Reaction of α-Chloro-α,α-diphenylacetanilide (I) with Triphenylmethylsodium.—Oxygen and moisture were excluded from the system as described in the sodium hydride reaction. To a stirred solution of 0.285 g. (1 mmole) of α-chloro-α,α-diphenylacetanilide in 10 ml. of anhydrous ether maintained at −5 to 0° by means of an ice–salt-bath was added, dropwise, 0.9 mmole of a 1% solution of triphenylmethylsodium in anhydrous ether. The dark red color of the base was discharged immediately indicating a rapid reaction. After an additional 10 min. stirring, the ether was removed and replaced with chloroform. At no time during these operations was the temperature allowed to rise above 0°. The insoluble material was rapidly centrifuged and the yellow, supernatant solution was scanned in the infrared. No bands attributable to an α-lactam were observed. The same was true of the chloroform-insoluble material.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE 39, MASS.]

A Sterically Controlled Synthesis of Amino Acids

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RECEIVED JUNE 12, 1961

Catalytic hydrogenation of α-acetamido-β,β-dimethylacrylic acid L-α-methylbenzylamide in the presence of Raney nickel gave the saturated amide. Hydrolysis of this amide afforded D-valine of 39% optical purity. Reduction of α-benzamido-β,β-dimethylacrylic acid L-α-methylbenzylamide followed by hydrolysis of the saturated amide produced D-valine of 18% optical purity. Similar treatment of the D-α-methylbenzylamide gave L-valine of 18% optical purity. D-Phenylalanine of 6% optical purity was produced by the hydrogenation and subsequent hydrolysis of α-benzamidocinnamic acid L-α-methylbenzylamide.

One route for the biosynthesis of α-amino acids is through reductive amination or transamination of α-keto acids. A remarkable feature of this reaction is the high degree of stereospecificity shown. Although the *in vivo* synthesis doubtless operates under enzymatic control and probably by interaction with asymmetric species, it seemed of interest to determine the degree of asymmetric induction produced under non-enzymatic conditions. In particular the catalytic hydrogenation of compounds of the type I was studied.

By application of the rules proposed by Cram[1] and Prelog[2] it should be possible to predict the isomer which will be formed predominantly in the conversion of an asymmetric amide of an α-acylamino-α,β-unsaturated acid to the amino acid. Assuming, like Prelog,[2] that hydrogen is adsorbed on the surface of the catalyst and that the substrate approaches the catalyst surface with the least hindered side, one can predict the enantiomer that will predominate by the induction due to the optically active center already present in the molecule. Thus, it can be seen (Fig. 1) that by the use of L-α-methylbenzylamine, D-amino acid should predominate. Conversely, the use of D-α-methylbenzylamine should lead to a predominance of L-amino acid. Leithe[3] has established the absolute configuration of (−)-α-methylbenzylamine by degrading the phenyl group to carboxyl and obtaining L-alanine. α-Methylbenzylamine was chosen as the optically active portion of the molecule to facilitate separation of the products after hydrolysis.

Aminolysis of 4-isopropylidene-2-methyl-5-oxazalone with L-α-methylbenzylamine afforded α-acetamido-β,β-dimethylacrylic acid L-α-methylbenzylamide (Ia). Hydrogenation of Ia in the presence of Raney nickel in methanol gave N-acetylvaline L-α-methylbenzylamide (IIa). Hydrolysis of IIa with 20% hydrochloric acid gave valine (III) in 90% yield. The valine thus obtained had a

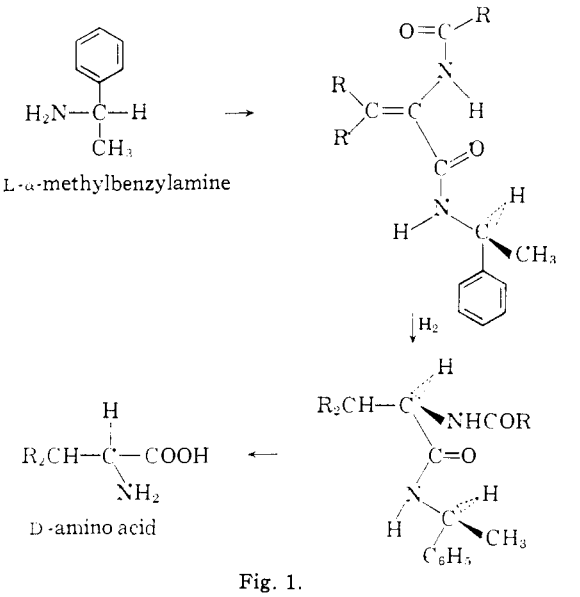


Fig. 1.

specific rotation of −11.3° in 6 *N* hydrochloric acid and −24.2° in glacial acetic acid. Based on the reported values for L-valine,[4] this corresponds to a 39% excess of D-valine.

