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68. Zen-ichi Horii, Tatsuo Sakai, and Yasumitsu Tamura: Studies on Oxytetracycline and Related Compounds. XIII.*[1] Synthesis and Stereoisomers of (α-Methylbenzyl)succinic Acid. (2).*[2]

(School of Pharmacy, University of Osaka[3])*

In the preceding work,*[1] three kinds of crystals corresponding to (α-methylbenzyl)-succinic acid were obtained and two of these were tentatively assigned as diastereoisomers, (Ia) and (Ib) shown in Chart 1, and the other as their mixture. The present work was undertaken to confirm these structural arrangements by preparing (Ia) and (Ib) by *cis*-addition of hydrogen to the double bond of *cis*- and *trans*-(α-methylbenzylidene)succinic acid (*cis*-IIa and *trans*-IIb).

(α-Methylbenzylidene)succinic acid (II) was prepared by the Stobbe reaction of acetophenone with diethyl succinate. When this reaction was carried out using sodium ethoxide in ethanol according to the Stobbe procedure,[1] the main reaction product was (IIb) (phenyl and carboxyl groups *trans*) and the yield of (IIa) (phenyl and carboxyl groups *cis* and named iso-(IIa) by Stobbe[1]) was very low. However, it was found that the yield of (IIa) could be improved by modifying the reaction condition. Thus, when the reaction was carried out by refluxing in *tert*-butanol in the presence of potassium *tert*-butoxide[2] and the resulting crystalline half-ester (IIIa) was separated from the oily isomeric half-ester (IIIb) by treatment with petroleum ether-benzene, (IIa) and (IIb) were obtained in about 1:2 ratio. The structure of these isomers had already been established by the works of Stobbe[3] and Haworth, *et al.*[4] that (IIa) was converted to 1-oxo-3-methyl-2-indeneacetic acid with sulfuric acid,[3] while (IIb) was converted to 1-hydroxy-4-methyl-3-naphthoic acid with aluminum chloride in nitrobenzene.[4]

Reduction of (IIa) and (IIb) was not effected with zinc powder in acetic acid[5] nor by catalytic reduction using Raney nickel catalyst in ethanol. However, it was found that the Schwenk-Papa reduction[6] proceeded on addition of Raney nickel alloy in small portions to a boiling 10% sodium hydroxide solution and (IIa) or (IIIa) was converted to a compound of m.p. 174° and (IIb) to a compound of m.p. 167° in quantitative yields. Catalytic reduction using palladium-charcoal or the same catalyst activated by platinum oxide in acetic acid gave the same result as with the Schwenk-Papa reduction. From the results of the reduction of (IIa) and (IIb), it could be concluded that the compound of m.p. 174° should be assigned (Ia) and the compound of m.p. 167°, (Ib). Reduction with sodium amalgam in acid medium converted both (IIa) and (IIb) into the compound of m.p. 147°, which proved to be a mixture of (Ia) and (Ib) on the basis of infrared spectrum as well as by melting point measurement and chemical evidences.

It is of considerable interest that the *cis*-reduction product was obtained by such a drastic reduction condition as the Schwenk-Papa method. To establish such stereospecifity of that reduction, some appropriate unsaturated compounds were chosen and

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*[1] Part XII: This Bulletin, **9**, 442 (1961).

*[2] Presented before the 79th Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April, 1959.

*[3] Toneyama, Toyonaka, Osaka-fu (堀井善一, 酒井立夫, 田村恭光).

1) H. Stobbe: Ann., **308**, 114 (1899).

2) W.S. Johnson, J.W. Peterson, W.P. Schneider: J. Am. Chem. Soc., **69**, 74 (1947).

3) H. Stobbe: Ber., **37**, 1619 (1904).

4) R.D. Haworth, B. Jones, Y.M. Way: J. Chem. Soc., **1943**, 10.

5) N. Campbell, A.E.S. Fairfull: *Ibid.*, **1949**, 1102.

6) D. Papa, E. Schwenk, B. Whiteman: J. Org. Chem., **7**, 587 (1942).

