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Further Study of Syntheses of *dl*-2, 3-Dicarboxycyclopentylacetic Acids

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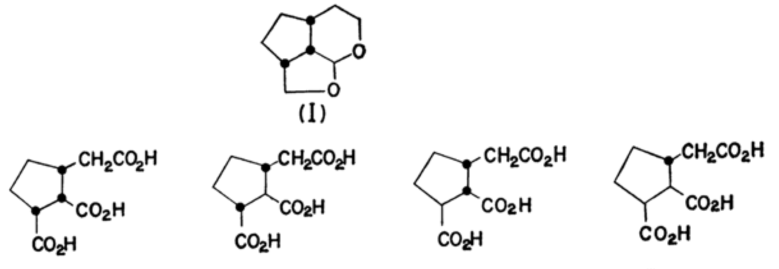
The assignment of the configuration of racemic *trans-trans* and *cis-cis*-2, 3-dicarboxycyclopentylacetic acid previously proposed has been confirmed by the syntheses of these compounds through other unambiguous reaction sequences. The *trans-cis*-isomer has been prepared by the epimerization of the 3-carboxyl group of the *cis-cis*-isomer, but the attempt to synthesize the fourth isomer (*cis-trans*) has been unsuccessful.

It has been reported that the chromic acid oxidation of tetrahydroanhydrodesoxyaucubigenin (I) gives the optically active *cis-cis*-2, 3-dicarboxycyclopentylacetic acid (IIa) as the key compound for determining the carbon framework of aucubin; from this the *trans-trans* (IIb) and *trans-cis** isomer (IIc) can be derived by the epimerization of either one of two carboxyl groups attached to the cyclopentane ring. Moreover, the stereochemistry of each isomer has been established, along with the chemical properties and the course of formation.[1]

The synthesis of *dl-trans-trans*-tricarboxylic acid (IIb), on the other hand, has been accomplished by one of the present authors[2] starting from the Michael condensation of dimethyl Δ^2-cyclopentene-1, 2-dicarboxylate (III) with diethyl malonate.[3] IIb was transformed to the isomer, the configuration of which has been presumed to be a *cis-cis* relation (IIa) because of its identity with the natural IIa (see below).

The present paper will describe the syntheses of IIa and IIb according to alternative reaction sequences[4] and the isomerization of IIa to IIc.



(I) (IIa) (IIb) (IIc) (IId)

Fig. 1

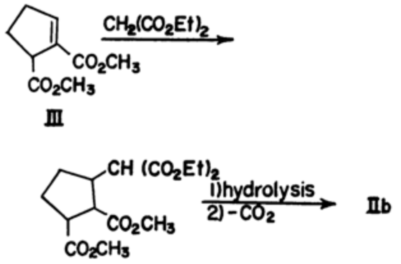
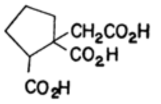


Fig. 2



(IV)

Fig. 3

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* In this and other designations in this paper the relationship between two carboxyl groups attached to the cyclopentane ring is given first, and that between the carboxymethyl group and the adjacent carboxyl group, second.

[1] a) S. Fujise, H. Obara and H. Uda, *Chem. & Ind.*, **1960**, 289; *J. Chem. Soc. Japan, Pure Chem. Sect.* (*Nippon Kagaku Zasshi*), **81**, 677 (1960). b) H. Uda, ibid., **81**, 1865 (1960).

[2] H. Obara, ibid., **81**, 1871 (1960).

[3] J. Grimshaw and H. R. Juneja (*Chem. & Ind.*, **1960**, 656) stated, without any evidence, that the migration of the double bond in III took place, giving the Δ^1-isomer, before the addition of diethyl malonate, and that, therefore, the final product was apparently 1, 2-dicarboxycyclopentylacetic acid (IV), not IIb. This possibility, however had already been excluded by the synthesis of IV through an unambiguous route,[2] and unlike III, the Δ^1-isomer undergoes the Michael addition accompanied by a migration of the double bond to the Δ^2-position, giving the same adduct as from III.[2]

[4] An attempt to prepare IIa by the Dieckmann cyclization of diethyl 3-ethoxycarbonylmethyladipate was unsuccessful. S. Fujise, H. Obara and K. Kurosawa, *J. Chem. Soc. Japan, Pure Chem. Sect.* (*Nippon Kagaku Zasshi*), **82**, 370 (1961).

