[Contribution from the Lederle Laboratories Division, American Cyanamid Co.]

BIOTIN. XI. THE STRUCTURE OF 2-ALKYLDIHYDROTHIOPHENE-3,4-DICARBOXYLIC ACIDS

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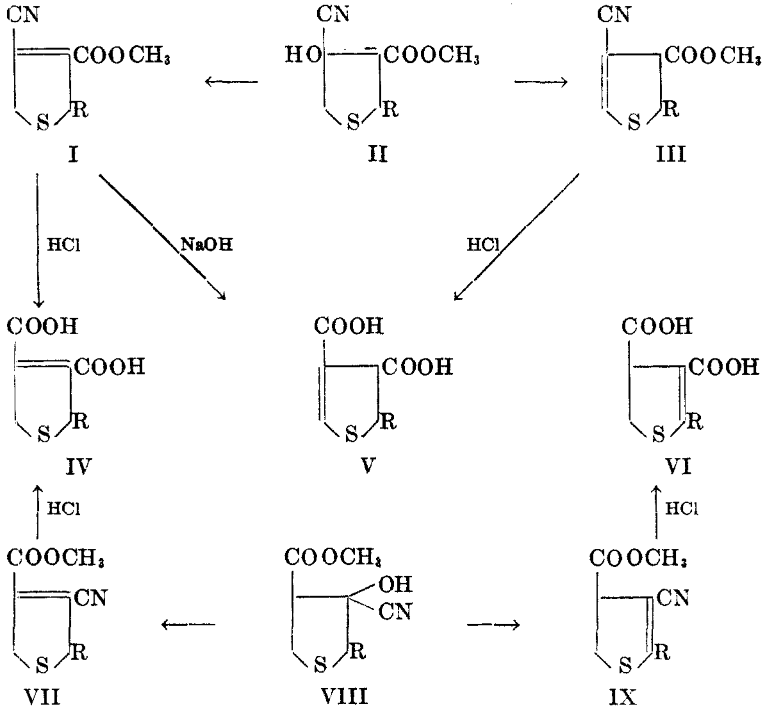
In some previous communications of this series (1, 2, 3), it was shown that dehydration and acid hydrolysis of cyanohydrin esters of types II and VIII gave 2-alkyldihydrothiophene-3,4-dicarboxylic acids in which the position of the double bond was unknown. The double bond has now been established to be in the 3,4-position.

3-Carbomethoxy-4-ketothiophane (4), on treatment with hydrogen cyanide, gave a cyanohydrin, II (R = H), which was dehydrated with phosphorus oxychloride and pyridine in benzene to a crystalline 3-carbomethoxy-4-cyanodihydrothiophene (I or III, R = H) in 70% yield. Acid hydrolysis of the cyano ester gave a dihydrothiophene-3,4-dicarboxylic acid, A, m.p. 183–184°, whereas alkaline hydrolysis gave an isomeric dihydrothiophene-3,4-dicarboxylic acid, B, m.p. 180–181° dec. An investigation showed that the absorption spectra (Figure 1) of the cyano ester and the diacid, A, were similar, but that of the diacid, B, was radically different, indicating that a shift of the double bond had taken place during the alkaline hydrolysis. Although the diacid, A, was readily



reduced with sodium amalgam to a mixture of the *cis* and *trans* isomers of thiophane-3,4-dicarboxylic acid, the diacid, B, was unaffected under the same conditions. However, the latter could be reduced to *trans*-thiophane-3,4-dicarboxylic acid[1] by increasing the temperature, time of reaction and quantity of sodium amalgam, thus demonstrating that the diacid, B, was truly a dihydrothiophene-3,4-dicarboxylic acid.