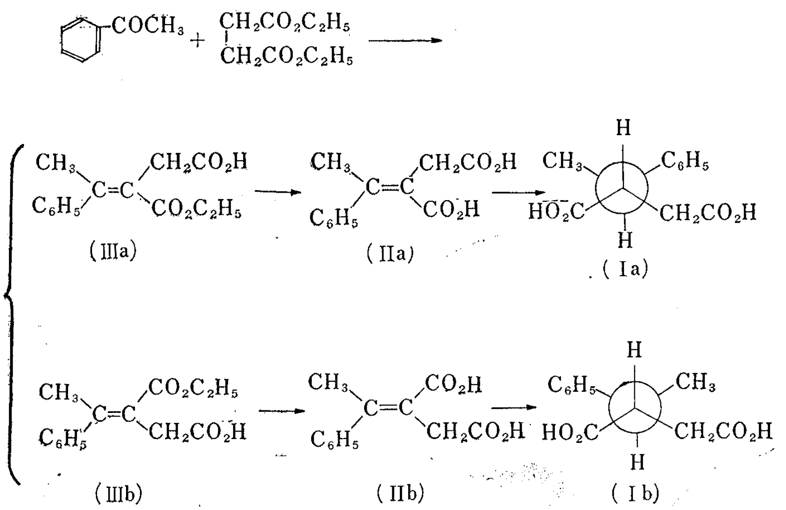

Chart 1.

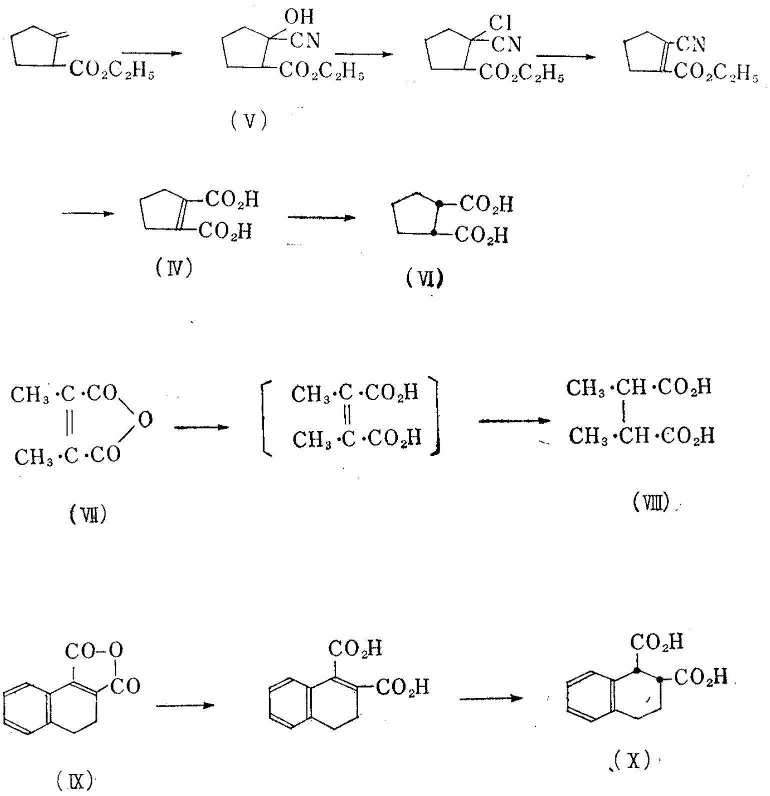

Chart 2.

subjected to that reduction. The compounds employed in the test were dimethylmaleic anhydride (Ⅶ), 3,4-dihydro-1,2-naphthalenedicarboxylic anhydride (Ⅸ), and 1-cyclopentene-1,2-dicarboxylic acid (Ⅳ). The reduction of (Ⅶ) gave *meso*-2,3-dimethylsuccinic acid (Ⅷ)[7,8] in over 60% yield. Similarly, (Ⅸ) was reduced to *cis*-1,2,3,4-tetrahydro-1,2-naphthalenedicarboxylic acid (Ⅹ) in a quantitative yield. The reduction of (Ⅳ) yielded the 1,2-cyclopentanedicarboxylic acid (Ⅵ) of m.p. 136°, which appeared to be the *cis*-isomer from comparison of the melting point with those of the *cis*- and *trans*-(Ⅵ) reported in a literature.[14]

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7) J.H. Golden, R.P. Linstead : J. Chem. Soc., **1958**, 1732.
8) N. Zelinsky : Ber., **21**, 3160 (1888).