Aminolysis of 4-isopropylidene-2-phenyl-5-oxazalone with L-α-methylbenzylamine in refluxing ethanol gave α-benzamido-β,β-dimethylacrylic acid L-α-methylbenzylamide (Ib). Hydrogenation of Ib over Raney nickel in methanol afforded a quantitative yield of N-benzoylvaline L-α-methylbenzylamine (IIb). Hydrolysis of IIb in 20% hydrochloric acid gave valine (III) in a yield of 90%. The valine obtained in this manner had a specific rotation of −5.2° in 6 *N* hydrochloric acid, −10.6° in glacial acetic acid, and −2.4° in water. These values correspond to an optical yield of 18% with the D-isomer once again in excess.

The same reaction sequence was carried out with D-α-methylbenzylamine. Hydrogenation of α-

(1) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

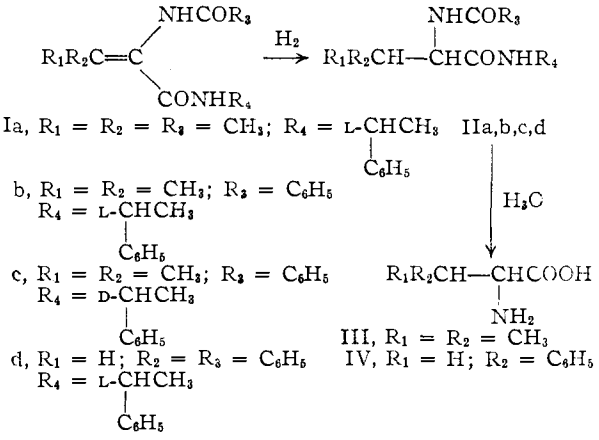
(2) V. Prelog, *Bull. soc. chim. France*, 987 (1956).

(3) W. Leithe, *Chem. Ber.*, **64**, 2831 (1931).

(4) J. P. Greenstein, S. M. Birnbaum and M. C. Otey, *J. Biol. Chem.*, **204**, 307 (1953).

benzamido-β,β-dimethylacrylic acid D-α-methylbenzylamide (Ic) gave a quantitative yield of the saturated amido-amide IIc. Hydrolysis of IIc in 20% hydrochloric acid gave valine (III) with a specific rotation of $-5.1°$ in 6 N hydrochloric acid, corresponding to an 18% excess of L-valine.

In each instance the identity and purity of the valine were confirmed by paper chromatography in 1-butanol, acetic acid, water. The synthetic valine



showed a single ninhydrin-positive spot of the same R_f value (0.43) as that of an authentic sample. α-Methylbenzylamine has an R_f of 0.64 in the same system. Thus, the observed rotation of the amino acid is not due to any contamination by the optically active amine. The synthetic valine showed a single spot at R_f 0.43 when the chromatograms were sprayed with a t-butyl hypochlorite solution followed by a starch–iodide solution. Therefore, there was no contamination of the valine by any unhydrolyzed amide which could account for the observed optical activity. Moreover, the constant value of the percentage of excess of a particular isomer in different solvents argues against any contamination by optically active species. In order to eliminate any possibility of diastereomer separation, the saturated amides were not recrystallized prior to hydrolysis.

α-Benzamidocinnamic acid L-α-methylbenzylamide (Id), prepared in 58% yield by aminolysis of 4-benzylidene-2-phenyl-5-oxazalone, was hydrogenated in the presence of Raney nickel to N-benzoylphenylalanine L-α-methylbenzylamide (IId). Hydrolysis of IId by 20% hydrochloric acid afforded phenylalanine (IV) in a yield of 91%. The specific rotation of the phenylalanine was 2.3° in water, indicative of an optical yield of 6%. The identity and purity of the phenylalanine were confirmed by paper chromatography and by comparison of the infrared spectrum of the synthetic phenylalanine with that of an authentic sample. The same precautions against diastereomer separation were taken as were mentioned previously.

