AN ABSTRACT OF THE THESIS OF

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Title: STUDY OF THE SYNTHESIS OF TRANS-CYCLOPENTANE-1,2-DICARBOXYLIC ACID

Abstract Approved: [redacted]
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The object of this study is the synthesis of trans-cyclopentane-1,2-dicarboxylic acid. Five procedures designed for the synthesis of this trans diacid are described in the literature. The procedure devised by Perkin in 1887, Fuson and Cole in 1938, and by Brenner in 1961 were investigated to determine which of these three offer the most practical method for the synthesis of trans-cyclopentane-1,2 dicarboxylic acid.

Perkin's procedure appears to be the most promising and the most practical procedure for the preparation of this diacid. This procedure consists of a three-step reaction. The starting materials diethyl malonate and 1,3-dibromopropane combine to form tetraethyl pentane-1,1,5,5-tetracarboxylate. This tetra ester upon being cyclized is hydrolyzed in a final step to produce trans-cyclopentane-1,2-dicarboxylic acid in a 7.4% yield. The crucial steps in this

procedure are the first and third reactions. After a modification of these crucial steps trans-cyclopentane-1,2-dicarboxylic acid was obtained in this laboratory in an over-all yield of 67%.

The procedure of Fuson and Cole starting with pimelic acid gave an over-all yield of 57.1% for the trans diacid. This method, however, is much more tedious involving five separate reactions.

Brenner's procedure starting with 2-carboethoxycyclohexanone gave trans-cyclopentane-1,2-dicarboxylic acid in an over-all yield of 67.2%. This procedure is far less practical than Perkin's for making the trans diacid on a large scale due to experimental complications and the tedious isolation of the product.

Study of the Synthesis of Trans-cyclopentane-1,2-dicarboxylic Acid

by

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STUDY OF THE SYNTHESIS OF TRANS-CYCLOPENTANE-1, 2-DICARBOXYLIC ACID

INTRODUCTION

Historical

Interest in the synthesis of the trans isomer of cyclopentane-1, 2-dicarboxylic acid stemmed from the discovery in 1950-52 of its ability to affect the permeability of cell membrane (11) and to inhibit succinic oxidase systems (12).

Trans-cyclopentane-1, 2-dicarboxylic acid was first reported by Perkin (9) in 1887 who synthesized this compound in a sequence of reactions starting with diethyl malonate. This ester was alkylated with 1, 3-dibromopropane to yield the ethyl ester of pentane-1, 1, 5, 5-tetracarboxylic acid (Figure 1, I).

Tetraethyl pentane-1, 1,5,5-tetracarboxylate was in turn treated with sodium ethoxide to convert it into the corresponding disodium salt which was then cyclized into the cyclic intermediate (Figure 1, II) through bromination. The cyclic tetra ester was then subjected to alkaline hydrolysis and decarboxylation yielding trans-cyclopentane-1, 2-dicarboxylic acid (Figure 1, III). This sequence of reactions are illustrated in Figure 1.

Although Perkin (9) published all the experimental details for these reactions he did not report any yield data for this procedure.

