Stereiosomerism. II. The Synthesis of Some *cis*- and *trans*-1,3-Cyclopentanedialkanoic Acids[1,2]

THOMAS L. WESTMAN AND ALFRED E. KOBER

Department of Chemistry, University of Florida, Gainesville, Florida 32603

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Previously we reported[3] the unequivocal synthesis of the isomeric 1,3-cyclohexanediacetic and dipropionic acids and a large-scale synthesis of *trans*-1,3-cyclohexanedipropionic acid by Wolff–Kishner reduction of 2,6-cyclohexanonedipropionic acid, the *cis* isomer being isolated in only trace quantities. We report here synthesis of the corresponding isomeric cyclopentanediacetic and dipropionic acids (**1a**–**2b**) and a convenient, large-scale synthesis of the *cis*- and *trans*-1,3-cyclopentanedipropionic acids.

Utilizing the readily available *cis*- and *trans*-1,3-cyclopentanedicarboxylic acids,[4a,b] the isomeric diacetic and dipropionic acids were prepared by Arndt–Eistert homologation as described previously.[3] The pertinent data for these compounds are recorded in Table I.

TABLE I

PHYSICAL AND ANALYTICAL DATA OF 1,3-CYCLOPENTANEDIALKANOIC ACIDS

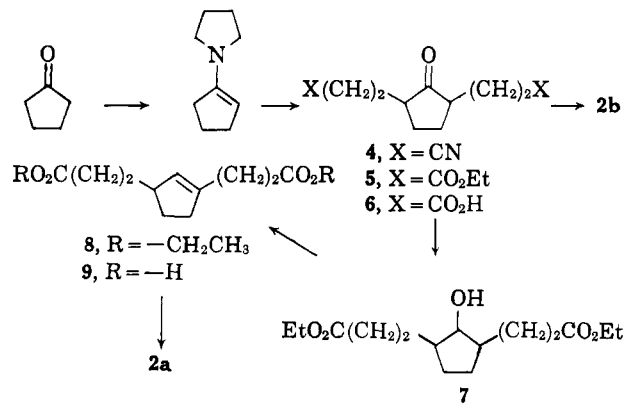
Acid	M.p., °C.[a]	Yield, %[b]	—Calcd., %— C	H	—Found, %— C	H
cis-Diacetic (**1a**)	141–142	23[c]	58.05	7.58	58.06	7.60
trans-Diacetic[e] (**1b**)	152–153	40[d]	58.05	7.58	58.36	7.84
cis-Dipropionic (**2a**)	100–101	26[c]	61.66	8.47	61.53	8.38
trans-Dipropionic (**2b**)	101–102	30[d]	61.66	8.47	61.86	8.55

[a] All samples were recrystallized three times from water. [b] Yields after one recrystallization. [c] Diazald used as diazomethane precursor. [d] DuPont EXR-101 used as diazomethane precursor. [e] R. W. Kierstead, R. P. Linstead, and B. C. L. Weedon [*J. Chem. Soc.*, 1803 (1953)] reported a compound, m.p. 135.5–137.5°, as *trans*-diacetic acid. The mode of their reaction sequence and the accord of **1b** being *trans*-diacetic acid suggests their compound is not *trans*-diacetic acid.

In part I of this series[3] a stereospecific synthesis of the isomeric dipropionic acids (**2a** and **2b**) was developed which utilized the enamine synthesis of Stork and coworkers.[5] In view of the applicability of this method to the cyclohexane series it seemed reasonable to anticipate similar results with the cyclopentane series.

When acrylonitrile was added to the pyrrolidine enamine of cyclopentanone in ethanol a 27% yield of the desired 2,5-cyclopentanonedipropionitrile (**4**), m.p. 66–67°, was obtained[6] along with a high-melting solid. This latter solid material was highly insoluble in most common solvents, its infrared spectrum displayed nitrile and five-ring ketone bands (2245 and 1740 cm.$^{-1}$, respectively), and its elemental analysis was low in carbon and hydrogen for a tripropionitrile adduct. No further investigations are planned for this material.