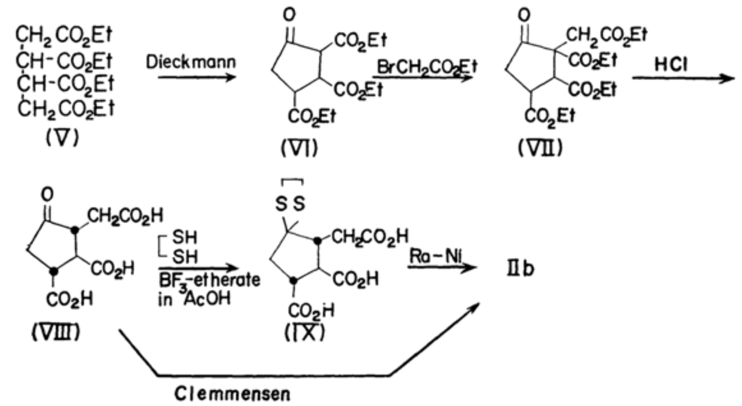

Fig. 4

2, 3, 4 - Triethoxycarbonylcyclopentanone (VI), which appeared to be the most satisfactory precursor for the synthesis of IIb, was prepared from tetraethyl butane-1, 2, 3, 4-tetracarboxylate (V) by the Dieckmann cyclization in a good yield. The condensation of the sodio derivative of VI with ethyl bromoacetate afforded a keto tetraester (VII), b. p. 195—210°C/2 mmHg; then VII was hydrolyzed and decarboxylated to yield 2, 3-dicarboxy-5-oxo-cyclopentylacetic acid (VIII), m.p. 215—216°C, by refluxing it with 6 N hydrochloric acid. The conversion of VIII into IIb was achieved by transforming it into a thioketal (IX) and then subjecting the IX to desulfurization with Raney nickel or directly by the Clemmensen reduction. The IIb thus obtained, m. p. 160°C, was identical with a sample of IIb which had been prepared from III, as has been mentioned above; this was determined by a comparison of the infrared spectra and by a mixed melting point determination. Since three substituents of VIII or of the Michael addition product of III will be preferentially oriented towards sterically less hindered (in another words, thermodynamically more stable) directions in such a strongly basic reaction condition, IIb must have the expected *trans-trans* arrangement.

In a series of experiments on the naturally-derived compounds, the *trans-trans* isomer (IIb), prepared by the epimerization of the triester of the *cis-cis*-tricarboxylic acid (IIa), produced the same dimeric trianhydride (X) as that obtained from IIa, involving the anomalous isomerization of one carboxyl group towards the sterically unfavorable side, upon being treated with boiling acetic anhydride; X returned to IIa on hydrolysis.[1b] This process has been applied to the racemic IIb, giving an isomer.[2] However, there has been no definite evidence about the stereochemistry of this isomer; the assignment of *cis-cis* relationship as in the natural IIa has been tentatively made only on the basis of the course of formation and its identity with the natural IIa. In order to clarify this point, an alternative synthesis of IIa was carried out. The catalytic hydrogenation of the unsaturated lactone ester (XI) afforded the corresponding saturated compound, *cis-cis*-2-(2′-hydroxyethyl)-5-carboxycyclopentylcarboxylic acid δ-lactone (XII), resulting from the *cis* attack of hydrogen on the double bond from the side opposite an allylic substituent.[5] The chromic acid oxidation of XII gave the desired *cis-cis* isomer (IIa), m. p. 176—177°C,[5,6] which was identical with a sample of IIa derived from IIb via the dimeric trianhydride (X) as shown by a study of the infrared spectra and by a mixed melting point determination. These results provide convincing evidence for the correctness of the assumed reaction course from IIb to IIa via X and for the stereochemistry of IIa.