1-Cyclopentene-1,2-dicarboxylic acid (IV) used in the reduction was prepared by the modified method of Sen-Gupta[9] from ethyl 2-cyano-2-hydroxycyclopentanecarboxylate (V), which was obtained by the reaction of ethyl 2-oxocyclopentanecarboxylate with acetone cyanehydrin.[10] (V) was chlorinated, followed by dehydrochlorination with 2,4,6-collidine, to give ethyl 2-cyano-1-cyclopentene-1-carboxylate, which was hydrolyzed to (IV).

Experimental

Iso-(α-methylbenzylidene)succinic Acid (IIa)——To a refluxed solution of 19.4 g. (0.50 mole) of K in 420 cc. of *tert*-BuOH, a mixture of 54 g. (0.45 mole) of acetophenone and 117.3 g. (0.67 mole) of diethyl succinate was added dropwise with stirring in N_2 atmosphere and the mixture was refluxed for 40 min. To the resulting orange-yellow solution, a mixture of 42 cc. of conc. HCl and 300 cc. of H_2O was added with cooling. The aqueous layer was extracted with Et_2O. The organic layer and the Et_2O extract were combined and the solvent was removed in a reduced pressure on a water bath. The residue was basified weakly with 5% NaOH solution under ice-cooling, the alkaline solution was washed several times with Et_2O, acidified with 15% HCl, and extracted with Et_2O. The extract was dried over anhyd. Na_2SO_4 and the solvent was distilled off giving 102 g. of a pale brown oil. The oil was dissolved in warm petr. ether containing a small amount of benzene and the resulting solution was allowed to stand overnight in a refrigerator. The separated crystals were collected and recrystallized from petr. ether containing a little Et_2O to 25 g. of colorless crystals, m.p. 105~110°. Further recrystallization furnished the analytical sample of m.p. 110~112°. *Anal.* Calcd. for $C_{14}H_{16}O_4$ (IIIa) : C, 67.74; H, 6.45. Found : C, 67.83; H, 6.21.

A mixture of 1.2 g. of (IIIa) and 90 cc. of 2% $Ba(OH)_2$ solution was refluxed for 2.5 hr. The whole reaction mixture was acidified with 10% HCl and extracted with AcOEt. The extract was dried over Na_2SO_4 and concentrated to 1 g. of pale yellow crystals, m.p. 162° (decomp.), which were recrystallized from H_2O to colorless needles, m.p. 177~179° (decomp.), which was not depressed when it was mixed with a sample of (IIa) prepared by the Stobbe method.[2] *Anal.* Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found : C, 65.60; H, 5.82.

(α-Methylbenzylidene)succinic Acid (IIb)——Distillation of the solvent from the mother liquor of (IIIa) gave 68 g. of the crude (III) as a viscous pale brown oil. The oil was boiled with 2% $Ba(OH)_2$ solution. The precipitate was collected, washed with H_2O, and acidified with 10% HCl to give pale brown needles, m.p. 161~163° (decomp.), which was recrystallized from H_2O to colorless needles (IIb), 171~172° (decomp.), which was not depressed when admixed with a sample of (IIb) prepared by the Stobbe procedure.[1] *Anal.* Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found : C, 65.81, H, 5.65.

(α-Methylbenzyl)succinic Acid (Ia)——i) To a stirred mixture of 100 mg. of (IIa) and 10 cc. of 10% NaOH solution heated on a boiling water, bath 500 mg. of Raney Ni alloy was added in small portions. The precipitate was filtered off and an equal volume of conc. HCl was added dropwise to the filtrate with ice-cooling. The acid solution was extracted with Et_2O, the extract was washed with H_2O, dried over anhyd. Na_2SO_4, and concentrated, giving a pale yellow solid, m.p. 170~173°. Recrystallization from H_2O or a mixture of AcOEt and petr. benzine furnished colorless crystals, m.p. 172~174°, in a quantitative yield. The melting point was not depressed when this was mixed with a sample of (Ia), m.p. 172~174°, which was reported in the preceding paper.*1 *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found : C, 64.79; H, 6.52. IR $\nu_{C=O}$ 1720 cm^{-1} (Nujol).