The ketodinitrile (**4**) was converted directly to the known[7] ketodipropionic acid ester (5) in 87% yield by treatment with absolute ethanol and sulfuric acid, followed by addition of water. Hydrolysis of this diester gave the known 2,5-cyclopentanonedipropionic acid (**6**)[7] in 85% yield.



Wolff–Kishner reduction (Huang-Minlon modification[8]) of the ketodinitrile (**4**) or keto diacid (**6**) gave an 86% yield of *trans*-1,3-cyclopentanedipropionic acid (**2b**). As in the case of the reduction of 2,6-cyclohexanonedipropionic acid,[3] the reduction of **4** and **6** appears to be a stereoselective process and, in this case, no *cis* diacid (**2a**) was found.

As noted previously,[3] the Wolff–Kishner reduction of α,α'-disubstituted cyclic ketones appears to yield predominately *trans*-1,3-disubstituted products. The configurations of the ketodinitrile (**4**) or keto diacid (**6**) are not known, but might be presumed *cis*. A further complicating factor is the well-known mobility between conformations of cyclopentane derivatives.[9] Furthermore, before an explanation of this apparent stereoselective reduction may be offered it is also necessary to determine whether a "2-alkyl ketone effect" exists for cyclopentanones and also what effects hydrazone formation and stereochemistry play in the reduction sequence. Such studies are in progress and will be reported elsewhere.

Reduction of the keto diester (**5**) with sodium borohydride in ethanol gave the hydroxy diester (**7**) in 81% yield. This alcohol was dehydrated by refluxing in benzene with *p*-toluenesulfonic acid, the water formed in the reaction being removed by azeotropic distillation, to yield the olefinic diester (**8**). Hydrolysis of the diester gave the olefinic diacid (**9**) in an over-all yield of 54%. The configuration and/or isomeric composition of the hydroxy diester (**7**) could not be reliably determined either by gas–liquid chromatog-

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(2) A portion of this work was presented at the Annual Meeting of the Southeastern Regional Section of the American Chemical Society, Nov. 14, 1963, Charlotte, N. C.

(3) T. L. Westman, R. Paredes, and W. S. Brey, Jr., *J. Org. Chem.*, **28**, 3512 (1963).

(4) (a) S. F. Birch, W. J. Oldham, and E. A. Johnson, *J. Chem. Soc.*, 818 (1947); (b) K. T. Pospischill, *Chem. Ber.*, **31**, 1951 (1898).

(5) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(6) Addition of ethyl acrylate to this enamine under conditions expected to yield the diadduct (**5**)[3] consistently gave a material of undetermined structure, b.p. 208° (0.1 mm.).

(7) N. J. Leonard and W. J. Middleton, *J. Am. Chem. Soc.*, **74**, 5114 (1952).

(8) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(9) E. L. Eliel, "The Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc. New York, N. Y., 1962, pp. 248–252.

raphy or analysis of the n.m.r. spectrum.[10] The position of the double bond in the olefinic diacid (**9**) is also not known with certainty since the vinyl proton signal in the n.m.r. spectrum of this compound was not sufficiently resolved for analysis.

Hydrogenation of the olefinic diacid (**9**), using 5% rhodium on alumina and acetic acid as solvent, gave the pure *cis*-dipropionic acid (**2a**) in 86% yield. The apparent stereoselectivity of this reduction suggests that the double bond is in the 1-position since this would allow the 3-alkyl side chain to have a maximum steric effect during the course of the reduction.

Experimental[11]

2,5-Cyclopentanonedipropionitrile (4). A.—The preparation of the pyrrolidine enamine of cyclopentanone followed the general procedure of Stork, *et al.*[5] In general, the enamine was used in crude form and was not distilled.

