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The Preparation of *cis*-3, 4-Ureylenethiophane*[1]

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The preparation of *cis*-3, 4-ureylenethiophane (23) was attempted through three different routes. *cis*-3-Carbomethoxyamino-4-carbomethoxythiophane (20A), which had been obtained by the Lossen rearrangement of *N*-phenylsulfonyloxythiophane-*cis*-3, 4-dicarboximide (19), was selectively hydrolyzed to *cis*-3-carbomethoxyamino-4-carboxythiophane (21A), the modified Curtius rearrangement of which gave *N*-carbomethoxy-*cis*-3, 4-ureylenethiophane (22A). The alkaline hydrolysis of 22A afforded 23. However, an attempt to prepare 23 through two sulfone derivatives, (6) and (14), was unsuccessful.

In connection with our study of the synthesis of biotin, *cis*-1, 2-ureylenecyclopentane and its 3-methyl derivative have been previously synthesized.[1] This paper will deal with the improved synthesis of *cis*-3, 4-ureylenethiophane (23), the compound lacking only the side chain of biotin. The synthesis was attempted through different routes.

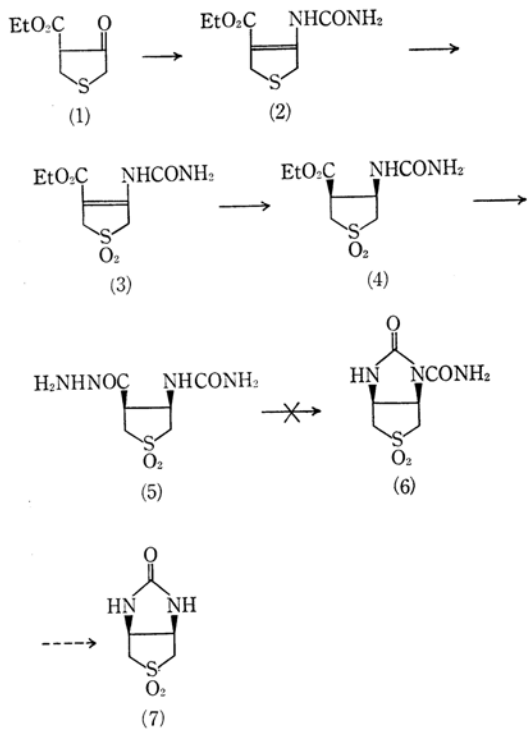

Chart 1

Since the catalytic hydrogenation of 3-ureido-4-carbethoxy-2, 5-dihydrothiophene (2) to 3-ureido-4-carbethoxythiophane (8) using 5% palladium charcoal or rhenium heptaselenide[2] as a catalyst has been found to be unsuccessful by repeated experiments carried out in our laboratory, the route to 23 *via cis*-3, 4-ureylenethiophane-1, 1-dioxide (7) was devised as a first route; it is shown in Chart 1. 3-Ureido-4-carbethoxy-2, 5-dihydrothiophene (2) was obtained by the condensation of 3-carbethoxy-4-ketotetrahydrothiophene (1)[3] with urea. The oxidation of the dihydrothiophene 2 to 3-ureido-4-carbethoxy-2, 5-dihydrothiophene-1, 1-dioxide (3) was carried out using 30% hydrogen peroxide in acetic acid. The hydrogenation of the 2, 5-dihydroester 3 over Raney nickel in absolute ethanol afforded a mixture of two isomers, *cis* and *trans* of 3-ureido-4-carbethoxythiophane-1, 1-dioxide (4); one isomer (4a) melted at 173—174°C, and the other one (4b), at 193—194°C. The molar ratio of these isomers in the product varied more or less with the reduction temperature and with the delicate nature of the catalyst, which was in turn affected by the conditions of alloy decomposition.

The 4a and 4b isomers were converted by heating them with 100% hydrazine hydrate at 100°C for 30 min into the corresponding hydrazides, 5a, (mp 173—174°C) and 5b (mp 203—205°C) respectively (see Chart 2). When the hydrazide, 5a, was heated with a small amount of hydrazine at 60°C for 90 min, 5a was transformed into another hydrazide, 5b. Since the *trans* isomer is generally much more stable than the corresponding *cis* isomer, and since the *cis* isomer is converted by heating it with a base into the *trans* isomer, the above results demonstrate that the lower melting hydrazide, 5a, has the *cis*-configuration and that the higher melting one, 5b, has the *trans*-configuration.

