[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL UNIVERSITY MEDICAL COLLEGE, AND FROM THE LEDERLE LABORATORIES]

BIOTIN. II. 3,4-*trans*-DIAMINOTHIOPHANE

GEORGE BOSWORTH BROWN; B. R. BAKER, SEYMOUR BERNSTEIN,
AND S. R. SAFIR

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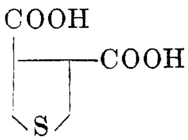
The syntheses of two isomeric 3,4-diaminothiophanes have been previously reported by one of these laboratories. Curtius degradation (1) of a thiophane-3,4-dicarboxhydrazide (II) yielded the diurethan (III) of a 3,4-diaminothiophane, both of unknown configuration. A second isomer of 3,4-diaminothiophane was synthesized (2) by the treatment of a 2,3-diaminobutane-1,4-disulfuric acid with sodium sulfide.

Through the characterization of the *cis*- and *trans*- forms of thiophane-3,4-dicarboxylic acid (I), it has now been demonstrated that the dihydrazide, II, and diurethan, III, have a *trans* relationship of the 3,4-substituents. The isomer of 3,4-diaminothiophane obtained in the second synthesis (2) must therefore have the *cis* configuration.

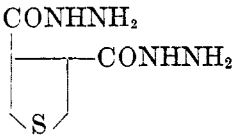
The thiophane-3,4-dicarboxylic acids (I) were prepared by extension of the earlier method from 3,3,4,4-tetracarbethoxythiophane (1) and by the recently described general method from 3-keto-4-carbethoxythiophanes (3). The identity of the dicarboxylic acids, I, synthesized by each method proves that under the conditions employed, the Dieckmann cyclization[1] of ethyl β-(carbethoxymethylthio)propionate takes place predominately in the desired direction.

3-Carbethoxy-4-ketothiophane was converted to the cyanohydrin and dehydrated with phosphorus oxychloride in pyridine to 3-carbethoxy-4-cyanodihydrothiophene. Acid hydrolysis resulted in a dihydrothiophene-3,4-dicarboxylic acid which was smoothly reduced with sodium amalgam in dilute aqueous alkali to a mixture of the *cis* and *trans* isomers of thiophane-3,4-dicarboxylic acid (I).

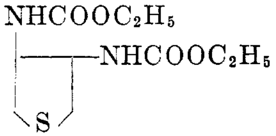
Esterification of the *cis-trans* diacid mixture and inversion by sodium methoxide followed by hydrolysis resulted in the formation of the pure *trans* diacid, m.p. 140–141°. The identical *trans* diacid was also obtained by cold alkaline hydrolysis of 3,4-dicarbethoxythiophane prepared by the earlier method (1). Acid hydrolysis of this diester gave a mixture of *cis* and *trans* isomers.



I



II



III

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[1] After this work was completed Woodward and Eastman (4) showed that high temperature Dieckmann cyclization of methyl β-(carbomethoxymethylthio)propionate yielded 3-carbomethoxy-4-ketothiophane whereas low temperatures favored the formation of 2-carbomethoxy-3-ketothiophane.

The mixture of *cis* and *trans* diacids from either source, when treated with acetyl chloride and then evaporatively distilled at 150° *in vacuo* gave the same thiophane-3,4-*cis*-dicarboxylic anhydride, m.p. 84–85°, which was easily hydrolyzed to the *cis* diacid, I, m.p. 134–135°. The latter, with acetyl chloride, readily reformed the *cis* anhydride in contrast to the *trans* diacid which gave a polymeric or mixed anhydride.

Esterified and treated with hydrazine, thiophane-3,4-*trans*-dicarboxylic acid (I) gave the corresponding *trans*-dihydrazide (II). That no inversion of configuration took place was demonstrated by acid hydrolysis back to the original *trans* diacid. However, when the *cis*-diacid was treated under the same conditions, the *trans*-dihydrazide was again formed, inversion of configuration having taken place.

Therefore, the 3,4-diaminothiophane synthesized from the *trans*-dihydrazide (II) must also have the *trans* configuration, as Curtius degradation has been reported to proceed without inversion (5). These results are similar to those obtained from the 2-alkylthiophane-3,4-dicarboxylic acids (3).

