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An Improved Synthesis of N,β-Dimethylleucine and the Resolution Thereof*1

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A diastereoisomeric mixture of racemic β-methylleucine was synthesized by the condensation of 2-benzyl-4(5*H*)-imidazolone with the methyl isopropyl ketone, followed by catalytic hydrogenation and hydrolysis. The separation of the mixture into *threo*-β-methyl-DL-leucine and *erythro*-β-methyl-DL-leucine was mainly achieved by fractional crystallization from water. The resolution of each diastereoisomer was also accomplished through salt-formation with (−)- and (+)-ephedrine alternately before or after the methylation of the amino group. The specific rotation and the NMR and IR spectra of one isomer, *threo*-N,β-dimethyl-L-leucine, corresponded closely with those reported for dimethylleucine isolated from nature.

N,β-Dimethylleucine was isolated from a hydrolysate of Ethamycin by Sheehan and his coworkers,[1] and later from Triostin C by Ōtsuka and Shōji.[2] The configuration at both centers of asymmetry of the amino acid was established as being comparable to that of L-alloisoleucine.[1,3] Although an attempt was made by Sheehan and Howell to synthesize the amino acid,[4],*2 it has not yet been done completely. In this paper, an improved synthesis of N,β-dimethyl-DL-leucine, a synthesis that might be appropriate for a method of preparation, and its favorable optical resolution using ephedrine are described.

Synthesis

2-Benzyl-4(5*H*)-imidazolone[5] (I), which can be easily produced by the condensation of ethyl phenylacetoimidinate with ethyl glycinate, may be expected to be a suitable material for the preparation of the

*1 This work was partially presented at the 20th and 21st Annual Meetings of the Chemical Society of Japan, Tokyo, April 1967 and Osaka, April 1968, and reported on *Tetrahedron Letters*, **1968**, 2015.

1) J. C. Sheehan, H. G. Zachau and W. B. Lawson, *J. Am. Chem. Soc.*, **80**, 3349 (1958).

2) H. Ōtsuka and J. Shōji, *J. Antibiotics*, **A16**, 52 (1963). More recently, the amino acid was also found in Triostin B_0 and in Quinomycin series by the same authors, *ibid.*, **A19**, 128 (1966); *Tetrahedron*, **23**, 1535 (1967).

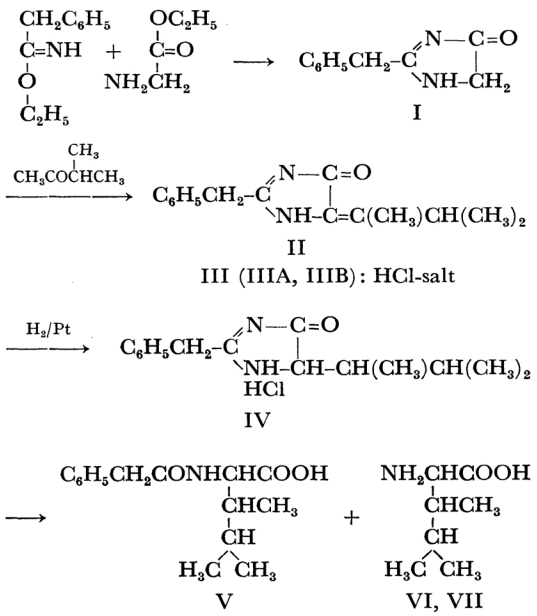
3) J. Shōji, K. Tori and H. Ōtsuka, *J. Org. Chem.*, **30**, 2772 (1965).

4) J. C. Sheehan and M. G. Howell, *ibid.*, **28**, 2279 (1963).

*2 In the preceding work to Sheehan, the diastereomixture of β-methyl-DL-leucine was also prepared by T. Kōnotsune, *Nippon Nogei Kagaku Kaishi* (*J. Agr. Chem. Soc. Japan*), **36**, 389 (1962), from the reactios of *s*-butyl crotonate, Grignard reagent of isopropyl bromide, and bromine, followed by hydrolysis and amination. But the over-all yield was as low as about 10%.

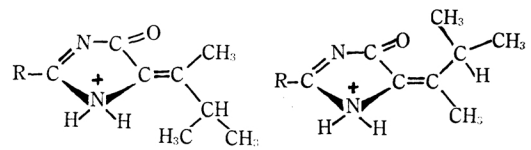
5) H. Finger and W. Zeh, *J. prakt. Chem.*, [2] **82**, 50 (1910); H. Lehr, S. Karlan and M. W. Goldberg, *J. Am. Chem. Soc.*, **75**, 3640 (1953); A. R. Kidwai and G. M. Devasia, *J. Org. Chem.*, **27**, 4527 (1962).

