The Stereochemistry of 3-Hydroxy-2-methylbutyric Acid

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Four stereoisomers of methyl 3-hydroxy-2-methylbutyrate (I), (+)-*threo*-I, (−)-*threo*-I, (+)-*erythro*-I, and (−)-*erythro*-I, were prepared, and their absolute configurations were determined. The configurations of (+)-*threo*-I, $[\alpha]_D^{20}$ +36.80° (*c* 5, methanol) and (+)-*erythro*-I, $[\alpha]_D^{20}$ +14.32° (*c*, 5, methanol) were assigned to (2*S*, 3*S*) and (2*S*, 3*R*) respectively.

The present work was undertaken in connection with two other studies. One is the study of the stereo-differentiating (asymmetric) hydrogenation of methyl 2-methyl-3-oxobutyrate (III) into methyl 3-hydroxy-2-methylbutyrate (I) over an asymmetrically modified nickel catalyst.[1] In this study, the determinations of $[\alpha]_D$ and the absolute configuration of each stereoisomer of I are essential for the evaluation of the reaction. The other is the study of the stereochemistry of the CH_3–CH(OH)–CH(CH_3)– group of sex pheromones of sawflies.[2]

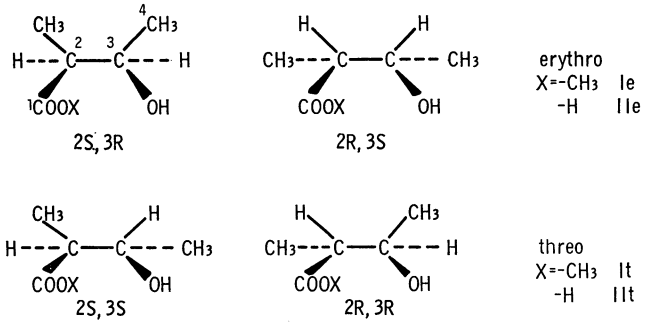


Fig. 1.

The configurations of four stereoisomers of I are shown in Fig. 1. The pair of (2*R*, 3*R*)- and (2*S*, 3*S*)-I was conventionally designated as the *threo* isomer (It), and that of (2*R*, 3*S*)- and (2*S*, 3*R*)-I, as the *erythro* isomer (Ie). Optically active I ($[\alpha]_D$+22°) was first isolated from the degradation product of tetrin B by Rinehart and co-workers.[3] The configuration at C-3 of this compound was assigned to *S*, but that at C-2 was not made clear. Masken and Polgar reported that each diastereomer of I showed a different retention time in GLC and assigned the diastereomer with long retention time to Ie based on the NMR and IR spectroscopic analyses.[4] However, neither the optical resolution of Ie and It nor the determination of the absolute configurations of optically active Ie and It has been reported.

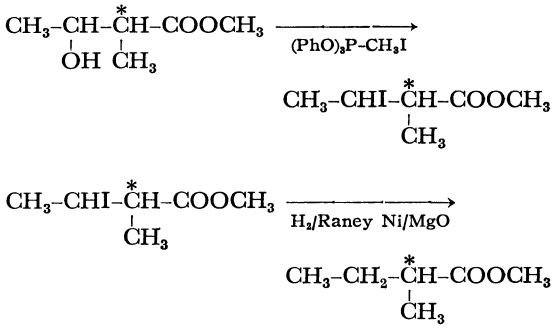
Results and Discussion

Diastereoisomeric I consisting of Ie and It in a ratio of 6 to 4 was obtained by the hydrogenation of methyl 2-methyl-3-oxobutyrate (III) over DL-tartaric acid-modified Raney nickel.[5] It is better to use modified Raney nickel for this hydrogenation, since unmodified Raney nickel is easily corroded by III and often loses its catalytic activity in the course of the hydrogenation.[6]

After the hydrolysis of I into 3-hydroxy-2-methylbutyric acid (II), II was converted to cyclohexylammonium salt. The recrystallization of the cyclohexylammonium salt from ethanol gave one of the diastereomers of II in a pure state. GLC and NMR analyses of its methyl ester indicated that the resulting isomer corresponded to the *erythro* isomer (IIe) assigned by Masken and Polgar. The cyclohexylammonium salt in the combined mother liquid was converted to sodium salt by treatment with sodium hydroxide. The recrystallization of the sodium salt from a methanol–acetone mixture gave the other diastereomer, IIt, in a pure state.