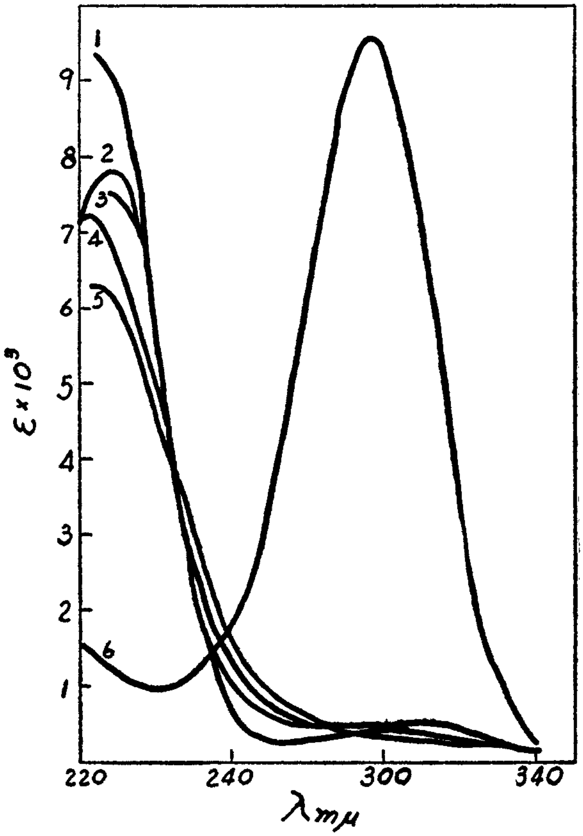


FIG. 1. 1: Diacid "A"; 2: I, R = H; 3: VII, R = $-CH_2COOH$; 4: IV, R = $-(CH_2)_4$-COOH; 5: IV, R = $-CH_2COOH$; 6: Diacid "B". Absorption curves determined in water.

Some similar observations have been made on the cyclohexene-1,2-dicarboxylic acids by Baeyer (5). The $\Delta^{1,2}$ isomer was readily reduced with sodium amalgam to cyclohexane-1,2-dicarboxylic acid, whereas the $\Delta^{2,3}$ isomer could not be reduced under the same conditions. Furthermore, the $\Delta^{1,2}$ isomer was rearranged to the $\Delta^{2,3}$ isomer under the influence of hot strong alkali. The same type of result has been observed with the cyclopentene-1,2-dicarboxylic acids (6).

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[1] The surprising observation that only the *trans* isomer was formed in this reaction was readily understood when it was found that the pure *cis* isomer could be rearranged to *trans* under the stringent alkaline conditions necessary for the reduction.

In both ring systems the positions of the double bonds were proven beyond doubt. If an analogy can be carried to the dihydrothiophene-3,4-dicarboxylic acids, then the diacid, A, should have the structure IV (R = H) and the diacid, B, that of V (R = H).

A comparison of the absorption spectra of the diacids, A and B, with that of maleic acid (Figure 2) indicated that A had the HOOC—C═C—COOH linkage, as both A and maleic acid absorbed strongly in the 215–225 mμ region, but only weakly in 275–305 mμ region. In contrast, β-ethylthiocrotonic acid (7), 2-propyl-4-butylthio-2,5-dihydrothiophene-3-carboxylic acid and the diacid, B, each had a maximum in the 275–305 mμ region, but only low absorption in the 220–230 mμ region, indicating that the diacid, B, had the —S—C═C—COOH linkage. Thus, the absorption spectra also indicate that the diacid, A, has structure IV (R = H) and the diacid, B, that of V (R = H).

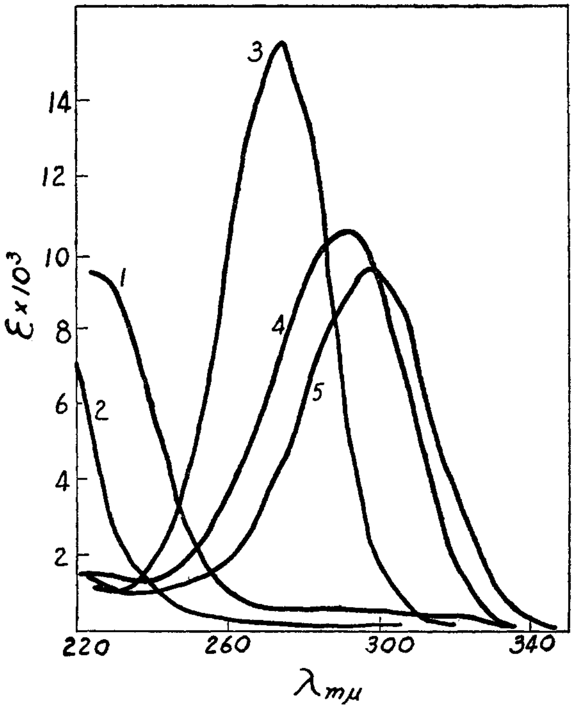
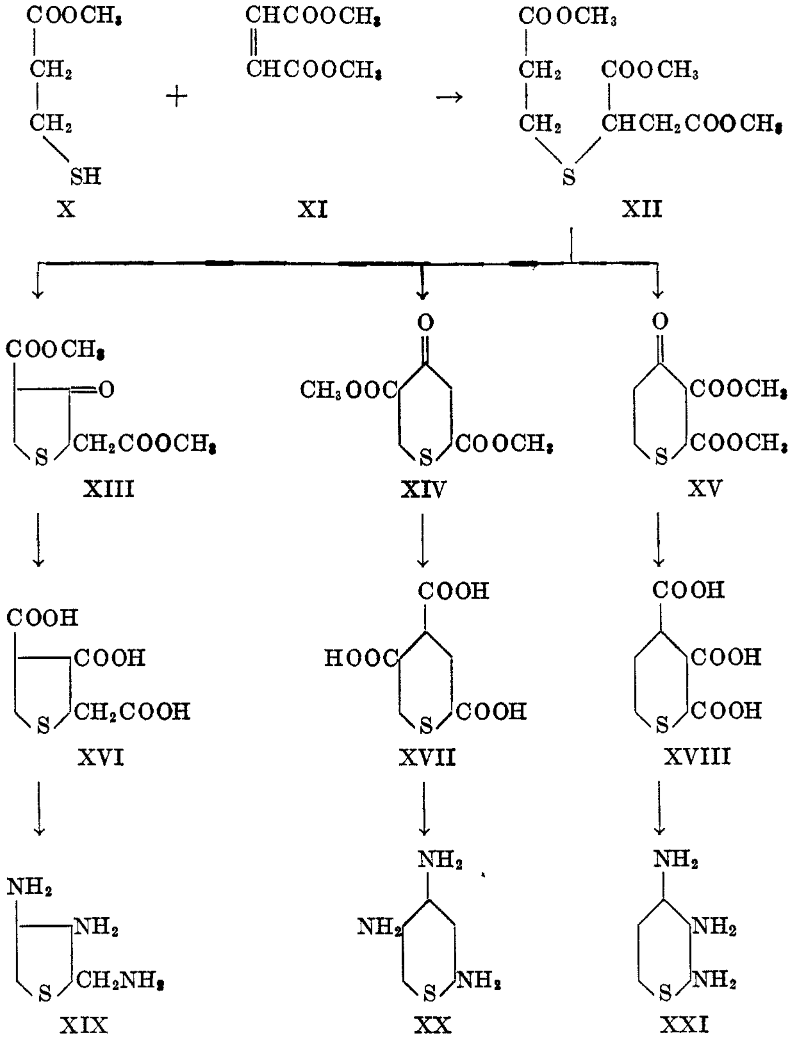