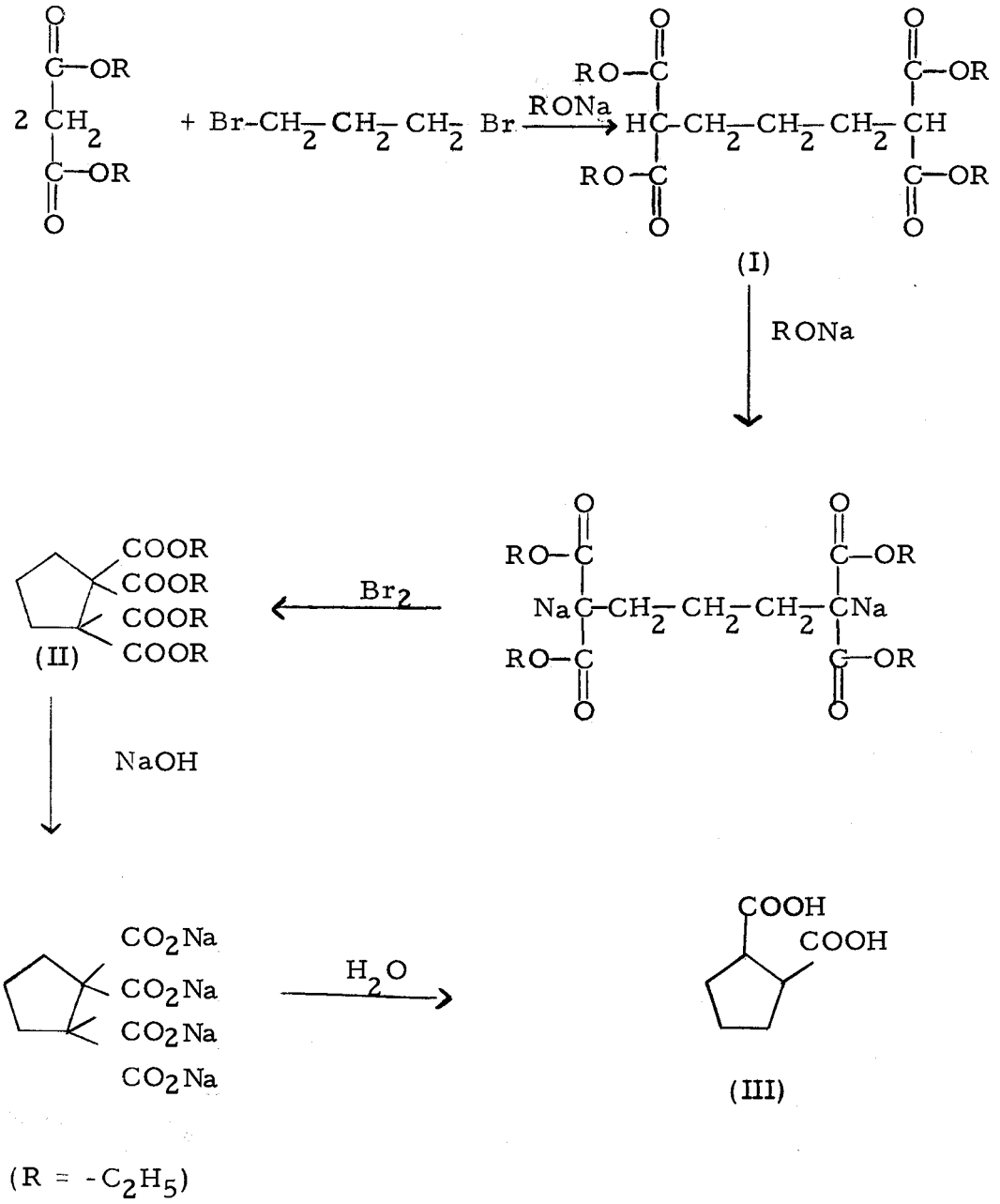


Figure 1. Trans-cyclopentane-1,2-dicarboxylic acid synthesis from the alkylation of diethyl malonate.

In 1894 Perkin (10) published an article in which he pointed out that certain aspects of his procedure were not entirely satisfactory referring specifically to the basic hydrolysis of the tetraethyl cyclic ester (Figure 1, II). This step was described as being time consuming with excess loss of material. As a consequence he recommended a modification in which he hydrolyzed this material using aqueous acetic and sulfuric acids. Refluxing for two days followed by steam distillation to remove the acetic acid and alcohol resulted in the crystallization of the crude product (Figure 1, III) which he separated, collected and purified by recrystallization from water using charcoal. Although Perkin (10) reported better yields in less time no actual data was given.

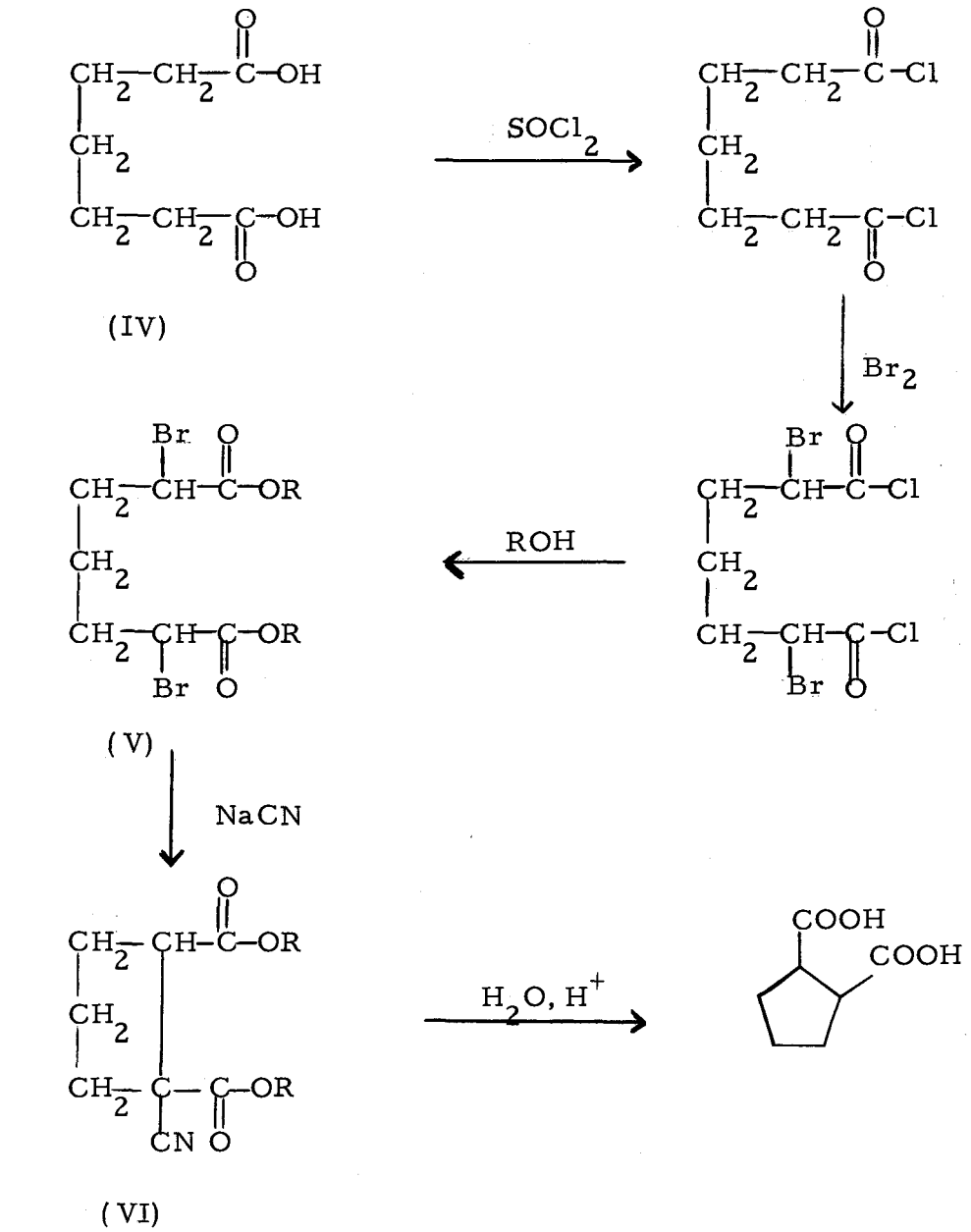
Sixty years later with the announcement of the discovery of certain biological properties of trans-cyclopentane-1, 2-dicarboxylic acid Bailey and Sorenson (2) further improved the synthesis of the acid starting with the modified hydrolysis procedure as described by Perkin (10).