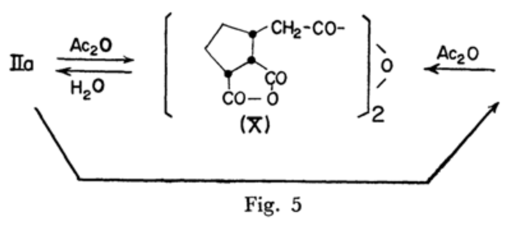

Fig. 5

The procedure which was employed in the conversion of the natural IIa to another isomer, IIc,[1b] appeared to be most suitable for the synthesis of the third isomer, *trans-cis*-tricarboxylic acid (IIc). Upon being heated over its melting point, IIa was converted into an anhydride carboxylic acid (XIII) with a loss of water; it was then esterified with diazomethane to yield an anhydride ester (XIV). The methanolysis of XIV, followed by the epimerization of the resulting diester carboxylic acid (XV, $R=CH_3$), without purification, with sodium methoxide in boiling methanol,

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[5] For a preliminary communication, see K. Kurosawa and S. Fujise, *Chem. & Ind.*, **1963**, 1688; for a full publication, see K. Kurosawa, H. Obara and H. Uda, This Bulletin, **39**, 530 (1966).

[6] The reported melting point of IIa is 161—162°C.[2] A further purified sample melts at 173—174°C.

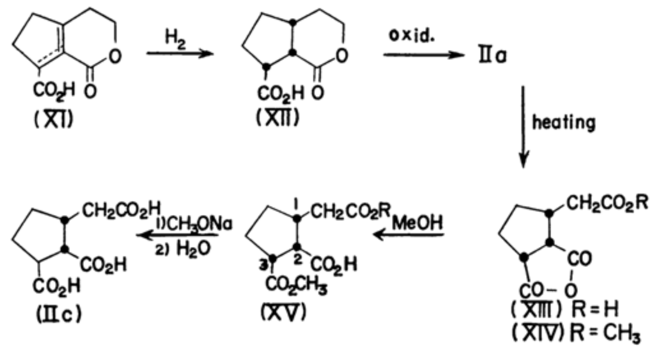

Fig. 6

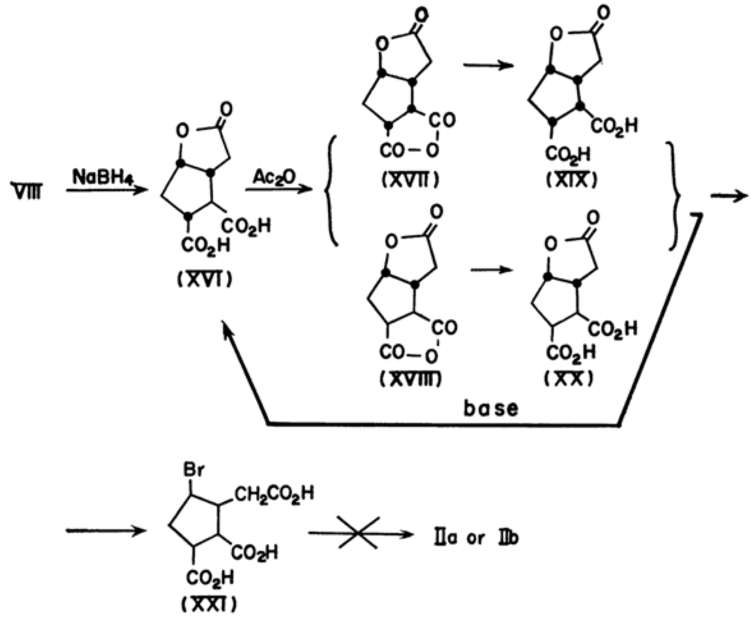

Fig. 7

and then the hydrolysis by addition of water produced the desired isomer (IIc) m. p. 156—157°C.⁷⁾ The method of synthesis and the chemical behavior⁸⁾ indicate that IIc must have a *trans-cis* configuration.