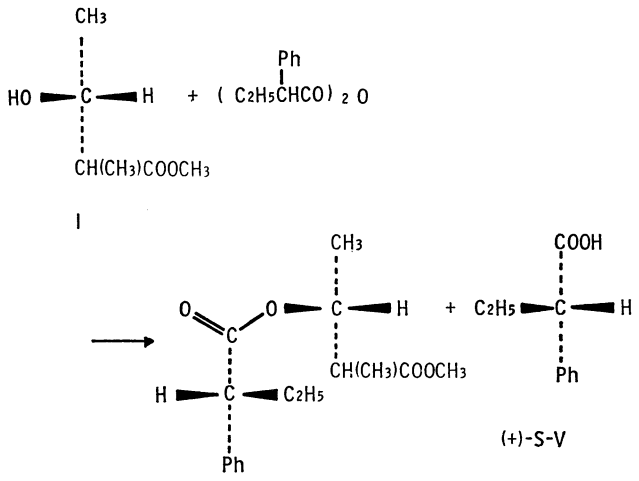
The optical resolution of each diastereomer was accomplished in the usual manner. The resulting isomer and resolving reagent were as follows: (+)-IIe and (+)-IIt by quinine, (−)-IIe by quinidine, and (−)-IIt by cinchonidine.

All the isomers of II were converted to their methyl ester (I) by the treatment of diazomethane. Thus, (+)-IIe was converted to (+)-Ie, (−)-IIe to (−)-Ie, (+)-IIt to (+)-It, and (−)-IIt to (−)-It. The configuration at the C-2 position of I was correlated to that of (+)-(*S*)-methyl 2-methylbutyrate (IV).[7] The conversion of I to IV was carried out in two steps:



From (+)-Ie and (−)-It, (+)-(*S*)-IV and (−)-(*R*)-IV were obtained respectively. Therefore, the configurations at the C-2 position of (+)-Ie and (+)-It are *S* while those of (−)-Ie and (−)-It are *R*.

The configuration at the C-3 position of I was determined by Horeau's method.[8] When an excess amount of (±)-2-phenylbutyric anhydride was treated with (+)-Ie, (+)-(*S*)-2-phenylbutyric acid was recovered. It was empirically demonstrated that when the configuration of I was that shown in Scheme 1, the recovered 2-phenylbutyric acid (V) had the (+)-(*S*)-enantiomer in excess. Therefore, the configuration at the C-3



Scheme 1.

position of (+)-Ie could be assigned to *R*. In the same manner, the reactions with both (+)-It and (−)-Ie gave (−)-(*R*)-V. Thus, the configurations at 3-C of (+)-It and (−)-Ie were assigned to *S*.

Table 1. Absolute configuration and optical rotation of methyl 3-hydroxy-2-methylbutyrate (I)

Isomer[a)]	Absolute configuration	$[\alpha]_D^{20}$ (*c* 5, methanol)
(+)-*threo*-I	(2*S*,3*S*)	+36.80°
(−)-*thero*-I	(2*R*,3*R*)	
(+)-*erythro*-I	(2*S*,3*R*)	+14.32°
(−)-*erythro*-I	(2*R*,3*S*)	

a) The sign of each isomer shows the direction of α_D^{20} observed in neat.

The configuration and optical rotation of each isomer are listed in Table 1. The relative configurations at C-2 and C-3 assigned by Masken are consistent with the present results.