titled compound because of its stability and because its reactivity with the desired ketone is sufficient. The condensation of I with methyl isopropyl ketone was successfully worked up, with the latter in a twofold excess, to give 2-benzyl-5-(α-methyl isobutylidene)-4-imidazolone (II), which was isolated as its stable hydrochloride (III) by passing dry hydrogen chloride through the solution of II in ethyl alcohol. The subsequent catalytic reduction of III over Adams' platinum oxide as a catalyst afforded 2-benzyl-5-(α-methyl isobutyl)-4-imidazolone (IV). In contrast with the favorable use of the above catalyst, palladium black did not respond when used similarly. Upon the hydrolysis of IV with aqueous barium hydroxide, the diastereoisomers of β-methylleucine (VI, VII) and *N*-phenylacetyl-β-methylleucine (V), which was considered to be a hydrolysis intermediate, were given in 52 and 44% yields respectively (Scheme 1). Since the solubility



Scheme 1

of VI in water was much less than that of the other isomer, VII, the isomer VI was obtained in a pure state by repeated fractional crystallization from water. Although it was difficult to isolate the more soluble VII in the pure form, VII was separated from contaminated VI as follows: a reverse relationship in solubility was here observed between the diastereoisomeric amino acids (VI and VII) and their *N*-acetyl derivatives (VI′ and VII′), and the final purification of VII was achieved by the fractional crystallization of its *N*-acetyl derivative (VII′), followed by deacetylation. The above *N*-acetylation was carried out by using a precise equiamount of acetic anhydride in a caustic alkali solution in order to avoid any equalization of asymmetry at the α-carbon atom through the formation of azlactone, which is likely to arise through the action of acetic anhydride in glacial acetic acid.[6],*3 VI was also obtained exclusively from the intermediate V by hydrolysis either with aqueous barium hydroxide or with 6N hydrochloric acid. Thus, the ultimate ratio of fairly pure VI and VII was about 2:1 (in 57 and 28% yields respectively). The predominantly-formed diastereoisomer VI was found to be a racemate of the desired *threo*-form, thus favoring our synthetic purpose. The result is probably due to steric hindrance exerted by the carbonyl group present in the imidazolone on the isopropyl of methyl isobutylidene in the molecule II. In the route from I to IV, IIIA rather than IIIB is preferably formed, followed by the *cis*-addition of hydrogen by catalytic reduction (Scheme 2). Consideration using the Dreiding model led



IIIA IIIB

R: $C_6H_5CH_2$

IIIA: Preferably formed structure, which expected to afford VI by *cis*-addition of hydrogen, followed by hydrolysis.

IIIB: Less prefered structure anticipated to form VII.

Scheme 2

us to understand the condensation containing the above sterically-controlled synthesis and enabled us to predict that, by subsequent catalytic hydrogenation, the preferably-formed VI would be racemic *threo*-β-methylleucine. Characteristic differences between VI and VII are observed from their IR spectra showing absorptions in the region of 1700—1600 cm^{-1}, though there was only a minor difference in the finger-print region; VI has two absorption bands at 1668 and 1628 cm^{-1}, with the former band much stronger than that of the latter, in contrast with the single band, at 1625 cm^{-1}, in VII. In addition, VI′ showed a carboxyl stretching band at 1733 cm^{-1} and a carbonyl band of amide at 1633 cm^{-1}, but the corresponding bands of VII′

6) J. P. Greenstein, S. M. Birnbaum and L. Levinton *Biochem. Prep.*, **3**, 84 (1953).

*3 When excess acetic anhydride in a warm alkali solution was used, epimerization was reported to occur at the α-carbon atom of isoleucine by W. A. H. Huffman and A. W. Ingersoll (*J. Am. Chem. Soc.*, **73**, 3366 (1951)). However, under the conditions described in this paper, VI and VII were acetylated without any considerable epimerization.

shifted to 1708 and 1615 cm^{-1} respectively.*4 There are, moreover, two characteristic bands in the 1200—1300 cm^{-1} region for VI′; one of these, at 1258 cm^{-1}, is much stronger than the other, at 1265 cm^{-1}; there is only the single band at 1418 cm^{-1} in the case of V′.

According to the method of Quitt and his coworkers,[7] the *N*-methylation of VI was accomplished through the formation of an *N*-benzyl derivative (VIII). The *N*-benzyl-*N*-methyl derivative (IX) thus formed was then hydrogenated to give *threo*-*N,β*-dimethyl-DL-leucine (X). Similarly, the other isomer, *erythro*-*N,β*-dimethyl-DL-leucine, was obtained through the isomeric intermediates, corresponding to VIII and IX, from VII. The observation that the relative configurations at the α- and β-carbon atoms of the diastereoisomers are reflected in their NMR spectra[3] was used as a basis for speculation concerning the steric structures of X and its isomer: the coupling constant at the α-proton of compound X, assumed above to be *threo*-form, was 3.9 cps, and that of the latter was 4.8 cps; these values corresponded to the values of the coupling constants (4.05 and 4.80 cps) reported in the literature for *N,γ*-dimethyl-DL-alloisoleucine and *N,γ*-dimethyl-DL-isoleucine. The IR spectra of X was, of course, distinct from that of the other isomer, and it was in good agreement with that of *N,γ*-dimethyl-DL-alloisoleucine over the whole region. The solubility behavior of both the diastereoisomers in such solvents as water, lower alcohols, and acetone was also comparable with that reported in the literature.[4]