These investigators (2) first modified the procedure by the trans esterification of acetic acid with the tetraethyl cyclopentane tetracarboxylic acid ester (Figure 1, II) removing the ethyl acetate product by careful fractionation, thus driving the reaction to completion. The resultant tetracarboxylic acid decarboxylated under these conditions to yield the desired trans-cyclopentane-1, 2-dicarboxylic

acid in 70% yield.

In 1949 Cason and Allen (5) investigated the reaction of diethyl malonate with 1, 3-dibromopropane as the first step in the synthesis of cyclobutane-carboxylic acid. In this work it was demonstrated that the use of excess of diethyl malonate led to decreasing yields of the cyclic derivative in favor of the tetraethyl ester of pentane-1, 1, 5, 5-tetracarboxylic acid (Figure 1, I). On the basis of these results Bailey and Sorenson (2) made a second modification of the original Perkin's synthesis by employing 12:1 ratio of diethyl malonate to 1, 3-dibromopropane. Using this huge excess of malonate these investigators (2) were able to prepare tetraethyl pentane-1, 1, 5, 5-tetracarboxylate in 81% yield.

In 1938 Fuson and Cole (6) synthesized trans-cyclopentane-1, 2-dicarboxylic acid by a procedure starting with pimelic acid (Figure 2, IV). This acid was converted to the ester via the acid chloride which was in turn brominated and then esterified to yield diethyl 2, 5-dibromopimelate (Figure 2, V). The reaction of this intermediate with sodium cyanide effected ring closure leading to diethyl 1-cyano-1, 2-cyclopentanedicarboxylate (Figure 2, VI). The hydrolysis of this derivative under refluxing conditions for two days gave the desired product in 51% yield. The reactions leading to trans-cyclopentane-1, 2-dicarboxylic acid synthesis by this procedure are shown in Figure 2.



(IV)

(V)

(VI)

(R = $-C_2H_5$) .

Figure 2. Trans-cyclopentane-1, 2-dicarboxylic acid synthesis from pimelic acid.

Later in 1945 Fuson et al. (7) modified this procedure by extending the time of the hydrolysis to four days. These workers (7) reported a 92% yield for the hydrolysis product.

In 1955 Birch et al. (3) prepared trans-cyclopentane-1, 2-dicarboxylic acid in yields ranging from 70 to 80%. This synthesis was carried out through the condensation of ethyl α,δ-diiodovalerate (Figure 3, VIII) with diethyl malonate followed by the hydrolysis and decarboxylation of the cyclopentane 1, 1, 2-tricarboxylic ethyl ester (Figure 3, IX) formed with concentrated hydrochloric acid. These investigators (3) obtained the ethyl ester of diiodovaleric acid (Figure 3, VIII) through a sequence of reactions starting with ethyl tetrahydrofuroate (Figure 3, VII). The complete sequence of these reactions is given in Figure 3.

Brenner (4) in 1961 reported the synthesis of trans-cyclopentane-1, 2-dicarboxylic acid starting with 2-carboethoxy cyclohexanone (Figure 4, X). This cyclohexanone derivative was converted to the 6-bromo-2-carboethoxycyclohexanone (Figure 4, XI) through bromination. Following treatment with an ethanolic solution of sodium hydroxide this compound rearranged so as to produce the cyclopentane dicarboxylic acid in 91% yield. This procedure is illustrated with the corresponding equations in Figure 4.

In the same year that Birch et al. (3) published their work Owen and Peto (8) reported 61% yield for the trans-cyclopentane-1, 2-