FIG. 2. 1: Diacid "A"; 2: maleic acid (12); 3: β-ethylthiocrotonic acid; 4: 2-propyl-4-*n*-butylthio-2,5-dihydrothiophene-3-carboxylic acid; 5: Diacid "B".

That the above suppositions were correct was verified by chemical proof. Dehydration and acid hydrolysis of the isomeric cyanohydrin esters, II and VIII, should give isomeric unsaturated diacids, V and VI, respectively if dehydration has taken place towards the sulfur atom. However, if dehydration forms a double bond in the 3,4 position, then the identical diacid, IV, should be obtained from both cyanohydrins. This was tested with R = —CH_2COOCH_3. The products obtained in both cases were indeed identical, proving that the double bond was in the 3,4 position.



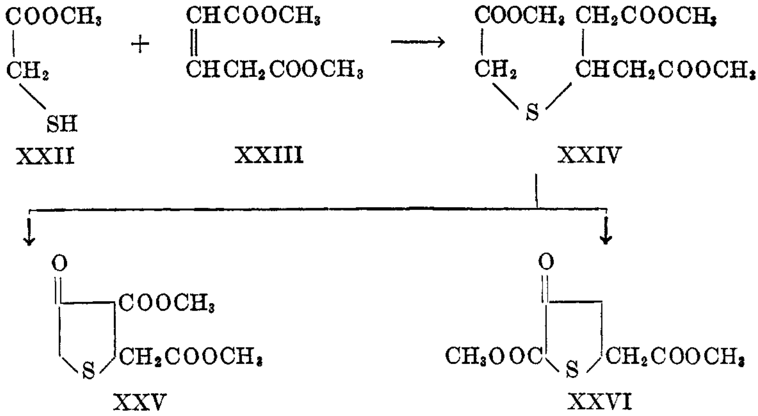
Methyl β-mercaptopropionate (X) condensed smoothly with methyl maleate in the presence of piperidine. The resultant thiotriester, XII, was cyclized by the Dieckmann method to 2-carbomethoxymethyl-3-keto-4-carbomethoxythiophane (XIII). The latter, converted to the cyanohydrin, VIII (R = —CH_2COOCH_3), was dehydrated with phosphorus oxychloride and pyridine in benzene to the crystalline 2-carbomethoxymethyl-3-cyano-4-carbomethoxy-2,5-dihydrothiophene (VII, R = —CH_2COOCH_3). Acid hydrolysis resulted in

2-carboxymethyl-2,5-dihydrothiophene-3,4-dicarboxylic acid (IV, R = —CH_2-COOH), m.p. 211–213°dec.