Optical Resolution

The resolution of the *N*-benzyloxycarbonyl derivative of X is desirable for the purpose of its peptide formation; it was achieved through salt-formation alternately using (−)- and (+)-ephedrine hemihydrate.*5 *N*-Benzyloxycarbonyl-*threo*-*N,β*-dimethyl-DL-leucine (XI), prepared according to the Schotten-Baumann technique from X with benzyloxycarbonyl chloride, was combined with (−)-ephedrine hemihydrate in ethyl acetate in concentrations of 1.0 and 0.56 M respectively, thus affording exclusively a salt of the L-isomer: *N*-benzyloxycarbonyl-*threo*-*N,β*-dimethyl-L-leucine·(−)-ephedrine salt ($[\alpha]_D = -75.0°$) (XIIL) in over a 90% yield. The further addition of the antipodal base, (+)-ephedrine hemihydrate, to the mother liquor gave an optically-pure *N*-benzyloxycarbonyl-*threo*-*N,β*-dimethyl-D-leucine·(+)-ephedrine salt ($[\alpha]_D = +73.5°$) (XIID). A suspension of XIIL in ethyl acetate was treated with 2N hydrochloric acid to give *N*-benzyloxycarbonyl-*threo*-*N,β*-dimethyl-L-leucine ($[\alpha]_D = -75.9°$) (XIIIL). The XIIIL was dissolved in 30% hydrogen bromide in glacial acetic acid to afford *threo*-*N,β*-dimethyl-L-leucine ($[\alpha]_D = +38.3°$) (XIVL); this was then neutralized with triethylamine in ethyl alcohol. In a similar way, the other isomer, *threo*-*N,β*-dimethyl-D-leucine ($[\alpha]_D = -39.3°$) (XIVD), was obtained from XIID through *N*-benzyloxycarbonyl-*threo*-*N,β*-dimethyl-D-leucine ($[\alpha]_D = +75.3°$) (XIIID). The XIIID isomer, with a specific rotation of +72°, was also obtained directly from the mother liquor of XIIL, without any intermediate formation of salt, XIID. In this case, the effective washing of the solution of ethyl acetate with water to remove a small amount of contaminating salt was essential in order to increase the optical purity of the product. Unlike the case of XI, *N*-benzyloxycarbonyl-*erythro*-*N,β*-dimethylleucine did not react with ephedrine to deposit salt from a solution in such a solvent as ethyl acetate, lower alcohols, acetone, benzene, or ether. The resolution was, however, accomplished in the case of *N*-benzyloxycarbonyl-*erythro*-β-methyl-DL-leucine (XV). The salts, *N*-benzyloxycarbonyl-*erythro*-β-methyl-L-leucine·(−)-ephedrine ($[\alpha]_D = -17.6°$) (XVIL) and *N*-benzyloxycarbonyl-*erythro*-β-methyl-D-leucine·(+)-ephedrine ($[\alpha]_D = +17.7°$) (XVID), were obtained from the ethereal solution by a way similar to that used for the *threo*-form. They were reduced to *erythro*-β-methyl-L-leucine ($[\alpha]_D = +38.9°$, in 5N hydrochloric acid) (XVIIL) and its antipode, XVIID ($[\alpha]_D = -39.4°$, in 5N hydrochloric acid), and finally *N*-methylation was performed to afford *erythro*-*N,β*-dimethyl-L-leucine ($[\alpha]_D = +38.0°$) (XVIIIL) and *erythro*-*N,β*-dimethyl-D-leucine ($[\alpha]_D = -38.3°$) (XVIIID) respectively. The L-isomer without an *N*-methyl group, XVIIL, was comparable to β-methyl-L-leucine, with a

Table 1.

Compound	$[\alpha]_D^{23\text{-}25}$	Solvent	Coupling constant at the α-proton signal in NMR (cps)
XIVL	+31.5° (+33.15°)[1] (+28.4°)[3]	Water	3.9 (4.0)[3]
	+38.3° (+39.2°)[1] (+41.9°)[3]	5N HCl	
XIVD	−31.8°	Water	3.9
	−39.3°	5N HCl	
XVIIIL	+38.0°	5N HCl	4.8
XVIIID	−38.3°	5N HCl	4.8

*4 Those spectra for VI′ and VII′ are in good agreement in whole region with the corresponding those of Sheehan's.[4]

7) P. Quitt, J. Hellerbach and K. Vogler, *Helv. Chim. Acta*, **46**, 327 (1963). Further studies on the *N*-methylation of amino acids have more extensively been done in the same way by M. Ebata, Y. Takahashi and H. Ōtsuka, This Bulletin, **39**, 2535 (1966).

*5 Extensive studies on the resolution of benzyloxycarbonylamino acids by use of ephedrine will be the subject in next paper.

specific rotation of +38°, prepared by Sheehan from the racemate of the less soluble acetyl derivative in water through digestion by acylase. In this connection, the racemic acetyl derivative VI′, which afforded the desired XIVL, was more soluble in water. All of the four possible optical active isomers have here been successfully prepared, as is indicated in Table 1. Among these, only XIVL has been found to be identical with natural amino acid in all respects, including optical rotation value and NMR and IR spectra.