The following is an approach to the synthesis of the remaining *cis-trans* enantiomer (IId). The reduction of the keto tricarboxylic acid (VIII) with sodium borohydride afforded predominantly a lactone dicarboxylic acid (XVI), m. p. 192—193°C. The treatment of XVI with boiling acetic anhydride produced a single lactone anhydride, m. p. 164—165°C, accompanied by the rearrangement of one carboxyl group, the infrared spectrum of which manifested both succinic-type anhydride and γ-lactone carbonyl absorption (1850 and 1769 cm^{-1} ⁹⁾ respectively). This compound is represented as the formula XVII or XVIII, according to the isomerization of either one of the two carboxyl groups. Thus, a lactone dicarboxylic acid, m. p. 198—199°C, isomeric with XVI and obtained by hydrolysis, possesses the structure XIX or XX respectively; this isomeric lactone carboxylic acid could be isomerized back to the starting material (XVI) on treatment with

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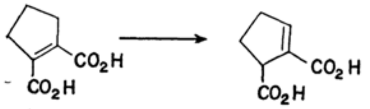
7) The facts that the XV (R=H) naturally derived from XIII could undergo intramolecular anhydride (glutaric-type) formation, without isomerization, with hot acetic anhydride and that, after epimerization, the yield of the *trans-trans* isomer (IIb), evidently produced through the esterification of the C-2 carboxyl group,¹ᵇ⁾ was very low prove the preferential ester-formation of the C-3 carboxyl group of the anhydride group in XIV on methanolysis and also indicate that the exclusive epimerization of the ester group takes place.

8) In addition to the glutaric-type anhydride formation in XV (R=H),⁷⁾ the thermostability of the natural IIc (no change upon heating) confirms the relative configuration of the three substituents of IIc to be *trans-cis*, since, if the configuration of the C-2 and C-3 carboxyl groups is *cis*, they must easily produce a succinic-type anhydride like IIa → XIII.¹ᵇ⁾

9) A succinic-type anhydride usually shows two carbonyl absorption bands, near 1855 and 1775 cm^{-1}. The latter hand in this compound presumably overlap with the lactone absorption.

base. Supposing that the epimerization of a carboxyl group takes place in the same mode as in the case of IIb→X during anhydride formation, the isomeric lactone dicarboxylic acid must be XIX with a *cis-syn-cis* configuration, whereas the epimerization of the other carboxyl group gives the alternative *cis-anti-cis* isomer (XX). The latter possibility seems to be sterically more favorable and has not, therefore, been eliminated. If this compound is actually XX, the expected *cis-trans* isomer (IId) would be obtained by the displacement of the hydroxyl group with hydrogen. The reaction of the compound (XIX or XX) with hydrogen bromide in anhydrous ethanol yielded a non-crystalline substance, which was supposed to be a bromotricarboxylic acid (XXI) because of the disappearance of lactone carbonyl absorption in its infrared spectrum. Successive attempts to reduce XXI to IIa or IId by means of zinc - hydrochloric acid or by means of catalytic hydrogenation under various conditions were all unsuccessful. Consequently, the preparation of IId or even the confirmation of the stereochemistry of the isomerized lactone dicarboxylic acid (XIX or XX) have not yet been accomplished.

Finally, a few remarks regarding the characterization of the Δ^1- and Δ^2-cyclopentene-1, 2-dicarboxylic acids, XXII and XXIII, used for the synthetic work[2] would be appropriate. The Δ^2- compound (XXIII), m. p. 144—145°C, has been obtained from the Δ^1-isomer (XXII), m. p. 177—178°C, by treatment with boiling concentrated aqueous potassium hydroxide, involving a double-bond migration.[2,10] The further purification of this isomerized substance, m. p. 144—145°C, indicated that it was still a mixture of Δ^1- (XXII) and Δ^2-isomers (XXIII), which could be separated in the pure state. The structures of XXII and XXIII were verified beyond doubt by infrared and nuclear magnetic resonance spectroscopy. The former (XXII): 179—180°C, ν^{KBr}: 1685, 1620, 1585 and 1550 cm^{-1}, δ[11] $= 2.97$ (triplet, 4H, $-CH_2-C=$) and 1.67 (quintet, 2H, $-CH_2-$), pK_a : 3.36 and 7.18. The latter (XXIII): m. p. 178—179°C, ν^{KBr}: 1700, 1672 and 1636 cm^{-1}, $\delta = 4.12$ (diffused singlet, 1H, $-CH=$) and 2.48 (multiplet, 5H, $-CH_2-$ and $-CH-$), pK_a: 4.03 and 5.92 respectively.



