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**Studies in the Propiothiolactone Series. II.\***  
**Preparation of DL- $\alpha$ -Succinimido- and L- $\alpha$ -(p-Toluenesulfonamido)- $\beta$ -propiothiolactone**

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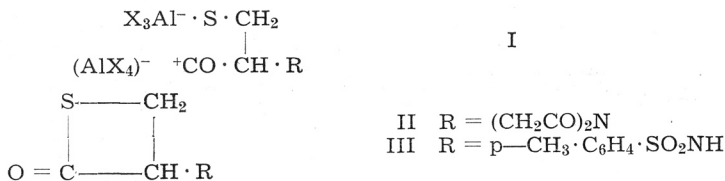
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The compounds mentioned in the title were prepared *via* debenzylation and subsequent cyclization of  $\alpha$ -succinimido- and  $\alpha$ -(p-toluenesulfonamido)- $\beta$ -benzylthiopropionyl chlorides with aluminum bromide in benzene at room temperature.

The reaction of *S*-benzyl-*N*-phthaloyl-*L*-cysteinyl chloride with two moles of aluminum halides in benzene has been shown by work in laboratories to yield *L*- $\alpha$ -phthalimido- $\beta$ -propiothiolactone.<sup>1</sup> The formation of propiothiolactone presumably proceeds through the intermediate formation of the betaine structure I, in which the zwitterion character of the betaine leads to the internal approach of the reactive centres and thus to the formation of propiothiolactone. This reaction seems to be a general method for the preparation of propiothiolactone derivatives.

In continuation of this work we have prepared: DL- $\alpha$ -succinimido- $\beta$ -propiothiolactone (II) and L- $\alpha$ -(p-toluenesulfonamido)- $\beta$ -propiothiolactone (III). These compounds were prepared by debenzylation and subsequent cyclization of the corresponding  $\beta$ -benzylthiopropionyl chloride with aluminum bromide in benzene at room temperature. The reaction was accomplished after 30 minutes and propiothiolactones were isolated as crystalline products after the removal of diphenylmethane with petroleum ether.



The hitherto undescribed *S*-benzyl-*N*-succinoyl-DL-cysteine was synthesized from *S*-benzyl-*L*-cysteine and succinic acid anhydride following essentially the method described by Scheiber and Reckleben for the preparation of *N*-succinoyl-glycine.<sup>2</sup> *N*-Succinoyl derivative was isolated in a yield of 21% and was racemic. No attempt was made so far to prepare the optically active *S*-benzyl-*N*-succinoylcysteine.

\* Paper I, D. Fleš, A. Markovac-Prpić and V. Tomašić, *J. Am. Chem. Soc.* 80 (1958) 4654.

The compounds II and III are rather stable and can be crystallized from the common organic solvents. The *N*-tosyl derivative III was however very sensitive toward the action of dilute alkalis and formed a white, insoluble precipitate when a benzene solution was treated with 5% bicarbonate solution. On the basis of elemental analysis it was supposed the most probable structure to be the one corresponding to a linear polythioester, similar to the one obtained in the series of *N*-phthaloyl derivative.<sup>1</sup> The phthalimido-polythioester was obtained by debenylation of *S*-benzyl-*N*-phthaloyl-*L*-cysteinyl chloride with one mole of aluminum chloride. It is worthwhile to note that thermal polymerization of  $\beta$ -propiolactone gave a similar polyester.<sup>3</sup>

