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

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In connection with previous work on the studies of degradation products of oxytetracycline, synthetic methods for preparing (α-methylbenzyl)succinic acid (I), which is an important intermediate in this work, are described. Previously, Stobbe[1] prepared (I) by reduction of the Stobbe condensation product of acetophenone and diethyl succinate. Present work was undertaken to find another route suited for the present purpose and two synthetic methods, A and B shown in Chart 1, were investigated.

Method A

As an exploratory experiment, the synthesis of benzylsuccinic acid (Ⅶ) was carried out. Ethyl β-phenylbutyrate (Ⅷ) was prepared by dehydration and reduction of the Reformatsky reaction product[2] of acetophenone with ethyl bromoacetate. Condensation of (Ⅷ) and diethyl oxalate was tried in two different reaction conditions of (a) refluxing an ether solution of (Ⅷ) and diethyl oxalate for 24 hours in the presence of sodium ethoxide and (b) the so-called forcing reaction.[3]

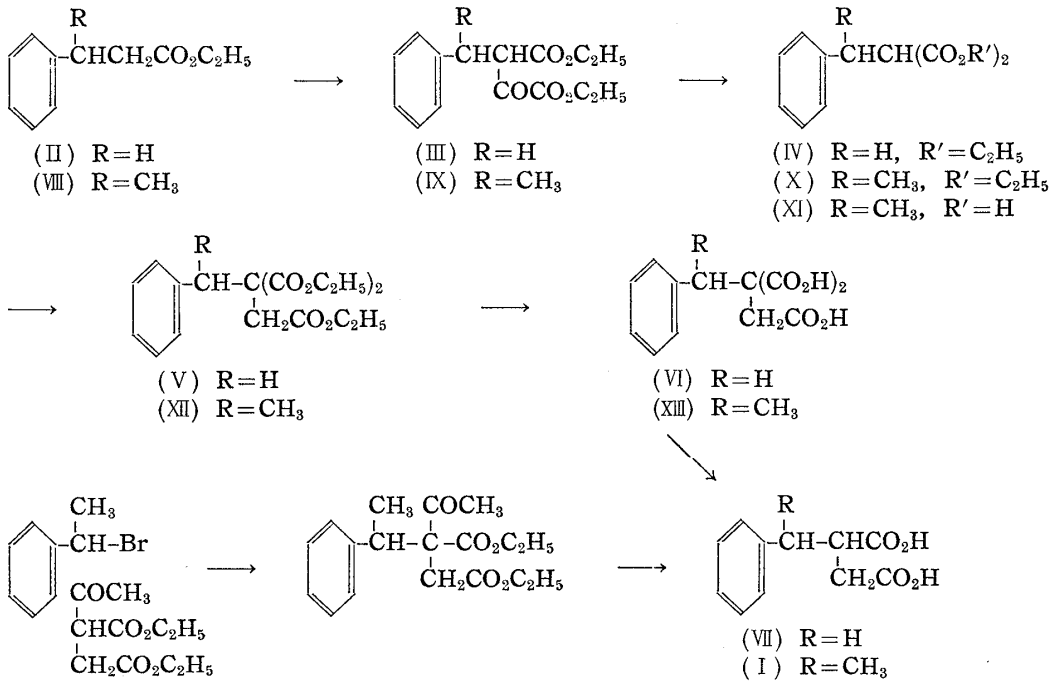

Chart 1.

*1 Part Ⅺ. Z. Horii, I. Ninomiya, Y. Tamura : This Bulletin, **7**, 444 (1959).

*3 Presented before the 77th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April, 1957.

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1) H. Stobbe : Ann., **308**, 114 (1899).
2) Org. Reactions, **1**, 1 (1942).
3) R. R. Briese, S. M. McElvain : J. Am. Chem. Soc., **55**, 1697 (1933).

In the preparation of ethyl α-ethoxalyl-β-phenylpropionate (III), no significant difference in yield was observed between the two reaction conditions, (a) and (b). The oxalyl ester (IX) was obtained from (VIII) in a satisfactory yield only by the forcing reaction. Decarbonylation of (III) and (IX) was easily accomplished by heating in the presence of soft glass powder[4] in a reduced pressure, giving diethyl benzylmalonate (IV) or diethyl (α-methylbenzyl)malonate (X), respectively.