Experimental

All melting points are uncorrected. The infrared spectra were recorded with a Koken DS-301 spectrometer using a sodium chloride prism in Nujol mulls. The NMR spectra were taken with a Nihon Denshi JNM-C-60H spectrometer on a solution in deuterium oxide, using sodium 2,2-dimethyl-2-silapentane-5-sulfonate as a reference at room temperature. The optical rotation values were measured with a Jasco DIP-SL-type polarimeter.

2-Benzyl-4(5*H*)-imidazolone (I). Prepared from ethyl phenylacetoimidinate and ethyl glycinate according to the method reported in the literature. I was obtained, in a 70% yield, as needles with a melting point of 142—143°C (lit.[5] mp 143°C).

2-Benzyl-5(α-methyl isobutylidene)-4-imidazolone (II). A) A mixture of finely-powdered I (25 g, 0.144 mol) and 25 g (0.288 mol) of methyl isopropyl ketone was refluxed under a nitrogen atmosphere for 6 hr at 120—130°C in an oil bath. After cooling (when the reaction mixture had solidified), the reaction mixture was triturated with 20—30 m*l* of petroleum ether and then filtered to give a crude material (mp 72—79°C) in an 89% yield (30.8 g). The material was dissolved in 300 m*l* of benzene and decolorized with active charcoal. Benzene was removed by concentration *in vacuo* to afford, in an 81% yield, colorless crystals with a melting point of 104—120°C (28.1 g). It was difficult to obtain crystals with a constant melting point, though it was possible to recrystallize them from either ether or ether-petroleum ether.

B) To the reaction mixture obtained from 68 g (0.39 mol) of I and 67 g (0.78 mol) of the ketone under conditions similar to those used in the A) procedure, 400 m*l* of ethyl alcohol were added; then dry hydrogen chloride was passed through the solution obtained above under cooling in a water bath until it was saturated. Then the mixture was sealed tightly with a stopper and stored in a refrigerator. After several hours, the deposited crystals were collected on a glass-fritted funnel and washed with much ether to give an almost pure hydrochloride of II (mp 207—210°C) in a 78% yield (85 g); this substance was designated III. It was recrystallized from ethyl alcohol-ether to afford pure crystals with a melting point of 208—210°C. Found: C, 64.52; H, 6.59; N, 9.96%. Calcd for $C_{15}H_{19}ON_2Cl$: C, 64.22; H, 6.83; N, 10.04%.

Racemic β-Methylleucine and Its Separation into Two Diastereoisomers (VI and VII). In a suspension of Adams' platinum oxide (200 mg) in 500 m*l* of alcohol, enough hydrogen was absorbed, and then 55 g (0.197 mol) of III were added. Hydrogenation was continued, with the aid of mechanical shaking, for 40 min, by which time about an equiamount of hydrogen (4400 m*l*) had been absorbed. After the removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give an oily product (IV). A solution of the oil in 2000 m*l* of water containing 372 g (1.18 mol) of barium hydroxide octa-hydrate was refluxed for 40—50 hr. After cooling, 351 m*l* of 6N sulfuric acid were slowly added; the precipitate was filtered and washed several times with hot water. The combined filtrate was concentrated *in vacuo* up to about 100 m*l*, and then the solution was washed twice with 100-m*l* portions of ether. The aqueous layer was concentrated *in vacuo* to give a crystalline residue. To the solution of the dried residue in 150 m*l* of ethyl alcohol, there were added about 20 m*l* of triethylamine to afford 15 g (52.4%) of a crystalline solid. The crystals were redissolved by warming them in 70 m*l* of water and decolorized with active charcoal; then the colorless solution obtained was allowed to stand over night at room temperature. The colorless crystals thus deposited were filtered, washed with alcohol, and then recrystallized several times from water to give 3.4 g (11.9%) of fine crystals. This compound did not change over 270°C; it was designated VI. Found: C, 57.64; H, 10.68; N, 9.41%. Calcd for $C_7H_{15}O_2N$: C, 57.90; H, 10.41; N, 9.65%.

To the mother liquor obtained after the removal of VI, there was added about twice as much acetone to give the other crystals. Repeated fractional crystallization from a small amount of water and acetone afforded a somewhat sterically impure material (mp over 270°C) in a 34.2% (9.8 g) yield. The material obtained was designated VII; it differed from VI in its crystalline form. Found: C, 57.73; H, 10.24; N, 9.72%.

The previously-filtered precipitate, after hydrolysis with barium hydroxide and subsequent neutralization with sulfuric acid, was placed in a 1-*l* Erlenmeyer flask; then it was treated by effective shaking with 200 m*l* of 1N sodium hydroxide, filtered, and washed with 1N sodium hydroxide. The combined filtrate was acidified to pH 4 with concentrated hydrochloric acid. The deposited product was collected by filtration and then recrystallized from benzene to give pure *N*-phenylacetyl-*threo*-β-methyl-DL-leucine (V), which had a melting point of 151.5—152.5°C, in a 43.5% (21.2 g) yield. Found: C, 68.15; H, 7.69; N, 5.66%. Calcd for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.04; N, 5.32%.