(XXII) (XXIII)

Fig. 8

Experimental

Tetraethyl Butane-1, 2, 3, 4-tetracarboxylate (V). —Commercial *cis*-Δ^4-cyclohexene-1, 2-dicarboxylic acid anhydride (100 g.) was dissolved into a solution of 75 g. of sodium carbonate, 2 kg. of cracked ice and 3 l. of water. To this solution 500 g. of well pulverized potassium permanganate was added portion by portion with efficient stirring; then the reaction mixture was stirred for 10 hr. with the temperature kept below 50°C. The precipitated manganese dioxide was filtered off, and the light brown filtrate was acidified (Congo red) with concentrated hydrochloric acid and evaporated to dryness. The residual solid was dried in vacuo over sulfuric acid and then extracted with boiling acetone three times; the acetone extracts were concentrated to a small volume, giving 55 g. of crude crystals. The second crop (21 g.) was obtained from the mother liquor. Recrystallization from acetone yielded 60 g. (39%) of pure butanetetracarboxylic acid, m. p. 188—189°C.

A solution of 380 g. of the above tetracarboxylic acid in 1.5 l. of ethanol containing 1 ml. of concentrated sulfuric acid was refluxed for 15 hr. The ethanol was removed by distillation, and the residue was again esterified with fresh ethanol by refluxing for an additional 15 hr. The ethanol was distilled off, and the residual oil was allowed to distill in vacuo. Tetraester (V), b. p. 178—183°C/1.0 mmHg; 395 g., 70%, was thus obtained.

2, 3, 4-Triethoxycarbonylcyclopentanone (VI).— To a suspension of 2.5 g. (0.11 g.atom) of finely-granulated sodium metal in 150 ml. of hot toluene there was carefully added 38 g. (0.11 mol.) of the tetraester (V) with vigorous stirring, so as to maintain a gentle refluxing and continuous evolution of hydrogen; after the addition of sodium, the stirring was continued for 2 hr. under refluxing. Then the cooled reaction mixture was poured into ice water containing an almost equimolar amount of acetic acid or hydrochloric acid with vigorous stirring. The water layer was separated and extracted with toluene two times. The combined toluene extracts were washed with water, dried over anhydrous sodium sulfate, and freed from toluene. The residual liquid was distilled in vacuo to give 25.5 g. of triethoxycarbonylcyclopentanone (VI), b. p. 175—182°C/2—3 mmHg (a slight decomposition was observed).

2, 3, 4-Triethoxycarbonyl-2-ethoxycarbonylmethylcyclopentanone (VII). — The sodio-derivative of VI was prepared from 85 g. (0.29 mol.) of VI and 7 g. (0.30 g.atom) of well-granulated metallic sodium in 400 ml. of anhydrous toluene in the usual manner. To this solution there was added dropwise 62 g. of ethyl bromoacetate with stirring and water-cooling, and the reaction mixture was heated under reflux for 6 hr. Then the mixture was poured into ice water, and the water layer was extracted with the same solvent three times. The combined toluene extracts were washed with dilute sodium bicarbonate solution and water, and then dried over anhydrous sodium sulfate and freed from toluene to give viscous liquid. Distillation in vacuo afforded 84 g. (76%) of 2, 3, 4,-triethoxycarbonyl- 2 -ethoxycarbonylmethylcyclopentanone (VII), b. p. 195—210°C/2.0 mmHg, ν^{neat} 1760 and 1733 cm^{-1}. The additional absorption bands at

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[10] A. Hassell and C. K. Ingold, *J. Chem. Soc.*, **1962**, 1465; B. L. Nandi, *J. Indian Chem. Soc.*, **11**, 213 (1934).