Experimental

The analytical GLC was carried out with a Shimadzu GC-4A gas chromatograph using a 3-m, 5-mm o.d. glass column packed with 5% NPGS on Chromosorb W at stated temperatures. The preparative GLC was carried out with a Shimadzu GC-3HA instrument using a 3-m, 8-mm o.d. stainless column packed with the same packing.

The optical rotations were measured with a Perkin Elmer 241 polarimeter at 20 °C under the stated conditions.

The NMR spectra were taken with a Hitachi R-24 spectrometer at 60 MHz. The IR spectra were taken with a Shimadzu IR-27G spectrometer. All the chemicals except as stated below were obtained from commercial sources and were used without further purification.

Methyl 2-Methyl-3-oxobutyrate (III). This was prepared from methyl acetoacetate and methyl iodide, bp 75—78 °C. GLC (at 90 °C) indicated a 98% purity; retention time, 9.1 min. Also there was 2% of methyl 2,2-dimethyl-3-oxobutyrate; retention time, 7.9 min.

Diastereoisomeric Methyl 3-Hydroxy-2-methylbutyrate (I). In an autoclave (1000 ml capacity), 300 g of III and 23 g of Raney nickel modified with DL-tartaric acid were placed. Hydrogen was added until the pressure reached 110 kg/cm², and then heating was commenced. After the temperature of the reaction mixture had become 65 °C, this temperature was maintained until the end of the reaction; after 24 h there was no fall in the pressure. After the removal of the catalyst, the distillation of the product gave 271 g of crude I, bp 79—81 °C/18 mmHg. GLC (at 90 °C) indicated that the products consisted of 39% of It (retention time 12.8 min), 58% of Ie (retention time 14.1 min), and 4% of unidentified impurities (retention times 11.0 and 15.2min).

Separation of threo-*I (It) and* erythro-*I (Ie).* The crude I (271 g) was saponified with 30% aqueous sodium hydroxide (300 ml) at room temperature. Most of the water was evaporated under reduced pressure, and the residue was acidified with 12M hydrochloric acid (120 ml) and they extracted with three 300 ml portions of ether. The evaporation of the ether from the combined extract gave 224 g of crude 3-hydroxy-2-methylbutyric acid (II). This was dissolved in 350 ml of ethanol and mixed with 180 g of cyclohexylamine under nitrogen. On cooling the solution overnight, a part of the salt was crystallized. Two successive recrystallizations of the crystalline part from 95% ethanol gave 166 g of cyclohexylammonium salt of IIe, mp 148 °C, Found: C, 59.74; H, 10.81; N, 6.34%. Calcd for $C_{11}H_{23}NO_3 \cdot (1/4)H_2O$: C, 59.56; H, 10.68; N, 6.31%. The attempts to eliminate the water from the sample resulted in failure, since the salt was decomposed with the evolution of cyclohexylamine on heating *in vacuo*. Small portions of the salt were acidified, and the liberated acid was converted to methyl ester with diazomethane. The GLC (at 90 °C) of the ester showed a single peak corresponding to the *erythro*-isomer; retention time, 14.3 min.

The mother liquids of the original crystallization and the first recrystallization were combined and concentrated to dryness. The residue was dissolved in 150 ml of 30% aqueous sodium hydroxide and washed with two 150 ml portions of ether. After reducing the water from the aqueous layer on a rotatory evaporator, the remaining dense sirup (*ca.* 70 ml) was mixed with 1100 ml of a methanol–acetone (1 : 5) mixture and crystallized at 0 °C. Two successive recrystallizations from methanol gave 48 g of sodium salt of IIt, mp 210—215 °C. The salt was too hygroscopic for the elemental analysis to be performed with a completely dried sample. The results of the elemental analysis were as follows; Found: C, 41.51; H. 6.52%. Calcd for $C_5H_9O_3Na \cdot (1/4) \cdot H_2O$: C, 41.52; H, 6.62, GLC (at 90 °C) of methyl ester derived from the sample showed a single peak of the *threo-isomer*; retention time, 12.5 min.

