UDC 615.779.931-011

## 69. Zen-ichi Horii, Tatsuo Sakai, and Yasumitsu Tamura: Studies on Oxytetracycline and Related Compounds. XIV.[*1] Synthesis and Stereoisomers of ($\alpha$-Methylbenzyl)succinic Acid. (3).[*2]

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

In continuation of previous works[*1,1)] on the synthesis of ($\alpha$-methylbenzyl)succinic acid (VII), examinations were made on a course of synthesis leading to (VII) via the malic acid (XI) from ethyl $\alpha$-ethoxalyl-$\beta$-phenylbutyrate (IX), which was previously prepared from $\beta$-phenylpropionic acid.[2)]

As a preliminary experiment, preparation of benzylsuccinic acid (I) was carried out. Reduction of ethyl $\alpha$-ethoxalyl-$\beta$-phenylpropionate (II) with aluminum amalgam in hydrous ether yielded diethyl 3-benzylmalate (III) in 60% yield. Hydrolysis of (III), followed by boiling of the resulting 3-benzylmalic acid (IV) with acetic anhydride gave benzylidenesuccinic anhydride (V). The structure of (V) was determined from its ultraviolet spectrum and this arrangement is also consistent with the result obtained by Robertson, *et al.*,[2)] that 3-($p$-methoxybenzyl)malic acid was converted to $p$-methoxybenzylidenesuccinic anhydride on treatment with acetic anhydride.[3)] Benzylidenesuccinic acid (VI) obtained by boiling (V) with water was hydrogenated to (I) in a quantitative yield by catalytic reduction using Raney nickel in ethanol.

Finding that the synthetic route attempted for the model compound gave satisfactory results, preparation of ($\alpha$-methylbenzyl)succinic acid by an analogous reaction was carried out. Condensation of ethyl $\beta$-phenylbutyrate (VIII) with diethyl oxalate was carried out by the forcing reaction method using sodium ethoxide. The reaction procedure was essenti-

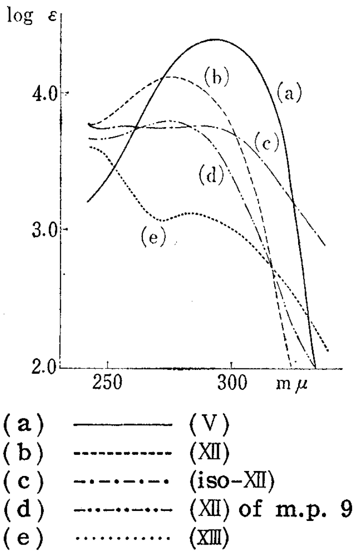


Fig. 1. Ultraviolet Absorption Spectra (in $CHCl_3$)

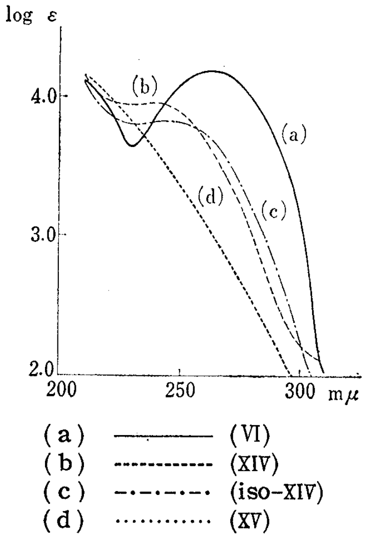


Fig. 2. Ultraviolet Absorption Spectra (in EtOH)

---

[*1] Part XIII: This Bulletin, **9**, 446 (1961).

