BIOTIN. VIII. PENTHIANE-3,4-DICARBOXYLIC ACID

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It was recently demonstrated (1) that treatment of a 2-alkylthiophane-3,4cis-dicarboxylic ester (I) with hydrazine resulted in the formation of a 2-alkylthiophane-3,4-trans-dicarboxhydrazide (II), inversion of configuration having taken place. As carbocyclic cis-diesters form dihydrazides with retention of configuration (2), it seemed of interest to investigate whether inversion in this reaction was limited to the thiophane nucleus, cf. I, or was a property of sulfur containing rings in general. It has now been found that the penthiane nucleus, cf. X, behaves in an analogous fashion.



3-Carbethoxy-4-ketopenthiane (III) (3), when treated with hydrogen cyanide gave a cyanohydrin, IV, which could be dehydrated with phosphorus oxychloride and pyridine to 3-carbethoxy-4-cyano- Δ^3 -penthiene (V). Acid hydrolysis of the latter failed to form the unsaturated diacid, VI, but resulted in a polymeric product. Acid hydrolysis of the cyanohydrin, IV, (R = Me or Et) proceeded smoothly to a mixture of stereoisomeric 4-hydroxypenthiane-3,4-dicarboxylic acids (VII), which was dehydrated with acetic anhydride in excellent yield to Δ^3 -penthiene-3,4-dicarboxylic anhydride (VIII). The crystalline anhydride, on reduction with sodium amalgam in aqueous alkali, gave a mixture of the *cis* and *trans* forms of penthiane-3,4-dicarboxylic acid (IX).

The pure *trans*-diacid was obtained by esterifying the *cis*-trans mixture and treatment with methanolic sodium methoxide followed by alkaline hydrolysis. The *cis*-diacid, IX a, was obtained from this same mixture by boiling with propionic anhydride, distillation, and hydrolysis of the *cis*-anhydride.

When heated with hydrazine, both the *cis* and *trans*-3,4-dicarbomethoxypenthianes (X) gave the same dihydrazide, XI. That the latter had the *trans* configuration was demonstrated by acid hydrolysis back to *trans*-penthiane-3,4dicarboxylic acid (IX b).

Curtius degradation of *trans*-penthiane-3,4-dicarboxhydrazide (XI) to the *trans*-diurethan, XII, and subsequent hydrolysis with hydrobromic acid resulted in *trans*-3,4-diaminopenthiane dihydrobromide (XIII), characterized as its dicarbamido derivative (XIV) and dibenzoate (XV).

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EXPERIMENTAL

3-Carbethoxy-4-ketopenthiane (III). This compound was prepared by Dieckmann cyclization of ethyl β , β' -thiodipropionate in 32-35% yield according to the method of Bennett and Scorah (3). The corresponding methyl ester was obtained in 28% yield, b.p. 134-136° (12 mm.) and solidified after a few days.

Anal. Calc'd for C₇H₁₀O₃S: C, 48.2; H, 5.7.

Found: C, 47.8; H, 5.1.

3-Carbethoxy-4-cyano- Δ^3 -penthiene (V). To a mixture of 8.2 g. of 3-carbethoxy-4-ketopenthiane (III) and 8 cc. of liquid hydrogen cyanide cooled in an ice-bath was added 0.1 cc. of 50% potassium hydroxide. After fifteen hours at 0°, the mixture was acidified with 0.7 cc. of 85% phosphoric acid and the excess hydrogen cyanide removed *in vacuo*. The residual cyanohydrin, IV, dissolved in 30 cc. of benzene and decanted from the syrupy phosphates, was treated with 37 cc. of dry pyridine and 4 cc. of phosphorus oxychloride. The heat of reaction maintained a temperature of 42° for one hour. After being refluxed for two hours, the mixture was poured into iced hydrochloric acid and ether. The separated organic layer was washed successively two times each with cold 3 N hydrochloric acid, cold 3% potassium hydroxide and finally water. After removal of the solvent, the residue was distilled, yellow oil, b.p. 125-128° (1 mm.); yield, 6.2 g. (74%).

Anal. Calc'd for $C_9H_{11}NO_2S$: N, 7.1. Found: N, 7.4.

Hydrolysis of the cyano ester, V, with a boiling mixture of hydrochloric and acetic acids gave anomalous results. The glassy product appeared to be polymeric in nature instead of the diacid, VI, as it failed to distil when converted to the methyl ester and it was unaffected by sodium amalgam in dilute alkali.