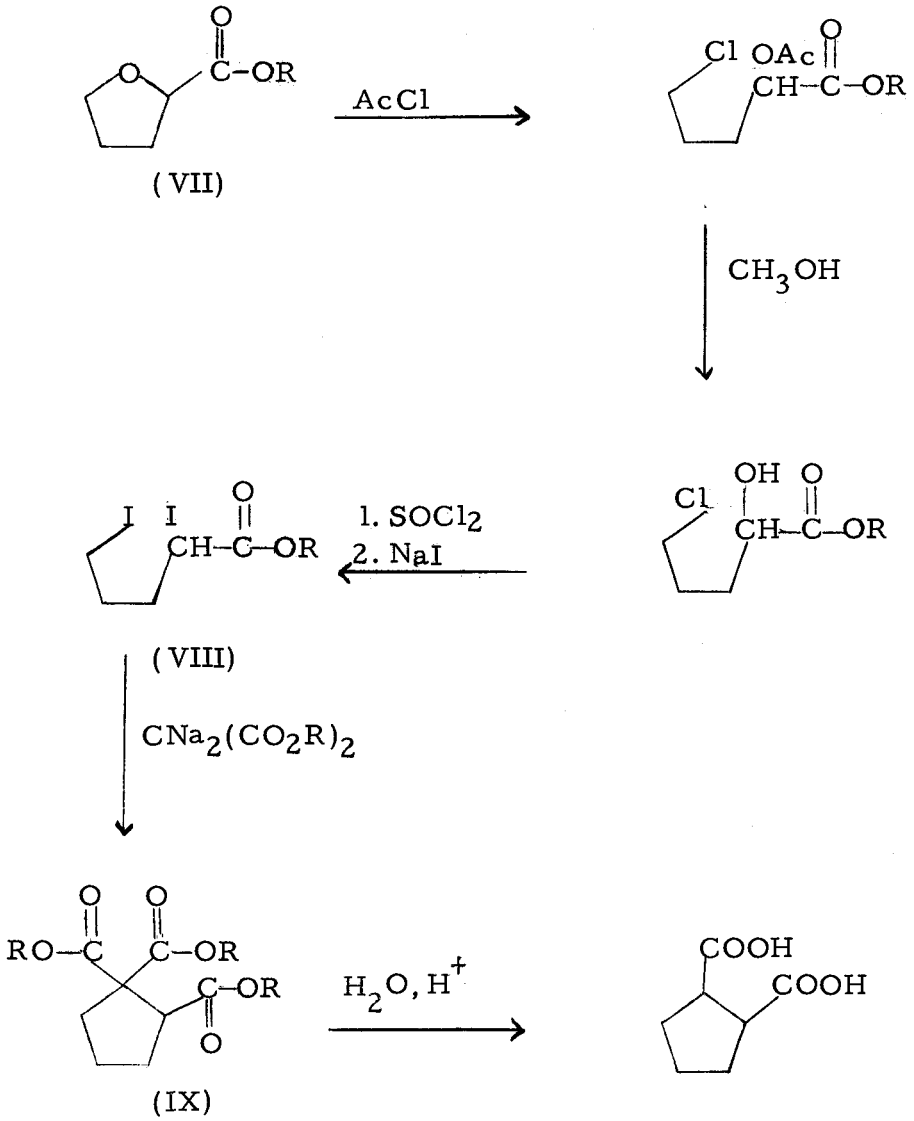


Figure 3. Trans-cyclopentane-1, 2-dicarboxylic acid synthesis from ethyl tetrahydrofuroate.

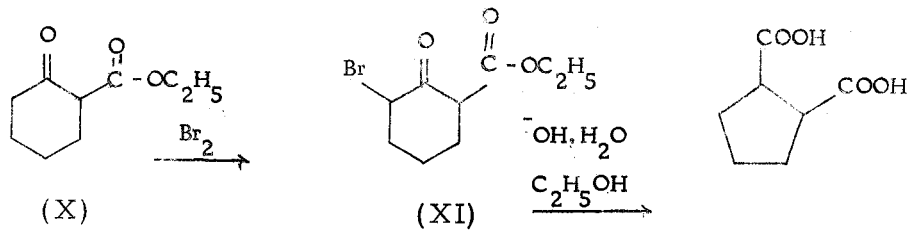


Figure 4. Trans-cyclopentane-1, 2-dicarboxylic acid synthesis from 2-carboethoxycyclohexanone.

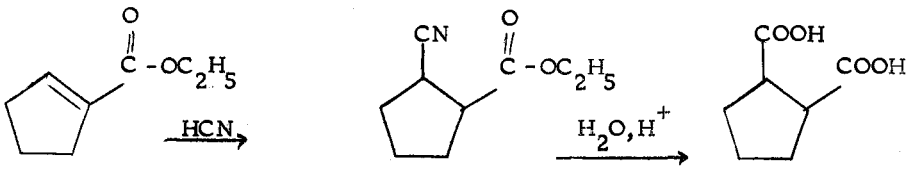


Figure 5. Trans-cyclopentane-1, 2-dicarboxylic acid synthesis from ethyl cyclopent-1-ene-1-carboxylate.

dicarboxylic acid by following the method proposed by Aspinall and Baker (1). According to these investigators(1) this acid can be prepared by the addition of hydrogen cyanide to the double bond of ethyl cyclopent-1-ene-1-carboxylate (Figure 5, XII) followed by hydrolysis with hydrochloric acid of the cyano ester (Figure 5, XIII) formed in the reaction. This method is illustrated in Figure 5.

Preparation of Derivatives of Trans-cyclopentane-1,2-dicarboxylic Acid

Owen and Peto (8) were able to prepare several cyclopentane derivatives starting with the sequence of reactions illustrated in Figure 5 for the preparation of the trans-cyclopentane-1,2-dicarboxylic acid. These workers esterified this acid with methanol-sulfuric acid to produce the trans-dimethyl ester (Figure 5, XIV) in 77% yield. The reduction of this ester with lithium aluminum hydride afforded trans-1,2-bishydroxymethylcyclopentane (Figure 5, XV).

Although cyclic compounds containing two trans-fused five membered ring are not very common Owen and Peto (8) synthesized the cyclic oxide trans-3-oxabicyclo [3.3.0] octane (Figure 6, XVII) in 67% yield. They esterified trans-1,2-bishydroxymethylcyclopentane (Figure 6, XV) with methanesulphonyl chloride in pyridine to form the trans-dimethanesulphonate derivative (Figure 6, XVI) which in turn was hydrolyzed in aqueous alkaline medium to yield the cyclic oxide.

In the same investigation these workers (8) carried out the synthesis of the sulfur counterpart of the cyclic oxide trans-3-thiabicyclo [3.3.0] octane (Figure 6, XXIII). This preparation was made by treating trans-1,2-bishydroxymethylcyclopentane (Figure 6, XV) with toluene-p-sulphonyl chloride to form trans-ditoluene-p-sulphonate (Figure 6, XXI) which was then treated with potassium thiolacetate and thiolacetic acid in ethanol to give trans-1,2-di

(acetylthiomethyl)cyclopentane (Figure 6, XXII). This bisthiolacetate was hydrolyzed to the dithiol and the resulting solution when treated with Raney nickel gave the trans-3-thiabicyclo [3.3.0] octane (Figure 6, XXIII).

Another derivative synthesized by Owen and Peto (8) was trans-2-methylcyclopentylmethanol (Figure 6, XX). This compound was made starting from the already prepared cyclic oxide (Figure 6, XVII). The tetrahydrofuran ring of the trans cyclic oxide was submitted to a fission with acetyl bromide to produce trans-2-bromomethylcyclopentylmethyl acetate (Figure 6, XVIII) which after reaction with potassium thiol acetate gave trans-2-acetylthiolcyclopentylmethyl acetate (Figure 6, XIX). This compound was dethionated with Raney nickel which after hydrolysis formed trans-2-methylcyclopentylmethanol. The complete sequence for these reactions are illustrated in Figure 6.