*1 Studies on the Syntheses of Heterocyclic Compounds. Part I. This paper was presented at the 20th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1967.

1) T. Takaya, H. Yoshimoto and E. Imoto, This Bulletin, in press.

2) H. S. Broadbent and C. W. Whittle, *J. Am. Chem. Soc.*, **81**, 3587 (1959).

3) G. B. Brown, B. R. Baker, S. Bernstein and S. R. Safir, *J. Org. Chem.*, **12**, 155 (1947).

Therefore, the configuration of the lower and higher melting esters, 4a and 4b, should be the *cis*- and *trans*-esters respectively. These conclusions are in accordance with Auers-Skita's rule that the *trans* isomer has, in general, a higher melting point than the corresponding *cis* isomer.

The treatment of the *cis*- and *trans*-esters, 4a and 4b, with 4 N hydrochloric acid gave the dihydrouracil derivative (9), which was then converted into the *trans*-hydrazide, 5b, by refluxing 9 with hydrazine hydrate; 9 was also sometimes obtained as a by-product upon the catalytic hydrogenation of 3 at higher temperatures, along with the *cis*- and *trans*-esters, 4a and 4b.

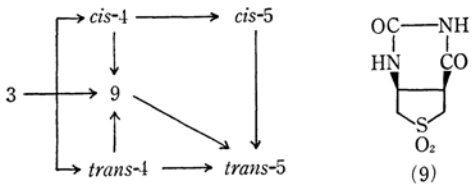

Chart 2

The Curtius rearrangement of the *cis*-hydrazide, 5a, was unsuccessful, giving only a resinous product, although the same rearrangement of the *cis*-2-ureidocyclopentanecarboxylic acid hydrazide proceeded smoothly to form *N*-carbamoyl-1, 2-ureylenecyclopentane.[1]

The failure of the Curtius rearrangement of the *cis*-hydrazide 5a as well as the difficulties of handling the sulfones 3, 4a and 5a due to their low solubilities in organic solvents, prompted us to attempt the second route, shown in Chart 3.

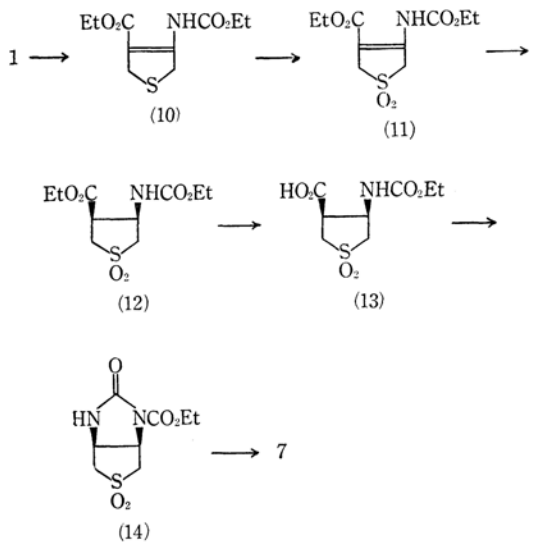

Chart 3

The condensation of the ketoester 1 with urethane was carried out by refluxing it in benzene in the presence of acid to give 3-carbethoxyamino-4-carbethoxy-2, 5-dihydrothiophene (10),[4] which was then oxidized to 3-carbethoxyamino-4-carbethoxy-2, 5-dihydrothiophene-1, 1-dioxide (11) by perbenzoic acid.[5] The hydrogenation of 2, 5-dihydrourethane 11 over Raney nickel gave two isomeric urethanes, *cis*- and *trans*-urethanes 12a (mp 98—99°C) and 12b (mp 140—141°C). The configuration of the urethanes 12a and 12b will be described later. The yield of the *cis*-urethane 12a increased with the decrease in the reduction temperature. The hydrolysis of the crude urethane 12 with dilute hydrochloric acid gave a mixture of the corresponding *cis*- and *trans*-acids, 13a and 13b. The *cis*-acid 13a was more soluble, and the *trans*-acid 13b, less soluble, in water. The modified Curtius rearrangement of *cis*-acid 13a, (mp 160—162°C) devised by Weinstock[6] afforded *N*-carbethoxy-*cis*-3,4-ureylenethiophane-1,1-dioxide (14) (mp 238—240°C (decomp.)). The alkaline hydrolysis of 14 to 7 was unsuccessful because of the decomposition of 14.