4-Hydroxypenthiane-3,4-dicarboxylic acid (VII). 3-Carbethoxy-4-ketopenthiane (III) (8.2 g.) was converted to the cyanohydrin, IV, as described above. The latter was refluxed for nineteen hours with 16 cc. of acetic acid and 40 cc. of concentrated hydrochloric acid. After evaporation to dryness *in vacuo*, the mixture was diluted with 30 cc. of water twice and evaporated to dryness each time. The residue was extracted with acetone and filtered from ammonium chloride. The filtrate was again evaporated to dryness *in vacuo*. The residual mixture of isomers was an amber gum; yield, 10.0 g. (99%).

Anal. Calc'd for $C_7H_{10}O_5S$: C, 40.7; H, 4.9.

Found: C, 40.3; H, 4.7.

In larger runs it was necessary to add the keto ester in portions to the hydrogen cyanide and potassium hydroxide in order to keep the temperature from rising above 15°.

 Δ^3 -Penthiene-3,4-dicarboxylic anhydride (VIII). A mixture of 131 g. of crude 4-hydroxypenthiane-3,4-dicarboxylic acid (VII) and 650 cc. of acetic anhydride was refluxed for two and one-half hours, then evaporated to dryness *in vacuo*. The residue, dissolved in chloroform, was filtered through Celite to remove some insoluble tarry material, the solvent removed and the residue distilled, b.p. 134-136° (1 mm.); yield, 96 g. (94% based on the original keto ester, III). The distillate solidified in the receiver and was purified for analysis by recrystallization from benzene-petroleum ether; cream colored crystals, m.p. 82-83°.

Anal. Calc'd for C₇H₆O₂S: C, 49.3; H, 3.5.

Found: C, 49.1; H, 3.1.

cis- and trans-Penthiane-3,4-dicarboxylic acid. (IX). A solution of 95 g. of Δ^3 -penthiane-3,4-dicarboxylic anhydride (VIII) in 820 cc. of 5% sodium hydroxide was stirred with 1550 g. of 2% sodium amalgam at 80° for two hours. After decantation from the mercury, the solution was strongly acidified, saturated with salt, and extracted with ethyl acetate (6 l., in several portions. The combined extracts, dried with anhydrous magnesium sulfate were evaporated to dryness *in vacuo*. The semi-crystalline residue weighed 92 g. (87%) and was used without further purification. For analysis a sample was recrystallized from acetone-benzene, white crystals, m.p. 154-160°.

Anal. Calc'd for $C_7H_{10}O_4S$: C, 44.2; H, 5.3.

Found: C, 43.8; H, 5.6.

Esterification by the continuous drying method (1) using chloroform, methanol, and sulfuric acid gave the dimethyl ester, X, as a nearly colorless oil, b.p. $155-159^{\circ}$ (12 mm.).

trans-Penthiane-3,4-dicarboxylic acid (IX b). A solution of 3.5 g. of cis- and trans-3,4dicarbomethoxypenthiane (X) in 10 cc. of methanol containing 50 mg. of sodium was refluxed for two and one-half hours to invert the cis ester present to trans. To one-half of the solution was added 1.5 g. of potassium hydroxide. After being refluxed for about ten minutes, a crystalline potassium salt began to separate, which was dissolved by the addition of 3 cc. of water. The solution was refluxed for two hours, acidified, saturated with salt, and extracted several times with ethyl acetate. The dried extracts on evaporation in vacuo gave 1.5 g. of crystals which were recrystallized from acetone-benzene, m.p. 173-178°; yield, 1.1 g. (72%). Several more recrystallizations gave white crystals, m.p. 175.5-177°.

Anal. Calc'd for $C_7H_{10}O_4S$: C, 44.2; H, 5.3. Found: C, 44.6; H, 5.8. cis-Penthiane-3,4-dicarboxylic acid (IX a). A solution of 11 g. of cis- and trans-penthiane-3,4-dicarboxylic acid (IX) in 57 cc. of propionic anhydride was refluxed for two hours. The excess propionic anhydride was removed *in vacuo* and the residue distilled. The orange distillate of somewhat impure cis-penthiane-3,4-dicarboxylic anhydride boiled at 122-128° (1 mm.); yield, 5 g. (49%).

Anal. Calc'd for C7H 8O3S: C, 48.8; H, 4.7.

Found: C, 50.0; H, 4.6.

The anhydride was heated on the steam-bath with excess dilute sodium hydroxide for thirty minutes. The solution was acidified, saturated with salt and extracted several times with ethyl acetate. The dried extracts were evaporated and the residue recrystal-lized from acetone-benzene, white crystals, m.p. 166-167.5°; yield, 0.7 g. Further recrystal-lization raised the m.p. to 167-168°. A mixture with *trans*-penthiane-3,4-dicarboxylic acid (IX b) melted at 159-160°.

Anal. Calc'd for $C_7H_{10}O_4S$: C, 44.2; H, 5.3.