ii) A solution of 150 mg. of (IIa) in 8 cc. of AcOH was hydrogenated in the presence of 150 mg. of 5% Pd-C at atmospheric pressure. One molar equivalent of H_2 was absorbed in about 5 hr. The catalyst was filtered off and the filtrate was concentrated in a reduced pressure. The residual white solid, m.p. 169~174°, was recrystallized from H_2O, giving colorless prisms, m.p. 172~174°. *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found : C, 64.40; H, 6.35.

iii) A solution of 0.6 g. of (IIIa) in 20 cc. of 6% NaOH solution was heated to 90° on a water bath and 2.0 g. of Raney Ni alloy was added in small portions with stirring. The reaction mixture was heated at 90° on a water bath for an additional 1 hr. and worked up as in procedure (i). A white solid, m.p. 160~168°, was obtained in a quantitative yield. Recrystallization from H_2O furnished colorless plates, m.p. 172~174°.

(α-Methylbenzyl)succinic Acid (Ib)——i) 1 g. of (IIb) was subjected to the Schwenk-Papa reduction using 60 cc. of 5% NaOH solution and 3 g. of Raney Ni alloy by the same procedure as in

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9) S. C. Sen-Gupta, N. N. Saha : J. Indian Chem. Soc., **29**, 331 (1952); S. C. Sen-Gupta : *Ibid.*, **17**, 183 (1940).

10) I. N. Nazarov, A. A. Akhrem, A. V. Kamernitskü : Zhur. Obshchei Khim., **25**, 1345 (1955) (C. A., **50**, 4950).

the synthesis of (Ia) by procedure (i). The pale yellow solid obtained was recrystallized from H_2O or from a mixture of AcOEt and petr. benzine and furnished colorless crystals, m.p. 166∼167°. The melting point was not depressed when this was mixed with a sample of (Ia), m.p. 166∼167°, which was reported in the preceding paper.[*1] *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found : C, 64.69; H, 6.45. IR $\nu_{C=O}$ 1700 cm^{-1} (Nujol).

ii) A solution of 150 mg. of (IIb) in 15 cc. of AcOH was hydrogenated in the presence of 15 mg. of PtO_2 and 100 mg. of 5% Pd-C at atmospheric pressure. One molar equivalent of H_2 was absorbed in 10 hr. The reaction mixture was filtered and the filtrate was evaporated in a reduced pressure, giving 150 mg. of a white solid. Recrystallization from H_2O furnished colorless plates, m.p. 166∼167°. The melting point was not depressed when this was mixed with a sample of (Ib), prepared by procedure (i). *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found : C, 64.58; H, 6.48.

(α-Methylbenzyl)succinic Acid of m.p. 147°——To a solution of 0.2 g. of (IIa or IIb) in 50 cc. of H_2O, 50 g. of 3% Na-Hg was added in small portions over a period of 1 hr., while the reaction mixture was kept weakly acid by addition of 30% H_2SO_4. The aqueous layer was extracted with Et_2O, the extract was dried, and concentrated, yielding a white solid of m.p. 140∼152°. Several recrystallizations from benzene furnished crystals of m.p. 146∼147°, which was not depressed when this was mixed with a sample of (I), prepared in the preceding work.[*1] *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found : C, 64.38; H, 6.41. IR $\nu_{C=O}$ 1703 cm^{-1} (Nujol).

Reduction of Dimethylmaleic Anhydride (VII) by the Schwenk-Papa Method——100 mg. of dimethylmaleic anhydride[11] (VII) was hydrogenated by the Schwenk-Papa method using 400 mg. of Raney Ni alloy and 5% NaOH solution. Upon working up the reaction mixture in the same manner as described for the preparation of (Ia), 100 mg. of a pale yellow solid, m.p. 171∼183° (decomp.), was obtained. Recrystallization from H_2O furnished 60 mg. of colorless crystals, m.p. 193.5∼194° (decomp.). The melting point was not depressed when this was mixed with an authentic sample of *meso*-2,3-dimethylsuccinic acid (VIII), m.p. 194°, obtained by the Zelinsky method.[8] *Anal.* Calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found : C, 49.40; H, 7.10. Concentration of the above mother liquor gave a second crop of crystals of m.p. 178∼183° (decomp.), which was recrystallized from H_2O to 15 mg. of colorless crystals, m.p. 193∼194°.