B.—The crude enamine (from 252 g., 3 moles, of cyclopentanone) was dissolved in 1 l. of absolute ethanol and the mixture was cooled (ice bath), with stirring, and 500 ml. (*ca.* 400 g., 7.5 moles) of acrylonitrile was added dropwise.[12] After the addition was complete the mixture was warmed to room temperature and then refluxed for 5 hr. after which time 250 ml. of water was added and refluxing was continued for an additional hour. The solvent and other volatile materials were removed *in vacuo* (100° at 30 mm.) and a crystalline material formed during the initial reflux period was collected by suction filtration and washed with chloroform.[13] The chloroform wash and an additional 500 ml. of chloroform were added to the liquid reaction product and this resulting solution was washed with three 200-ml. portions of 3 *N* hydrochloric acid, followed by water. After drying over anhydrous magnesium sulfate the chloroform was removed *in vacuo* to yield a thick viscous oil which deposited 106 g. of crystalline 2,5-cyclopentanedipropionitrile after standing several days in the refrigerator. Removal of further liquid from the residual oil (mononitrile?) by distillation up to 180° (0.3 mm.), followed by allowing the viscous residue to stand in the refrigerator overnight, gave an additional 47 g. of the dinitrile. The combined yield of 2,5-cyclopentanonedipropionitrile was 153 g. (27%), m.p. 63–65°, after washing the crystalline material with 50% ethanol, followed by drying in a vacuum desiccator. An analytical sample of this material had m.p. 66–67° after two recrystallizations from 95% ethanol.

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.23; H, 7.36; N, 14.56.

The initial crystalline material formed during the reaction was recrystallized twice from acetone, m.p. 178–179°, and submitted for analysis.

Anal. Calcd. for $C_{14}H_{17}N_3O$ (2,2,5-cyclopentanonetripropionitrile): C, 69.11; H, 7.04. Found: C, 68.13; H, 6.49.

2,5-Cyclopentanonedipropionic Acid (6).—2,5-Cyclopentanonedipropionitrile (**4**) (47 g., 0.25 mole) was refluxed for 3 hr. with 500 ml. of concentrated hydrochloric acid. At the end of this period the solution was evaporated to dryness *in vacuo* (steam bath) and the solid residue was triturated with 250 ml. of ethanol. Removal of ammonium chloride by filtration and evaporation of the ethanol yielded 48 g. (85%) of 2,5-cyclopentanonedipropionic acid (**6**), m.p. 121–122.5° after two recrystallizations from dioxane–hexane (lit.[7] m.p 122°).

***trans*-1,3-Cyclopentanedipropionic Acid (2b) *via* Wolff–Kishner Reduction of 4.**—2,5-Cyclopentanonedipropionitrile (**4**, 57 g., 0.3 mole) was mixed with potassium hydroxide (84 g., 1.5 moles) dissolved in 600 ml. of diethylene glycol. Hydrazine hydrate (85%, 42 ml., *ca.* 1.2 moles) was added and the mixture was refluxed for 1.5 hr. (*ca.* 135°) after which time the condenser was removed and the mixture was heated to 200–220° and maintained at this temperature for about 4 hr., or until the evolution of nitrogen had ceased. After the mixture was cooled, 600 ml. of water was added and this solution was extracted once with ether. The basic, aqueous solution was acidified by the addition of 600 ml. of 6 *N* hydrochloric acid and extracted with five 200-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate followed by removal of the ether to yield 55.0 g. (86%) of *trans*-1,3-cyclopentanedipropionic acid (**2b**), m.p. 96–97° after one recrystallization from water. A mixture melting point of this material with the *trans*-dipropionic acid (m.p. 101–102°) previously prepared *via* the Arndt–Eistert sequence (*vide supra*) was 98–100°. A mixture melting point of this acid with the *cis*-dipropionic acid (**2a**, m.p. 100–101°) was 88–94°. The infrared spectra of the two samples of *trans*-dipropionic acid were identical, except for band intensities.

Following essentially the same procedure as described above, 2,5-cyclopentanonedipropionic acid (**6**) was converted, in comparable yield as above, to the *trans*-dipropionic acid (**2a**).