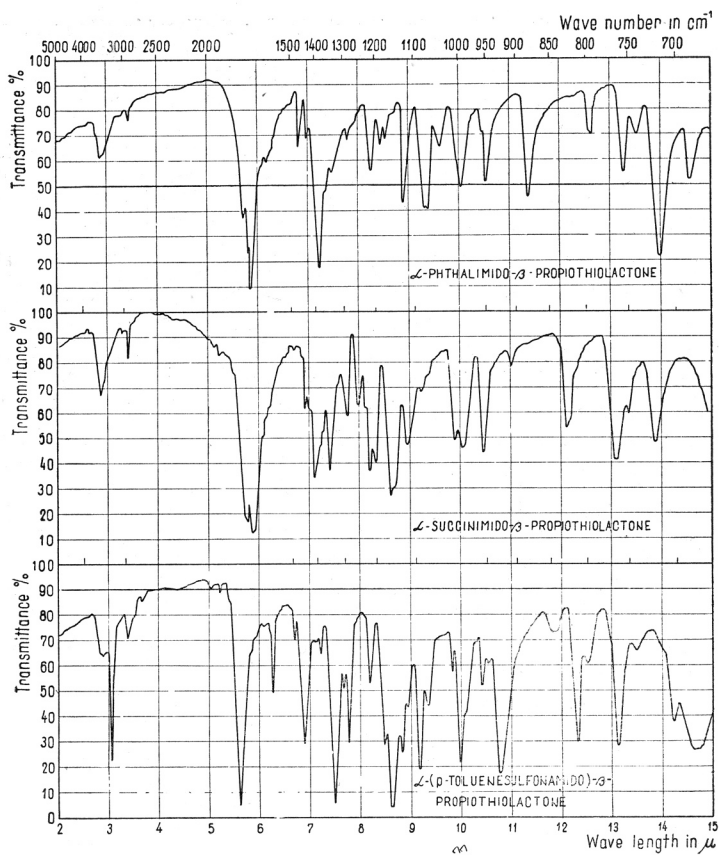


Fig. 1. The infrared absorption spectra

The infrared spectra of  $\alpha$ -phthalimido-<sup>1</sup>,  $\alpha$ -succinimido- and  $\alpha$ -(*p*-toluenesulfonamido)- $\beta$ -propiolactones were recorded on a Perkin-Elmer Mod. 21 spectrophotometer, using KBr pelleting technique (Fig. 1). The limited number of the compounds examined does not allow for a more detailed search for bands due to the thiolactone ring vibrations, but it appears interesting to note the frequency of the C-O stretching band. With propiolactone III, it is possible to locate easily this band at  $1780\text{ cm}^{-1}$ , whereas with the other two

compounds this region of the spectrum is obscured by the imide carbonyl bands. Nevertheless, by comparing the spectra of the two propiothiolactones with the spectra of phthalimide and with succinimide respectively, it is possible to locate the thiolactone carbonyl bands at  $1770\text{ cm}^{-1}$  (phthalimido-propiothiolactone) and at  $1762\text{ cm}^{-1}$  (succinimidopropiothiolactone). Hence, the carbonyl band in the propiothiolactone system seems to appear between  $1760$  and  $1780\text{ cm}^{-1}$ . This range has been found to be characteristic of the five membered lactones<sup>4</sup> whereas the carbonyl of the  $\beta$ -lactones should absorb at higher frequencies. The replacement of the oxygen atom by sulfur seems to result in a lowering of the carbonyl frequency, perhaps through a reduction of the ring strain.

There is another band in the spectra of the propiothiolactones which does not appear with related amides and imides. It is near  $1000\text{ cm}^{-1}$  and may be brought in connection with the  $\overset{\text{C}}{\text{(lactone)}}\text{-N}$  stretching vibration, in agreement with the assignments in the spectra of some amines and amides.<sup>5</sup>

## EXPERIMENTAL\*

*S-Benzyl-N-succinoyl-DL-cysteine*

A well powdered mixture of 4 g. (0.019 mole) of *S*-benzyl-L-cysteine and 2 g. (0.02 mole) of succinic anhydride was placed in a round-bottomed flask equipped with a thermometer, and the reaction mixture was immersed into an oil bath heated to  $190^\circ$ . When inside temperature reached  $180^\circ$  the heating was disconnected and the temperature of the reaction mixture kept for 20 minutes at  $160\text{--}70^\circ$ . The dark-brown mass was treated with 5 ml. of ethyl acetate, 100 ml. of benzene followed by 30 ml. of petroleum ether (b. p.  $40\text{--}60^\circ$ ) was added, and the reaction mixture kept overnight in a refrigerator. The solvent was decanted, evaporated *in vacuo*, and the residue crystallized from 5 ml. of benzene to give 1.4 g. of white crystalline product melting at  $120^\circ$ . The crude product was recrystallized from 4 ml. of benzene and a yield of 1.2 g. (21%) was obtained; m. p.  $127\text{--}130^\circ$ . An analytical sample was recrystallized from benzene to a melting point of  $129\text{--}130^\circ$   $[\alpha]_{\text{D}}^{20} 0^\circ$  (c. 1.665% in EtOH).