A suspension of 2.9 g (0.011 mol) of V in 40 m*l* of 6N hydrochloric acid was refluxed for 14 hr. After cooling, the deposited crystals were filtered off and the filtrate was concentrated *in vacuo* to give a residue. The residue was dissolved in 15 m*l* of ethyl alcohol and neutralized with 2 m*l* of triethylamine. Then the crystals were filtered and washed with ethyl alcohol to afford VI quantitatively (1.6 g). V also afforded VI exclusively upon further treatment in aqueous barium hydroxide for 31 hr at the refluxing temperature.

Acetylation of Amino Groups of VII and VI. A solution of 4.9 g (0.0337 mol) of sterically-impure VII in 8.48 m*l* of 4N sodium hydroxide was cooled to 0—5°C in an ice bath and stirred mechanically. Then, 8.48 m*l* of 4N sodium hydroxide and 3.18 m*l* (0.0337 mol) of acetic anhydride were added, at rates to maintain a

slight basicity and a temperature of about 5°C, over a 30-min period. Stirring was then continued for a further 30 min at room temperature. The solution was acidified by the addition of about 6 m*l* of 6N hydrochloric acid. White crystals deposited immediately; they were filtered to give an *N*-acetyl derivative (5.95 g, 94%). The product was repeatedly recrystallized from water to give 5.40 g of the less soluble *N*-acetyl-*erythro*-*β*-methyl-DL-leucine (VII′), which had a melting point of 169—170°C (lit.[4] 171.8—172.2°C). Found: C, 57.55; H, 9.34; N, 7.34%. Calcd for $C_9H_{17}O_3N$: C, 57.73; H, 9.15; N, 7.48%. IR: 1708, 1616, and 1553 cm^{-1}.

The combined mother liquor was concentrated to dryness to give a crystalline residue. This was repeatedly recrystallized from water and acetone to afford 0.386 g of the more soluble *N*-acetyl-*threo*-*β*-methyl-DL-leucine (VI′), which had a melting point of 159—160°C (lit.[4] 157—157.5°C). Found: C, 58.05; H, 8.91; N, 7.35%. IR: 1733, 1633, 1550, and 1418 cm^{-1}.

The VII′ and VI′ thus obtained were reduced to pure VII and VI by a usual acid hydrolysis, followed by neutralization with triethylamine. On the other hand, pure VI and VII were also acetylated in a similar way to afford VI′ and VII′ respectively; the yields were in the range of 91—95%, and no epimerization was to be seen in either case.

***N*-Benzyl-*threo*-*β*-methyl-DL-leucine (VIII).** A) According to the method of Quitt,[7] 2.9 g (0.02 mol) of VI was treated with 2.1 m*l* (0.02 mol) of freshly-distilled benzaldehyde and then with 0.23 g (0.006 mol) of sodium borohydride, while the temperature was maintained between 20 and 22°C. Then the same amounts of benzaldehyde and sodium borohydride were added to the reaction mixture; from it 4.7 g (100%) of VIII (mp 205—207°C) were then obtained. Recrystallization from an ethyl alcohol-water mixture (2:1) afforded pure crystals with a melting point of 213°C (4.0 g). Found: C, 71.48; H, 8.87; N, 5.75%. Calcd for $C_{14}H_{21}O_2N$: C, 71.45; H, 9.00; N, 5.95%.

B) When catalytic hydrogenation using palladium black as a catalyst was used instead of reduction with sodium borohydride, VIII was usually obtained in a yield relatively lower (as much as 70%) than in the case of A).

***N*-Benzyl-*erythro*-*β*-methyl-DL-leucine.** In a way similar to the procedure of VIII, A), this compound was obtained in an 87% yield; mp 225°C. The recrystallization was performed from methyl alcohol. A mixed-melting-point determination with VIII was depressed to 200—205°C. Found: C, 71.47; H, 8.76; N, 6.09%.

***N*-Benzyl-*threo*-*N,β*-dimethyl-DL-leucine (IX) and Its Dicyclohexylammonium Salt.** According to the method of Quitt,[7] 3 g (0.0128 mol) of finely-powdered VIII were treated with 1.8 m*l* (0.037 mol) of formic acid and 1.5 m*l* (0.018 mol) of 38% formaline. IX was thus obtained almost quantitatively as an oily product; it was often crystallized when left standing for long period of times and furnished crystals with a melting point of 56—57°C. The oil was converted to its dicyclohexylammonium salt from an acetone solution for its characterization. Recrystallization from ethyl alcohol gave a pure product in an 82% yield; mp 139°C. Found: C, 75.16; H, 10.75; N, 6.39%. Calcd for $C_{27}H_{46}O_2N_2$: C, 75.30; H, 10.77; N, 6.51%.