[11] Measured in a pyridine solution at 60 Mc. Chemical shifts are given in p.p.m. units, using tetramethylsilane as an internal standard.

1685 and 1638 cm^{-1} can be attributed to an *O*-alkylated by-product.

2, 3 - Dicarboxy - 5 - oxo-cyclopentylacetic Acid (VIII).—The mixture of VII and *O*-alkylated by-product from the preceding experiment (5 g.) was refluxed with 50 ml. of 6 N hydrochloric acid for 6 hr.; then the solvent was removed under reduced pressure. The residual viscous material crystallized when treated with ethyl acetate, and recrystallization from ethyl acetate gave 1.8 g. (47%) of a pure keto tricarboxylic acid (VIII), m. p. 215—216°C, ν^{KBr} 1747 (cyclopentanone) and 1700 cm^{-1} (carboxyl).

Found: C, 47.21; H, 4.45. Calcd. for $C_9H_{10}O_7$: C, 46.96; H, 4.38%. pK_{a_1} 3.32, pK_{a_2} 4.76, pK_{a_3} 5.92.

***trans* - *trans* - 2, 3 - Dicarboxycyclopentylacetic Acid (IIb).**—Keto tricarboxylic acid (VIII) (1.0 g.) was treated with 1.5 ml. of ethane dithiol and 1.5 ml. of boron trifluoride etherate, and then the mixture was allowed to stand at room temperature for 24 hr. The separated amorphous solid was collected by filtration, yielding 1 g., m. p. 190°C (decomp.) (no ketonic band in infrared); this was then subjected to desulfurization without purification. The above thioketal was refluxed with Raney nickel, prepared from 30 g. of alloy, in 100 ml. of 70% aqueous ethanol for 4 hr. Removal of the catalyst, followed by acidification and then evaporation of the solvent, gave crude crystals. Pure *trans-trans*-2,3-dicarboxycyclopentylacetic acid (IIb), 0.1 g., m. p. 160°C, was obtained by recrystallization from ethyl acetate, and showed an infrared spectrum completely identical with that of a sample prepared by the previously-reported procedure, starting from the Michael addition of dimethyl Δ^2-cyclopentene-1, 2-dicarboxylate (III) and diethyl malonate,2) and there was no depression in a mixed melting point determination.

***cis-cis*-2,3-Dicarboxycyclopentylacetic Acid (IIa).**—A solution of *cis-cis*-2-(2′-hydroxyethyl)-5-carboxycyclopentylcarboxylic acid δ-lactone (XII)5) (1.5 g.) in 250 ml. of glacial acetic acid was treated with a solution of 2.0 g. of chromium trioxide and 3.5 ml. of concentrated sulfuric acid in 7 ml. of water; the oxidation was then allowed to proceed at room temperature for three days. The excess oxidant was decomposed by addition of methanol, almost all of the acetic aicd was removed by distillation under reduced pressure with the aid of water, and then the solution was neutralized with a minimum amount of solid sodium bicarbonate, keeping the Congo red acidity. The resulting solution was saturated with sodium chloride and extracted continuously with ether for 65 hr. Evaporation of the ether extract gave 0.9 g. (51%) of *cis-cis*-2, 3-dicarboxycyclopentylacetic acid (IIa). The pure sample recrystallized from ethyl acetate had a melting point of 176—177°C.

Found: C, 50.00; H, 5.63. Calcd. for $C_9H_{12}O_6$: C, 50.00; H, 5.60%.

The infrared spectrum of this substance was completely indistinguishable from that of the sample obtained from IIb by isomerization via dimeric trianhydride (X),2) and the mixed melting point of these samples was not depressed.