The Dieckmann cyclization of XII can theoretically take place to give the thiophane, XIII, and/or the penthianes, XIV and XV. That the cyclization formed the thiophane keto ester, XIII, was proved as follows:[2]

2-Carboxymethyl-2,5-dihydrothiophene-3,4-dicarboxylic acid (IV, R = —CH_2COOH) was reduced with sodium amalgam to the thiophane tricarboxylic acid, XVI, m.p. 191°. This acid was degraded, *via* the trihydrazide and the triurethan, to the stable triamine, XIX, identified as its trihydrobromide, tripicrate, and triuramido derivatives. If the Dieckmann cyclization had formed either of the penthiane keto esters, XIV or XV, then the above sequence of reactions would have resulted in the hydrolytically unstable triamines, XX and XXI, respectively. A molecule in which thio and amine groups are attached to the same carbon atom has been shown by Brown and Kilmer (9) to be unstable, as this linkage is cleaved on hydrolysis of the urethan derivative, with the formation of ammonia.

Methyl glutaconate (XXIII) readily added methyl thioglycolate (XXII) with formation of the thiotriester, XXIV. Dieckmann cyclization of the latter in hot toluene proceeded in 60% yield to the keto esters, XXV and XXVI. Ferric chloride titration (4) indicated that the product contained 87% of the desired keto ester, XXV. This was converted to 2-carboxymethyl-2,5-dihydrothiophene-3,4-dicarboxylic acid (IV, R = —CH_2COOH) *via* the intermediates II and I (R = —CH_2COOCH_3). The product melted at 211–213°dec. and gave no depression in m.p. when mixed with the triacid obtained from the isomeric cyanohydrin, VIII (R = —CH_2COOCH_3).



XXII XXIII XXIV

XXV XXVI

The absorption spectra (Fig. 1) of the cyano esters, VII (R = —CH_2COOCH_3, —$(CH_2)_4COOCH_3$ and H), the triacids, IV (R = —CH_2COOH or —$(CH_2)_4$-COOH), and the dihydrothiophene-3,4-dicarboxylic acid, A, were almost identi-

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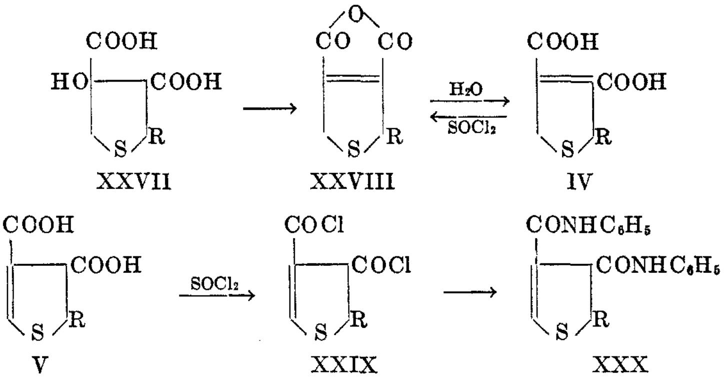
[2] There was a good probability that the reaction would give a thiophane rather than a penthiane ring as methyl β,β′-thiodipropionate does not cyclize appreciably with the conditions used.

cal, showing that in all these molecules the double bond was in the 3,4 position.[3]

A reagent which could be used to distinguish between a 2,5-dihydrothiophene-3,4-dicarboxylic acid (IV) and its 2,3-dihydro isomer was thionyl chloride. With the model compounds (R = H), IV formed an anhydride (XXVIII) whereas V (R = H), formed a diacid chloride characterized as its dianilide, XXX (R = H).[4]



Treatment of 3-hydroxythiophane-3,4-dicarboxylic acid (XXVII, R = H) with acetic anhydride gave a mixture of 2,5-dihydrothiophene-3,4-dicarboxylic anhydride (XXVIII, R = H) and 3-acetoxythiophane-3,4-dicarboxylic anhydride. As this dehydration took place to give a double bond in the 3,4-position, it is probable that the similar dehydration of 2-(γ-phenoxypropyl)-3-hydroxythiophane-3,4-dicarboxylic acid and XXVII (R = $C_6H_5O(CH_2)_3$—) also took place (8) to give the same diacid with a double bond in the 3,4 position.

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EXPERIMENTAL

3-Cyano-4-carbomethoxy-2,5-dihydrothiophene (I, R = H). To 80 cc. of liquid hydrogen cyanide and 0.5 cc. of 50% potassium hydroxide cooled in an ice-bath was added in portions a solution of 148 g. of 3-keto-4-carbomethoxythiophane (4) in 50 cc. of methanol, maintaining the temperature at 10–20°. After fifteen hours at 0–5°, the mixture was acidified with 3 cc. of 85% phosphoric acid and evaporated to dryness *in vacuo;* yield of crude cyanohydrin (II, R = H), 178 g.