***N*-Benzyl-*erythro*-*N,β*-dimethyl-DL-leucine and Its Dicyclohexylammonium Salt.** Similarly, this compound was prepared from *N*-benzyl-*erythro*-*β*-methyl-DL-leucine as crystals with a melting point of 134—135°C in an 87% yield. Found: C, 72.68; H, 9.29; N, 5.66%. Calcd for $C_{15}H_{23}O_2N$: C, 72.25; H, 9.30; N, 5.62%. The dicyclohexylammonium salt of the material was obtained in an 81% yield; mp 127—128°C. A mixed-melting-point determination with the salt of IX was depressed to 120—122°C. Found: C, 75.38; H, 10.43; N, 6.38%.

***threo*-*N,β*-Dimethyl-DL-leucine (X).** The oily IX prepared from 3 g (0.0128 mol) of VIII was hydrogenated with palladium black as a catalyst in 60 m*l* of 90% acetic acid; then it was concentrated to afford crystals. Recrystallization from an ethyl alcohol-water mixture (2:1) and then a water-dioxane mixture gave pure X with a melting point of over 270°C in a 98% yield. Found: C, 60.40; H, 11.15; N, 8.89%. Calcd for $C_8H_{17}O_2N$: C, 60.34; H, 10.76; N, 8.80%.

***erythro*-*N,β*-Dimethyl-DL-leucine.** The same procedure as in the case of the preparation of X was used. The product was obtained from *N*-benzyl-*erythro*-*N,β*-dimethyl-DL-leucine in a 94% yield; mp>270°C. Found: C, 59.87; H, 10.38; N, 8.83%.

***N*-Benzyloxycarbonyl-*threo*-*N,β*-dimethyl-DL-leucine (XI).** To a solution of 8.8 g (0.55 mol) of X in 14 m*l* (0.055 mol) of 4N sodium hydroxide, there were added 16.7 m*l* (0.066 mol) of 4N sodium hydroxide and 10 g (0.059 mol) of benzyloxycarbonyl chloride according to the Schotten-Baumann procedure; the subsequent reaction proceeded well with concurrent stirring and cooling at 0—5°C in an ice bath. The reaction was continued for 1 hr at 0—5°C and then for an additional hour at room temperature. The reaction mixture was washed with 15 m*l* of ether, and then the aqueous layer was neutralized with 6N hydrochloric acid to pH 4. The oily product which was thus deposited was extracted twice with 30-m*l* portions of ethyl acetate, and the combined extract was washed with dilute hydrochloric acid and water. The ethyl acetate layer was dried over anhydrous sodium sulfate. The filtrate was evaporated to dryness to give 13.7 g of an oily residue. The oil was purified by redissolving it in an aqueous solution of sodium hydrogen carbonate and by washing it with ether, followed by a treatment similar to that described above. The oily product thus obtained was triturated with petroleum ether to afford a crystalline solid, which was then recrystallized from ether-petroleum ether to give 12 g (75%) of XI with a melting point of 79°C. Found: C, 65.78; H, 7.70; N, 4.94%. Calcd for $C_{16}H_{23}O_4N$: C, 65.51; H, 7.90; N, 4.78%.

***N*-Benzyloxycarbonyl-*threo*-*N,β*-dimethyl-L-leucine·(−)-ephedrine Salt (XIIL) and *N*-Benzyloxycarbonyl-*threo*-*N,β*-dimethyl-D-leucine (XIIID).** XI (8.3 g, 0.028 mol) and (−)-ephedrine hemihydrate (2.7 g, 0.0155 mol) were dissolved in 28 m*l* of warming ethyl acetate. The mixture was then allowed to stand for 24 hr at room temperature. The deposited crystals were filtered and washed with ethyl acetate to give 6.1 g (94%) of XIIL; mp 157°C. Recrystallization from an ethyl alcohol-ethyl acetate mixture (1:1) afforded 5.7 g of the pure material with a melting point of 160—161°C, $[\alpha]_D^{24} = -75.0°$ (*c* 0.40, in ethyl alcohol). Found: C, 68.26; H, 8.24; N, 6.27%. Calcd for $C_{26}H_{38}O_5N_2$: C, 68.09; H, 8.35; N, 6.11%.

The mother liquor obtained after the removal of XIIL was washed twice with a small amount of 2N hydrochloric acid and water. The organic layer was dried over anhydrous sodium sulfate. The filtrate was concentrated to dryness to give a crystalline residue in a 94% (3.9 g) yield; mp 90—91°C. Recrystallization from benzene - petroleum ether afforded 3.4 g of almost optically-pure XIIID; mp 94—95°C, $[\alpha]_D^{24}=+72°$ (*c* 1.00, in ethyl alcohol).

***N*-Benzyloxycarbonyl-*threo*-*N*,*β*-dimethyl-D-leucine·(+)-ephedrine Salt (XIID).** To a solution of 0.70 g (0.0024 mol) of XIIID ($[\alpha]_D^{24}=+72°$) in 1.5 m*l* of ethyl acetate, there was added a solution of 0.42 g (0.0024 mol) of (+)-ephedrine hemihydrate in 1.0 m*l* of ethyl acetate. The mixture was set aside for 24 hr at room temperature, and then the crystals deposited were filtered, washed with ethyl acetate, and dried to afford XIID (mp 155—157°C) in an 89% (0.975 g) yield. Recrystallization from an ethyl alcohol - ethyl acetate mixture (1 : 1) gave crystals with a melting point of 159—160°C and $[\alpha]_D^{25}=+73.5°$ (*c* 0.30, in ethyl alcohol). Found: C, 67.97; H, 8.31; N, 6.16%.