Optical Resolution of IIe. When a solution of cyclohexylammonium salt of IIe (150 g) in 1500 ml of water was passed through a column packed with 500 ml of Amberlite IR-120 (H^+ type), 2000 ml of an acidic eluate were collected. To the eluate 220 g of quinine was added, after which the mixture was stirred until the added base was completely dissolved. After the decoloration of the solution with activated charcoal, it was evaporated to dryness under reduced pressure to give crude quinine salt. Ethanol was added to the crude salt in portions at the boiling temperature until the salt was completely dissolved (*ca.* 180 ml of ethanol was required); on cooling, crystals of the quinine salt were precipitated. Recrystallization from ethanol was carried out in the manner described above. The progress of resolution was followed by the measurement of the optical rotation of the sodium salt derived from a small portion of quinine salt by treatment with aqueous sodium hydroxide. After three recrystallizations, the rotation reached a steady value, are unchanged by two further recrystallizations. The quinine salt of IIe

obtained amounted to 50 g; mp 140—141 °C, $[\alpha]_D^{20}$ −134 °C (*c* 1, H_2O). This was dissolved in 100 ml of water and treated with 5% aqueous sodium hydroxide with stirring until the pH of the mixture became 10. The removal of the liberated quinine by filtration and the evaporation of the filtrate gave a dense sirup, which was then dissolved in 50 ml of ethanol. After removing the insoluble matter by filtration, the filtrate was mixed with 250 ml of acetone to give 15 g of (−)-sodium salt of IIe as crystals, $[\alpha]_D^{20}$ −7.20 ° (*c* 10, H_2O), +13.61 ° (*c* 5, 3 M HCl).

The sodium salt (98 g), $[\alpha]_D^{20}$ +2.0 (*c* 10, H_2O), recovered from the combined mother liquids of the first and second crystallizations was dissolved in 1500 ml of water, after which the solution was passed through a column packed with 500 ml of Amberlite IR-120 (H^+ type). Into the acidic eluate (1700 ml), a 280-g portion of quinidine was added, and the mixture was stirred until all the base had dissolved. After removing the insoluble matter, the solution was evaporated to dryness to give crude quinidine salt. Four successive recrystallizations of the salt from acetone gave 110 g of quinidine salt of optically pure IIe; $[\alpha]_D^{20}$ 172 ° (*c* 10, H_2O), mp 100 °C. This was then converted to (+)-sodium salt of IIe in a yield of 30 g; $[\alpha]_D^{20}$ +7.53 ° (*c* 10, H_2O), −13.74 ° (*c* 10, 3M HCl).

(+)-Methyl erythro *3-Hydroxy-2-methylbutyrate (Ie).* The acid liberated from 10 g of (−)-sodium salt of IIe by treatment with 24 ml of 10 M HCl was extracted with three 30-ml portions of ether, and the combined extract was dried over anhydrous magnesium sulfate. After the solvent had been reduced, a slight excess of ethereal diazomethane was added to solution at 5 °C, and the mixture was kept at room temperature for 20 min. After the excess of diazomethane had then been decomposed with HCl, the solution was washed with water, dried over magnesium sulfate, and concentrated. The distillation of the condensate under reduced pressure gave 8.5 g of (+)-Ie, bp 75 °C/15 mmHg; α_D^{20} +11.30 ° (neat); GLC (at 90 °C); single peak; retention time, 14.0 min; NMR ($CDCl_3$, TMS), δ 1.18 (3H, d, J=6.4 Hz), 1.19 (3H d, J=7.0 Hz), 2.46 (1H, broad signal), 2.51 (1H, m), 3.70 (3H, s), 4.06 (1H, m), IR (neat) 3550, 2990, 2940, 1730, 1200, 1085, 1032 cm^{-1}. This product contains *ca.* 1% of water, as estimated from the results of the elemental analysis. A-2g portion of the product was boiled in 30 ml of dry benzene in order to remove the water as the benzene azeotrope and was then distilled at atmospheric pressure to give an analytical sample; bp 183 °C/763 mmHg; Found; C, 54.60; H, 9.46%. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15%. $[\alpha]_D^{20}$ +14.32 (*c* 5, CH_3OH), −4.04 (*c* 5, $CHCl_3$). The GLC, NMR, and IR data of the sample were identical with those listed above.