The malonic ester (IV) was condensed with ethyl bromoacetate in the presence of sodium ethoxide, giving ethyl 2-ethoxycarbonyl-2-benzylsuccinate (V) in 52% yield, but the condensation of (X) with ethyl bromoacetate was effected only in the presence of sodium hydride[5] and gave the tricarboxylic ester (XII) in 50% yield. The tricarboxylic ester (V or XII) was hydrolyzed in alkaline solution and the free acid (VI or XIII) obtained was decarboxylated by fusion in an oil bath to give (I) or (VII).

Several recrystallizations of (I) from a mixture of ethyl acetate and benzene gave two kinds of crystals melting at 174° and 147°. The former is less soluble than the latter in the recrystallization solvent used.

Mothod B

A toluene solution of (1-bromoethyl)benzene and diethyl acetylsuccinate was heated under reflux for 25 hours in the presence of sodium.[6] Alkaline hydrolysis of the condensation product using 15% sodium hydroxide solution gave (I). (1-Chloroethyl)benzene failed to react with ethyl acetylsuccinate under the same reaction condition as that for the reaction of (1-bromoethyl)benzene. Three kinds of crystals melting at 174°(Ia), 167°(Ib), and 147°(Ic) were isolated by recrystallization of (I). Both compounds (Ia) and (Ib) were proved to correspond to a pair of diastereoisomers of (I) and (Ic) to a mixture of the diastereoisomers. The reason why this conclusion was drawn will be discussed in detail in the following paper.

Experimental

Synthesis of Benzylsuccinic Acid (Method A)

Ethyl α-Ethoxalyl-β-phenylpropionate (III)——a) A mixture of 40 g. (0.27 mole.) of diethyl oxalate and EtONa (prepared from 2.7 g. of Na) was stirred and to the resulting clear yellow solution, 20 g. (0.11 mole.) of ethyl β-phenylpropionate was added. The reaction mixture was kept at 50° in a pressure of 100 mm. Hg for 3.5 hr. with stirring. Under this condition, EtOH formed during the condensation reaction was removed from the mixture through an efficient fractionating column. The reaction mixture was decomposed with H_2O and the organic layer was extracted several times with 3% NaOH solution until the organic layer gave negative $FeCl_3$ coloration. The combined alkaline solution was acidified with conc. HCl and extracted with Et_2O. The Et_2O extract was washed with saturated $NaHCO_3$ solution and dried over anhyd. Na_2SO_4. Removal of the solvent gave 21.5 g. (70%) of pale yellow oil (III), which was used without further purification for the preparation of (IV).

b) To a suspension of EtONa (prepared from 4.0 g. of Na) in 80 cc. of dehyd. Et_2O, a solution of 40 g. (0.27 mole) of diethyl oxalate in 45 cc. of anhyd. Et_2O was added dropwise and the mixture was stirred for 30 min. A solution of 30 g. (0.17 mole.) of ethyl β-phenylpropionate in 15 cc. of dehyd. Et_2O was added dropwise to this clear yellow solution and the mixture was refluxed for 24 hr. with stirring. After decomposition of the product with ice-water, the organic layer was separated, the alkaline layer was washed twice with Et_2O, and the aqueous layer, after acidification with conc. HCl, was extracted with Et_2O. The extract was washed with saturated $NaHCO_3$ solution, dried over anhyd. Na_2SO_4, and concentrated, yielding 34 g. (73%) of pale yellow oil (III). A solution of (III) in EtOH gave a dark red $FeCl_3$ reaction and gave green Cu salt on addition of aqueous cupric acetate solution. Recrystallization of the Cu salt from EtOH furnished green needles of m.p. 144~145°. *Anal.* Calcd. for $C_{30}H_{34}O_{10}Cu$: C, 58.13; H, 5.39. Found : C, 58.33; H, 5.36.

4) F. F. Blick, R. F. Feldkamp : *Ibid.*, **66**, 1087 (1944).
5) V. H. Wallingford, M. A. Thorpe, A. H. Homeyer : *Ibid.*, **64**, 580 (1942); O. Wiss, H. Fuchs : Helv. Chim. Acta, **35**, 407 (1952).
6) R. D. Haworth, B. Jones, Y. M. Woy : J. Chem. Soc., **1943**, 10.

Ethyl Benzylmalonate (IV)——A mixture of 10.0 g. of (III) and 2.0 g. of soft glass powder was heated gradually to 190~200° in an oil bath in a reduced pressure and kept at this temperature for about 1 hr. until the evolution of CO ceased. Soft glass powder was filtered off and distillation of the filtrate gave 5.5 g. (62%) of colorless oil, b.p_2 134~135°. *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.12; H, 7.08.