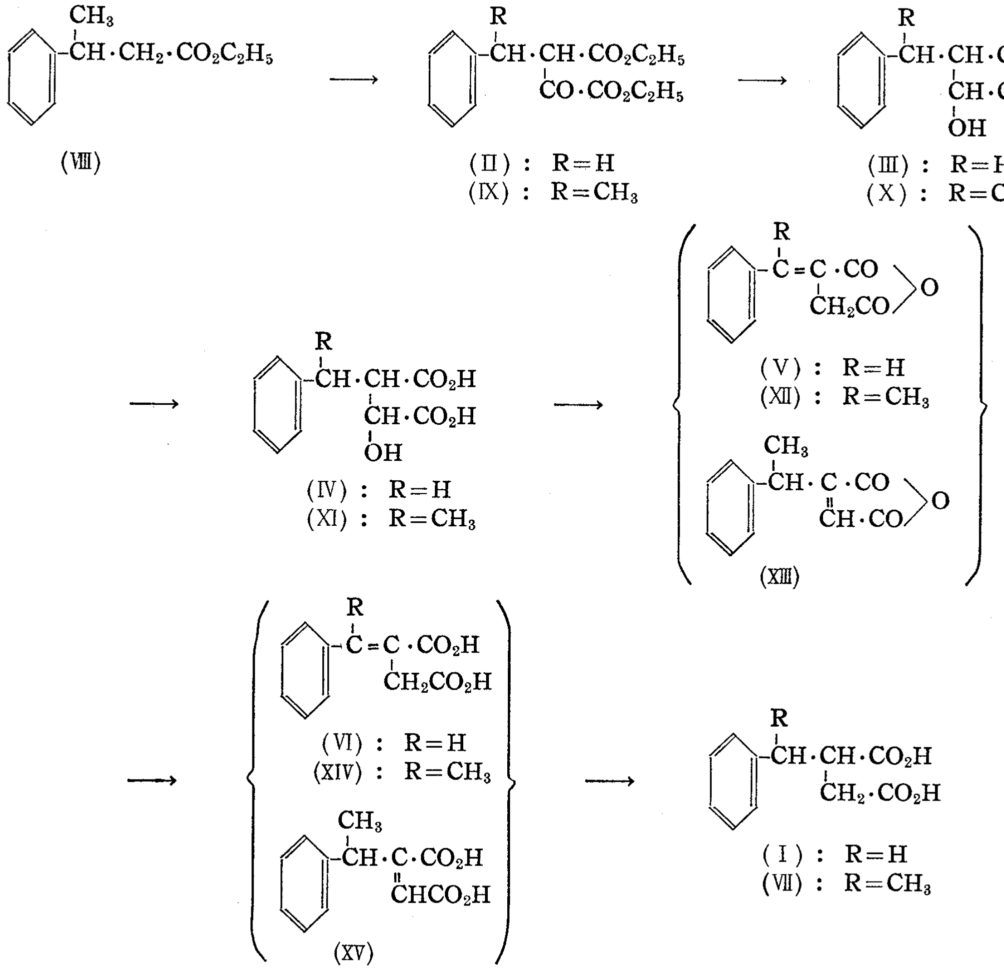
[*2] Presented before the 77th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April, 1957.

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

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

2) A. L. J. Buckle, A. McGookin, A. Robertson: J. Chem. Soc., **1954**, 3981.

3) R. Fittig: Ann., **305**, 19 (1899).



ally the same as that reported in a previous paper,$^{1)}$ except that the reaction temperature was 50° instead of 90° to avoid decarbonylation which might result during the reaction when the yield was only 30%. Diethyl 3-($\alpha$-methylbenzyl)malate (X) was reduced with aluminum amalgam, followed by hydrolysis, to 3-($\alpha$-methylbenzyl)malic acid (XI). The malic acid (XI) was dehydrated as in the preliminary experiment.

Refluxing of the malic acid (XI) in acetic anhydride for 10 hours yielded the crude crystalline anhydride, from which three kinds of crystals melting at 138°, 114°, and 91° were isolated on recrystallization. By direct comparison of their melting points and ultraviolet spectra with those of the authentic samples prepared by the Stobbe method, the compound of m.p. 138° was assigned to the *cis*-isomer of ($\alpha$-methylbenzylidene)succinic anhydride (XII) (phenyl and carboxyl groups *cis*) and the one of m.p. 114° to *trans*-(XII). These structural arrangements were supported by further transformation of the two anhydrides to the known corresponding dicarboxylic acids.[*1] The compound of m.p. 91° proved to be a mixture of the *cis*- and *trans*-(XII) by separation into these two components.

In a different experiment, when (XI) was refluxed in acetic anhydride for 3 hours, the crude anhydride was obtained as an oil, from which a small amount of ($\alpha$-methylbenzyl)-maleic anhydride (XIII), m.p. 51~53°, was isolated. Hydrolysis of (XIII) yielded ($\alpha$-methylbenzyl)maleic acid (XV), m.p. 114°, in a quantitative yield. The structures assigned to (XIII) and (XV) were supported by their ultraviolet spectra as well as further reduction by the Schwenk-Papa method to a mixture of diastereomers of ($\alpha$-methylbenzyl)succinic acid[*1] (VII), m.p. 147°. The Schwenk-Papa reduction of the oily anhydride or the catalytic reduction of the crude unsaturated dicarboxylic acid obtained by hydrolysis of the oily anhydride provided (VII) of m.p. 147°, accompanied with (VII) of m.p. 174°*1 in the former reduction. Formation of this (VII) of m.p. 174° would indicate that the benzylidenesuccinic anhydride (XII) besides the maleic anhydride (XIII) was present in the oily anhydride.

