was cooled and 0.111 g of dicyclohexylcarbodiimide[13] was added. The suspension was stirred for 22 hr; filtration afforded 0.179 g of dicyclohexylurea and triethylamine hydrochloride. Lyophilization produced an oily solid, which showed five spots by tlc on silica gel G (7.5 cm) with benzene–methanol (10:1). Column chromatography produced a solid which only showed three spots by tlc on silica gel G (7.5 cm) with benzene–methanol (10:1). A test[14] for β-

(10) Melting points were determined with a Kofler hot-stage microscope. Infrared spectra were recorded on a Perkin-Elmer Model 237 recording spectrophotometer. The nmr spectra were recorded on a Varian A-60. Microanalytical data were supplied by Dr. S. M. Nagy and his associates.

(11) Purchased from Nutritional Biochemicals Corp.

(12) J. C. Sheehan and D. A. Johnson, *J. Am. Chem. Soc.*, **76**, 158 (1954).

(13) Purchased from Eastman Organic Chemicals.

(14) A test was developed in this laboratory for reactive β-lactams, including penicillins. It is based upon the fact that reactive β-lactams are cleaved by ammonia to yield the corresponding amino amides, which move much more slowly than the β-lactams on thin layer plates. Two tlc plates are spotted identically. One of them is stored in an ammonia atmosphere for 15 min. Both plates are then chromatographed in benzene–methanol (10:1) and developed by iodine. The plate treated with ammonia will no longer show the spot corresponding to the β-lactam, but will show a much slower moving spot that is not present on the plate not treated with ammonia.

lactams using tlc was positive for one of these spots (R_f 0.45). The infrared spectrum of the mixture showed a band at 1760 cm^{-1}.

t-**Butyl α-Phthalimidopropionate-3-imino-N-γ-thiolactone (11).**—To a solution of 1.54 g (0.01 mole) of homocysteine thiolactone hydrochloride[15] (10) was added 31 ml (0.015 mole) of 0.5 *N* sodium hydroxide. To this solution (pH 8.0) was added a hot solution (70°) of 2.89 g (0.01 mole) of 1 in 38 ml of absolute ethanol. After cooling, the reaction mixture was aerated with nitrogen and the flask sealed. Storage at room temperature for 14 days produced a solid (11) which was collected by filtration; 2.44 g (63%). Recrystallization from 95% ethanol produced a very pale yellow solid; mp 178–180°. The infrared spectrum had absorption at 1780, 1750, 1720, 1700, and 1650 cm^{-1}.

Anal. Calcd for $C_{19}H_{20}N_2O_5S$: C, 58.76; H, 5.16; N, 7.22; S, 8.20. Found: C, 58.97; H, 5.26; N, 7.41; S, 8.14.

(15) Purchased from Nutritional Biochemicals Corp.

The Reaction of α-Chloro-α,α-diphenylacetanilide with Sodium Hydride. II.[1] The Identification of a Dimeric Product

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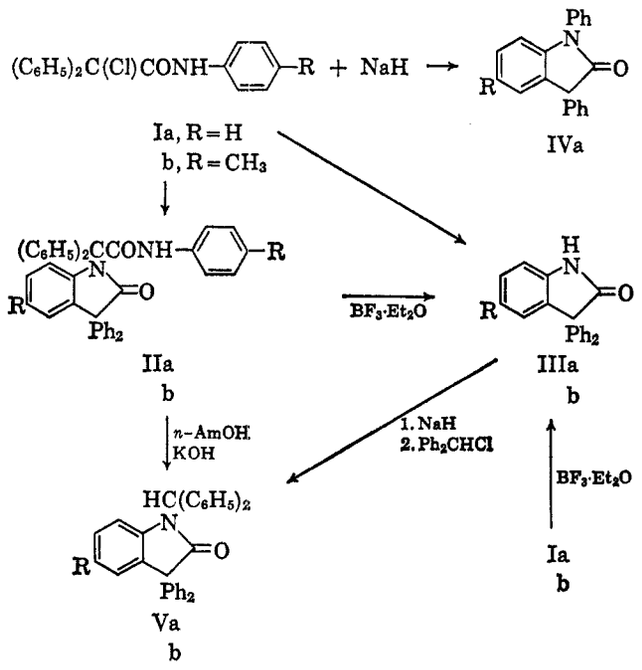
A previous investigation in this laboratory has shown that the reaction of α-chloro-α,α-diphenylacetanilide (Ia) (Scheme I) with sodium hydride gives three