The configuration of the isomers of the urethanes, 12a and 12b, were determined in the following way. The oxidation of the *cis*-urethane (20B, R=Et) with perbenzoic acid gave the corresponding sulfone derivative (mp 96—97.5°C), which was proved, by a mixed-melting-point determination and by a comparison of their infrared spectra, to be identical with the low-melting urethane, 12a. These results clearly demonstrate that the low melting urethane, 12a, has a *cis*-configuration, and that the high melting urethane, 12b, has a *trans*-configuration. The product, 14, obtained by the modified Curtius rearrangement of *cis*-13a was identical in its mixed melting point and infrared spectra with that of the compound obtained by the oxidation of *N*-carbethoxy-*cis*-3, 4-ureylenethiophane (22B, R=Et) with perbenzoic acid. Since 14 could not be converted to 7 as has been described above, all attempts to prepare *cis*-3, 4-ureylenethiophane 23 *via* 7 were abandoned. At this point the third route, shown in Chart 4 was devised. The catalytic hydrogenation and diimide reduction of 3, 4-dicarboxy-2, 5-dihydrothiophene (15) to *cis*-3, 4-dicarboxythiophane (16a) were unsuccessful. The reduction of the diacid 15 with a sodium amalgam gave *trans*-dicarboxylic acid (16b), which was converted to *cis*-anhydride (17) by refluxing it with acetic anhydride. The treatment of the anhydride 17 with hydroxylamine gave the *N*-hydroximide (18), which was then treated with

4) Catalytic hydrogenation of 10 to 3-carbethoxyamino-4-carbethoxythiophane using 5% palladium charcoal or rhenium heptaselenide as a catalyst was also unsuccessful in our experiments.

5) Oxidation of 10 with 30% hydrogen peroxide in acetic acid led to 3-carbethoxyamino-4-carbethoxythiophene. Details of this oxidation will be reported in the near furure.

6) J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).

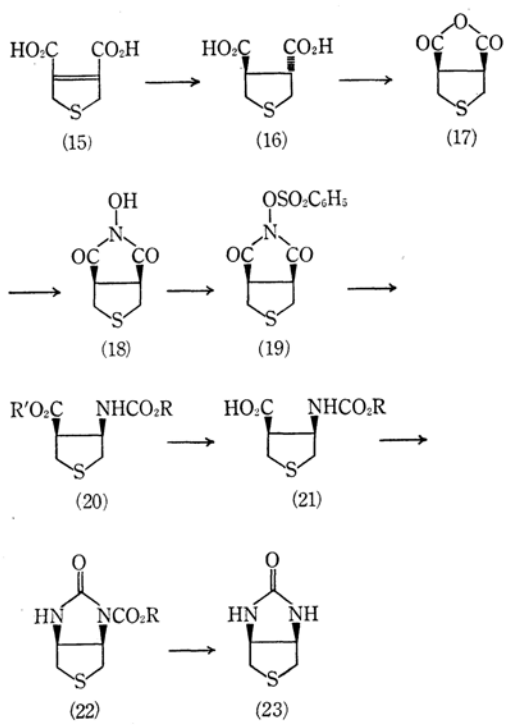

Chart 4

benzenesulfonyl chloride to give the *O*-benzenesulfonyl compound (19). 3-Carbomethoxyamino-4-carbomethoxythiophane (20A, R=Me) was obtained by the Lossen rearrangement of 19 with triethylamine. The selective hydrolysis of 20A afforded 3-carbomethoxyamino-4-carboxythiophane (21A, R=Me). The modified Curtius rearrangement of 21A gave the *N*-carbomethoxy-*cis*-3, 4-ureylenethiophane (22A, R=Me), which was then hydrolyzed by 10% barium hydroxide to give *cis*-3, 4-ureylenethiophane (23).