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EXPERIMENTAL

Ethyl β-(carbethoxymethylthio)propionate. To a mixture of 228 g. of ethyl thioglycolate (3) and 2 cc. of piperidine was added 350 cc. of ethyl acrylate in portions with ice cooling so that the temperature was 30–40°. An additional 2 cc. of piperidine was added in two portions after ten and twenty minutes. At the end of fifteen hours the mixture was distilled: colorless oil, b.p. 154–155° (12 mm.); yield 407 g. (97%).

The ethyl acrylate may be reduced to a 5% excess without appreciable lowering of the yield, but a 1:1 ratio gives only 90%.

After this work was completed, Buchman and Cohen (7) as well as Woodward and Eastman (4) mentioned this method but gave no experimental details. The b.p. of this compound has been recorded as 148–150° (10 mm.) by Karrer and Schmidt (6).

3-Carbethoxy-4-ketothiophane. A. To the dry sodium ethoxide from 2.7 g. of sodium, obtained by evaporating an ethanolic solution to dryness *in vacuo*, was added 20.4 g. of ethyl β-(carbethoxymethylthio)propionate in 100 cc. of dry benzene. The mixture was distilled from a bath at 125° through a Vigreux column. In thirty minutes 70 cc. of distillate, b.p. 68–78°, was obtained, distillation stopped, and the solid sodium enolate began to separate. After thirty minutes more at 125°, the mixture was cooled in an ice-bath and diluted with ice-water and ether. The aqueous layer was acidified with acetic acid and the ether layer extracted once more with water. The combined acidified extracts were in turn extracted with benzene, washed successively with water, dilute sodium bicarbonate and water. Distillation gave 7.7 g. (48%) of a colorless liquid, b.p. 90–93° (1 mm.).

Anal. Calc'd for $C_7H_{10}O_3S$: C, 48.2; H, 5.8; S, 18.4.
Found: C, 48.2; H, 5.7; S, 18.3.

The semicarbazone formed white needles from dilute ethanol, m.p. 171–173°.

Anal. Calc'd for $C_8H_{13}N_3O_3S$: C, 41.5; H, 5.7; N, 18.2.
Found: C, 41.6; H, 6.1; N, 17.6.

After this work was completed Buchman and Cohen (7) reported the b.p. of the keto ester as 96° (4 mm.) and the m.p. of the semicarbazone as 176°, but gave no experimental details.

B. To the dry sodium ethoxide from 17.5 g. of sodium was added 82.5 g. of ethyl thioglycolate in 200 cc. of benzene. Most of the sodium ethoxide dissolved on shaking. To the mixture was added dropwise with shaking, 77 cc. of ethyl acrylate over a period of ten minutes. After being refluxed for two and one-half hours, the benzene solution was extracted with ice-water and worked up as in part *A*; yield, 68 g. (48%), b.p. 105–122° (5 mm.), but mainly at 110–115°.

The cyclization can also be carried out on ethyl β-(carbethoxymethylthio)propionate with sodium ethoxide in boiling benzene for two hours; yield, 55% of a product boiling at 107–111° (6 mm.).

3-Carbethoxy-4-cyanodihydrothiophene. To 40 cc. of liquid hydrogen cyanide (3) and 0.5 cc. of 50% potassium hydroxide solution cooled in an ice-bath was added 130 g. of 3-carbethoxy-4-ketothiophane in portions so that the temperature was maintained at 5–15°. After twenty hours at 0–5° the mixture was acidified with 1.5 cc. of 85% phosphoric acid and the excess hydrogen cyanide was removed *in vacuo*. The residue, dissolved in 200 cc. of benzene, was dried with sodium sulfate and the drying agent rinsed with 170 cc. of benzene. The solution was diluted with 370 cc. of dry pyridine and 160 cc. of phosphorus oxychloride was added. The temperature was maintained at 40–45° with occasional cooling until the reaction was no longer exothermic. After a total of six hours the mixture was poured into iced hydrochloric acid, the organic layer was washed with dilute hydrochloric acid, iced 3% sodium hydroxide, dilute acetic acid, and then distilled. The product, b.p. 122–125° (1 mm.), partially solidified in the receiver; yield, 114 g. (84%).

Anal. Calc'd for $C_8H_9NO_2S$: C, 52.5; H, 5.0; N, 7.6.
Found: C, 52.7; H, 4.8; N, 7.1.