Reduction of 3,4-Dihydro-1,2-naphthalenedicarboxylic Anhydride (IX) by the Schwenk-Papa Method——1 g. of the anhydride[12] (IX) dissolved in 30 cc. of 10% NaOH solution was reduced by the Schwenk-Papa method using 3 g. of Raney Ni alloy. On working up the reaction mixture in the same manner as for (Ia), colorless needles were obtained in a quantitative yield. Recrystallization from H_2O furnished colorless needles, m.p. 184∼185°, which was not derpessed when this was mixed with an authentic sample of *cis*-1,2,3,4-tetrahydro-1,2-naphthalenedicarboxylic acid (X), obtained by the method of Auwers and Möller.[13] *Anal.* Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found : C, 65.34; H, 5.42.

1-Cyclopentene-1,2-dicarboxylic Acid (IV)——A mixture of 20 g. (0.13 mole) of ethyl 2-oxocyclopentanecarboxylate (V), 40 g. (0.45 mole) of acetone cyanohydrin, 25 cc. of MeOH, 0.5 g. of anhyd. K_2CO_3, and 2 drops of 10% KCN solution was allowed to stand overnight. The pale yellow solution obtained was filtered and the filtrate was acidified with 10% H_2SO_4 to Congo red. The inorganic salt that separated was filtered off and the filtrate was distilled in a reduced pressure, giving 10.8 g. of ethyl 2-cyano-2-hydroxycyclopentanecarboxylate as a colorless viscous oil, b.p_{12} 147°.[*4]

To a solution of ethyl 2-cyano-2-hydroxy-1-cyclopentene-1-carboxylate obtained as above in two volumes of dehyd. benzene, a mixture of benzene and $SOCl_2$ was added dropwise with ice-cooling. The reaction mixture was allowed to stand overnight and worked up as usual. The yellow viscous oil, b.p_4 115∼140°, of ethyl 2-cyano-2-chlorocyclopentanecarboxylate here obtained was heated with 2,4,6-collidine for 2 hr. on a water bath. Et_2O was added to the cooled collidine solution and the separated collidine hydrochloride was filtered off. Distillation of the Et_2O solution yielded ethyl 2-cyano-1-cyclopentene-1-carboxylate as a pale yellow viscous oil, b.p_4 115∼130°, in 20% yield (from ethyl 2-oxocyclopentanecarboxylate). The oil obtained was boiled with conc. HCl, giving crystals. Recrystallization from H_2O gave colorless plates, m.p. 174∼176°. *Anal.* Calcd. for $C_7H_8O_4$: C, 53.84; H, 5.16. Found : C, 53.85; H, 5.12.

Reduction of 1-Cyclopentene-1,2-dicarboxylic Acid (IV) by the Schwenk-Papa Method——One-half g. of (IV) was dissolved in 15 cc. of 10% NaOH solution and reduced on a boiling water bath by the Schwenk-Papa method using 1.5 g. of Raney Ni alloy. Upon working up the reaction mixture

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[*4] In a similar procedure, ethyl 2-cyano-2-hydroxycyclohexanecarboxylate, b.p_5 130°, was prepared from ethy 2-oxocyclohexanecarboxylate in 60% yield.

11) N. Zelinsky, S. Krapivin : Ber., **22**, 646 (1889).

12) Org. Syntheses, Coll. Vol. **2**, 194 (1948).

13) K. Auwers, K. Möller : J. prakt. Chem., [2] **109**, 124 (1925); K. Alder, K. Triebeneck : Chem. Ber., **87**, 237 (1954).

in the same manner as for (Ia), a white solid of m.p. 120° was obtained. Recrystallization from H_2O furnished 0.25 g. (50%) of colorless needles, m.p. 136°. Perkin[14] reported that the melting point of *cis*-1,2-cyclopentanedicarboxylic acid (VI) was 140° and that of *trans*-(VI) was 181°. *Anal.* Calcd. for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found : C, 53.21; H, 6.44.

Summary

The configuration of the diastereoisomers, (Ia) and (Ib), of (α-methylbenzyl)succinic acid was determined by preparing them by the *cis*-reduction of *cis*- and *trans*-(α-methylbenzylidene)succinic acid, (IIa) and (IIb). It was also found that the Schwenk-Papa reduction of (IIa) and (IIb) proceeded stereospecifically and *cis*-addition of hydrogen to the double bond was observed. This stereospecificity of the reduction was further confirmed in other cases.

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[14] W. H. Perkin, Jr. : J. Chem. Soc., **65**, 572 (1894).