Experimental[7]

3-Ureido-4-carbethoxy-2, 5-dihydrothiophene (2). By treating 3.48 g of 3-carbethoxy-4-ketotetrahydrothiophene (1) with 1.20 g of urea in the manner described in the following paper,[1] 3.54 g (82%) of 2 were obtained, mp 201—203°C.

Found: C, 44.17; H, 5.27; N, 12.91%. Calcd for $C_8H_{12}O_3NS$: C, 44.44; H, 5.60; N, 12.96%.

3-Ureido-4-carbethoxy-2, 5-dihydrothiophene-1, 1-dioxide (3). A peracetic acid solution was prepared from 5.7 m*l* of 30% hydrogen peroxide, 40 m*l* of acetic acid, and 20 m*l* of acetic anhydride by letting it stand at room temperature overnight. Six grams of 2 were dissolved in the peracetic acid solution, and the mixture was maintained at 45°C for 24 hr. The solid thus precipitated was collected by filtration. When the filtrate was concentrated to a small volume (about 10 m*l*), a small amount of the solid was obtained. The combined solids (4.5 g) were recrystallized from 99% ethanol to give 3.65 g (53%) of the product, 3, mp 186—187°C.

Found: C, 38.58; H, 4.77; N, 11.21%. Calcd for $C_8H_{12}O_5N_2S$: C, 38.71; H, 4.87; N, 11.29%.

3-Ureido-4-carbethoxythiophane-1, 1-dioxide (4). The sulfone 3 (300 mg) was hydrogenated over Raney nickel in 100 m*l* of absolute ethanol under a hydrogen pressure of 100 atm at 40—45°C for 3 hr. After the removal of the catalyst, the solution was concentrated to dryness, and the residue was recrystallized from 99% ethanol to give 150 mg (50%) of the *cis*-ester (4a), mp 173—174°C.

Found: C, 38.58; H, 5.78; N, 11.01%. Calcd for $C_8H_{14}O_5N_2S$: C, 38.40; H, 5.64; N, 11.20%.

The concentration of the mother liquor gave a small amount of the *trans*-ester (4b), mp 193—194°C.

Found: C, 38.10; H, 5.78; N, 11.18%. Calcd for $C_8H_{14}O_5N_2S$: C, 38.40; H, 5.64; N, 11.20%.

The molar ratio of the *cis*- and *trans*-esters varied from 1 : 0 to 0 : 1 with the nature of the catalyst, which was affected by the conditions of the preparation, and with the hydrogenation temperature.

***cis*-3-Ureidothiophane-1, 1-dioxide-4-carboxylic Acid Hydrazide (5a).** A mixture of 62 mg of the *cis*-ester, 4a, and 57 mg of 100% hydrazine hydrate was heated on a water bath for 30 min. After about 10 min, a clear solution was obtained. Upon cooling the solution, 53 mg (90%) of the *cis*-hydrazide 5a (mp 173—174°C (decomp.)) was obtained.

Found: C, 30.24; H, 5.18; N, 23.66%. Calcd for $C_6H_{12}O_4N_4S$: C, 30.52; H, 5.12; N, 23.72%.

***trans*-3-Ureidothiophane-1, 1-dioxide-4-carboxylic Acid Hydrazide (5b).** The *trans*-ester 4b (50 mg) was worked up in the manner described above to give 35 mg (74%) of *trans*-hydrazide 5b (mp 203—205°C (decomp.)).

Found: C, 30.58; H, 5.16; N, 23.62%. Calcd for $C_6H_{12}O_4N_4S$: C, 30.52; H, 5.12; N, 23.72%.

Conversion of *cis*-Hydrazide 5a to *trans*-Hydrazide 5b. A mixture of 50 mg of *cis*-hydrazide, 5a, and 0.05 m*l* of 100% hydrazine hydrate was heated at 60°C for 90 min. After a few minutes, a clear solution was obtained. Upon cooling the solution, 40 mg (80%) of *trans*-hydrazide 5b (mp 203—205°C) were obtained. This *trans*-hydrazide, 5b, was identical in all respects (infrared spectrum and mixed melting point) with the product obtained by treating the *trans*-ester 4b and hydrazine.