Diethyl 2,5-Cyclopentanonedipropionate (5).—2,5-Cyclopentanonedipropionitrile (**4**, 140 g., 0.74 mole) was mixed with 170 ml. (*ca.* 3 moles) of absolute ethanol and 300 ml. of dry benzene. Concentrated sulfuric acid (289 g., 3 moles) was added cautiously and the mixture was then refluxed for 12 hr. After cooling to room temperature, the mixture was poured onto 800 ml. of water–ice mixture, the benzene layer separated, and the aqueous solution extracted with ether. The combined ether–benzene extracts were dried over anhydrous magnesium sulfate and the solvent was removed to yield 181 g. (87%) of crude diethyl 2,5-cyclopentanonedipropionate (**5**). Distillation of this material gave pure diethyl ester (**5**), b.p. 170–171° (0.55 mm.), $n^{20}D$ 1.4612 [lit.[7] b.p. 161–162° (0.4 mm.), $n^{20}D$ 1.4633].

Diethyl 2,5-Cyclopentanoldipropionate (7)—To a solution of 48 g. (0.17 mole) of diethyl 2,5-cyclopentanonedipropionate (**5**) in 400 ml. of absolute ethanol, cooled in an ice bath, was added, with stirring, 4 g. (0.1 mole) of sodium borohydride over a 15-min. period. Stirring was continued for an additional 2 hr., the mixture was poured into 800 ml. of ice water and the aqueous mixture was extracted with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate and the solvent then removed to yield an oil. Vacuum distillation of this oil gave 39 g. (81%) of diethyl 2,5-cyclopentanoldipropionate (**7**), b.p. 175–176°(0.55 mm.), $n^{20}D$ 1.4686.

A satisfactory analysis of this material could not be obtained. Similarly, attempts to prepare solid derivatives of this compound also were unsuccessful.

1,3-Cyclopentan-1-enedipropionic Acid (9).—Diethyl 2,5-cyclopentanoldipropionate (**7**, 10 g., 0.035 mole) was dissolved in 50 ml. of dry benzene and 1 g. of *p*-toluenesulfonic acid was added. The mixture was refluxed overnight under a water separator, or until no further water was formed. The benzene solution was then washed with sodium bicarbonate solution, followed by water, and then dried over anhydrous magnesium sulfate. The benzene was then removed *in vacuo* to give an oil which was extracted with pentane to leave behind unchanged alcohol diester (**7**) which is insoluble in pentane. The pentane was removed *in vacuo* to give 8.4 g. (90%) of crude diethyl 1,3-cyclopentan-1-enedipropionate (**8**). The crude diester (**8**, 8.4 g., 0.031 mole) was added to a solution of 7.0 g. (0.125 mole) of potassium hydroxide in 50 ml. of methanol and this mixture was refluxed, with stirring, for 3 hr. After this time, the solution was evaporated to dryness and the residue was dissolved in a minimum amount of water. This basic, aqueous solution was extracted once with ether and then acidified with 6 *N* hydrochloric acid. The acidified aqueous solution was extracted with ether, the ether solution dried over anhydrous magnesium sulfate, and the solvent removed to yield 5.1 g. (77%) of crude 1,3-cyclopent-1-enedipropionic acid (**9**). An analytical sample was obtained by three recrystallizations from water, m.p. 81–82°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.05; H, 7.49.

***cis*-1,3-Cyclopentanedipropionic Acid (2a) *via* Reduction of 9.**—Crude 1,3-cyclopentan-1-enedipropionic acid (**9**, 20.0 g., 0.094 mole), m.p. 77–79°, was dissolved in 200 ml. of glacial acetic acid along with 1.5 g. of 5% rhodium on alumina. Hydrogenation was performed using a modified Paar apparatus at an initial pressure of 30 lb. Hydrogen uptake was complete in *ca.* 3 hr. (0.09 mole hydrogen), the mixture was filtered and poured into 500 ml. of water, and the aqueous solution was extracted with ether. After drying the ether extracts over anhydrous magnesium sulfate, the solvent was removed *in vacuo* to yield crude product, containing traces of acetic acid. The acetic acid was removed by azeotropic distillation with heptane to yield 17.3 g.