***N*-Benzyloxycarbonyl-*threo*-*N*,*β*-dimethyl-L-leucine (XIIIL).** To a suspension of 4.8 g (0.0105 mol) of the XIIL salt in 15 m*l* of ethyl acetate, there were added 7.8 m*l* (0.0156 mol) of 2N hydrochloric acid (7.8 m*l*, 0.0156 mol), and the mixture was shaken effectively in a separatory funnel. After washing further with water, the ethyl acetate layer was dried over anhydrous sodium sulfate. The ethyl acetate was evaporated to dryness to afford 3 g (98%) of crystals; mp 94—96°C. Recrystallization from benzene - petroleum ether gave 2.8 g of XIIIL with a melting point of 98—99°C, $[\alpha]_D^{26}=-75.9°$ (*c* 1.10, in ethyl alcohol). Found: C, 65.25; H, 7.99; N, 4.89%. Calcd for $C_{16}H_{23}O_4N$: C, 65.51; H, 7.90; N, 4.78%.

***N*-Benzyloxycarbonyl-*threo*-*N*,*β*-dimethyl-D-leucine (XIIID).** Following the method used for the preparation of XIIIL, from 3.2 g (0.007 mol) of XIID, 1.9 g (93%) of XIIID with a melting point of 98—99°C was obtained. $[\alpha]_D^{25}=+75.3°$ (*c* 0.7, in ethyl alcohol). Found: C, 65.72; H, 8.04; N, 4.79%.

***threo*-*N*,*β*-Dimethyl-L-leucine (XIVL).** A) To 1.0 g (0.0034 mol) of XIIIL, 3.5 g of 30% hydrogen bromide in glacial acetic acid was added. The reaction mixture was then set aside in a tight-stoppered vessel for 1 hr at room temperature. There after 30 m*l* of ether were added to complete the precipitation of the product, which was collected on a glass-fritted funnel and washedwith ether. The yield of the hydrobromide was 0.75 g (92%), and its melting point was 209—210°C. Free amino acid XIVL was obtained by treatment with triethylamine in a solution of 4 m*l* of ethyl alcohol, followed by recrystallization from a water - ethyl alcohol mixture (1 : 1). The yield was 0.43 g (86% from hydrobromide), and it had a melting point of over 270°C; $[\alpha]_D^{25}=+38.3°$ (*c* 0.90, in 5N hydrochloric acid), $[\alpha]_D^{25}=+31.5°$ (*c* 0.50, in water). Found: C, 60.39; H, 10.57; N, 8.93%. Calcd for $C_8H_{17}O_2N$: C, 60.34; H, 10.74; N, 8.80%.

B) A solution of 1.0 g (0.0034 mol) of XIIIL in 10 m*l* of glacial acetic acid was hydrogenated using 200 mg of palladium black as a catalyst under mechanical shaking for 5 hr. After the catalyst had then been removed by filtration, the filtrate was evaporated to dryness to give a crystalline residue and dried in a vacuum desiccator over concentrated sulfuric acid and solid sodium hydroxide. The residue was recrystallized from water and dioxane to give 0.47 g (87%) of XIVL with a melting point of over 270°C; $[\alpha]_D^{25}=+37.3°$ (*c* 0.70, in 5N hydrochloric acid), $[\alpha]_D^{23}=+29.1°$ (*c* 0.90, in water).

***threo*-*N*,*β*-Dimethyl-D-leucine (XIVD).** A way similar to the method A) used in the preparation of XIVL was used. From the reaction of 1.0 g (0.0034 mol) of XIIID and 3.5 g of 30% hydrogen bromide in glacial acetic acid, followed by neutralization with amine, XIVD with a melting point of over 270°C was obtained in almost the same yield. $[\alpha]_D^{25}=-39.3°$ (*c* 0.60, in 5N hydrochloric acid), $[\alpha]_D^{25}=-31.8°$ (*c* 0.40, in water). Found: C, 60.56; H, 10.63; N, 9.01%.

***N*-Benzyloxycarbonyl-*erythro*-*β*-methyl-DL-leucine (XV).** By the usual method of Schotten-Baumann, a pure product with a melting point of 62—64°C was obtained from VII in an 84% yield. The recrystallization was performed from benzene-petroleum ether. Found: C, 64.37; H, 7.42; N, 5.18%. Calcd for $C_{15}H_{21}O_4N$: C, 64.49; H, 7.58; N, 5.01%.