## Experimental

**Diethyl 3-Benzylmalate (III)**——A mixture of 5.0 g. of crude ethyl $\alpha$-ethoxalyl-$\beta$-phenylpropionate[3] (II), 30 cc. of hydr. $Et_2O$, and Al-Hg was stirred at room temperature until the mixture gave negative $FeCl_3$ reaction. The reaction mixture was filtered and the residue was washed well with warm $Et_2O$. The filtrate and the $Et_2O$ washings were combined, washed with $H_2O$, and dried over anhyd. $Na_2SO_4$. Distillation gave 2.7 g. (60%) of a colorless oil, b.p$_2$ 165°. *Anal.* Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found : C, 63.89; H, 6.92.

**3-Benzylmalic Acid (IV)**——(III) (2.2 g.) was hydrolysed by boiling with a mixture of 5 cc. of EtOH and 12 cc. of 10% NaOH solution for 2.5 hr. in a water bath. Upon working up the reaction mixture as usual, 1.6 g. (91%) of a colorless viscous oil was obtained. It solidified when dried over $P_2O_5$. Recrystallization from a mixture of $Et_2O$ and benzene gave colorless crystals, m.p. 127~129°. *Anal.* Calcd. for $C_{11}H_{12}O_5$ : C, 58.92; H, 5.40. Found : C, 58.92; H, 5.39.

**Benzylidenesuccinic Anhydride (V)**——A solution of 2.5 g. of (IV) in 15 cc. of $Ac_2O$ was refluxed for 3 hr. in an oil bath, and the solution was concentrated in a reduced pressure to about one-fourth the original volume. When cooled, 1.6 g. (76%) of yellow crystals, m.p. 145~152°, were obtained. Recrystallization from AcOEt furnished pale yellow crystals, m.p. 163~166°. This compound readily decolorized $KMnO_4$ solution. *Anal.* Calcd. for $C_{11}H_8O_3$ : C, 70.21; H, 4.29. Found : C, 70.89; H, 4.49. UV : $\lambda_{max}^{CHCl_3}$ 293 mμ (log $\varepsilon$ 4.37).

**Benzylidenesuccinic Acid (VI)**——A suspension of 0.7 g. of (V) in $H_2O$ was refluxed for 1.5 hr. in an oil bath, cooled, and the separated white crystals, m.p. 182° (decomp.), were collected. Yield, 0.7 g. (91%). Recrystallization from $H_2O$ furnished crystals of m.p. 185° (decomp.). *Anal.* Calcd. for $C_{11}H_{10}O_4$ : C, 64.07; H, 4.89. Found : C, 63.74; H, 4.81. UV : $\lambda_{max}^{EtOH}$ 263 mμ (log $\varepsilon$ 4.21).

**Benzylsuccinic Acid (I)**——A solution of 0.5 g. of (VI) in 30 cc. of MeOH was shaken in the presence of Raney Ni catalyst in $H_2$ atmosphere at atmospheric pressure. When a calculated amount of $H_2$ was absorbed, the catalyst was filtered off and MeOH was evaporated to leave 0.5 g. (99%) of white crystals, m.p. 156~161°, which was raised to 161° by recrystallization from $H_2O$.

**Diethyl 3-($\alpha$-Methylbenzyl)malate (X)**——A solution of EtONa (prepared from 3.5 g. of Na), 75 g. (0.51 mole.) of diethyl oxalate, and 26.0 g. (0.135 mole.) of (VIII) was heated at 50° for 3 hr. in a reduced pressure with stirring. EtOH formed during the course of the reaction was removed through an efficient fractionating column. After cool, the reaction mixture was poured into a mixture of conc. HCl, ice-water, and $Et_2O$. The $Et_2O$ layer was washed with $NaHCO_3$ solution and extracted several times with cold 2% NaOH solution until $FeCl_3$ reaction became negative. The combined alkaline extract was acidified with 15% HCl with ice cooling. Then the acid solution was extracted with $Et_2O$. The $Et_2O$ extract was washed successively with $NaHCO_3$ solution and $H_2O$, dried over anhyd. $Na_2SO_4$, and $Et_2O$ was evaporated, giving 11.9 g. (50%) of a pale yellow oil (crude IX).