(10) *Cf.* also the difficulties encountered in the analysis of similar cyclohexane derivatives, ref. 3.

(11) All melting points are corrected; boiling points are uncorrected.

(12) The addition of acrylonitrile is accompanied by the generation of considerable heat and caution must be exercised, particularly for large-scale reactions.

(13) This material is very difficultly soluble in common solvents.

(86%) of crude *cis*-1,3-cyclopentanedipropionic acid (**2a**) which had m.p. 98–99° after one recrystallization from water. A mixture melting point of this acid with an analytical sample of *cis*-1,3-cyclopentanedipropionic acid (m.p. 100–101°) was 98–99°. A mixture melting point of this acid with an analytical sample of the *trans*-dipropionic acid (**2b**, m.p. 101–102°) was 87–92°. The infrared spectra of the two samples of *cis*-1,3-cyclopentanedipropionic acid were identical except for band intensities.

The Preparation of *o*-Amino-Substituted Arylphosphonic Acids[1]

LEON D. FREEDMAN AND G. O. DOAK

Department of Chemistry, North Carolina State of the University of North Carolina at Raleigh, Raleigh, North Carolina

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Twelve years ago we described the preparation of *o*-aminophenylphosphonic acid by the copper-catalyzed reaction between *o*-bromophenylphosphonic acid and aqueous ammonia.[2] Recently, Lukin and Kalinina[3] have reported that they were unable to prepare *o*-aminophenylphosphonic acid by this reaction but obtained instead a 41% yield of *o*-hydroxyphenylphosphonic acid. In their procedure they isolated the phosphonic acid as a copper complex which was converted to the free acid by means of hydrogen sulfide. They reported further that the acid thus obtained gave a negative test for the amino group (by diazotization and coupling) and gave carbon, hydrogen, and phosphorus analyses in reasonable agreement with the theoretical values for *o*-hydroxyphenylphosphonic acid.[4]

In view of the results reported by Lukin and Kalinina, we have re-examined the matter and have found that the phosphonic acid obtained by the procedure they described contains nitrogen and is in fact identical with the *o*-aminophenylphosphonic acid prepared by us in 1952. The properties of *o*-hydroxyphenylphosphonic acid, which has recently been prepared by an unambiguous method,[5] are quite different from those of the material described by the Russian investigators. Thus the *o*-hydroxy compound has m.p. 124–127°, is extremely soluble in water, and gives a purple color with aqueous ferric chloride; by contrast, the acid described by Lukin and Kalinina has m.p. 178–179°, is only moderately soluble in water, and gives an orange-brown color with ferric chloride. Their inability to diazotize their material is surprising, since Miyata[6] has recently obtained an azo compound by diazotizing *o*-aminophenylphosphonic acid (prepared by the amination of *o*-bromophenylphosphonic acid with aqueous ammonia) and coupling the resulting diazonium salt with chromotropic acid.

Although Lukin and Kalinina are therefore mistaken about the identity of the phosphonic acid they obtained, their method of isolation is highly recommended. It is more convenient and gives more consistent results than the tedious isolation procedure we originally described.[2] Other *o*-amino-substituted arylphosphonic acids can also be isolated as copper complexes. Thus we have prepared two new compounds, 2-amino-4-tolyl- and 2-amino-5-tolylphosphonic acids, and found that they form insoluble copper complexes. It is of interest that Lukin, Kalinina, and Zavarikhina[7] have reported that 2-amino-5-chlorophenylphosphonic acid can be isolated as a copper complex; compounds in which the amino group is *meta* or *para* to the phosphono (PO_3H_2) group apparently do not form insoluble copper complexes.[8]

In the course of this work, it was found that *o*-chloro-substituted arylphosphonic acids can be converted to the corresponding *o*-amino compounds under the same conditions used with the *o*-bromo-substituted arylphosphonic acids. This result is of some interest since chloro-substituted anilines (from which the phosphonic acids are made) are usually much less expensive than are the corresponding bromo-substituted anilines.