Dihydrothiophene-3,4-dicarboxylic acid. A mixture of 113 g. of 3-carbethoxy-4-cyanodihydrothiophene, 230 cc. of acetic acid, and 560 cc. of concentrated hydrochloric acid was refluxed for thirteen hours, diluted to 2 l. with water and clarified with Norit. Saturated with salt, the solution was extracted with three 500-cc. portions of ethyl acetate. The extracts, dried with magnesium sulfate, were evaporated to dryness *in vacuo* and the residue was crystallized from benzene; yield 79 g. (74%), m.p. 165–180°. Recrystallization from acetone-benzene gave white crystals which melted at 169–185°. This may be a mixture of isomers.

Anal. Calc'd for $C_6H_6O_4S$: C, 41.3; H, 3.4; S, 18.4.
Found: C, 41.6; H, 2.7; S, 18.4.

cis and trans-Thiophane-3,4-dicarboxylic acids (I). A solution of 300 g. of dihydrothiophene-3,4-dicarboxylic acid in 2600 cc. of 5% sodium hydroxide was stirred with 4.6 kg. of 2% sodium amalgam. The heat of reaction raised the temperature to 75° for about thirty minutes. The mixture was stirred ninety minutes more at 70–80°. The decanted solution was acidified, saturated with salt and extracted three times with ethyl acetate. The solvent was removed *in vacuo* and the residue was crystallized from benzene, white crystals, m.p. 102–120°; yield, 260 g. (87%) of a mixture of *cis* and *trans* isomers.

Thiophane-3,4-trans-dicarboxylic acid (I). *A.* A mixture of 5.5 g. of 3,4-dicarbethoxythiophane, obtained by the bis-malonic ester method (1), 1.9 g. of sodium hydroxide, 35 cc. of water, and 5 cc. of alcohol was allowed to stand at room temperature for three hours, then acidified and continuously extracted with benzene. Concentration gave 3.7 g. (82%) of the *trans* acid in the form of white leaflets, m.p. 131–134°, resolidifies and remelts at 140–141° (cor.). Recrystallization from acetone-benzene did not change the m.p. After standing for eighteen months the acid had changed over completely to the high-melting form, m.p. 140–141°.

Anal. Calc'd for $C_6H_8O_4S$: C, 40.8; H, 4.6.
Found: C, 40.9; H, 4.7.

When this same diester was hydrolyzed by boiling with dilute ethanolic hydrochloric acid, a mixture of *cis* and *trans* isomers, m.p. 110–124°, was obtained.

B. A solution of 25 g. of thiophane-3,4-dicarboxylic acid (m.p. 102–120°, obtained by reduction of dihydrothiophene-3,4-dicarboxylic acid) and 2.5 cc. of concentrated sulfuric acid in 100 cc. of absolute ethanol and 100 cc. of benzene was refluxed twenty-four hours under a Soxhlet apparatus containing anhydrous magnesium sulfate in the thimble. After being washed with water, the solution was evaporated *in vacuo*. The residue was refluxed for one hour with 60 cc. of absolute ethanol containing 1.5 g. of sodium, then diluted with 25 g. of potassium hydroxide in 75 cc. of water and refluxed an additional hour. Acidified with 60 cc. of concentrated hydrochloric acid, the solution was extracted with 300 cc. of ethyl acetate in three portions and the extracts dried with magnesium sulfate. Evaporation *in vacuo* and trituration with benzene gave 21.5 g. (85%) of *trans* acid, m.p. 133–136°.

A similar preparation was recrystallized from acetone-benzene, white leaflets, m.p. 132–134°, resolidifies and remelts at 139–141° (uncor.). A mixture of the latter with preparation *A* gave no depression in m.p.

Thiophane-3,4-cis-dicarboxylic anhydride. A mixture of 1.5 g. of thiophane-3,4-dicarboxylic acid (m.p. 105–116°, obtained above by acid hydrolysis method *A*) and 15 cc. of acetyl chloride was refluxed for five hours, solution being complete in fifteen minutes. After removal of the volatile material *in vacuo*, the residue was evaporatively distilled for ten hours at 150° and 20 mm. onto a cold finger; white crystals, m.p. 84–85° (cor.); yield, 0.70 g. (50%).

Anal. Calc'd for $C_6H_6O_3S$: C, 45.6; H, 3.8.
Found: C, 45.5; H, 3.7.