Conversion of the Dihydrouracil (9) to the *trans*-Hydrazide 5b. A solution of 76 mg of 9 and 0.07 m*l* of 100% hydrazine hydrate was heated at 60°C for 30 min, concentrated to dryness *in vacuo*, and triturated with 95% ethanol. The precipitate was filtered off and washed with ethanol to give 65 mg (75%) of *trans*-hydrazide 5b (mp 201—204°C), which was identical in infrared spectrum with the product obtained from the *trans*-ester 4b and hydrazine.

The Dihydrouracil (9) (mp 299—301°C (decomp.)) was obtained in a 65—75% yield from either the *cis*-ester 4a or the *trans*-ester 4b by treating it with 4 N hydrochloric acid over a steam bath. However, the *trans*-ester 4b necessitated more or less prolonged heating (3 hr) as compared with the *cis*-ester, 4a (1 hr) in this transformation.

7) All melting points are uncorrected.

Found: C, 35.60; H, 4.23; N, 13.51%. Calcd for $C_6H_8O_4N_2S$: C, 35.30; H, 3.95; N, 13.72%.

Attempted Curtius Rearrangement of the *cis*-Hydrazide (5a). To a solution of 164 mg of *cis*-hydrazide, 5a, in 5 m*l* of ice-cooled 2 N hydrochloric acid, there was stirred, drop by drop, a solution of 65 mg of sodium nitrite in 1 m*l* of water. The mixture was stirred at −5−0°C for 2 hr, and then evaporated to dryness at room temperature under a reduced pressure of 5 mmHg. The residue dissolved in 15 m*l* of absolute ethanol was refluxed for 30 min, and the sodium chloride precipitated was removed by filtration. The filtrate was concentrated to dryness. The residue thus obtained was a resinous material and did not show the characteristic bands for the ureylene ring of the IR spectrum.

3-Carbethoxyamino-4-carbethoxy-2,5-dihydrothiophene (10). A mixture of 10.5 g of the ketoester 1, 6.3 g of urethane, 1 g of *p*-toluenesulfonic acid, and 200 m*l* of dry benzene was refluxed for 15 hr in a Soxhlet apparatus containing sodium sulfate in a thimble. The mixture was then washed thoroughly with water to remove the *p*-toluenesulfonic acid and the excess urethane. The evaporation of the solvent gave 14.0 g (95%) of the product, 10. This crude product was purified by chromatography using an alumina column and chloroform as an eluent, or by recrystallization from methanol-water to give an analytical sample (mp 70—71.5°C).

Found: C, 48.87; H, 6.08; N, 5.80%. Calcd for $C_{10}H_{15}O_4NS$: C, 48.97; H, 6.17; N, 5.71%.

3-Carbethoxyamino-4-carbethoxy-2,5-dihydrothiophene-1,1-dioxide (11). 6.81 g of 10 were dissolved in 261 m*l* of 5.4 N perbenzoic acid in chloroform, and the solution was maintained at room temperature for 24 hr. The solution was then washed successively with dilute aqueous sodium thiosulfate, dilute aqueous sodium bicarbonate, and water. The evaporation of the solvent gave the crude sulfone, 11. This sulfone was submitted to chromatography over an alumina column, using chloroform as an eluent, to give 4.6 g (57%) of the pure sulfone, 11 (mp 89—90°C), which was then further purified by recrystallization from chloroform-ligroin (mp 90—91°C).

Found: C, 43.56; H, 5.20; N, 4.81%. Calcd for $C_{10}H_{15}O_6NS$: C, 43.32; H, 5.45; N, 5.05%.

3-Carbethoxyamino-4-carbethoxythiophane-1,1-dioxide (12). One gram of 11 was hydrogenated in 120 m*l* of absolute ethanol over Raney nickel under a hydrogen pressure of 100 atm at 40—50°C for 3 hr. After the catalyst had been removed by filtration, the solvent was evaporated to dryness. The residue was recrystallized from chloroform-petroleum ether or from ether to give 0.9 g (90%) of the *cis*-ester, 12a (mp 98—99°C).