Experimental[9]

***o*-Aminophenylphosphonic Acid.**—*o*-Bromophenylphosphonic acid[10] (23.7 g.), 18 g. of freshly prepared cuprous oxide, and 400 ml. of concentrated aqueous ammonia were allowed to react under the exact conditions specified by Lukin and Kalinina.[3] On acidification of the reaction mixture to pH 4, a greenish precipitate was obtained, which was removed by filtration and dissolved in 100 ml. of 4 *N* hydrochloric acid. Hydrogen sulfide was then passed into the solution to precipitate copper sulfide. The filtrate from the copper sulfide was decolorized with charcoal and treated with solid sodium carbonate until just alkaline to congo red (pH 3.7). The light gray precipitate thus obtained was washed with cold water and then dried *in vacuo*. The yield was 10.1 g. (58%), m.p. 189–193°. Mixture melting point with authentic *o*-aminophenylphosphonic acid[2] was 190–196°.

Anal. Calcd. for $C_6H_8NO_3P$: N, 8.09; P, 17.89. Found: N, 7.91; P, 17.69.

Some of the reaction conditions described in ref. 3 are not essential to the success of the above preparation. Thus, J. T. Baker reagent grade cuprous oxide is as satisfactory as the freshly prepared material. Furthermore, it is not necessary to pass ammonia gas through the reaction mixture (as Lukin and Kalinina have specified) in order to keep the ammonia concentration constant; equally good results are obtained by simply heating the stirred mixture of phosphonic acid, cuprous oxide, and aqueous ammonia for 18 hr. at 70–80°. It has also been found that *o*-chlorophenylphosphonic acid[11] can be substituted for *o*-bromophenylphosphonic acid in the above reaction.

2-Amino-4-tolylphosphonic Acid.—2-Bromo-4-tolylphosphonic acid[12] (12.6 g.) and 9.0 g. of cuprous oxide were added to 200 ml. of aqueous ammonia (*d* 0.90) in a three-necked flask equipped with a sealed stirrer, a reflux condenser, and a thermometer. The mixture was stirred and heated at 70–80° for 18 hr. The copper complex was isolated as described above and then dissolved in 400 ml. of 4 *N* hydrochloric acid. After the

(1) This work was supported by Research Grant GM-09479 from the National Institutes of Health, U. S. Public Health Service.

(2) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **74**, 753 (1952).

(3) A. M. Lukin and I. D. Kalinina, *Zh. Obshch. Khim.*, **30**, 1597 (1960).

(4) It should be noted that the theoretical values for carbon, hydrogen, and phosphorus do not differ greatly for *o*-aminophenylphosphonic acid and *o*-hydroxyphenylphosphonic acid. The analytical results reported by Lukin and Kalinina are in satisfactory agreement with the theoretical values for *o*-aminophenylphosphonic acid.

(5) L. D. Freedman, G. O. Doak, and E. L. Petit, *J. Org. Chem.*, **25**, 140 (1960).

(6) H. Miyata, *Bull. Chem. Soc. Japan*, **36**, 127 (1963).

(7) A. M. Lukin, I. D. Kalinina, and G. B. Zavarikhina, *Zh. Obshch. Khim.*, **30**, 4072 (1960).

(8) A. M. Lukin and I. D. Kalinina, *Dokl. Akad. Nauk SSSR*, **137**, 873 (1961).

(9) Melting points were determined as previously described [G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **73**, 5658 (1951)]. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(10) G. O. Doak and L. D. Frreedman, *ibid.*, **75**, 683 (1953).

(11) G. O. Doak and L. D. Freedman, *ibid.*, **73**, 5658 (1951).

(12) The preparation of 2-bromo-4-tolylphosphonic acid has been previously described [L. D. Freedman, H. Tauber, G. O. Doak, and H. J. Magnuson, *ibid.*, **75**, 1379 (1953)] but was erroneously called "2-Br-5-CH_3-$C_6H_3PO_3H_2$."