Some Derivatives of Aspartic and Glutamic Acids

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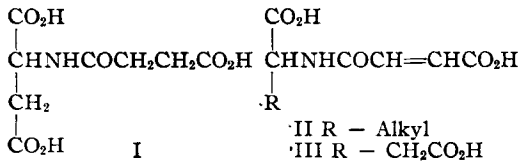
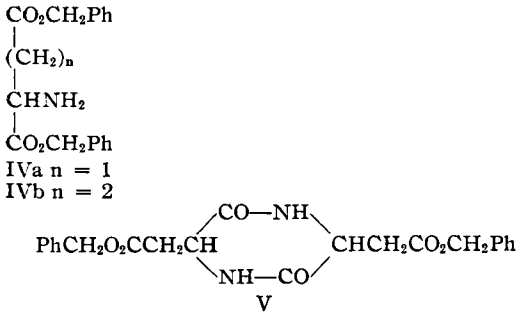
N-Acylation of L-glutamic and L-aspartic acids was carried out under mild conditions *via* their benzyl esters. Anomalous racemization was observed with some aspartic acid derivatives.

In connection with some research on the biogenesis of diaminopimelic acid (1) a sample of N-(β-carboxypropionyl)-L-aspartic acid (I) was required. It has been reported (2) that amino acids in aqueous solution react with maleic anhydride in benzene solution to give the N-acylated derivative II in good yield

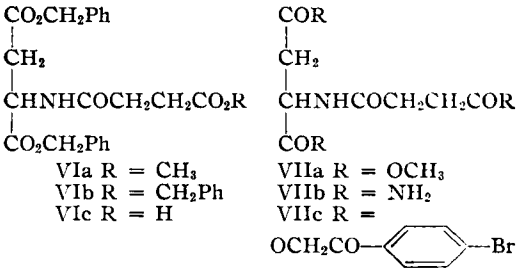


We attempted the preparation of N-(β-carboxyacroyl)-L-aspartic acid (III) by this method with the aim of hydrogenating it to the desired aspartic acid derivative, I; however, neither L-aspartic acid nor its disodium salt reacted with maleic anhydride or succinic anhydride (3). β-Carbomethoxypropionyl chloride and disodium aspartate (4) also failed to lead to the desired product.

In the hope that acylation might be more successful in a homogeneous reaction mixture, it was decided to use dibenzyl L-aspartate (IVa) which is soluble in organic solvents. This ester was obtained as a viscous oil which on long standing deposited a crystalline solid. The diketopiperazine structure V has been assigned to this on the basis of elemental analyses, molecular weight, and infrared spectrum



Dibenzyl L-aspartate (IVa) reacted readily with β-carbomethoxypropionyl chloride and β-carbobenzyloxypropionyl chloride to give the N-acylated products VIa and VIb, respectively. Hydrogenolysis of VIb gave an amorphous product whose infrared spectrum showed the presence of the amide and carboxyl functions expected of I. It was found that IVa condensed with succinic anhydride to give the N-acylated compound VIc in excellent yield. Hydrogenolysis of VIc afforded I as an amorphous material



On treatment of I with diazomethane an oily trimethyl ester (VIIa) was obtained; this gave a crystalline amide (VIIb) by reaction with alcoholic ammonia. Compound I was further characterized by the preparation of a crystalline *p*-bromophenacyl ester (VIIc).

N-Phthaloyl amino acids are of importance in peptide synthesis. Some amino acids, such as L-aspartic and L-glutamic acids, undergo racemization during phthaloylation by the fusion method. Alternative multi-step procedures have been described for the preparation of N-phthaloyl derivatives of L-aspartic and L-glutamic acids (5–10). The availability of dibenzyl L-aspartate made it possible to explore yet another mild method of phthaloylation that has been described recently (11, 12). This method, which involves phthaloylation in toluene solution in presence of triethylamine, was also applied to esters of L-glutamic acid.

EXPERIMENTAL[1]

Benzyl esters of amino acids were prepared as their *p*-toluene-sulfonate salts by using the method of Cipera and Nicholls (13). The free esters, obtained in high yield on shaking the salts with cold sodium bicarbonate solution, were optically active and could

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[1] All melting points are uncorrected.

be used for acylation without further purification. β-Benzyl L-aspartate was prepared by using the procedure described for γ-benzyl L-glutamate (14).