Dehydration of 107 g. of the crude cyanohydrin in the same way as described for the corresponding ethyl ester (1) resulted in 75 g. (82%) of product, b.p. 120–125° (1 mm.), m.p. 44–50°. Recrystallization from heptane-benzene gave 65 g. (70%) of white crystals, m.p. 55–57°.

Anal. Calc'd for $C_7H_7NO_2S$: C, 49.7; H, 4.2; N, 8.3.
Found: C, 49.9; H, 4.3; N, 8.5.

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[3] The structures postulated by Surrey, Hammer, and Suter (10) for a similar series of compounds with R = phenyl do not agree with these results.

[4] Similarly, Baeyer (5) observed that Δ^1-tetrahydrophthalic acid formed an anhydride much more easily than did the isomeric Δ^2-tetrahydrophthalic acid.

2,5-Dihydrothiophene-3,4-dicarboxylic acid (IV, R = H). A mixture of 5 g. of I (R = H), 15 cc. of acetic acid, and 25 cc. of concentrated hydrochloric acid was refluxed for sixteen hours, then evaporated to dryness *in vacuo.* The residue was extracted with hot acetone, filtered from ammonium chloride, and again evaporated to give 4.9 g. of solid, m.p. 163–170°. Recrystallization from acetone-benzene resulted in 4 g. (77%) of white crystals, m.p. 183–184°.

Anal. Calc'd for $C_6H_6O_4S$: C, 41.3; H, 3.5.
Found: C, 41.4; H, 4.0.

Reduction with sodium amalgam in dilute alkali at 70–80° as previously described (1) gave a nearly quantitative yield of a mixture of the *cis* and *trans* isomers of thiophane-3,4-dicarboxylic acid.

4,5-Dihydrothiophene-3,4-dicarboxylic acid (V, R = H). A solution of 5 g. of I (R = H) in 25 cc. of alcohol was refluxed with 10 g. of sodium hydroxide in 25 cc. of water for sixteen hours. The solution was acidified, clarified by filtration, and extracted three times with ethyl acetate. Dried with magnesium sulfate, the extracts were evaporated to dryness *in vacuo.* The residual solid (5 g., m.p. 165–172°) was recrystallized from acetone-benzene, white crystals, m.p. 180–181° dec.; yield, 3.3 g. (64%). A mixture with 2,5-dihydrothiophene-3,4-dicarboxylic acid (IV, R = H) (isomer A) melted below 150°.

Anal. Calc'd for $C_6H_6O_4S$: C, 41.3; H, 3.5.
Found: C, 41.5; H, 3.8.

Reduction of 4,5-dihydrothiophene-3,4-dicarboxylic acid (V, R = H). Attempted reduction of this compound (isomer B) with sodium amalgam in dilute alkali at 70–80° as previously described (1) resulted in recovery of 94% of somewhat impure starting material, m.p. 165–168° dec., identified by mixed m.p.

A solution of 3.3 g. of isomer B in 60 cc. of 1 *N* sodium hydroxide was stirred with 125 g. of 2% sodium amalgam on the steam-bath for four hours. The reaction mixture was worked up as usual (1); yield after recrystallization from benzene, 2.1 g. (64%), m.p. 124–125°, resolidifies and remelts at 134–135°. A mixture with an authenic sample of *trans*-thiophane-3,4-dicarboxylic acid (1) gave no depression in the m.p. By retreatment of the filtrate with sodium amalgam as just described, an additional 0.40 g. (12%) of *trans* diacid was obtained with the same m.p.

When pure *cis*-thiophane-3,4-dicarboxylic acid (1) was heated with 20% alkali on the steam-bath for four hours, 60% of *trans*-thiophane-3,4-dicarboxylic acid was obtained, m.p. and mixed m.p. 135–136°.

2-Propyl-3-carbomethoxy-4,4-dibutylthiothiophane. A mixture of 50 g. of 2-propyl-3-carbomethoxy-4-ketothiophane (8) and 50 cc. of *n*-butyl mercaptan was treated with hydrogen chloride gas until turbid (about five minutes). After twenty-two hours, during which a layer of water separated, the oil was dissolved in benzene and washed twice each with 10% sodium hydroxide and water. Distillation gave 50 g. (55%) of product, b.p. 158–162° (1 mm.), n_D^{26} 1.5373.

Anal. Calc'd for $C_{17}H_{32}O_2S_3$: C, 56.1; H, 8.9.
Found: C, 56.6; H, 8.8.

2-Propyl-4-n-butylthio-2,5-dihydrothiophene-3-carboxylic acid. A solution of 5.6 g. of the above mercaptal in 25 cc. of alcohol and 6 g. of potassium hydroxide in 6 cc. of water was refluxed for sixteen hours, diluted with water, acidified, and extracted with benzene. The benzene layer was extracted with 5% sodium hydroxide and water. The latter two were combined and acidified. The oil was extracted with benzene. The residue on evaporation was recrystallized from dilute alcohol, then benzene-petroleum ether, white crystals, m.p. 137–137.5°.