Found: C, 42.89; H, 5.86; N, 5.05%. Calcd for $C_{10}H_{17}O_6NS$: C, 43.01; H, 6.14; N, 5.02%.

When hydrogenation was carried out at 70—80°C, the *trans*-ester 12b (mp 140—141°C) was obtained after recrystallization from chloroform-ligroin,

Found: C, 43.24; H, 6.07; N, 5.00%. Calcd for $C_{10}H_{17}O_6NS$: C, 43.01; H, 6.14; N, 5.02%.

The hydrogenation of 11 often gave a mixture of *cis*- and *trans*-isomers, 12a and 12b. The separation of the *cis-trans* mixture into each isomer was difficult.

Another Method of Synthesizing and Identifying the *cis*-Ester 12a. A mixture of 1.827 g of 18, 1.8 m*l* of triethylamine, and 30 m*l* of absolute ethanol was refluxed for 90 min and then diluted with 100 m*l* of water. The solution was extracted 4 times with 70 m*l* of ether. The extracts were washed with dilute hydrochloric acid and water which had been saturated with sodium chloride. After drying over sodium sulfate, the evaporation of the ether gave 1.27 g (88%) of the rearranged product, *cis*-carbethoxyamino-4-carbethoxythiophane (20B). To a solution of 3.7 m*l* of 0.43 N perbenzoic acid in chloroform, 93 mg of this 20B were added. The solution was allowed to stand at room temperature for 5 days, diluted with 20 m*l* of chloroform, and washed successively with dilute aqueous sodium thiosulfate, dilute aqueous potassium hydroxide, and water. The removal of the solvent gave 82 mg of the corresponding sulfone, mp 96—97.5°C (chloroform-ligroin). This sulfone was identical in all respects (IR spectrum and mixed melting point) with the *cis* ester, 12a (mp 98—99°C) obtained by the catalytic reduction of 11.

3-Carbethoxyamino-4-carboxythiophane-1,1-dioxide (13). A *cis-trans* mixture of 12 (1.47 g) was hydrolyzed with 40 m*l* of 4 N hydrochloric acid by heating it over a steam bath for 2 hr. The solution was then cooled in a refrigerator: *trans*-acid 13b was crystallized out and filtered off to give 0.85 g of *trans*-acid 13b (mp 204—206°C (from water)).

Found: C, 38.16; H, 4.96; N, 5.40%. Calcd for $C_8H_{13}O_6NS$: C, 38.25; H, 5.22; N, 5.58%.

The filtrate was extracted 4 times with 50 m*l* of ethyl acetate. The extract was dried over sodium sulfate and concentrated to dryness. The recrystallization of the residue (0.35 g) from ethyl acetate-petroleum ether gave *cis*-acid 13a (mp 160—162°C).

Found: C, 38.54; H, 5.14; N, 5.55%. Calcd for $C_8H_{13}O_6NS$: C, 38.25; H, 5.22; N, 5.58%.

The Modified Curtius Rearrangement of *cis*-Acid 13a to *N*-Carbethoxy-*cis*-3,4-ureylenethiophane-1,1-dioxide (14B, R=Et). Into a solution of 460 mg of *cis*-acid 13a in 40 m*l* of acetone at −10°C there was stirred, drop by drop, a mixture of ethyl chloroformate in 4 m*l* of acetone. The reaction mixture was then stirred for 40 min at the same temperature, and to this mixture there was added at −10°C, drop by drop, 175 mg of sodium azide in 5 m*l* of water. The above mixture was also further stirred for 40 min at the same temperature. After the reaction mixture had been diluted with water, the organic material was extracted 4 times with 80 m*l* of ethyl acetate, and the extract was dried over sodium sulfate. The dried extract was refluxed for 1 hr to decompose the acid azide. The removal of the solvent gave 210 mg of the crude product, which was extracted twice with 30 m*l* of hot absolute ethanol. After the evaporation of the solvent, the residue (mp 225—232°C (decomp.)) was recrystallized from methanol to give the product, 14B (mp 236—239°C (decomp.)).