A mixture of 11 g. of (IX), 60 cc. of $Et_2O$, and Al-Hg (prepared from 15 g. of Al) was worked up as in the synthesis of (III) and 6 g. (55%) of a pale yellow oil, b.p$_4$ 175°, was obtained. *Anal.* Calcd. for $C_{16}H_{22}O_5$ : C, 65.29; H, 7.53. Found : C, 65.55; H, 7.52.

**3-($\alpha$-Methylbenzyl)malic Acid (XI)**——(X) (4.5 g.) was hydrolysed by boiling with a mixture of 10 cc. of EtOH and 30 cc. of 10% KOH solution, and worked up as usual, giving 3.3 g. (91%) of white crystals, m.p. 99°. *Anal.* Calcd. for $C_{12}H_{16}O_6 \cdot H_2O$ (XI) : C, 56.24; H, 6.29. Found : C, 56.20; H, 6.24.

When this acid was dried over $P_2O_5$ at 50° for 36 hr., crystals of m.p. 130~134° were obtained. *Anal.* Calcd. for $C_{12}H_{14}O_5$ : C, 60.50; H, 5.92. Found : C, 60.39; H, 5.79.

**Dehydration of (XI) to (XIV) or (XV)**——1) A solution of 3.1 g. of (XI) and 20 cc. of $Ac_2O$ was refluxed for 3 hr. in an oil bath. Distillation of $Ac_2O$ from the solution in a reduced pressure gave 2.6 g. of a brown viscous oil (A).

i) When 1.5 g. of (A) was allowed to stand overnight, a crystalline substance separated. This was recrystallized from petr. benzine containing a small amount of benzene to 150 mg. of (XIII) as colorless plates, m.p. 40~44°. Two additional recrystallizations from petr. benzine gave colorless plates, m.p. 51~53°. *Anal.* Calcd. for $C_{12}H_{10}O_3$ (XIII) : C, 71.28; H, 4.99. Found : C, 71.08; H, 4.92. UV : $\lambda_{max}^{CHCl_3}$ 284 mμ (log $\varepsilon$ 3.11).

(XIII) (100 mg.) was hydrolyzed by boiling with 2 cc. of 10% NaOH solution for 30 min. in a water bath and worked up as usual. Pale brown crystals (about 100 mg.) obtained were recrystallized from a mixture of benzene and petr. benzine to colorless plates, m.p. 112~114°. *Anal.* Calcd. for $C_{12}H_{12}O_4$ (XV) : C, 65.44; H, 5.49. Found : C, 65.79; H, 5.24. UV : $\lambda_{max}^{CHCl_3}$ 242 mμ (log $\varepsilon$ 3.638).

ii) A suspension of 0.5 g. of (A) in 7 cc. of $H_2O$ was heated for 1 hr. in a water bath, $H_2O$ was distilled off completely in a water bath in a reduced pressure. To the residual clear orange viscous oil 2 cc. of benzene was added and allowed to stand overnight in a refrigerator to give 0.2 g. of colorless crystals, m.p. 101~110°. Recrystallization from benzene furnished colorless plates, m.p. 112~114°, which was not depressed when mixed with a sample of (XV) described above.

2) A solution of 3.5 g. of (XI) in 25 cc. of $Ac_2O$ was refluxed for 10 hr. in an oil bath and $Ac_2O$ was distilled off in a reduced pressure. Recrystallization of the brown oil (2.9 g.) here obtained from a mixture of benzene and petr. benzine gave the following results :

i) a) Pale yellow blades (0.35 g.) were obtained from the relatively less-soluble fraction. Several recrystallizations from $CS_2$ furnished colorless blades, m.p. 137~138°. *Anal.* Calcd. for $C_{12}H_{10}O_3$ (iso-(XII)) : C, 71.28; H, 4.99. Found : C, 71,55; H, 5.03. UV $\lambda_{max}^{CHCl_3}$ mμ (log ε) : 260~261 (3.778), 283~285 (3.781). It was shown to be identical by the mixed melting point test and comparison of the ultraviolet spectra with iso-(XII) prepared by the Stobbe method.[4]

b) A solution of the iso-(XII) in $H_2O$ was refluxed for 1 hr. and $H_2O$ was distilled off. Recrystallization of the residue from $H_2O$ gave colorless prisms, m.p. 178~179° (decomp.), in a quantitative yield. It was identical with respect to ultraviolet spectrum and mixed melting point with iso-(XIV) obtained by the Stobbe method.[4] *Anal.* Calcd. for $C_{12}H_{12}O_4$ (iso-XIV) : C, 65.44; H, 5.49. Found : C, 65.30; H, 5.69. UV : $\lambda_{max}^{EtOH}$ 244 mμ (log ε 3.829).