Anal. Calc'd for $C_{12}H_{20}O_2S_2$: C, 55.3; H, 7.7.
Found: C, 55.6; H, 7.4.

The yield was poor, and most of the starting material could be recovered.

Methyl β-carbomethoxy-β,β′-thiodipropionate (XII). To a mixture of 580 g. of methyl β-mercaptopropionate (8) and 5 cc. of piperidine was added dropwise with stirring and ice-cooling 640 cc. of methyl maleate, at such a rate that the temperature was 35–40° (twenty minutes). The solution was allowed to stand for one hour, and was distilled. After a fore-run of methyl fumarate, the product was obtained as a colorless oil, b.p. 155–165° (1 mm.); yield, 1244 g. (98%). The b.p. varies considerably with bath temperature.

Anal. Calc'd for $C_{10}H_{16}O_6S$: C, 45.5; H, 6.1.
Found: C, 46.0; H, 6.1.

2-Carbomethoxymethyl-3-keto-4-carbomethoxythiophane (*XIII*). To a solution of 100 g. of XII in 300 cc. of toluene and 35 cc. of methanol was added 25 g. of commercial sodium methoxide. The mixture was refluxed for two hours. The sodium methoxide dissolved soon after the b.p. was reached. Cooled to 5°, the reaction mixture was diluted with ice and water. The separated aqueous layer was immediately run into iced hydrochloric acid and the toluene extracted once more with ice-water. The oily keto ester was extracted with toluene, the extract was washed with aqueous sodium bicarbonate and water. Distillation gave 46 g. (52%) of a colorless oil, b.p. 135–155° (1 mm.), mainly at 145°. The product, which was suitable for the next step, solidified on standing. Several recrystallizations from benzene-petroleum ether gave white crystals, m.p. 71–74°.

Anal. Calc'd for $C_9H_{12}O_5S$: C, 46.6; H, 5.2.
Found: C, 46.4; H, 5.5.

In larger runs the yield was 35–45%. Without the methanol, the sodium methoxide became coated and the yield was poor.

2 - Carbomethoxymethyl - 3 - cyano - 4 - carbomethoxy - 2,5 - dihydrothiophene (*VII*, *R* = $-CH_2COOCH_3$). To 121 g. of molten XIII super-cooled to 20° was added quickly 40 cc. of hydrogen cyanide and 0.5 cc. of 50% potassium hydroxide. The mixture rapidly became homogeneous on swirling in an ice-bath. After fifteen hours at 0°, the mixture was acidified with 3 cc. of 85% phosphoric acid and volatile material was removed *in vacuo* on the steam-bath. The crude cyanohydrin, VIII (R = $-CH_2COOCH_3$) was dehydrated with 100 cc. of phosphorus oxychloride and 390 cc. of pyridine in 390 cc. of benzene in the same manner as described for I (R = H) except that the reaction was allowed to proceed for four hours. Distillation gave 90.4 g. (68%) of product, b.p. 155–165° (1 mm.), which solidified in the receiver. Recrystallization from benzene-heptane resulted in light yellow crystals, m.p. 88–89.5°.

Anal. Calc'd for $C_{10}H_{11}NO_4S$: C, 49.8; H, 4.6; N, 5.8.
Found: C, 49.4; H, 4.7; N, 6.1.

2-Carboxymethyl-2,5-dihydrothiophene-3,4-dicarboxylic acid (*IV*, *R* = $-CH_2COOH$). A mixture of 41.2 g. of recrystallized VII (R = $-CH_2COOCH_3$), 90 cc. of acetic acid, and 200 cc. of concentrated hydrochloric acid was refluxed for sixteen hours, then worked up as described for VII (R = H); yield of white crystals, 22.3 g. (56%), m.p. 211–213° dec.

Anal. Calc'd for $C_8H_8O_6S$: C, 41.3; H, 3.5.
Found: C, 41.7; H, 3.4.

2-Carboxymethylthiophane-3,4-trans-dicarboxylic acid (*XVI*). A solution of 25 g. of IV (R = $-CH_2COOH$) in 250 cc. of 5% sodium hydroxide was stirred with 400 g. of 2% sodium amalgam on the steam-bath for three hours. After the addition of 14 g. of sodium hydroxide, the mixture was heated on the steam-bath for fifteen hours. The solution was decanted from the mercury, acidified, saturated with salt and extracted with four 125-cc. portions of ethyl acetate. The combined extracts, dried with magnesium sulfate and Norited, were concentrated *in vacuo* until the product began to crystallize, then diluted with one volume of benzene; yield, 11.7 g. (47%), m.p. 183–185°. Recrystallization from acetone-ethyl acetate gave white crystals, m.p. 191–191.5°. Analytical values obtained for carbon and hydrogen on this molecule were quite variable.