Found: C, 44.6; H, 4.7.

trans-Penthiane-3,4-dicarboxhydrazide (XI). (A). A mixture of 1.75 g. of the cis and trans isomers of 3,4-dicarbomethoxypenthiane (X) was converted to the trans ester as described under trans-penthiane-3,4-dicarboxylic acid. To the methanol solution was added 1.5 cc. of 85% hydrazine hydrate. After being refluxed for ninety minutes, the mixture was cooled and the product removed; yield, 1.2 g. (69%). Recrystallization from 60% propanol gave white needles, m.p. 206-208°.

Anal. Calc'd for C₇H₁₄N₄O₂S: C, 38.5; H, 6.5; N, 25.7.

Found: C, 38.4; H, 6.2; N, 25.8.

A solution of 0.5 g. of the above hydrazide in 6 N hydrochloric acid was heated on the steam-bath for one hour. Extraction with ethyl acetate and evaporation gave the free acid which was recrystallized from acetone-benzene; white crystals, m.p. 175-177°. The m.p. was not depressed on admixture with *trans*-penthiane-3,4-dicarboxylic acid (IX b), but depressed to 154-159° when mixed with the *cis* acid (m.p. 166-167°) (IX a).

(B). The cis-3,4-dicarbomethoxypenthiane (X a) prepared from 70 mg. of pure cisdiacid (IX a) and an excess of ethereal diazomethane was refluxed one hour with a little methanol containing excess hydrazine hydrate. The product which separated on cooling melted at 204-206° alone or when mixed with *trans*-penthiane-3,4-dicarboxhydrazide (XI).

trans-3, 4-Dicarbethoxyaminopenthiane (XII). To a solution of 7.5 g. of trans-penthiane-3, 4-dicarboxhydrazide (XI) in 97 cc. of 1 N hydrochloric acid was added 100 cc. chloroform. The mixture was stirred in an ice-bath and treated dropwise with 4.7 g. of sodium nitrite in 30 cc. of water over a period of one hour. After being stirred at 0° for an additional thirty minutes, the mixture was separated and the aqueous layer extracted with chloroform. The combined chloroform solutions were dried with calcium chloride at 0° for twenty minutes, then diluted with 75 cc. of absolute ethanol and refluxed for one hour. After removal of the solvent the residue was recrystallized from ethanol to give 4.0 g., m.p. 172-173°, and 2.0 g., m.p. 165-168°, of white crystals (total 63%).

Anal. Calc'd for C₁₁H₂₀N₂O₄S: C, 47.8; H, 7.3; N, 10.1.

Found: C, 47.7; H, 6.9; N, 10.3.

When the sodium nitrite was added over a period of ten minutes, the yield dropped to about 25% and much free nitrous acid was evolved.

trans-3,4-Diaminopenthiane dihydrobromide (XIII). A mixture of 0.75 g. of trans-3,4dicarbethoxyaminopenthiane (XII) and 7 cc. of 48% hydrobromic acid was refluxed for ten minutes, when solution was complete. It was clarified with Norit and cooled to 5°. The dihydrobromide formed white crystals, m.p. 295° dec.; yield, 0.7 g. (88%).

Anal. Calc'd for C₅H₁₄Br₂N₂S: C, 20.4; H, 4.8; N, 9.5.

Found: C, 20.3; H, 4.7; N, 9.3.

trans-3,4-Dicarbamidopenthiane (XIV). A solution of 100 mg. of trans-3,4-diaminopenthiane dihydrobromide (XIII) and 100 mg. of potassium cyanate in 3 cc. of water was allowed to stand for several hours. The white crystals which separated were recrystallized from water, m.p. 248°; yield, 50 mg. (67%). Anal. Calc'd for $C_7H_{14}N_4O_2S$: C, 38.5; H, 6.5; N, 25.7. Found: C, 39.0; H, 6.2; N, 25.6.

trans³-, 4-Dibenzoylaminopenthiane (XV). This compound was prepared from benzoyl chloride and trans-3, 4-diaminopenthiane dihydrobromide (XIII) by the usual Schotten-Baumann procedure. It was purified by recrystallization from pyridine, white crystals, m.p. 314-316°.

Anal. Calc'd for $C_{19}H_{20}N_2O_2S: C, 67.1; H, 5.9; N, 8.2.$ Found: C, 66.7; H, 5.8; N, 8.1.

SUMMARY

The cis and trans forms of penthiane-3,4-dicarboxylic acid have been synthesized and characterized.

cis-3,4-Dicarbomethoxypenthiane, when treated with hydrazine, gave transpenthiane-3,4-dicarboxhydrazide. An inversion of configuration took place in the same manner as in the analogous thiophane series.

Several derivatives of trans-3,4-diaminopenthiane have been described.

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