***N*-Benzyloxycarbonyl-*erythro*-*β*-methyl-L-leucine-(−)-ephedrine (XVIL) and *N*-Benzyloxycarbonyl-*erythro*-*β*-methyl-D-leucine·(+)-ephedrine (XVID).** To a solution of 5.58 g (0.02 mol) of XV in 6.0 m*l* of ether, there was added a solution of 1.91 g (0.011 mol) of (−)-ephedrine hemihydrate in 4.0 m*l* of ether. The reaction mixture was then allowed to stand overnight in a refrigerator to form a gelatinous material. The product was collected by filtration after it had been crushed to pieces with a glass rod and a small amount of ether had been added. A somewhat crude (−)-salt (1.6 g) (mp 120—124°C) was thus obtained. The ethereal mother liquor was washed wih 2N hydrochloric acid and then with water, and dried over anhydrous sodium sulfate. The ethereal solution was evaporated to dryness under reduced pressure; then the residue thus obtained was redissolved in 6.0 m*l* of ether. To the solution, there was added a solution of 1.91 g of (+)-ephedrine hemihydrate in 4.0 m*l* of ether. Then (+)-salt (1.4 g) (mp 124—125°C) was obtained by a way similar to that described above. The same treatment was possible again reciprocally with (−)- and (+)-ephedrine hemihydrate. Optically-active (−)-salt consisting of (−)-ephedrine was combined and recrystallized from ethyl acetate to give 2.0 g (45%) of a pure material with a melting point of 124—125°C; $[\alpha]_D^{25}=-17.6°$ (*c* 0.74 in ethyl alcohol). Found: C, 67.50; H, 8.09; N, 6.28%. Calcd for $C_{25}H_{36}O_5N_2$: C, 67.54; H, 8.16; N, 6.30%.

In the same way, optically-pure (+)-salt with a melting point of 124—125°C was obtained in a 49.5% (2.2 g) yield; $[\alpha]_D^{25}=+17.7°$ (*c* 0.95 in ethyl alcohol). Found: C, 67.60; H, 8.14; N, 6.32%. The mixed-melting-point of minus and plus salt was depressed to 101—104°C.

***erythro*-*β*-Methyl-L-leucine (XIIL) and the D-Isomer (XIID).** To a suspension of 1.9 g (0.0034 mol) of (−)-salt in 10 m*l* of ethyl acetate, there were added 3.4 m*l* of 2N hydrochloric acid; then the mixture was shaken in a separatory funnel. The organic layer was treated as usual to give 1.3 g of an oily residue. The oil was dissolved in 3.4 g of 30% hydrogen bromide in glacial acetic acid, after which the mixture was allowed to stand for 1 hr at room temperature and then

for 24 more hour in a refrigerator after the addition of 100 m*l* of ether. The deposited crystals were collected by filtration on a glass-fritted funnel and washed with ether. Recrystallization from ethyl alcohol and ether afforded a pure material with a melting point of 195—196°C in a 69% (0.66 g) yield. Similarly, from 2.18 g of (+)-salt D-isomer hydrobromide was obtained in a 73% (0.8 g) yield; mp 203—205°C. A solution of 0.6g of hydrobromide of the L-isomer in ethyl alcohol was neutralized with triethylamine. The crystals thus obtained were collected and recrystallized from water and dioxane to give 0.28 g (73% from hydrobromide) of the amino acid XVIIL; $[\alpha]_D^{24}=+38.9°$ (*c* 0.485, in 5N hydrochloric acid), $[\alpha]_D^{25}=+29.7°$ (*c* 0.37, in water). Found: C, 57.92; H, 10.38; N, 9.70%. From 0.65 g of the hydrobromide of the D-isomer, free amino acid XVIID was obtained in a 67% (0.3 g) yield; $[\alpha]_D^{25}=-39.4°$ (*c* 0.38, in 5N hydrochloric acid). Found: C, 57.82; H, 10.34; N, 9.62%.

***erythro*-*N*,*β*-Dimethyl-L-leucine (XVIIIL) and the D-Isomer (XVIIID).** The methylation of the amino groups of XVIIL and XVIID was accomplished, step by step, by *N*-benzylation, *N*-methylation, and subsequent catalytic hydrogenolysis, in a way similar to that used for the corresponding racemic *threo*-isomer. *N*-Benzyl-L-isomer: mp 218—219°C, 74% yield. Found: C, 71.62; H, 8.95; N, 5.82%. *N*-Benzyl-D-isomer: mp 218—219°C, 43% yield. Found: C, 71.70; H, 8.93; N, 6.03%. The mixed-melting-point of the two isomers was depressed to 208—210°C. *N*-Benzyl-*N*-methyl-L-isomer: mp 102—105°C, 68% yield. Found: C, 72.41; H, 9.08; N, 5.60%. *N*-Benzyl-*N*-methyl-D-isomer: mp 102—105°C, 74% yield. Found: C, 72.20; H, 9.40; N, 5.55%. The mixed-melting-point of these two isomers was depressed to 76—80°C. *erythro*-*N*,*β*-Dimethyl-L-leucine: mp>270°C, 51% yield; $[\alpha]_D^{25}=+38.0°$ (*c* 0.50, in 5N hydrochloric acid). Found: C, 60.52; H, 10.48; N, 8.91%. *erythro*-*N*,*β*-Dimethyl-D-leucine: mp >270°C, 52% yield; $[\alpha]_D^{25}=-38.3°$ (*c* 0.60, in 5N hydrochloric acid). Found: C, 60.18; H, 10.51; N, 8.76%.