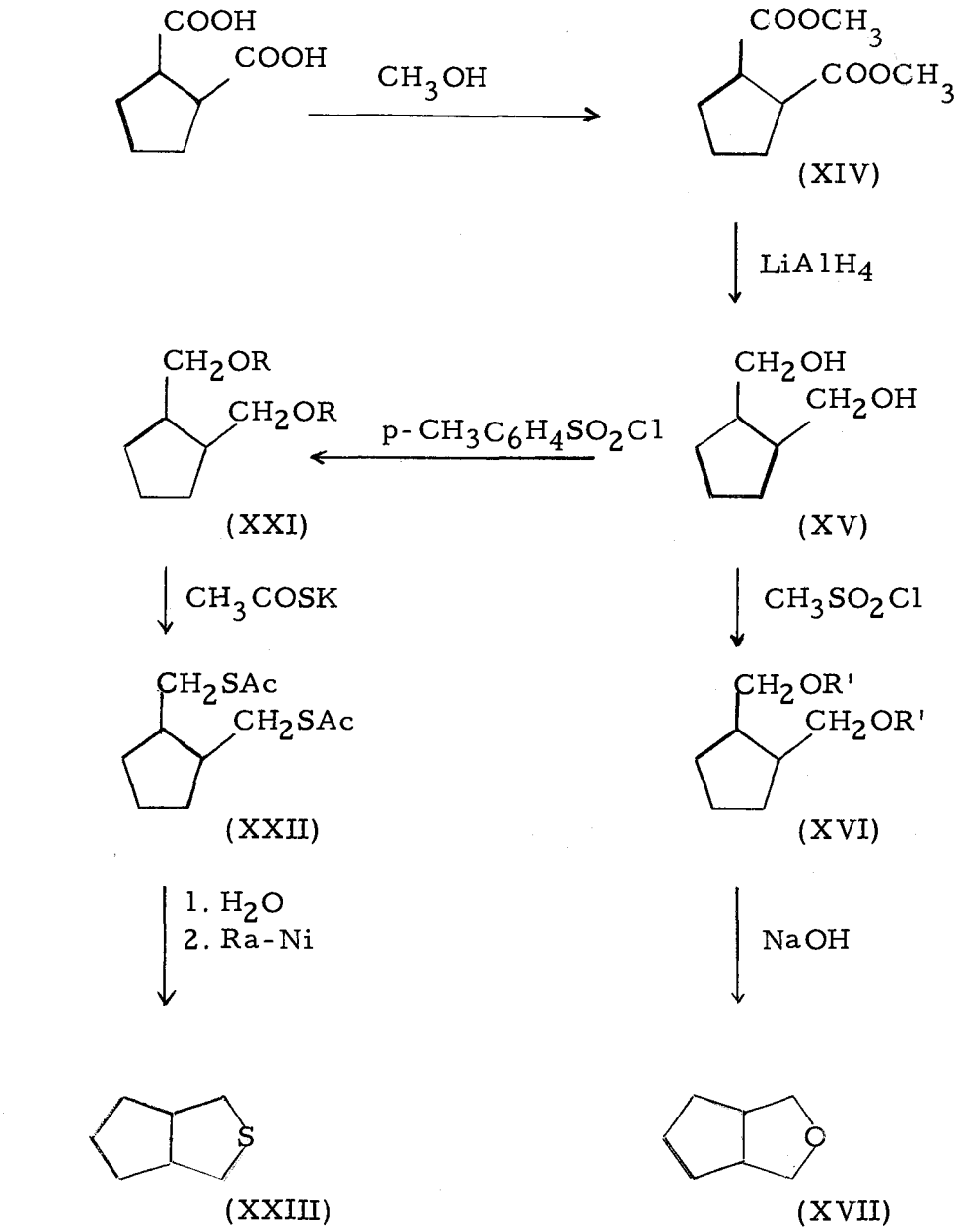


Figure 6. Preparation of derivatives of trans-cyclopentane-1, 2-dicarboxylic acid.

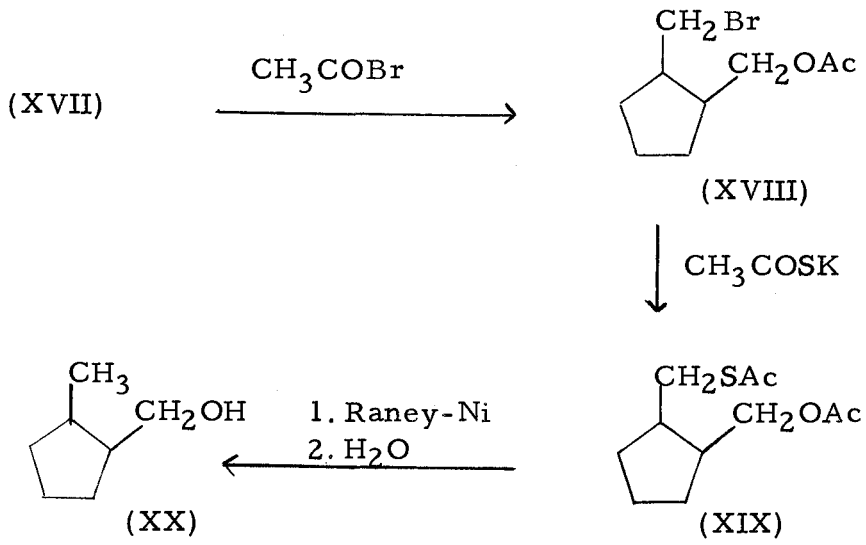


Figure 6. Continued.

DISCUSSION

In this laboratory we have studied the synthesis of trans-cyclopentane-1,2-dicarboxylic acid. From the methods already mentioned the procedure proposed by Aspinall and Baker (1) does not appear promising since the starting material ethyl cyclopent-1-ene-1-carboxylate is difficult to obtain.

To prepare trans-cyclopentane-1,2-dicarboxylic acid following the procedure suggested by Birch et al. (3) it is necessary to procure ethyl α,δ-diiodovalerate as the starting material. This compound is not commercially available so that it is necessary to synthesize it. In the same investigation these workers (3) noted that this diiodovalerate ethyl ester could be synthesized starting with ethyl tetrahydrofuroate which is also a not readily available material.

