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# THE SYNTHESIS OF N,β-DIMETHYL-L-LEUCINE

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N,β-Dimethylleucine was first found in nature by Sheehan and his co-workers(1) from the hydrolyzate of ethamycin, and proved to have the L-configuration at α-asymmetric carbon atom. Although Sheehan and Howell(2) synthesized this amino acid by Strecker reaction starting from 2,3-dimethylbutyraldehyde, whole stereochemical character has not been discussed. Since this starting material is unfavorable because of its instability, we attempted to synthesize this amino acid from methyl isopropyl ketone and 2-benzyl-4(5H)-imidazolone(3). In this paper the synthesis and the resolution of N,β-dimethylleucine are described.

1) Synthesis of N,β-dimethylleucine.

2-Benzyl-4(5H)-imidazolone(I) was condensed with methyl isopropyl ketone and then the product obtained was treated with hydrogen chloride in ethanol to give 2-benzyl-5-(α-methylisobutylidene)-4-imidazolone hydrochloride(II), m.p. 208-210°, in high yield(80%). Catalytic reduction of II in the presence of Adam's platinum oxide, followed by hydrolysis with barium hydroxide for 40 hours and by treatment with triethylamine gave a mixture of β-methylleucine(diastereoisomeric mixture, III and IV) and N-benzylcarbonyl-β-methylleucine(V), m.p. 150-153°. Since this derivative V could be hydrolyzed to III in quantitative yield by refluxing with 6N hydrochloric acid for 15 hours, total yield of diastereoisomeric pair of β-methylleucine(III,IV) reached to Ca. 80% and the consequent molar ratio of III and IV in the product was 2 : 1. The diastereoisomers of β-methylleucine were separated each other by the recrystallization from water. This separation was confirmed by the comparison of the infrared spectrum of each diastereoisomer, which showed significant differences between both isomers, especially in the region of 1600 to

1300 $cm^{-1}$. III: m.p. above 270°. Anal. 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 %. IV: m.p. above 270°. Found: C, 57.73; H, 10.21; N, 9.72 %.

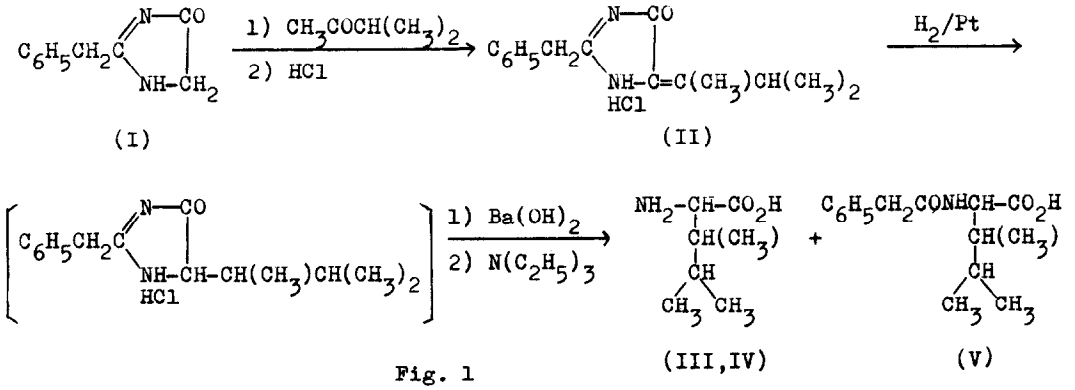


Fig. 1

N-Methylation of β-methylleucine(III,IV) was carried out by the method reported by Quitt et al.(4). One of the isomer III was treated with benzaldehyde and then reduced with sodium borohydride to give N-benzyl derivative, m.p. 208-209°, in quantitative yield. Subsequent methylation of this derivative with formic acid-formaldehyde, followed by hydrogenolysis using palladium black gave N,β-dimethylleucine(VI), m.p. above 270°, in high yield(Fig. 2). Anal. 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 %. Similarly, IV was converted to corresponding isomer of N,β-dimethylleucine(VII), m.p. above 270°. Anal. Found: C, 59.87; H, 10.38; N, 8.83 %. The infrared spectra of VI and VII were exactly identical with those reported in literature (2,5) in whole regions.

(III,IV) ⟶ N-benzyl-β-methylleucine ⟶ N,β-dimethylleucine(VI,VII)

Fig. 2

Recently Shoji et al.(5) isolated N,β-dimethylleucine from the antibiotic triostin C and elucidated its stereochemical feature by NMR spectroscopy. From the result of their study they deduced that N,β-dimethylleucine from triostin C was identical with that obtained from ethamycin and should be assigned to N,γ-dimethyl-L-alloisoleucine.

The diastereoisomeric forms of N,β-dimethylleucines(VI,VII) which were synthesized here could be confirmed by the comparison of spectral data as follows.

The synthetic compounds(VI,VII) were found to be identical with N,γ-dimethylallo-isoleucine and N,γ-dimethylisoleucine respectively, in infrared and NMR spectra(5). Moreover, the infrared spectrum of VI in $D_2O$ was virtually identical with that of the amino acid from triostin C. From these results we have concluded that the conformation of VI is identical with that of naturally occurring N,β-dimethyl-leucine.

2) Resolution of N,β-dimethyl-DL-leucine.

Carbobenzoxy N,β-dimethyl-DL-leucine(VIII), m.p. 79°, which was prepared by carbobenzoxylation of VI by the usual way, was mixed with l(-)-ephedrine in ethyl acetate (molar ratio, 1 : 0.6) to give crystalline carbobenzoxy N,β-dimethyl-L-leucine·ephedrine salt(IX), m.p. 161°, $[\alpha]_D^{24}$ -75.0°(c 0.4, EtOH). The filtrate from this salt was treated with d(+)-ephedrine at room temperature to give carbobenzoxy N,β-dimethyl-D-leucine·ephedrine salt(X), m.p. 159-160°, $[\alpha]_D^{25}$ +73.5°(c 0.3, EtOH). The salt(IX) was treated with hydrochloric acid to give carbobenzoxy N,β-dimethyl-L-leucine, m.p. 99°, $[\alpha]_D^{26}$ -75.9°(c 1.1, EtOH), which was then decarbobenzoxylated with hydrogen bromide in glacial acetic acid and treated with triethylamine to yield N,β-dimethyl-L-leucine, $[\alpha]_D^{23}$ +31.5°(c 0.5, $H_2O$), $[\alpha]_D^{25}$ +38.3° (c 0.9, 5N HCl). These values of specific rotations are agreement with those of N,β-dimethylleucine from ethamycin as well as triostin C. Since naturally occurring N,β-dimethylleucine certainly belongs to the L-amino acid series, it is obvious that the compound here obtained is N,β-dimethyl-L-leucine. By the similar procedure, X was converted to carbobenzoxy N,β-dimethyl-D-leucine, m.p. 99°, which was then decarbobenzoxylated to give N,β-dimethyl-D-leucine, $[\alpha]_D^{25}$ -31.8°(c 0.4, $H_2O$), $[\alpha]_D^{25}$ -39.3°(c 0.6, 5N HCl).

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