Reaction of Epoxides. III. The Synthesis of 2-Amino-5-substituted 4,5-Dihydrothiophene from Substituted Propylene Sulfides and Ethyl Cyanoacetate

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Snyder\(^3\) has reported that alkene sulfides reacted with ethyl cyanoacetate in the presence of sodium ethoxide to give ethyl 2-iminothiophene-3-carboxylate. However, there are only a few instances regarding simple alkene sulfides, such as ethylene, propylene and isobutylene sulfide. Guss\(^4\) has also shown that the reaction of styrene sulfides with sodium derivative of ethyl cyanoacetate gave a product believed to be ethyl 2-imino-4(or 5)-phenylthiophene-3-carboxylate, though the structure of this product was not determined.

In order to extend this cyclization for the general synthesis of thiophene derivatives, the reaction of some substituted propylene sulfides with ethyl cyanoacetate was attempted in the present study. The materials employed are 3-piperidino-, \(^5\) 3-morpholino-, \(^6\) and 3-phenoxypropylene sulfides \(^1\). Although entirely satisfactory procedure was found for this condensation, the best results were obtained by heating these propylene sulfides (I) with ethyl cyanoacetate in the presence of an equivalent amount of sodium ethoxide under reflux for 2 hr to give the expected products (II or III). Almost same results were also obtained when treating at room temperature for 6 hr.

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\begin{align*}
\text{R-CH}_2\text{CH-CH}_2\text{CNCH}_2\text{COOC}_2\text{H}_5 & \xrightarrow{\text{NaOC}_2\text{H}_5} \text{R-CH}_2\text{CH-CN=NH or} \\
\text{R-CH}_2\text{CH-CN=NH} & \xrightarrow{\text{Raney Ni}} \text{CH}_2\text{C-NH} \\
\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH} & \quad \text{R=O, N-} \\
\end{align*}
\]

Chart 1

In this condensation, two isomeric products are possible to form due to the difference of the orientation in the ring opening of the cyclic sulfide.\(^7,8\) Regarding the orientation, Snyder\(^3\) has evidently proved that, in the reaction of propylene and isobutylene sulfides with ethyl cyanoacetate, the structure of the products obtained is type II by alkaline hydrolysis,

2) Location: Ot-hon-machi, Kumamoto.
oxidation and desulfurization followed by the comparison with the known compounds. On the other hand, no evidence for the structure of the reaction product between styrene sulfide and ethyl cyanoacetate has been provided. For the establishment of the structure of the present product, infrared (IR), nuclear magnetic resonance (NMR), and mass spectra were measured. Mass spectra showed the molecular ion peak agreed with the assigned structure. NMR spectra exhibited the multiplet assignable to the methylene hydrogen in the thiophane ring in the region of 6.80–7.40 \( \tau \), no support for the establishment of the structure II or III being obtained. An unquestionable proof for the structure II resulted from the desulfurization of phenoxy derivative with Raney nickel alloy. The desulfurization was carried out in aqueous alkali under conditions such that hydrolysis first occurred. The product obtained was \( \gamma \)-phenoxypropylmalonic acid, which was identified with the authentic sample prepared by heating \( \gamma \)-bromopropyl phenyl ether with diethyl malonate followed by hydrolysis. The IR spectra exhibited the absorption of the ester carbonyl group at near 1640 cm\(^{-1}\), which shift in much lower frequency in comparison with the normal ester carbonyl absorption. This suggests that the tautomeric isomer (IV) of the imino ester (II) forms a hydrogen bond between the amino group and ester carbonyl group.

\[
\begin{align*}
R-\text{CH}_2\text{CH}_2\text{C}=\text{NH} & \quad \text{II} \\
\text{H}_2\text{C} & \quad \text{C}=\text{COOC}_2\text{H}_5 \\
R-\text{CH}_2\text{CH}_2\text{C}=\text{NH}_2 & \quad \text{IV} \\
\text{H}_2\text{C} & \quad \text{C}=\text{COOC}_2\text{H}_5 \\
\hline
\end{align*}
\]

Chart 2

Support for the chelation was also obtained from the NMR spectra which showed a signal corresponding to two hydrogens at near 4.00 \( \tau \) assignable to the amino group. By these results, it is presumed that the structure would be stabilized by means of the formation of intramolecular hydrogen bond.

**Experimental**

**Piperidinopropylene Sulfide**—To a solution of 76 g of thiourea in 350 ml of \( \text{H}_2\text{O} \) was added slowly 49 g of \( \text{H}_2\text{SO}_4 \). To the solution was added dropwise with vigorous stirring 141 g of piperidinopropylene oxide at 5–10° over a period of 2 hr. After stirring for an additional 15 min and cooling, a solution of 106 g of \( \text{Na}_2\text{CO}_3 \) in 450 ml of \( \text{H}_2\text{O} \) was added to the solution and the mixture was stirred for several hours at room temperature. The oily product isolated from the reaction mixture was separated and the water layer was repeatedly extracted with ether. The combined oily product and ethereal layer were dried over \( \text{Na}_2\text{SO}_4 \) and evaporated. The residue was distilled under reduced pressure to give 102.4 g (85.2%) of colorless liquid boiling at 72–74°/0.17 mm Hg. *Anal. Calcd. for C\(_6\)H\(_{10}\)NS: C, 61.08; H, 9.61; N, 8.91. Found: C, 61.00; H, 9.42; N, 8.99.*