Financial support through a grant from the USPH (C-2239-Bio.) is gratefully acknowledged.

Experimental[5]

α-Acetamido-β,β-dimethylacrylic Acid L-α-Methylbenzylamide (Ia).—To a solution of 2.05 g. (0.015 mole) of 4-isopropylidene-2-methyl-5-oxazalone[6] in 15 ml. of dry benzene was added 1.78 g. (0.015 mole) of L-α-methylbenzylamine[7] ($[\alpha]^{25}D$ $-39.2°$, neat). The reaction mixture was allowed to reflux for 90 minutes. After *ca.* 45 minutes a colorless solid began to precipitate. The benzene was removed under reduced pressure and the residue was dissolved in warm methanol. The yellow methanolic solution was poured into 50 ml. of N hydrochloric acid to precipitate 1.8 g. (46%) of the crude amide, m.p. 195–197°. Recrystallization from ethanol–water gave an analytical sample, m.p. 197–199°, $[\alpha]^{25}D$ $-50°$ (c 0.46, ethanol).

Anal. Calcd. for $C_{15}H_{20}O_2N_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.23; H, 7.82; N, 11.20.

N-Acetylvaline L-α-Methylbenzylamide (IIa).—A solution of 1 g. (3.85 mmoles) of α-acetamido-β,β-dimethylacrylic acid L-α-methylbenzylamide in 80 ml. of methanol was hydrogenated over ~1 g. of freshly prepared Raney nickel[8] at 25° and atmospheric pressure. The reaction ceased after the uptake of the theoretical amount of hydrogen. The total reaction time was 1 hour. The catalyst was removed by suction filtration through Celite 503 and the filtrate was evaporated to dryness under reduced pressure to give 1 g. (100%) of the N-acetylvaline L-α-methylbenzylamide, m.p. 185–202°. Three recrystallizations from ethanol gave an analytical sample of colorless needles, m.p. 188–189°.

Anal. Calcd. for $C_{15}H_{22}O_2N_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.71; H, 8.42; N, 10.67.

Hydrolysis of N-Acetylvaline L-α-Methylbenzylamide.—A suspension of 487 mg. (1.86 mmoles) of crude N-acetylvaline L-α-methylbenzylamide in 5 ml. of 20% hydrochloric acid in a sealed ampoule under nitrogen was placed in an oven at 100° for 14 hours. The cooled reaction mixture was extracted with three 3-ml. portions of ether to remove a small amount of brown oil. The aqueous layer was concentrated to dryness under reduced pressure to a mixture of the hydrochlorides of valine and L-α-methylbenzylamine. The residue was dissolved in the minimum amount of water, made alkaline with N sodium hydroxide, and extracted five times with 3-ml. portions of ether to remove the amine. The aqueous layer was acidified to pH 5 with N hydrochloric acid and desalted on a column of Dowex 50W X-8 (200–400 mesh, washed with 2 N ammonium hydroxide, water, N hydrochloric acid, and water). The column was eluted with water until the eluate was shown to be free of halide ion. The amino acid was then eluted with 2 N ammonium hydroxide, the excess ammonia was removed under reduced pressure, and the aqueous solution lyophilized. The powder from the lyophilization was dissolved in water and the water was removed under reduced pressure at 40° to give 195 mg. (90%) of crystalline valine. Paper chromatography of the product in 1-butanol, water, acetic acid (25:25:6) showed a single ninhydrin-positive spot (R_f 0.44). The valine thus obtained had $[\alpha]^{25}D$ $-11.3 \pm 0.3°$ (c 3.7, 6 N hydrochloric acid) and $[\alpha]^{25}D$ $-24.2 \pm 0.2°$ (c 1.47, acetic acid).