ii) a) Concentration of the combined mother liquor of (i-a) gave 0.2 g. of pale yellow plates, m.p. 100~110° (from benzene-petr. benzine). Further recrystallization from $CS_2$ furnished colorless plates, m.p. 112~114°. It was identical with respect to ultraviolet spectrum and mixed melting point with (XII) obtained by the Stobbe method.[4] *Anal.* Calcd. for $C_{12}H_{10}O_3$ (XII) : C, 71.28; H, 4.99. Found : C, 71.38; H, 4.94. UV : $\lambda_{max}^{CHCl_3}$ 275 mμ (log ε 4.12).

b) A solution of (XII) in $H_2O$ was refluxed for 1 hr. and $H_2O$ was distilled off. Recrystallization of the residue from $H_2O$ gave colorless needles, m.p. 171~172° (decomp.). It was identical with respect to ultraviolet spectrum and mixed melting point with (XIV) obtained by the Stobbe method.[4] *Anal.* Calcd. for $C_{12}H_{12}O_4$ (XIV) : C, 65.44; H, 5.49. Found : C, 65.21; H, 5.31. UV : $\lambda_{max}^{EtOH}$ 235~238 mμ (log ε 3.962).

iii) The viscous oil obtained by concentration of the mother liquor of (ii-a) gave 1.2 g. of pale yellow-brown crystals, m.p. 80~92°, on treatment with a mixture of benzene and petr. benzine. Colorless crystals, m.p. 90~91°, were obtained by further recrystallization from the same solvent. *Anal.* Calcd. for $C_{12}H_{10}O_3$ : C, 71.28; H, 4.99. Found : C, 71.58; H, 5.02. UV : $\lambda_{max}^{CHCl_3}$ 275 mμ (log ε 3.78).

The product of m.p. 90~91° consisted of two kinds of crystals having different crystal forms; one of pale yellow blades as the minor component and the other of pale yellow granular crystals as the major component. Both types of crystals were separated manually with a needle and magnifying glass. Recrystallization from $CS_2$ gave colorless blades, m.p. 137~138°, from the minor component and colorless needles, m.p. 112~114°, from the major component. The melting points were not depressed when these components were mixed respectively with the samples of iso-(XII) and (XII).

**(α-Methylbenzyl)succinic Acid (VII)**——i) (XV) (20 mg.) was reduced by the Schwenk-Papa method*1 using 120 mg. of Raney Ni alloy and 1.5 cc. of 10% NaOH solution and 18 mg. (89%) of a pale brown solid was obtained. Two recrystallizations from a mixture of AcOEt and petr. benzine furnished colorless prisms, m.p. 143~146°, which was not depressed on admixture with (VII), described in a previous paper.[1]

ii) The crude anhydride (2.5 g.) of (XI), which was obtained by refluxing a solution of 3.2 g. of (XI) and 30 cc. of $Ac_2O$ for 3 hr., was hydrolyzed by boiling with 20 cc. of 3% NaOH solution for 3 hr. in an oil bath. Upon working up the reaction mixture as usual, 2 g. of a brown viscous oil was obtained. A solution of this oil in 30 cc. of EtOH was shaken in the presence of Raney Ni catalyst (prepared from 1.2 g. of Raney Ni alloy) in $H_2$ atmosphere at room temperature until one molar equivalent of $H_2$ was absorbed (in 6 hr.). The catalyst was filtered off and the solvent was evaporated, giving a brown viscous oil which crystallized from benzene to 1.7 g. (55%) of white crystals. Further recrystallization from benzene furnished white crystals, m.p. 145~147°. *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found : C, 64.98; H, 6.13.

## Summary

A method was investigated for the synthesis of (α-methylbenzyl)succinic acid (VII) by dehydration, hydrolysis, and hydrogenation of 3-(α-methylbenzyl)malic acid (XI). Dehydration of 3-(α-methylbenzyl)malic acid (XI) by boiling with acetic anhydride yielded *cis*- and *trans*-isomers of (α-methylbenzylidene)succinic anhydride (XII) and (α-methylbenzyl)maleic anhydride (XIII), which were converted to the corresponding dicarboxylic acids by hydrolysis with water.

(Received September 9, 1960)

---

[4] H. Stobbe : Ann., **308**, 114 (1899).