Ethyl 2-Ethoxycarbonyl-2-benzylsuccinate (V)——To a solution of 0.46 g. (0.02 mole.) of Na in 25 cc. of dehyd. EtOH, 5.0 g. (0.02 mole) of (IV) was added and the mixture was refluxed for 2 hr. in a water bath. After cool, 3.4 g. (0.02 mole) of ethyl bromoacetate was added dropwise to the viscous solution and the mixture was refluxed for 2 hr. At the end of the reaction, most of EtOH was distilled off. The residue was diluted with H_2O, dried over anhyd. Na_2SO_4, and distilled, giving 3.5 g. (52%) of colorless oil, b.p_1 152~162°. *Anal.* Calcd. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.52; H, 7.15.

2-Carboxy-2-benzylsuccinic Acid (VI)——A solution of 3.5 g. of (V), 17 cc. of EtOH, 3.5 g. of NaOH, and 17 cc. of H_2O was heated to reflux for 2 hr. in a water bath and most of EtOH was distilled off. The residue was diluted with H_2O, acidified with HCl, extracted with Et_2O. The Et_2O extract was reëxtracted with saturated $NaHCO_3$ solution. The alkaline solution was acidified with HCl, extracted with Et_2O, the extract was washed with H_2O, and dried over anhyd. Na_2SO_4. Evaporation of the dried extract gave 2.5 g. of white solid, which was purified by recrystallization from a mixture of AcOEt and petr. benzine, and then from H_2O, giving 1.8 g. (69%) of white crystals, m.p. 173° (decomp.). *Anal.* Calcd. for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.23; H, 4.78.

Benzylsuccinic Acid (VII)——800 mg. of (VI) was heated up to 170~180° in an oil bath. The crude product was recrystallized from H_2O, giving 500 mg. (76%) of white crystals, m.p. 159~161°. *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.18; H, 5.79.

Synthesis of (α-Methylbenzyl)succinic Acid (Method A)

Ethyl (α-Methylbenzyl)malonate (X)——A solution of 52 g. (0.35 mole) of diethyl oxalate and 17.3 g. (0.09 mole) of ethyl β-phenylbutyrate was added to EtONa (prepared from 2.3 g. of Na) and the mixture was heated for 1.5 hr. in a water bath (bath temp., 60°) in a reduced pressure of 70 mm. Hg and then for 1.5 hr. in a water bath (bath temp., 90°) in a pressure of 5 mm. Hg with stirring. Excess of diethyl oxalate and EtOH formed during the reaction were distilled off through an efficient fractionating column. After cool, the product was decomposed with dil. H_2SO_4 and extracted with Et_2O. The Et_2O extract was washed with $NaHCO_3$ solution and H_2O, and dried over anhyd. Na_2SO_4. Distillation of Et_2O and diethyl oxalate from the extract gave crude (IX) as an oil, which gave dark red $FeCl_3$ reaction and formed a green oil of Cu salt with aqueous cupric acetate solution. Crude (IX) was mixed with 6 g. of soft glass powder, heated to about 200° in an oil bath in a reduced pressure, and kept at 200° until the evolution of CO ceased. After completion of the reaction (1 hr.), glass powder was filtered off and the filtrate was distilled in a reduced pressure, giving 12.1 g. (50%) of colorless oil (X), b.p_7 146~148°. A solution of (X), 10% NaOH solution, and EtOH was refluxed for 2 hr. and worked up as usual. A white solid obtained was recrystallized from H_2O, yielding colorless crystals, m.p. 142~144° (decomp.). *Anal.* Calcd. for $C_{11}H_{12}O_4$ (XI): C, 63.45; H, 5.81. Found: C, 63.38; H, 5.60.

Ethyl 2-Ethoxycarbonyl-2-(α-methylbenzyl)succinate (XII)——A mixture of 8 g. of diethyl carbonate, 2.4 g. (0.009 mole) of (X), and 0.22 g. (0.009 mole) of NaH was stirred for 1.5 hr. To this mixture 3 g. (0.018 mole.) of ethyl bromoacetate was added and the whole was stirred for 5 hr. on a boiling water bath. After cool, an excess of NaH was decomposed with a small amount of AcOH and the mixture diluted with H_2O was extracted with Et_2O. The Et_2O extract was washed with H_2O, $NaHCO_3$ solution, and H_2O. Distillation of the dried extract gave 1.7 g. (55%) of viscous pale yellow oil, b.$p_{4.5}$ 176~178°. *Anal.* Calcd. for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 64.95; H, 7.32.