SCHEME I

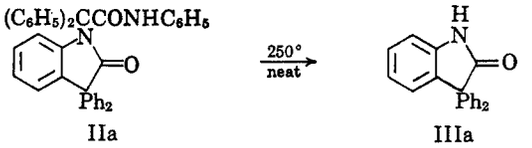


products. Two of the products were previously identified as 3,3-diphenyloxindole (IIIa) and 1,3-diphenyloxindole (IVa).[1] Subsequent investigation has shown the identity of the third and major product to be 2-[1′-(3′,3′-diphenyloxindolyl)]-2,2-diphenylacetanilide (IIa).[2] This compound is also now established as the major product obtained from the photochemical reaction of diphenyldiazomethane with phenyl isocyanate.[3]

While earlier attempts to establish the molecular weight of IIa by cryoscopic and mass spectrometric methods gave misleading values,[1,3] vapor pressure osmometry gave a molecular weight of 598 (570 calculated for $C_{40}N_{30}N_2O_2$). Saponification of IIa gave 1-(diphenylmethyl)-3,3-diphenyloxindole (Va).[2a,4] The structure of Va has now been confirmed in this laboratory by an independent and unambiguous synthesis utilizing the sodium hydride promoted alkylation of 3,3-diphenyloxindole (IIIa) with benzhydryl chloride. The previously reported quantitative conversion of IIa to IIIa by refluxing boron fluoride etherate has been confirmed.[1]

The reaction of α-chloro-α,α-diphenyl-N-*p*-tolylacetamide (Ib) with sodium hydride yields IIb and IIIb. The nmr spectrum of IIb shows the presence of two distinct methyl groups while the spectrum of IIIb shows a single methyl absorption. 5-Methyl-3,3-diphenyloxindole could be obtained in good yield by the treatment of Ib with refluxing boron fluoride etherate. The dimer was saponified giving 1-(diphenylmethyl)-5-methyl-3,3-diphenyloxindole (Vb) which was synthesized from 5-methyl-3,3-diphenyloxindole (IIIb) by treatment with sodium hydride and benzhydryl chloride.

Previous mass spectra of Ia taken on instruments utilizing a heated inlet system exhibit a molecular ion peak at *m/e* 285.[3] This is explained by the pyrolysis of IIa at 250° which gives 3,3-diphenyloxindole (IIIa) as the only isolable crystalline product. A high-



resolution mass spectrum, however, obtained utilizing a direct inlet system, shows several peaks characteristic of Ia.[5] The spectrum exhibits peaks corresponding to ions VI–XI, with *m/e* 119.0363, 120.0428, 167.0856, 284.1105, 286.1194, 450.1870, and 451.1963, respectively.

Experimental Section

Reaction of α-Chloro-α,α-diphenylacetanilide (Ia) with Sodium Hydride.[1]—The previously described procedure was followed and IIa was isolated: mp 214–215° (Kofler) (from acetone).

Anal. Calcd for $C_{40}H_{30}N_2O_2$: mol wt, 570.66. Found (vapor pressure osmometer,[7] benzene): mol wt, 598.

(1) Part I: J. C. Sheehan and J. W. Frankenfeld, *J. Am. Chem. Soc.*, **83**, 4792 (1961).

(2) (a) This structure was recently proposed by S. Sarel, J. T. Klug, E. Breuer, and F. D'Angeli [*Tetrahedron Letters*, **No. 24**, 1553 (1964)]. (b) The product of the reaction between α-chloro-α,α-diphenylacetanilide and sodium hydride was originally assigned an α-lactam structure, 1,3,3-triphenylaziridinone [S. Sarel and H. Leader, *J. Am. Chem. Soc.*, **82**, 4752 (1960)]. In ref 1 and 3, IIa was incorrectly identified as 2,2-diphenylindoxyl.

(3) J. C. Sheehan and I. Lengyel, *J. Org. Chem.*, **28**, 3252 (1963).

(4) C. H. Hassall and A. E. Lippman, *J. Chem. Soc.*, 1059 (1953).

(5) The high-resolution mass spectrum was determined on a CEC Type 21-110-A-1 mass spectrometer at 170° by the courtesy of Professor K. Biemann and Mr. P. Fennessy.

(6) Ultraviolet spectra were determined on a Cary Model 14 spectrophotometer; infrared spectra were determined on a Perkin-Elmer 237 spectrophotometer, and the nmr spectra were determined on a Varian A-60 spectrometer.

(7) Mechrolab vapor-pressure osmometer Model 310A.