**Morpholinopropylene Sulfide**—One mole (143 g) of morpholinopropylene oxide was allowed to react with 76 g of thiourea by the procedure described above. The product was distilled to give 102.9 g (94.7%) colorless liquid boiling at 71–73°/0.13 mm Hg. *Anal. Calcd. for C\(_6\)H\(_{10}\)ONS: C, 52.81; H, 8.23; N, 8.80. Found: C, 52.37; H, 8.18; N, 8.86.*

**Phenoxypropylene Sulfide**—To a solution of 97 g of KSCN in 100 ml of \( \text{H}_2\text{O} \) was added with stirring at 20–30° 150 g of phenoxypropylene oxide over a period of 1.75 hr. The mixture was continued to stir for an additional 2 hr and then stood overnight. The oily layer was separated from water layer and added to a solution of 50 g of KSCN in 100 ml of \( \text{H}_2\text{O} \). The mixture was stirred at 20–30° for 5 hr and combined to the water layer. The combined mixture was extracted with ether and the extracts were dried

over CaCl₂, evaporated and the residue was distilled under reduced pressure to give 68.0 g (41.6%) of colorless liquid boiling at 89—89°/0.14 mm. Anal. Calcd. for C₆H₈O₈S: C, 65.02; H, 6.06. Found: C, 64.91; H, 6.09

**Ethyl 2-Amino-5-piperidinomethyl-4,5-dihydrothiophene-3-carboxylate**—To a solution prepared by dissolving 2.3 g of Na in 300 ml of abs. EtOH was added 15 g of ethyl cyanoacetate. The mixture was refluxed during 15.7 g of piperidinopropylene sulfide was added dropwise over a period of 1 hr. Refluxing was continued for an additional 1 hr. After removal of the solution, by distillation under reduced pressure, the residue was poured into cold H₂O and extracted with ether. The extracts were dried over Na₂SO₄ and evaporated to dryness. Recrystallization of the residue from EtOH gave 6.1 g (22.6%) of colorless prisms melting at 86—88°. Anal. Calcd. for C₁₃H₁₉O₂N₃S: C, 57.76; H, 8.20; N, 10.36. Found: C, 57.87; H, 8.34; N, 10.38. IR ν max cm⁻¹: 3375, 3275 (NH₂); 1638 (CO).

**Ethyl 2-Amino-5-morpholinomethyl-4,5-dihydrothiophene-3-carboxylate**—One-tenth mole (15.9 g) of morpholinopropylene sulfide was allowed to react with 15 g of ethyl cyanoacetate in the presence of 2.3 g of Na by the procedure described above. The product was recrystallized from EtOH to give 7.3 g (26.8%) of colorless prisms melting at 115—117°. Anal. Calcd. for C₁₃H₂₁O₂N₃S: C, 52.93; H, 7.40; N, 10.29. Found: C, 52.78; H, 7.46; N, 10.06. IR ν max cm⁻¹: 3370, 3275 (NH₂); 1643 (CO). NMR (CDCl₃) δ: 8.85 (3H, triplet, CH₃), 7.65—7.35 (7H, multiplet, CH=CH-C―CH₂-CH), 7.40—6.80 (2H, multiplet, ring CH₂), 6.35 (4H, triplet, O-CH₂), 5.90 (2H, quartet, CH₂-Me), 3.85 (2H, NH₂). Mass Spectrum m/z: 272 (M⁺).

**Ethyl 2-Amino-5-phenoxyethyl-4,5-dihydrothiophene-3-carboxylate**—The reaction was carried out using 2.3 g of Na, 16.6 g of phenoxypropylene sulfide and 15 g of ethyl cyanoacetate by the procedure described above. The product was recrystallized from EtOH to give 11.1 g (39.8%) of colorless prisms melting at 105—106°. Anal. Calcd. for C₁₃H₁₄O₂N₂S: C, 60.20; H, 6.14; N, 5.02. Found: C, 59.91; H, 6.26; N, 4.98. IR ν max cm⁻¹: 3370, 3280 (NH₂); 1647 (CO). NMR (CDCl₃) δ: 8.78 (3H, triplet, CH₃), 7.14—6.90 (2H, multiplet, ring CH₂), 6.50—5.55 (3H, multiplet, O-CH₂-CH), 6.03 (2H, quartet, CH₂-Me), 3.98 (2H, NH₂), 3.40—2.75 (6H, multiplet, phenyl hydrogen). Mass Spectrum m/z: 279 (M⁺).

**γ-PhenoxypropyImalonic Acid from Ethyl 2-Amino-5-phenoxyethyl-4,5-dihydrothiophene-3-carboxylate**—Desulfurization of ethyl 2-amino-5-phenoxyethyl-4,5-dihydrothiophene-3-carboxylate with Raney nickel aluminum alloy by the procedure described by Schwenk gave γ-phenoxypropyImalonic acid, which was identified with an authentic sample by the mixed melting point determination and IR comparison.

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**Organic Photochemical Reactions. VIII.** Photocyclization of N-Acryloyl Heteroaromatic Amines

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As an extension of the photochemical cyclization of methacrylanilides, we attempted the photocyclization of N-acryloyl heteroaromatic amines. Irradiation of various N-substituted acrylamides in benzene solution through pyrex glass with a high pressure mercury arc lamp in an argon atmosphere at room temperature afforded photoproducts (I—X). De-