Preparation of 14B by the Oxidation of 22B. To a solution of 216 mg of *N*-carbethoxy-*cis*-3,4-ureylene-thiophane (22B, R=Et) in 10 m*l* of chloroform, 10 m*l* of 0.43 N perbenzoic acid in chloroform were added. The solution was then allowed to stand overnight at room temperature. The solid which precipitated was collected by filtration and recrystal-

lized from ethanol to give 225 mg (90%) of 14b (mp 238—240°C (decomp.)). This sulfone, 14B, was identified by its infrared spectrum and by a mixed-melting-point determination with one of the sulfones obtained by the modified Curtius rearragnement of *cis*-3-carbethoxyamino-4-carboxythiophane-1, 1-dioxide 13a.

Found: C, 38.95; H, 4.88; N, 11.27%. Calcd for $C_8H_{12}O_5NS$: C, 38.71; H, 4.87; N, 11.29%.

***trans*-3, 4-Dicarboxythiophane (16b)** was prepared from 2, 5-dihydrothiophane-3, 4-dicarboxylic acid (15) according to the method of Baker and his co-worker[8] in a 98% yield; mp 137—139°C (from acetone-benzene), lit. mp 140—141°C.

***cis*-Thiophane-3, 4-dicarboxylic Anhydride (17).** A mixture of 25.0 g of 16b and 140 m*l* of freshly-distilled acetic anhydride was refluxed for 2 hr; careful fractional distillation then gave the product, 17 bp 145—150°C/1 mmHg) in a yield of 15.0 g (66%). This product was further purified by recrystallization from ether; mp 87—88°C, lit. mp 84—85°C.[8]

***N*-Hydroxy-*cis*-thiophane-3, 4-dicarboxyimide (18).** To a solution of 1.88 g of anhydride, 17, in 30 m*l* of dry methanol, there was added a solution of hydroxylamine prepared from 900 mg of hydroxylamine hydrochloride in 10 m*l* of dry methanol and 300 mg of sodium in 20 m*l* of dry methanol. The mixture was mechanically shaken for 14 hr at room temperature. The solvent was then removed at room temperature *in vacuo*, and the residue was recrystallized from dry ethyl acetate to give 1.31 g (64%) of the product, 18 (mp 148—150°C).

Found: C, 41.63; H, 3.82; N, 7.97%. Calcd for $C_6H_7O_3NS$: C, 41.62; H, 4.08; N, 8.09%.

***N*-Phenylsulfonyloxythiophane-*cis*-3, 4-dicarboximide (19).** To a solution of 3.98 g of 18 in 40 m*l* of 10% aqueous sodium carbonate, 4.43 g of benzenesulfonyl chloride were added, drop by drop, after which the mixture was stirred at room temperature. The solid which separated was collected by filtration and recrystallized from methanol to give 6.0 g (84%) of the product, 19 (mp 136—138°C).

Found: C, 46.25; H, 3.30; N, 4.18%. Calcd for $C_{12}H_{11}O_5NS_2$: C, 46.01; H, 3.54; N, 4.47%.

***cis*-3-Carbomethoxyamino-4-carbomethoxythiophane** (20A, R=Me). A mixture of 1.21 g of 19, 1.20 g of triethylamine, and 25 m*l* of dry methanol was refluxed for 1 hr and then diluted with 50 m*l* of water. The solution was extracted with ether, and the extract was washed with dilute hydrochloric acid and water, and then dried over sodium sulfate. The evaporation of the solvent gave 680 mg (82%) of the product, 20A (mp 81—83°C (from petroleum ether)).

Found: C, 44.10; H, 5.87; N, 6.39%. Calcd for $C_8H_{13}O_4NS$: C, 43.83; H, 5.98; N, 6.39%.

***cis*-3-Carbomethoxyamino-4-carboxythiophane (21A, R=Me).** A mixture of 680 mg of 20A and 8 m*l* of 3 N hydrochloric acid was heated over a steam bath until a clear solution was obtained (about 90 min). The solution was then extracted with ether, and the extract was dried over sodium sulfate. The removal of the solvent gave 500 mg (*ca.* 100%) of the product, 21A (mp 130—131°C (from benzene-petroleum ether)).