The methyl ester was prepared in 80% yield by the continuous drying method (8) using methanol, chloroform, and sulfuric acid; b.p. 160–165° (1 mm.). Recrystallization from methanol gave white crystals, m.p. 47°.

Anal. Calc'd for $C_{11}H_{16}O_6S$: C, 47.8; H, 5.8.
Found: C, 48.3; H, 6.0.

2-Carboxhydrazidomethylthiophane-3,4-trans-dicarboxhydrazide. A mixture of 2.7 g. of 2-carbomethoxymethyl-3,4-trans-dicarbomethoxythiophane and 5.4 cc. of 100% hydrazine hydrate was heated on the steam-bath with shaking. In three minutes a crystal paste had formed. After being heated fifteen minutes more, the mixture was triturated with methanol; yield, 2.5 g. (93%), m.p. 241° dec. Recrystallization from water-methanol gave white crystals of unchanged m.p.

Anal. Calc'd for $C_8H_{16}N_6O_3S$: C, 34.8; H, 5.8; N, 30.5.
Found: C, 34.5; H, 6.1; N, 30.2.

2-Carbethoxyaminomethyl-3,4-trans-dicarbethoxyaminothiophane. To a solution of 2.3 g. of the above trihydrazide in 100 cc. of 1 *N* hydrochloric acid and 50 cc. of chloroform was added dropwise with stirring and ice-cooling a solution of 2.0 g. of sodium nitrite in 50 cc. of water over a period of twenty-five minutes. After being stirred ten minutes more, the mixture was separated and the aqueous layer extracted once more with chloroform. The combined chloroform extracts, dried with calcium chloride at 0°, were diluted with 50 cc. of absolute ethanol and refluxed for one hour. After removal of the solvent, the residue was recrystallized from dilute alcohol; yield, 1.2 g. (40%), m.p. 201–204°.

Anal. Calc'd for $C_{14}H_{25}N_3O_6S$: C, 46.3; H, 7.0; N, 11.7.
Found: C, 46.7; H, 7.3; N, 11.8.

2-Aminomethyl-3,4-trans-diaminothiophane (XIX) trihydrobromide. A mixture of 300 mg. of the above triurethan and 6 cc. of 48% hydrobromic acid was refluxed twenty-five minutes. The solution was cooled in an ice-bath, the product was collected on a glass filter and washed with acetone. After drying at 100°, the yield was 255 mg. (79%), of crystals which sintered at 170–200° and decomposed at 293°. Recrystallization from 48% hydrobromic acid gave white needles which partially melted with gas evolution at 170°, resolidified and remelted at 302° dec.

Anal. Calc'd for $C_5H_{16}Br_3N_3S \cdot 2H_2O$: C, 14.1; H, 4.7; N, 9.9.
Found: C, 14.4; H, 5.4; N, 10.0.

The tripicrate formed orange-yellow crystals from dilute methanol, m.p. 224° dec.

Anal. Calc'd for $C_{23}H_{22}N_{12}O_{21}S$: N, 20.1. Found: N, 20.0.

The trihydrobromide gave a triuramido derivative with potassium cyanate in 85% yield: white crystals from water, m.p. 282° dec.

Anal. Calc'd for $C_8H_{16}N_6O_3S$: C, 34.8; H, 5.8; N, 30.5.
Found: C, 34.8; H, 5.9; N, 30.2.

Methyl β-(carbomethoxymethylthio)glutarate (XXIV). To a mixture of 58 g. of methyl thioglycolate and 82.5 g. of methyl glutaconate (11) was added 0.6 cc. of piperidine. The temperature was kept below 50° by ice-cooling. After standing for sixteen hours, the mixture was dissolved in chloroform, washed with water and distilled: colorless oil, b.p. 155–163° (1 mm.); yield, 83.6 g. (60%).

Anal. Calc'd for $C_{10}H_{16}O_6S$: C, 45.5; H, 6.1.
Found: C, 45.1; H, 6.1.

2-Carbomethoxymethyl-3-carbomethoxy-4-ketothiophane (XXV). From 40 g. of XXIV, 13.5 cc. of methanol, 120 cc. of toluene, and 10 g. of sodium methoxide was obtained, after refluxing for one hour, 21 g. (60%) of colorless oil, b.p. 137–143° (1 mm.), according to the procedure described for the isomeric keto ester (XIII). Ferric chloride titration (4) indicated that the keto ester was 87% pure, containing 13% of the isomeric XXVI.

Anal. Calc'd for $C_9H_{12}O_5S$: C, 46.6; H, 5.2.
Found: C, 46.8; H, 5.3.