*Anal.* 13.63 mg. subst.: 28.60 mg.  $\text{CO}_2$ , 5.98 mg.  $\text{H}_2\text{O}$   
 2.38 mg. subst.: 0.98 ml.  $\text{N}_2$  ( $25^\circ$ , 759 mm.)  
 $\text{C}_{14}\text{H}_{15}\text{NO}_4\text{S}$  (293.27) calc'd: C 57.33; H 5.16; N 4.78%  
 found: C 57.25; H 4.91; N 4.71%

*S-Benzyl-N-succinoyl-cysteinyl chloride*

*S*-Benzyl-*N*-succinoyl-cysteine (2 g., 0.007 mole) was refluxed one hour with 20 ml. of thionyl chloride. The excess of thionyl chloride was removed *in vacuo*, the residue repeatedly treated with benzene and finally dissolved in 10 ml. of benzene. The impurities were precipitated with 20 ml. of petroleum ether and the clear solution decanted and evaporated *in vacuo* gave 2.0 g. (94.5%) of a crystalline product. A sample for analysis was purified by crystallization from benzene-petroleum ether (4:3) in needles, m. p.  $73\text{--}75^\circ$ .

*Anal.* 9.84 mg. subst.: 19.56 mg.  $\text{CO}_2$ , 3.90 mg.  $\text{H}_2\text{O}$   
 $\text{C}_{14}\text{H}_{14}\text{ClNO}_3\text{S}$  (311.78) calc'd: C 53.93; H 4.53%  
 found: C 54.24; H 4.43%

*DL- $\alpha$ -Succinimido- $\beta$ -propiothiolactone (II)*

$\alpha$ -Succinimido- $\beta$ -benzylthiopropionyl chloride (2 g., 0.0064 mole) dissolved in 250 ml. of benzene was added at once into a solution of 5.6 g. (0.021 mole) of  $\text{AlBr}_3$  in 50 ml. of benzene. The reaction mixture was kept for one hour at room temperature and was hydrolyzed with 30 g. of ice and 6 ml. of concentrated hydrochloric

\* Melting points are uncorrected.

acid. The aqueous layer was separated and extracted with two 20-ml. portions of benzene, the combined benzene layers were washed with two 20 ml. portions of water and dried over magnesium sulfate. The benzene was removed under reduced pressure and the residue (2.2 g.) triturated with two 10-ml. portions of petroleum ether (b. p. 40—60°). Evaporation of petroleum ether gave 0.47 g. (44%) of diphenylmethane. The residue obtained after trituration with petroleum ether (1.7 g.) was dissolved in 2 ml. of ethyl acetate and 1 ml. of petroleum ether, and after standing overnight in a refrigerator 0.71 g. (60%) of crystalline propiothiolactone II was collected, m. p. 93—95°. A sample for analysis was recrystallized from methanol and finally from ethanol to a melting point of 95—97°.

*Anal.* 8.64 mg. subst.: 14.48 mg. CO<sub>2</sub>, 2.85 mg. H<sub>2</sub>O  
 C<sub>7</sub>H<sub>7</sub>NO<sub>3</sub>S (185.13) calc'd.: C 45.41; H 3.81%  
 found: C 45.73; H 3.68%

#### L- $\alpha$ -(p-Toluenesulfonamido)- $\beta$ -propiothiolactone (III)

S-Benzyl-N-(p-toluenesulfonyl)-L-cysteinyl chloride<sup>6</sup> (4.9 g., 0.013 mole) in 80 ml. benzene was treated with 15 g. (0.056 mole) of AlBr<sub>3</sub> in 80 ml. of benzene, and the reaction mixture worked up as before. The residue after trituration with petroleum ether was dissolved in 13 ml. benzene and 5 ml. petroleum ether, yielding 2.2 g. (67%) of propiothiolactone III, m. p. 99—101°. A sample was recrystallized for analysis from a mixture of benzene-petroleum ether; needles melting at 101—102°,  $[\alpha]_D^{20}$  —5.2° (c 6.285% in dioxane).

*Anal.* 14.50 mg. subst.: 24.87 mg. CO<sub>2</sub>, 5.20 mg. H<sub>2</sub>O  
 C<sub>10</sub>H<sub>11</sub>NO<sub>3</sub>S<sub>2</sub> (257.20) calc'd.: C 46.70; H 4.31%  
 found: C 46.80; H 4.01%

#### Conversion of the propiothiolactone III to L-cystine

The propiothiolactone III (0.2 g., 0.00078 mole) was refluxed for 4 hours with 2 ml. of glacial acetic acid and 2 ml. of hydriodic acid, and the reaction mixture was kept overnight at room temperature. The mixture of acids was evaporated *in vacuo*, the last traces of acids removed by successive treatment with water, the residue dissolved in 10 ml. of water, extracted with ether, water evaporated to dryness, the residue dissolved in 2 ml. of water and adjusted to pH 4.5 with a saturated sodium acetate solution. The solution was exposed to air and after several days 46 mg. (49.5%) of L-cystine separated; m. p. 252° (decompn.),  $[\alpha]_D^{20}$  —201° (c 2.325% in N—HCl). Reported m. p. 258—261° (decompn.)<sup>7</sup>  $[\alpha]_D^{24.91}$  —212.9° (c 0.9947% in 1.02N—HCl).<sup>8</sup> Paper chromatography of the compound gave the same spot with ninhydrine as the authentic specimen of L-cystine.