Similarly, the mixed isomeric thiophane-3,4-dicarboxylic acids obtained by reduction of dihydrothiophene-3,4-dicarboxylic acid gave the same anhydride, m.p. and mixed m.p. 83–84°.

Thiophane-3,4-cis-dicarboxylic acid (I). A sample of the corresponding *cis*-anhydride was heated with a little water until solution was complete, then evaporated to dryness *in vacuo*. The residue was recrystallized from acetone-benzene, white blades, m.p. 134–135° (cor.). A mixed m.p. with thiophane-3,4-*trans*-dicarboxylic acid was 105–109°.

Anal. Calc'd for $C_6H_8O_4$: C, 40.8; H, 4.6.
Found: C, 40.8; H, 4.3.

A few mg. of the *cis*-acid was refluxed for one hour with 1 cc. of acetyl chloride. Evaporation and trituration with benzene gave the *cis*-anhydride, m.p. 82–85°. The *cis*-diacid was again regenerated by water treatment. On the other hand the pure *trans*-acid gives a polymeric or mixed anhydride with acetyl chloride which gives the *trans* acid on hydrolysis. The mixed anhydride when heated to 150° is rearranged to the *cis*-anhydride.

Thiophane-3,4-trans-dicarboxhydrazide (II). A. A solution of 500 mg. of thiophane-3,4-*trans*-dicarboxylic acid in 2 cc. methanol was treated with an excess of ethereal diazomethane. The solution was evaporated and the residue refluxed for thirty minutes with 1 cc. of 100% hydrazine hydrate in 5 cc. of absolute ethanol. During this time the product separated from solution. The mixture was diluted with 5 cc. of absolute ethanol, cooled in an ice-bath and the dihydrazide collected on a filter; yield, 450 mg. (80%) of white needles, m.p. 223–224°. Admixture with the thiophane-3,4-dicarboxhydrazide previously described (1) gave no depression in the m.p.

A solution of 230 mg. of the above hydrazide in 4 cc. of 6 *N* hydrochloric acid was heated on the steam-bath under reflux for twenty-four hours. After dilution with 10 cc. of water and saturation with salt, the solution was extracted twice with ethyl acetate. The dried extracts were evaporated *in vacuo* and the residue crystallized from benzene, white leaflets, m.p. 131–134°, resolidifies and remelts at 138–139°; yield, 165 mg. (83%). A mixed m.p. with thiophane-3,4-*trans*-dicarboxylic acid was the same, while a mixed m.p. with the *cis*-diacid was 87–96°, thus indicating the *trans* configuration of the hydrazide.

B. When 20 mg. of thiophane-3,4-*cis*-dicarboxylic acid was esterified with diazomethane and treated with hydrazine under the same conditions used for *trans* ester, the *trans*-hydrazide, m.p. 218–220°, was obtained. It gave no depression in m.p. when mixed with preparation *A*.

3,4-trans-Diaminothiophane dihydrobromide. A mixture of 1.0 g. of 3,4-*trans*-dicarbethoxyaminothiophane (1) and 10 cc. of 48% hydrobromic acid was refluxed for forty minutes. In five minutes solution was complete and in ten minutes the product began to crystallize out. The mixture was cooled to 5°, the product collected on a glass filter and washed with alcohol and ether, white crystals, m.p. > 350°; yield, 1.05 g. (95%).

Anal. Calc'd for $C_4H_{12}Br_2N_2S$: N, 10.0. Found: N, 9.8.

The dihydrobromide is readily soluble in cold water, insoluble in cold 48% hydrobromic acid, hot alcohol, or hot acetic acid. It is somewhat soluble in hot 48% hydrobromic acid.

3,4-trans-Diuramidothiophane. A solution of 100 mg. of 3,4-*trans*-diaminothiophane dihydrobromide and 90 mg. of potassium cyanate in 2 cc. of water was allowed to stand at room temperature for eight hours. The white leaflets were removed by filtration and recrystallized from 50% alcohol, m.p. 249–250° dec.; yield, 70 mg. (83%).

Anal. Calc'd for $C_6H_{12}N_4O_2S$: N, 27.4. Found: N, 27.6.

SUMMARY

The *cis* and *trans* forms of thiophane-3,4-dicarboxylic acids have been characterized.

The configuration of one of the previously known 3,4-diaminothiophanes has been established as *trans*.

NEW YORK, N. Y.
PEARL RIVER, N. Y.

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