The semicarbazone formed white crystals from dilute methanol, m.p. 159–164°.

Anal. Calc'd for $C_{10}H_{15}N_3O_5S$: C, 41.7; H, 5.1; N, 14.5.
Found: C, 41.9; H, 5.6; N, 14.5.

2 - Carbomethoxymethyl - 3 - carbomethoxy - 4 - cyano - 2,5 - dihydrothiophene (*I, R* =

$-CH_2COOCH_3$). This compound was prepared in 77% yield in the same manner as described for the isomeric cyano ester (VII, R = $-CH_2COOCH_3$); yellow oil, b.p. 145–158° (1 mm.). A center cut at 147° was used for analysis.

Anal. Calc'd for $C_{10}H_{11}NO_4S$: C, 49.8; H, 4.6; N, 5.8.
Found: C, 49.7; H, 5.2; N, 5.6.

Acid hydrolysis as described for VII (R = $-CH_2COOCH_3$) gave 2-carboxymethyl-2,5-dihydrothiophene-3,4-dicarboxylic acid (IV, R = $-CH_2COOH$) in 37% yield, m.p. and mixed m.p. 211–213° dec.

2,5-Dihydrothiophene-3,4-dicarboxylic anhydride (XXVIII). A mixture of 0.50 g. of 2,5-dihydrothiophene-3,4-dicarboxylic acid, 5 cc. of benzene and 1.2 cc. of thionyl chloride was refluxed for twenty minutes, gas evolution being complete in ten minutes. Evaporation to dryness *in vacuo* and trituration with petroleum ether gave 0.35 g. (78%) of product, m.p. 164–166°. Recrystallization from benzene did not change the m.p.

Anal. Calc'd for $C_6H_4O_3S$: C, 46.2; H, 2.6.
Found: C, 46.2; H, 3.0.

4,5-Dihydrothiophene-3,4-dicarboxanilide (XXX, R = H). A mixture of 0.50 g. of 4,5-dihydrothiophene-3,4-dicarboxylic acid (V, R = H), 5 cc. of benzene, 1.2 cc. of thionyl chloride, and one drop of a solution of one drop of pyridine in 10 cc. of benzene was refluxed for ninety minutes, when gas evolution was complete. The solvent was removed *in vacuo*, leaving an oily acid chloride, which was converted to the dianilide with aniline in benzene; yield, 0.59 g. (63%), m.p. 183–188°. Recrystallization from benzene containing a little acetone afforded white crystals, m.p. 190–192°.

Anal. Calc'd for $C_{18}H_{16}N_2O_2S$: C, 66.7; H, 5.0; N, 8.6.
Found: C, 67.0; H, 5.2; N, 8.3.

3-Hydroxythiophane-3,4-dicarboxylic acid (XXVII, R = H). The cyanohydrin (II, R = H) from 35 g. of 3-keto-4-carbomethoxythiophane, 70 cc. of acetic acid, and 165 cc. of concentrated hydrochloric acid was refluxed for twenty-two hours. Diluted with 100 cc. of water, the solution was clarified with Norit, then evaporated to dryness *in vacuo*. The residue was dissolved in 100 cc. of water and the evaporation repeated. Extraction with acetone, filtration from ammonium chloride, and evaporation gave 43 g. (quant.) of *cis* and *trans* isomers as a buff-colored solid with a wide melting-point range.

This hydroxy diacid was refluxed two hours with 200 cc. of acetic anhydride, the excess anhydride was removed *in vacuo*, and the residue distilled at 1 mm. in a flask with a wide side arm. The distillate (35 g.), m.p. 113–153°, was recrystallized from benzene giving 14.2 g. (39%) of 2,5-dihydrothiophene-3,4-dicarboxylic anhydride (XXVIII, R = H), m.p. and mixed m.p. 163–166°. From the filtrate was isolated 8.8 g. (18%) of 3-acetoxythiophane-3,4-dicarboxylic anhydride, m.p. 85–90°.

Anal. Calc'd for $C_8H_8O_5S$: C, 44.4; H, 3.7.
Found: C, 44.8; H, 4.0.

SUMMARY

1. Dehydration of 2- or 5-alkyl-3-hydroxy-3-cyano-4-carbomethoxythiophanes forms cyano esters with a double bond in the 3,4 position of the thiophane nucleus.

2. Acid hydrolysis of 2- or 5-alkyl-3-cyano-4-carbomethoxy-2,5-dihydrothiophenes gives 2-alkyl-2,5-dihydrothiophene-3,4-dicarboxylic acids.

3. Hydrolysis of 3-cyano-4-carbomethoxy-2,5-dihydrothiophene with strong alkali yields 4,5-dihydrothiophene-3,4-dicarboxylic acid with rearrangement of the double bond to the 2,3 position.

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