(α-Methylbenzyl)succinic Acid (I)——a) A solution of 1.1 g. of (XII) and 35 cc. of 25% HCl was refluxed for 20 hr. After cool, 0.6 g. of colorless crystals separated out. Several recrystallizations from a mixture of AcOEt and benzene furnished 0.1 g. of colorless prisms (Ia) of m.p. 173°. *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.11; H, 6.38.

Concentration of the mother liquor gave 0.2 g. of colorless crystals (Ic) of m.p. 145~147° (from benzene). *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.05; H, 6.38.

b) A solution of 0.4 g. of (XII) and 15 cc. of 15% NaOH solution was heated to reflux for 20 hr. The reaction mixture was acidified with 10% HCl and extracted with Et_2O. The Et_2O extract was dried over anhyd. Na_2SO_4 and evaporated, yielding 0.25 g. of pale brown oil, which crystallized from a mixture of AcOEt and petr. benzine. Recrystallization gave colorless plates, m.p. 143° (decomp.). Elemental analysis showed that this was a mixture of (XIII) and (I).

This mixture of (XIII) and (I) was heated to 160° in an oil bath and vigorous evolution of gas resulted. The mixture was cooled and recrystallization of the product from benzene furnished colorless plates of m.p. 145~147°, which was not depressed on admixture with (Ic). *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.71; H, 6.38.

Synthesis of (α-methylbenzyl)succinic Acid (Method B)——To a solution of 60.5 g. (0.28 mole) of ethyl acetylsuccinate in 250 cc. of toluene, 6.5 g. (0.28 mole.) of Na was added and the mixture was warmed until in solution. To the resulting solution, 59.3 g. (0.32 mole.) of (1-bromoethyl)benzene was added dropwise at 100° with stirring. The reaction mixture was kept at 120~130° for 25 hr., acidified with 160 cc. of 10% HCl with ice-cooling, and extracted with Et_2O. The Et_2O extract was dried over anhyd. Na_2SO_4 and concentrated to give an oil, from which the fraction distilling below 80° in a pressure of 35 mm. Hg was removed. The residue (38 g.) here obtained was refluxed with 1.4 L. of 15% NaOH solution for 25 hr. The reaction mixture was acidified with HCl and extracted with Et_2O. The Et_2O extract was dried over anhyd. Na_2SO_4 and the solvent evaporated, giving 27 g. of viscous brown oil. On recrystallization from a mixture of AcOEt and benzene, 10.6 g. (17%) of white crystals were obtained. The separation of the product into the diastereoisomers was effected as follows :

i) Recrystallization of the product from 250 cc. of benzene furnished 1.5 g. of less-soluble colorless crystals of m.p. 168~169°. Further recrystatllization from a mixture of AcOEt and benzene or AcOEt alone gave colorless crystals (Ia) of m.p. 173~174°, which was not depressed when mixed with the sample of (Ia) prepared by method A. *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.82; H, 6.50.

ii) The mother liquor of (i) was concentrated to about one-half the original volume. The precipitate from the concentrated mother liquor was recrystallized from AcOEt, affording 1 g. of colorless crystals, m.p. 142~148°. Further recrystallization from benzene furnished colorless crystals (Ic) of m.p. 145~147°, which was not depressed when mixed with the sample of (Ic) prepared by method A. *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found : C, 64.65; H, 6.43.

iii) Evaporation of the solvent from the mother liquor of (ii) gave 7.3 g. of white crystals of m.p. 145~151°. Recrystallization from benzene and then from a mixture of AcOEt and benzene furnished 3 g. of white crystals, m.p. 165~167°. Recrystallization of this from H_2O yielded colorless crystals (Ib) of m.p. 166~167°. *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found : C, 64.64; H, 6.33.

Summary

(α-Methylbenzyl)succinic acid was synthesized by (A) condensation of ethyl bromoacetate and diethyl (α-methylbenzyl)malonate, and (B) condensation of (1-bromoethyl)benzene and ethyl acetylsuccinate, and its *threo*- and *erythro*-isomers were isolated.

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