#### Reaction of the propiothiolactone III with sodium bicarbonate

The propiothiolactone III (0.2 g., 0.00078 mole) was dissolved in 15 ml. of benzene and treated in a separatory funnel with 10 ml. of an aqueous 5% sodium bicarbonate solution. A white precipitate which was formed instantaneously was filtered off, washed with water, extracted with 15 ml. of boiling benzene, the insoluble part was filtered off and dried on air, yielding 0.15 g. of white powder melting at 175—180° (decompn. under sintering at 165°). The product was insoluble in common organic solvents, but was very soluble in dimethylformamide. The »polymer« was insoluble in melted camphor and *m*-dinitrobenzene.

*Anal.* 9.93 mg. subst.: 17.10 mg. CO<sub>2</sub>, 3.75 mg. H<sub>2</sub>O  
 (C<sub>10</sub>H<sub>11</sub>NO<sub>3</sub>S<sub>2</sub>)<sub>x</sub> calc'd.: C 46.70; H 4.31%  
 found: C 46.99; H 4.22%

A sample of the »polymer« (50 mg.) was refluxed for 24 hours with 2 ml. of glacial acetic acid and 2 ml. of hydriodic acid, and the reaction mixture worked up as it was described for the hydrolysis of the propiothiolactone III. Cystine which was obtained gave on paper chromatography the same spot with ninhydrine as the authentic sample of L-cystine. M. p. 253° (decompn.).

**Bis(N-p-toluenesulfonyl)-L-cystinyl-diglycine dimethyl ester**

A solution of 0.5 g. (0.002 mole) of the propiothiolactone III and 0.49 g. (0.0056 mole) of glycine methyl ester in 4 ml. dioxane was kept overnight at room temperature. The solvent was evaporated under reduced pressure, the residue dissolved in 50 ml. ethyl acetate, washed with two 10-ml. of water, dried over magnesium sulfate, and the solvent was evaporated *in vacuo*. The crystalline residue (0.4 g.) was recrystallized three times from ethyl acetate to a melting point of 177—178.5° (Kofler microscopic method),  $[\alpha]_D^{20}$  47.5° (c 1.820% in dioxane).

*Anal.* 10.19 mg. subst.: 16.92 mg. CO<sub>2</sub>, 4.32 mg. T<sub>2</sub>O  
 C<sub>26</sub>H<sub>34</sub>N<sub>4</sub>O<sub>10</sub>S<sub>4</sub> (690.82) calc'd.: C 45.20; H 4.96%  
 found: C 45.31; H 4.74%

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## IZVOD

**Studije u redu propiotiolaktona II. Sinteza DL- $\alpha$ -sukcinimido-  
i L- $\alpha$ -(p-toluensulfonamido)- $\beta$ -propiotiolaktona**

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U ranijem je radu<sup>1</sup> pokazano, da debenziliranje S-benzil-N-ftaloil-L-cisteinil klorida s jednim molom aluminijskoga triklorida daje optički aktivni ftalimido-politioester, a sa dva mola aluminijskog triklorida da nastaje L- $\alpha$ -ftalimido- $\beta$ -propiotiolakton. Predložen je reakcioni mehanizam, koji pretpostavlja nastajanje intermedijarne betainske strukture I. Primjenom iste metode priređeni su u okviru ovoga rada, DL- $\alpha$ -sukcinimido- $\beta$ -propiotiolakton (II) i L- $\alpha$ -(p-toluensulfonamido)- $\beta$ -propiotiolakton (III). Sinteza ovih spojeva provedena je u benzenu, kod sobne temperature, uz upotrebu aluminijskoga tribromida. Propiotiolakton III lagano se polimerizira u kontaktu s natrijskim bikarbonatom. Aciliranjem metilnog estera glicina, pomoću propiotiolaktona III, priređen je dimetilni ester bis(N-p-toluensulfonyl)-L-cistinil-diglicina.

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