Brenner's procedure (4) for the preparation of trans-cyclopentane-1,2-dicarboxylic acid is a two-step synthesis starting with 2-carboethoxycyclohexanone which is a readily obtainable material although rather expensive. This two-step sequence of reactions consists first in the preparation of the 6-bromo-2-carboethoxycyclohexanone via the bromination of 2-carboethoxycyclohexanone. The second step for this procedure involves the alkaline hydrolysis of the 6-bromo-2-carboethoxycyclohexanone intermediate to yield the trans-cyclopentane-1,2-dicarboxylic acid.

Fuson and Cole (6) prepared the trans isomer of this cyclopentane diacid following a sequence of reactions starting with pimelic acid which is readily available. This procedure consists of several steps; first, the synthesis of pimeloyl dichloride from the reaction of pimelic acid with thionyl chloride. This is followed by the preparation of 2, 5-dibromopimelic acid which results from the bromination of pimeloyl dichloride. Esterification of the dibromopimelic acid with absolute ethanol yields diethyl 2, 5-dibromopimelate. Upon cyclization of this diethyl dibromo ester with sodium cyanide and hydrolysis of the ethyl 1-cyano-1, 2-cyclopentanedicarboxylate the product trans-cyclopentane-1, 2-dicarboxylic acid is obtained.

The original Perkin's procedure (9) offers a good route since the starting materials diethyl malonate and 1, 3-dibromopropane are both inexpensive and readily available. This procedure is a three-step operation going from the reaction of the starting materials to the formation of trans-cyclopentane-1, 2-dicarboxylic acid. The crucial steps in this procedure center around the synthesis of tetraethyl pentane-1, 1, 5, 5-tetracarboxylate and the hydrolysis of the cyclopentane-1, 1, 2, 2-tetracarboxylic acid ethyl ester under conditions which would favor the trans over the cis dicarboxylic acid.

From the above considerations it appears that of the five reported procedures the methods of Brenner (4), Fuson (6) and Perkin

(9, 10) offer the best approach to the synthesis of the trans-cyclopentane-1,2-dicarboxylic acid.

Since it is the purpose of this investigation to study the synthesis of trans-cyclopentane-1,2-dicarboxylic acid it seems feasible to make a comparison of these three methods; to determine whether it would be possible to effect improvements in either of these three procedures that could lead to a more practical preparation of the desired diacid.

EXPERIMENTAL

Brenner's Procedure

Trans-cyclopentane-1, 2-dicarboxylic acid was prepared following the directions given by Brenner (4). The experimental details were as follows:

6-Bromo-2-carboethoxycyclohexanone: A given amount of bromine (0. 146 mole) was slowly added to a well agitated solution of 25.0g(0. 146 mole) of 2-carboethoxycyclohexanone in 10 ml of dry ether. During the addition the reaction mixture was cooled in an ice bath with salt. After the addition was complete the reacting mixture was diluted with ether and poured onto 20. 0 g of sodium carbonate and ice. The ether extract was separated by means of a dropping funnel, and after distillation of the ether, the oily fraction was distilled under reduced pressure to yield 29. 6 g (82%) of the product boiling at 123-125^{o}/4 mm.

Trans-cyclopentane-1, 2-dicarboxylic acid: Twelve g of 6-bromo-2-carboethoxycyclohexanone was refluxed for one hour with a solution of nine g of sodium hydroxide in ten ml water and 150 ml of ethanol. After that nitrogen was bubbled through the solution, most of the alcohol was evaporated, and the residue acidified with hydrochloric acid. The solution was then saturated with ammonium chloride. The crude product was extracted with ether and after

evaporation the residue was recrystallized from benzene-methanol solution to yield 4.7 g of the trans diacid (82%). The over-all yield was 67.2%.

Fuson and Cole Procedure

According to the directions given by Fuson and Cole (6) trans-cyclopentane-1,2-dicarboxylic acid was synthesized from pimelic acid. In the last step of this synthesis the modification of Fuson et al. (7) was followed.

Pimeloyl dichloride: A mixture of 60 g of pimelic acid and 100 ml of thionyl chloride was heated under reflux for about five hours. After the excess of thionyl chloride had been removed at reduced pressure the residue was distilled to yield 64.2 g (87.1%) of the compound boiling at 115-118°/6 mm.

2,5-Dibromopimeloyl chloride: A given amount of bromine (0.64 mole) was slowly added through a separatory funnel to 64.0 g (0.32 mole) of pimeloyl dichloride. The mixture was then heated on a water bath at 60-65° for a period of six hours.

Diethyl 2,5-dibromopimelate: An excess of absolute ethanol was carefully added to the cooled and well stirred crude product containing the 2,5-dibromopimeloyl chloride. The excess of ethanol was then removed at reduced pressure. The ester after the addition of water was extracted with ether washed with with dilute sodium

carbonate and upon distillation under reduced pressure yielded 114.5 g (89.7%) of diethyl 2,5-dibromopimelate b.p. 178-180/6 mm.

Ethyl 1-cyano-1,2-cyclopentane dicarboxylate: Fifty g of diethyl 2,5-dibromopimelate were mixed with 25 g of sodium cyanide and 30 ml of absolute ethanol. The mixture was refluxed for 60 hours. After this refluxing period the mixture was cooled and filtered. The filtrate distilled in vacuo gave the cyano compound in 81.6% yield (24.5 g) boiling at 135-136°/3.7 mm.

Trans-cyclopentane-1,2-dicarboxylic acid: Twenty eight g of ethyl 1-cyano-1,2-cyclopentane dicarboxylate were heated under reflux with 100 ml of concentrated hydrochloric acid for 90 hours. Upon completion of this reflux period the solid which separated on cooling was filtered and recrystallized from water using charcoal. The yield of the trans diacid m.p. 161-163° was 16.8 g (90.1%). The over-all yield from pimelic acid was 57.1%.