(−)-Methyl erythro *3-Hydroxy-2-methylbuthyrate (Ie).* By the same procedure mentioned before, 10 g of (+)-sodium salt of IIe was converted into (−)-Ie in a yield of 8.5 g, α_D^{20} −11.39° (neat). The bp, water content, retention time in GLC, and NMR and IR spectra were identical with those of the (+)-isomer.

Optical Resolution of IIt. A solution of sodium salt of IIt (98 g) in 1000 ml of water was passed through a column packed with 500 ml of Amberlite IR-120 (H^+ type). The acidic eluate (1700 ml) was mixed with 230 g of quinine and stirred until it was completely dissolved. The solution was then concentrated to 200 ml and allowed to stand overnight at 5 °C to give 137 g of quinine salt as crystals. After recrystallizing three times from water, the resulting 30-g portion of the salt (mp 154 °C, $[\alpha]_D^{20}$ −163 °(*c* 2, 50% ethanol)) was converted into (+)-sodium salt of IIt in a yield of 23 g, $[\alpha]_D^{20}$ +10.6 °(*c* 10, H_2O), +26.5 ° (*c* 5, 3M HCl).

The sodium salt (70 g, $[\alpha]_D^{20}$ −4.5 ° (*c* 10, H_2O)) recovered from the mother liquid was dissolved in 800 ml of water and treated with Amberlite IR-120 (H^+ type). The acid thus liberated was subjected to further resolution by the recrystallization of its cinchonidine salt from a mixture of acetone and 2-propanol (4 to 1). After recrystallizing five times, the salt was converted into (−)-sodium salt of IIt in a yield of 10 g, $[\alpha]_D^{20}$ −10.20 ° (*c* 10, H_2O), −26.30 ° (*c* 10, 3M HCl).

(+)- and (−)-Methyl 3-Hydroxy-2-methylbutyrate (It). (+)- and (−)-salt of IIt were converted into the methyl ester by the method described above.

From 10 g of (+)-sodium salt of IIt, 8.7 g of (+)-It were obtained; bp 83 °C/18 mmHg, water content, *ca.* 0.5%, α_D^{20} +34.80° (neat), GLC (at 90 °C), single peak; retention time, 13.0 min; NMR ($CDCl_3$, TMS) δ 1.18 (3H, d, J=7.2 Hz), 1.22 (3H, d, J=6.3 Hz), 1.19 (1H, broad signal), 2.47 (1H, m), 3.71 (3H, s), 3.82 (1H, m), IR (neat) 3550, 2990, 2960, 1730, 1200, 1100, 1045 cm^{-1}. The dehydrated analytical sample was prepared by the method described before; bp 181 °C/764 mmHg, Found: C, 54.51; H, 9.43%. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15%, $[\alpha]_D^{20}$ +36.80° (*c* 5, CH_3OH), +32.51° (*c* 5, $CHCl_3$). The GLC, NMR, and IR data of this sample were identical with those listed above.

From 10 g of (−)-sodium salt of IIt, 8.6 g of (−)-It were obtained; water content, *ca.* 1%, α_D^{20} −34.72° (neat). The GLC, NMR, and IR data of this compound were identical with those of the (+)-isomer.