α-Benzamido-β,β-dimethylacrylic Acid L-α-Methylbenzylamide (Ib).—4-Isopropylidene-2-phenyl-5-oxazalone[9] (20.1 g., 0.1 mole) was dissolved, with stirring, in 100 ml. of refluxing ethanol. After solution was complete 12.1 g. (0.1 mole) of L-α-methylbenzylamine was added and the orange solution was refluxed. The product crystallized in 15 minutes. After cooling in an ice-bath for 90 minutes the product was collected and washed with cold ethanol. The α-benzamido-β,β-dimethylacrylic acid L-α-methylbenzylamide (14.5 g., 45%) was recrystallized as needles from dioxane. An additional 1.6 g. (5%) was obtained from the mother liquor. The product had m.p. 217–218° and $[\alpha]^{27}D$

(5) All melting points are corrected. Optical rotations were measured with a Rudolph no. 344 polarimeter using a 1-dm. polarimeter tube except as stated otherwise. The reported optical rotations are the average of at least eight individual readings. We wish to thank Dr. D. N. McGregor for independent measurements of the optical rotations of the amino acids. We are indebted to Dr. S. M. Nagy for the microanalyses.

(6) B. Hems, D. Holland and F. Robinson in "The Chemistry of Penicillin," H. T. Clark, J. R. Johnson and Sir R. Robinson, editors, Princeton University Press, Princeton, N. J., 1949, p. 465.

(7) A. Campbell, A. H. J. Houston and J. Kenyon, *J. Chem. Soc.*, 93 (1947).

(8) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 181.

(9) G. R. Ramage and J. L. Simonsen, *J. Chem. Soc.*, 532 (1935).

$-24.8°$ (c 1.78, methanol). Two additional recrystallizations from dioxane gave an analytical sample.

Anal. Calcd. for $C_{20}H_{22}O_2N_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.75; H, 7.01; N, 8.81.

N-Benzoylvaline L-α-Methylbenzylamide (IIb).—A solution of 1 g. (3.1 mmoles) of α-benzamido-β,β-dimethylacrylic acid L-α-methylbenzylamide in 70 ml. of absolute methanol was hydrogenated over ~500 mg. of freshly prepared Raney nickel at 25° and atmospheric pressure. The reaction ceased after the uptake of the required amount of hydrogen and was complete in 1 hour. The catalyst was removed by suction filtration through Celite 503 and the filtrate was concentrated to dryness under reduced pressure to yield 1 g. (100%) of N-benzoylvaline L-α-methylbenzylamide, m.p. 190–202°. Two recrystallizations from ethanol gave an analytical sample, m.p. 202–204°, $[\alpha]^{27}D$ $-63.3°$ (c 1.94, methanol).

Anal. Calcd. for $C_{20}H_{24}O_2N_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.04; H, 7.41; N, 8.59.

Hydrolysis of N-Benzoylvaline L-α-Methylbenzylamide.—The crude N-benzoylvaline L-α-methylbenzylamide (514 mg., 1.6 mmoles) was suspended in 4 ml. of 20% hydrochloric acid, under nitrogen, in a sealed ampoule and placed in an oven at 100° for 15 hours. The cooled reaction mixture was extracted four times with 3-ml. portions of ether to remove the benzoic acid that had crystallized and some brown oil. Isolation as previously described afforded 169 mg. (90%) of crystalline valine. The identity of the valine was confirmed by paper chromatography in 1-butanol, acetic acid, water. The valine isolated in this manner had $[\alpha]^{25}D$ $-5.2 \pm 0.4°$ (c 3.26, 6 N hydrochloric acid), $[\alpha]^{25}D$ $-10.6 \pm 0.3°$ (c 1.9, acetic acid), and $[\alpha]^{25}D$ $-2.4 \pm 0.4°$ (c 1.4, water).

α-Benzamido-β,β-dimethylacrylic Acid D-α-Methylbenzylamide (Ic).—4-Isopropylidene-2-phenyl-5-oxazalone (2.5 g., 0.012 mole) was dissolved, with stirring, in 20 ml. of warm absolute ethanol. After solution was complete, 1.5 g. (0.012 mole) of D-α-methylbenzylamine[10] ($[\alpha]^{25}D$ 38.6°, neat) was added and the orange solution was refluxed for 75 minutes. A precipitate began to form after 45 minutes. The reaction mixture was poured into 50 ml. of 0.5 N hydrochloric acid and the crude acrylic acid amide was collected on a filter. Recrystallization from dioxane gave 1.65 g. (42%) of colorless needles, m.p. 214–217°. A second recrystallization from dioxane gave an analytical sample, m.p. 215–217° and $[\alpha]^{26}D$ 24.1° (c 1.32, methanol).