***trans-cis*-2, 3-Dicarboxycyclopentylacetic Acid (IIc)**—The *cis-cis* isomer (IIa) was heated over its melting point in a sublimation apparatus for half an hour and then distilled under diminished pressure. The resulting anhydride carboxylic acid (XIII) was treated with excess ethereal diazomethane. The anhydride methyl ester (XIV) (0.4 g.) thus obtained was refluxed in 4 ml. of anhydrous methanol for 1 hr., and, after removal of the methanol, a methanolic solution of sodium methoxide freshly prepared from 0.2 g. of metallic sodium and 10 ml. of anhydrous methanol was added and refluxing was continued for 2 hr. After water (3 ml.) had then been added, the reaction mixture was again refluxed for 30 min. to complete hydrolysis. The hydrolysate was worked up in the usual manner, i. e., evaporation of the methanol, dilution with water, acidification with mineral acid, and finally extraction with ethyl acetate, to give 0.25 g. of a crude product, m. p. 127—144°C. Recrystallization from ethyl acetate yielded pure *trans-cis*-2, 3-dicarboxycyclopentylacetic acid (IIc), m. p. 156—157°C, which revealed a different infrared spectrum from that of either IIa or IIb.

Found: C, 49.66; H, 5.56. Calcd. for $C_9H_{12}O_6$: C, 50.00; H, 5.60%.

2, 3-Dicarboxy-5-hydroxycyclopentylacetic Acid γ-Lactone (XVI).—To a solution of 0.2 g. of VIII in 5 ml. of water containing 0.15 g. of sodium hydroxide, there was added 0.1 g. of sodium borohydride; the reaction mixtrure was then stirred at 80°C for 2 hr. After acidification with concentrated hydrochloric acid, the solution was evaporated to dryness. The residual solid was treated with ethyl acetate, and then, after removal of the insoluble inorganic material by filtration, the filtrate was passed through a column of silica gel. Evaporation of the ethyl acetate gave 0.04 g. of a lactone dicarboxylic acid (XVI), m. p. 192—193°C, ν^{KBr} 1769 and 1685 cm^{-1}, pK_{a_1} 3.34, pK_{a_2} 5.51.

Found: C, 50.18: H, 4.82. Calcd. for $C_9H_{10}O_6$: C, 50.47; H, 4.71%.

2, 3-Dicarboxy-5-hydroxycyclopentylacetic Acid Anhydride γ-Lactone (XVII or XVIII).—A solution of 0.17 g. of XVI in 20 ml. of acetic anhydride was refluxed for 2 hr. After removal of the acetic anhydride under reduced pressure, the residual viscous liquid was distilled in vacuo using a sublimation apparatus and then treated with ethyl acetate to give a crystalline product. Recrystallization from ethyl acetate yielded 0.02 g. of pure anhydride lactone (XVII or XVIII), m. p. 164—165°C, ν^{KBr} 1850 and 1769 cm^{-1}.

Found: C, 55.25; H, 4.20. Calcd. for $C_9H_8O_5$: C, 55.10; H, 4.11%.

Isomeric 2, 3 - Dicarboxy-5-hydroxycyclopentylacetic Acid γ-Lactone (XIX or XX).—The anhydride lactone from the preceding experiment (0.17 g.) was treated with 5 ml. of water at 100°C for 30 min. and then dried up and recrystallized from ethyl acetate to give 0.13 g. (68%) of the isomeric lactone dicarboxylic acid (XIX or XX), m. p. 198—199°C, ν^{KBr} 1730 and 1692 cm^{-1}, pK_{a_1} 3.91, pK_{a_2} 5.92.

Found: C, 50.86; H, 4.69. Calcd. for $C_9H_{10}O_6$: C, 50.47; H, 4.71%.

Ethyl Diethoxycarbonyl - 5 - bromocyclopentylacetate (XXI).—The isomeric lactone dicarboxylic acid was treated overnight with anhydrous ethanol saturated with hydrogen bromide at room temperature. The hydrogen bromide and ethanol were then removed under reduced pressure to give a bromoester (XXI) (the lactone absorption disappeared) which, without further purification or characterization, was then subjected to reduction. However, the reduction of XXI with zinc - hydrochloric acid or with hydrogen catalytically under various conditions failed to produce any crystalline product.

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