Original Perkin's Procedure

Trans-cyclopentane-1,2-dicarboxylic acid synthesis according to the original Perkin's procedure (9) consisted of three steps. Synthesis of tetraethyl pentane-1,1,5,5-tetracarboxylate in the first step followed by the formation of tetraethyl cyclopentane-1,1,2,2-tetracarboxylate in the second step. The last step involved the hydrolysis of the cyclopentane tetracarboxylic acid ester to yield the

dicarboxylic pentane acid as the trans isomer.

Step one. A cool mixture of diethyl malonate and 1, 3-dibromopropane in the ratio 2:1 respectively was slowly added to a cooled solution of sodium ethoxide. After standing for a moment the reaction set in with evolution of heat. The sodium bromide which formed was dissolved with water and a few drops of sulfuric acid. After extraction with ether followed by distillation, the crude oil was subjected to a steam distillation in order to separate the tetraethyl pentanecarboxylic acid ester from any unchanged 1, 3-dibromopropane, unreacted diethyl malonate and from the by-product diethyl cyclobutane-1, 2-dicarboxylate. The tetraethyl pentanetetracarboxylic acid ester that remained in the flask was extracted with ether, washed with dilute sodium carbonate, dried over calcium chloride and purified by fractionation under reduced pressure. Following these directions tetraethyl pentane-1, 1, 5, 5-tetracarboxylate was obtained in 19-21% yield.

Step two. In order to prepare the cyclopentane tetracarboxylic acid ester intermediate Perkin (9) mixed a cooled solution of tetraethyl pentane-1, 1, 5, 5-tetracarboxylate in ether with a cooled ethereal solution of sodium ethoxide. After the disodium salt of the tetra ester separated bromine was added and the oil formed in this cyclization process was extracted with ether. Removing the ether left the crude tetraethyl cyclopentane-1, 1, 2, 2-tetracarboxylate.

Step three. To get the diacid Perkin (9) hydrolyzed the crude tetraethyl cyclopentane-1, 1, 2, 2-tetracarboxylate (without any further purification) with potassium hydroxide in a little alcohol. The potassium salt was treated with an excess of sulfuric acid and the free cyclopentane-1, 1, 2, 2-tetracarboxylic acid was extracted at least 20 times with ether. After drying the ethereal solution over calcium chloride followed by the usual work up, the cyclopentane-tetracarboxylic acid was obtained as a brownish syrup. This syrup-like tetra acid heated at 200-220° yielded trans-cyclopentane-1, 2-dicarboxylic acid in an impure form. In this investigation Perkin (9) gave a long procedure for purifying the trans-cyclopentane-1, 2-dicarboxylic acid. This step yielded 12.6% for the impure compound. At this point the over-all yield was 2.4-2.6%.

This original last step (9) years later was considered by Perkin (10) to be time and material consuming. In a new procedure (10) this step was modified in an attempt to get better yields for the trans diacid. In this modified procedure the crude tetraethyl cyclopentane-1, 1, 2, 2-tetracarboxylate was hydrolyzed in an aqueous solution of acetic and sulfuric acids in a reflux apparatus for two days. After the refluxing period the acetic acid and ethanol were removed by steam distillation. The brownish crust that remained in the flask was then purified by recrystallization using charcoal. Using this modification and after two days of refluxing trans-cyclo-

pentane-1, 2-dicarboxylic acid was obtained in 35.4% yield; the overall yield was calculated to be 6.7% to 7.4%.

Each of these steps of Perkin's procedure have been studied in this laboratory. Special attention was given to the first and third steps which are the most important in the synthesis of trans-cyclopentane-1, 2-dicarboxylic acid by this route.

The first step of the original procedure (9) for the synthesis of tetraethyl pentane-1, 1, 5, 5-tetracarboxylate was carried out using diethyl malonate in varying ratios. The yields of the tetra ester are given in Table 1. Run 1 to 4 were worked out following the original conditions (9) and in the same ratio. In run 5 a large excess of diethyl malonate was used under the same original conditions. Runs 6, 7, 8, 9 and 10 were further modified by allowing the formation of the enolate anion first. This step was made by adding cooled diethyl malonate to a cooled solution of sodium ethoxide in absolute alcohol. Using care 1, 3-dibromopropane was added dropwise to the solution. After the addition was completed the mixture was heated on a water bath with continued stirring for three hours. Under these conditions it was found that the best yield of tetraethyl pentane-1, 1, 5, 5-tetracarboxylate was obtained when the ratio 6:1 of diethyl malonate to 1, 3-dibromopropane was employed.

The second step for the formation of tetraethyl cyclopentane-1, 1, 2, 2-tetracarboxylate was carried out under the original conditions

Table 1. Yields of tetraethyl pentane-1, 1, 5, 5-tetracarboxylate from the alkylation of diethyl malonate with 1, 3-dibromopropane.

Run No.	Ratio of Reagents			Yield of Tetraethyl pentane-1, 1, 5, 5-tetracarboxylate (%)
	1, 3-Dibromopropane	Sodium	Diethyl Malonate	
1 to 4	1	2	2	19 - 21
5	1	8	8	32.6
6	1	2	5	78.3
7	1	2	6	84.6
8	1	2	7	84.2
9	1	2	8	73.68
10	1	2	12	71.6

(9). This cyclic intermediate product without any further purification was used in the third step.

Trans-cyclopentane-1, 2-dicarboxylic acid was prepared in the third step following the modified directions (10). Under these conditions the trans diacid was obtained in 35.4% yield. By increasing the reflux period to three days the yield was improved up to 41.7%. Changing the hydrolysing agent from the aqueous mixture of acetic and sulfuric acids to concentrated hydrochloric acid and increasing the reflux time to five days gave 79.2% yield of the cyclopentane dicarboxylic acid.

Based on these improvements for the first and third steps of the original (9) and modified (10) directions proposed by Perkin the following procedure for the synthesis of tetraethyl pentane-1, 1, 5, 5-tetracarboxylate and trans-cyclopentane-1, 2-dicarboxylic acid was devised.