Anal. Calcd. for $C_{20}H_{22}O_2N_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.29; H, 6.92; N, 8.59.

N-Benzoylvaline D-α-Methylbenzylamide (IIc).—A solution of 1 g. (3.1 mmoles) of α-benzamido-β,β-dimethylacrylic acid D-α-methylbenzylamide in 80 ml. of absolute methanol was hydrogenated over ~ 1 g. of freshly prepared Raney nickel at room temperature and atmospheric pressure. The reaction ceased after the uptake of the theoretical amount of hydrogen and was complete in 1 hour. The catalyst was removed by suction filtration through Celite 503 and the filtrate was concentrated to dryness under reduced pressure to yield 1 g. (100%) of N-benzoylvaline D-α-methylbenzylamide, m.p. 190–203°. Two recrystallizations from ethanol gave an analytical sample of colorless needles, m.p. 205–207°.

Anal. Calcd. for $C_{20}H_{24}O_2N_2$: N, 8.64. Found: N, 8.46.

Hydrolysis of N-Benzoylvaline D-α-Methylbenzylamide.—The crude N-benzoylvaline D-α-methylbenzylamide (505 mg., 1.56 mmoles) was suspended, under nitrogen, in 5 ml. of 20% hydrochloric acid in a sealed ampoule and placed in an oven at 100° for 15 hours. The cooled reaction mixture was treated as before. The valine obtained in this manner (136 mg., 75%) had $[\alpha]^{25}D$ 5.1 ± 0.3° (c 2.86, 6 N hydrochloric acid). The identity of the valine was confirmed by paper chromatography in 1-butanol, acetic acid, water. The valine showed a single ninhydrin-positive spot of R_f 0.43.

α-Benzamidocinnamic Acid L-α-Methylbenzylamide (Id).—4-Benzylidene-2-phenyl-5-oxazalone[11] (13.2 g., 0.053 mole) was suspended in 60 ml. of absolute ethanol containing 6.5 g. (0.054 mole) of L-α-methylbenzylamine. The oxazalone dissolved on warming. The reaction mixture was refluxed for 2 hours and filtered. α-Benzamidocinnamic acid L-α-methylbenzylamide crystallized on cooling. The product was recrystallized from ethanol to give 7.3 g. (37%) of needles, m.p. 181–183°. An additional 4 g. of product was obtained by concentration of the mother liquor.

Anal. Calcd. for $C_{24}H_{22}O_2N_2$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.67; H, 5.84; N, 8.06.

N-Benzoylphenylalanine L-α-Methylbenzylamide (IId).—A solution of 1 g. (2.7 mmoles) of α-benzamidocinnamic acid L-α-methylbenzylamide in 70 ml. of absolute methanol was hydrogenated over ~500 mg. of freshly prepared Raney nickel catalyst at room temperature and atmospheric pressure. The uptake of hydrogen ceased after one equivalent had been absorbed. The reaction was complete in 2.25 hours. The catalyst was removed by suction filtration through Celite 503 and the filtrate was concentrated to dryness under reduced pressure to yield 1 g. (100%) of N-benzoylphenylalanine L-α-methylbenzylamide, m.p. 159–185°. Three recrystallizations from ethanol gave an analytical sample, m.p. 181–183°. Admixture with starting material gave m.p. 157–178°.

Anal. Calcd. for $C_{24}H_{24}O_2N_2$: C, 77.39; H, 6.50; N, 7.52. Found: C, 77.22; H, 6.39; N, 7.87.

Hydrolysis of N-Benzoylphenylalanine L-α-Methylbenzylamide.—A suspension of N-benzoylphenylalanine L-α-methylbenzylamide (430 mg., 1.16 mmoles) in 4 ml. of 20% hydrochloric acid under nitrogen in a sealed ampoule was placed in an oven at 100° for 15 hours. The cooled reaction mixture was treated as described above to give 175 mg. (91%) of phenylalanine. The infrared spectrum is identical with that of an authentic sample of phenylalanine. The phenylalanine gave a single spot on paper chromatography in 1-butanol, acetic acid, water (R_f 0.55). The phenylalanine obtained in this manner had $[\alpha]^{25}D$ 2.3 ± 0.1° (length, 2 dm.; c 2.4, water).

(10) A. W. Ingersoll, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 506.

(11) H. Gillespie and H. Snyder, ref. 10, p. 489.