Methyl 3-Iodo-2-methylbutyrate. Partially resolved (+)-Ie (5g, α_D^{20} +7.08° (neat)) was mixed with methyl tris-(phenoxy)phosphonium iodide prepared from 15 g of triphenyl phosphite and 4.3 g of methyl iodide. The mixture was then stirred at 50 °C overnight. As the product we extracted four 20-ml portions of hexane. The combined extract was washed with a 30-ml portion of water, dried over anhydrous sodium sulfate, and concentrated to one tenth of its original volume under reduced pressure. The distillation of the condensate gave 1.2 g of a diastereomeric mixture of methyl 3-iodo-2-methylbutyrate, bp 98—102 °C/12 mmHg. GLC (at 130 °C) indicated a 97.5% purity as a diastereomeric mixture (retention times 6.2 and 6.7 min) and 2.5% of an unidentified impurity (retention time 5.7 min). The NMR spectra (CCl_4, TMS) showed those signals; δ 1.32 and 1.33 (d, J=7.1) for the $C\underline{H}_3$–CH–$COOCH_3$ of each diastereomer, 1.90 and 1.98 (d, J=6.4) for the $C\underline{H}_3$–CHI– of each diastereomer, 2.5 (m) for –$C\underline{H}(CH_3)$–, 3.75 (s) for –O–$C\underline{H}_3$, and 4.05 (m) for –CHI–. The spectra were consistent with the structure of methyl 3-iodo-2-methylbutyrate. The IR spectra did not show any OH stretching, indicating the absence of the starting material in the product.

Partially resolved (−)-It (5 g, α_D^{20} −19.1° (neat)) was converted into methyl 3-iodo-2-methylbutyrate (1.1 g) by the method discribed before. The GLC, NMR, and IR data of the product were identical with those of the product derived from (+)-Ie.

Hydrogenolysis of Methyl 3-Iodo-2-methylbutyrate. Into an atmospheric pressure hydrogenation vessel which had been filled with hydrogen, methyl 3-iodo-2-methylbutyrate derived from (+)-Ie (0.8 g), magnesium oxide (0.5 g), and a Raney nickel catalyst (1.8 g in 10 ml of methanol) were introduced. The mixture was shaken at 45 °C for 48 h under an atmospheric pressure of hydrogen. After the removal of the insoluble matter by filtration, the filtrate was subjected to flash distillation at 50 mmHg. The distillate collected in a cold trap was transferred into an evaporator fitted with a Snyder column and was concentrated to 1.5 ml on heating under atmospheric pressure. GLC (at 50 °C) indicated that the condensate consisted of methyl 2-methylbutyrate and methanol

in a ratio of 1 to 10, with an accompanying trace amount of a high-boiling substance. The preparative GLC (at 40 °C) of the condensate gave pure methyl 2-methylbutyrate (IV), $[\alpha]_D^{20}$ +14.4° (*c* 4, methanol). The GLC, NMR, and IR data of the product were identical with those of the authentic compound prepared from racemic 2-methylbutyric acid (Tokyo Kasei Kogyo Co., Ltd.)

In the same manner as has been presented before, methyl 3-iodo-2-methylbutyrate was converted into IV, $[\alpha]_D^{20}$ −11.7° (*c* 4, methanol). The GLC, NMR, and IR data of the product were identical with those of an authentic compound.

Kinetic Resolution of (±)-2-Phenylbutyric Anhydride with I. A solution of (±)-2-phenylbutyric anhydride (0.6), (+)-Ie (0.1 g), and pyridine (2 g) in 10 ml of benzene was kept at room temperature for 12 h and then a 15-ml portion of water was added. The mixture was stirred for 30 min, a 30-ml portion of dilute hydrochloric acid was added, and the new mixture was extracted with 50 ml of ether. The ether layer was washed with water and extracted with a 50-ml portion of a 5% aqueous sodium hydrogencarbonate solution. The aqueous extract was acidified with dilute hydrochloric acid, followed by extraction with ether. The ether extract was dried over anhydrous magnesium sulfate and then evaporated to dryness to give 0.16 g of 2-phenylbutyric acid, which had α_D^{20} +0.80° in 2 ml of benzene.

The reactions of (−)-Ie and (+)-It with 2-phenylbutyric anhydride were carried out as before. The values of α_D^{20} (0.16 g of a sample in 2 ml of benzene) of the recovered 2-phenylbutyric acid were −0.73° for (−)-Ie and −0.96° for (+)-It. The NMR and IR spectra of each acid were identical with those of an authentic compound (Wako Pure Chemical Industries, Ltd.).

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