Tetraethyl pentane-1, 1, 5, 5-tetracarboxylate: In a 1-liter three-necked flask carrying a separatory funnel, mechanical stirrer and a reflux condenser fitted with a calcium chloride tube, a solution of sodium ethoxide was prepared by adding 11.5 g of fresh-cut sodium in small pieces to 350 ml of dried absolute ethanol.[1]

[1] Sodium, 3.5 g, was added to 450 ml of 99.5% ethanol. After it has dissolved 13.8 g of ethylphthalate was added. The solution was heated to reflux for two hours and 350 ml of alcohol were distilled directly into the reaction flask.

The mixture was cooled in an ice bath and 240.25 g (1.5 mole) of cooled diethyl malonate were slowly added through the dropping funnel. 1,3-Dibromopropane, 50.50 g (0.25 mole), was added dropwise by means of the separatory funnel. After the addition was completed the reacting mixture was heated on a water bath and refluxed with stirring for three hours. Upon completion of the reflux period the alcohol was removed by distillation until the bulk of it had been recovered. After cooling 400 ml of water were added together with few drops of sulfuric acid to dissolve the sodium bromide produced in the reaction. The oily compound was then separated by extraction with three 200 ml portions of ethyl ether. The ether was removed by distillation and the reaction mixture was subjected to a rapid steam distillation until oily drops were no longer observed in the distillate.[2] The tetraethyl pentanetetracarboxylic acid ester that remained in the flask was cooled and extracted with two 100 ml portions of ether; this extract was dried over calcium chloride. The solution was filtered and after removal of the ether the residue was purified by vacuum distillation. The yield of product boiling at 185-190°/1.5 mm was 76.2 g (84.6%).

Tetraethyl cyclopentane-1,1,2,2-tetracarboxylate: Fifty four g

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[2] The steam distillation separates unchanged diethyl malonate together with diethyl cyclobutane-1,1-dicarboxylate formed as a side reaction from the desired tetraethyl pentane-1,1,5,5-tetracarboxylate.

of tetraethyl pentane-1, 1, 5, 5-tetracarboxylate was dissolved in 150 g of pure dry ether and then an ethereal solution[3] of sodium ethoxide containing 6.9 g of sodium was slowly added. The operation was effected in an ice bath and the reacting components were carefully cooled before mixing. After ten minutes 24 g of bromine was slowly added through a dropping funnel, the mixture being well agitated during the addition. After the addition was completed the product was allowed to stand for an hour and then mixed with an equal volume of water. The aqueous layer was extracted with ether and after distilling off the ether crude tetraethyl cyclopentane-1, 1, 2, 2-tetracarboxylate was obtained.

Trans-cyclopentane-1, 2-dicarboxylic acid: The crude tetraethyl cyclopentane-1, 1, 2, 2-tetracarboxylate was dissolved in 300 ml of concentrated hydrochloric acid and the mixture placed in a round bottomed flask fitted with a reflux condenser. The mixture was heated under reflux for five days. After this reflux period the crystalline compound that separated after cooling was collected. The crude material was decolorized with charcoal and recrystallized from water to give 17.3 g (73%) of white crystals of trans-cyclopentane-1, 2-dicarboxylic acid m. p. 161-163°. The mother liquor was

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[3] This solution was prepared by dissolving 6.9 g of sodium in as little alcohol as possible and then while still hot pouring it in about five times the volume of dry ether.

concentrated and the final yield was 18.8 g (79.2%). The over-all yield for this product was 67%

SUMMARY AND CONCLUSIONS

Of the five published procedures for the synthesis of the trans-cyclopentane-1, 2-dicarboxylic acid Birch et al. (3) and Aspinall and Baker (1) were not confirmed in this laboratory since the starting material ethyl α, δ-diiodovalerate and ethyl cyclopent-1-ene-1-carboxylate respectively are rather rare compounds which were not available. From the data given in the literature the procedure described by Birch et al. (3) gave an over-all calculated yield of 46.9% for the trans-cyclopentane-1, 2-dicarboxylic acid. On the other hand calculations made from the data given by Aspinall and Baker (1) and in the modification for the same procedure by Owen and Peto (8) starting with ethyl pent-1-ene-1-carboxylate indicated the trans-cyclopentane-1, 2-dicarboxylic acid could be affected in an over-all yield of 61%.

Of the three procedures investigated Brenner's (4) started with 2-carboethoxycyclohexanone, which upon bromination and hydrolysis of the 6-bromo-2-carboethoxycyclohexanone intermediate, gave a good yield for the synthesis of trans-cyclopentane-1, 2-dicarboxylic acid. In spite of the 67.2% over-all yield obtained for the trans diacid this procedure has the disadvantage of starting with 2-carboethoxycyclohexanone which is an expensive material. This fact makes this procedure impractical for synthesizing the trans diacid on a large scale. Also this procedure is somewhat complicated in the last

step of the Favorsky rearrangement leading to the isolation of the cyclic diacid.

The second procedure investigated was that of Fuson and Cole (6) with the modifications of Fuson et al. (7) which gave 57.1% over-all yield for the trans-cyclopentane-1,2-dicarboxylic acid. This procedure consisted of a sequence of five reactions starting with pimelic acid. This sequence of reactions was much more time consuming and gave a slightly decreased over-all yield for the trans-cyclopentane-1,2-dicarboxylic acid.

Trans-cyclopentane-1,2-dicarboxylic acid prepared by the original Perkin's procedure (9) as modified by himself (10) gave an over-all yield of 7.4%. Since this procedure was by far the simplest the crucial steps one and three were investigated. Both steps were modified thereby improving this method so as to give an over-all yield of 67% for the trans-cyclopentane-1,2-dicarboxylic acid.

On the basis of these studies the procedure of Perkin as modified by this laboratory appears to be the most practical for the synthesis of trans-cyclopentane-1,2-dicarboxylic acid.

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