Found: C, 41.15; H, 5.38; N, 6.84%. Calcd for $C_7H_{11}O_4NS$: C, 40.98; H, 5.40; N, 6.83%.

***N*-Carbomethoxy-*cis*-3, 4-ureylenethiophane (22A, R=Me).** Into a solution of 410 mg of 21A in a mixture of 8 m*l* of acetone and 2 m*l* of water, 222 mg of triethylamine in 4 m*l* of acetone were stirred, drop by drop, at −10°C. After ten minutes, 263 mg of ethyl chloroformate in 1 m*l* of acetone was stirred into the above solution at the same temperature, and the mixture was stirred a further 40 min. To the resulting solution 173 mg of sodium azide in 1 m*l* of water were added, drop by drop; then stirring was continued for 50 more min at −10°C. The reaction mixture was extracted 4 times with 30 m*l* of ether, and the extract was dried over sodium sulfate. The solvent was removed at room temperature under reduced pressure. The residue was dissolved in 70 m*l* of dry toluene, and the solution was heated over a steam bath for 1 hr. The solvent was concentrated to a small volume (about 5 m*l*), and the resultant colorless precipitate was collected to give 170 mg (42%) of the product, 22A (mp 179—180°C (from benzene)).

Found: C, 41.71; H, 4.77; N, 13.67%. Calcd for $C_7H_{10}O_3N_2S$: C, 41.58; H, 4.99; N, 13.86%.

***N*-Carbethoxy-*cis*-3, 4-ureylenethiophane (22B, R=Et).** A mixture of 1.15 g of crude 3-carbethoxyamino-4-carbethoxythiophane (20B, R=Et), prepared from 19 in the same manner as has been described for 20A, in 12 m*l* of 3 N hydrochloric acid was heated over a steam bath for 2.5 hr while nitrogen gas was bubbled in. The product was extracted 5 times with 60 m*l* of ether. After having been dried over sodium sulfate, the solvent was removed to dryness to give 780 mg (75%) of crude 3-carbethoxyamino-4-carboxythiophane (21B, R=Et) (mp 104—109°C) (4 recrystallizations from benzene-ligroin). To a solution of 600 mg of 21B (mp 104—109°C) in 12 m*l* of acetone, 304 mg of triethylamine in 2 m*l* of acetone were added. Into the above solution at −10°C there was then stirred, drop by drop, a solution of 360 mg of ethyl chloroformate in 2 m*l* of acetone; stirring was continued for 30 more min. To the above solution at −10°C there was then added, drop by drop, a solution of 237 mg of sodium azide in 2 m*l* of water. After the reaction mixture had been stirred at −10°C for 1 hr, the mixture was diluted with 10 m*l* of water, and the diluted solution was extracted 5 times with 50 m*l* of ether. The product was worked up in the manner described for the preparation of 22A to give 355 mg (60%) of the product, 22B (mp 186—187.5°C (from benzene)).

Found: C, 44.31; H, 5.49; N, 12.79%. Calcd for $C_8H_{12}N_2S$: C, 44.44; H, 5.60; N, 12.96%.

***cis*-3, 4-Ureylenethiophane (23).** A mixture of 96 mg of 22A, 6 m*l* of 10% barium hydroxide, and 3 m*l* of ethanol was heated for 3.5 hr over a steam bath. The mixture was acidified with 2 m*l* of 6 N hydrochloric acid, and the acidified solution was evaporated to dryness *in vacuo*. The residue was sublimated at the bath temperature of 170°C under a pressure of 0.3 mmHg to give 55 mg (80%) of the product, 23 (mp 229—231°C, (lit. mp 231°C)[8]).

Found: C, 41.58; H, 5.70; N, 19.20%. Calcd for $C_5H_8ON_2S$: C, 41.66; H, 5.59; N, 19.44%.

8) B. R. Baker, M. V. Querry, S. R. Safir, W. L. McEwen and S. Bernstein, *J. Org. Chem.*, **12**, 174 (1947).