Dibenzyl L-Aspartate *p*-Toluenesulfonate.—*p*-Toluenesulfonic acid monohydrate (60.0 Gm., 0.32 mole), L-aspartic acid (40.0 Gm., 0.30 mole), and benzyl alcohol (100 ml., 104 Gm., 0.96 mole) were placed in a 1-L. flask provided with a mechanical stirrer and a Dean-Stark water separator with condenser. The mixture was heated for 18 hours under vigorous reflux. Fifteen milliliters of water was collected during this period. The clear solution was cooled in ice and the precipitate removed by filtration. The crude product (131 Gm., yield 74%), recrystallized twice from water containing 5% of ethanol, yielded 82 Gm. (41%); m.p. 157–158°, $[\alpha]_D^{25}$ + 1° (95% EtOH).

Anal.—Calcd. for $C_{25}H_{27}NO_7S$: C, 61.85; H, 5.61; S, 6.59. Found: C, 61.44; H, 5.69; S, 6.61.

The preparation of dibenzyl DL-aspartate *p*-toluenesulfonate by a similar procedure has been described (15).

Dibenzyl L-Aspartate (IVa).—One hundred grams (0.206 mole) of dibenzyl L-aspartate *p*-toluenesulfonate was added to a cold mixture of 500 ml. of ether and 100 ml. of water in a separator and shaken. A cold, nearly saturated solution of 45.0 Gm. (0.363 mole) of sodium carbonate monohydrate was then added and the mixture shaken vigorously for a few minutes. The ether layer was separated and the aqueous layer was extracted several times with ether. The combined ether extracts were dried over anhydrous sodium sulfate. On removing the solvent under reduced pressure at room temperature, 57.4 Gm. (88%) of a slightly yellow oil (IVa) was obtained. Purification of this product by distillation under reduced pressure could not be accomplished because the compound decomposed at about 90° with the formation of succinic anhydride, m.p. 119°.

For identification, 3.0 Gm. of the oil IVa was converted to its hydrochloride (2.6 Gm., 60%) which was recrystallized from methanol-ether, m.p. 129.5 to 130° [lit. (16) m.p., 124–125°], $[\alpha]_D^{25}$ + 1 (95% ethyl alcohol).

Anal.—Calcd. for $C_{18}H_{20}ClNO_4$: C, 61.79; H, 5.76; Cl, 10.14; N, 4.01. Found: C, 61.70; H, 6.02; Cl, 9.93; N, 4.03.

After standing for several weeks at room temperature, the compound IVa deposited crystals which were removed by filtration. Compound V melted at 157–158° after washing with acetone and recrystallization from ethanol.

Anal.—Calcd. for $C_{22}H_{22}N_2O_6$: C, 64.38; H, 5.40; N, 6.83; mol. wt., 410. Found: C, 64.32; H, 5.57; N, 6.95; mol. wt., 434.

$\nu_{max.}^{Nujol}$ in cm.$^{-1}$: 3290, 3150 (N—H); 1735 (SH), 1730 (ester CO); 1688, 1655 (amide CO).

Hydrogenolysis of Dibenzyl L-Aspartate.—The ester IVa (3.13 Gm.) was dissolved in 25 ml. of absolute methanol and hydrogenated at an initial pressure of 20 lbs./sq. in. in the presence of 1.5 Gm. of 10% palladium-on-charcoal. The catalyst and the precipitate were removed by filtration and then extracted with 500 ml. of hot water. The clear aqueous solution was lyophilized. The rotation and infrared spectrum of the product were identical with that of L-aspartic acid.

β-Benzyl L-Aspartate.—Fifty milliliters of concentrated sulfuric acid followed by 500 ml. of benzyl alcohol were added carefully to 500 ml. of ether. The ether was removed under reduced pressure and 66.5 Gm. (0.50 mole) of L-aspartic acid was added. The solution was kept at room temperature for 20 hours, then cooled to 0°, and a mixture of 250 ml. of pyridine in 1000 ml. of ethanol (96%) was added under vigorous stirring. The precipitate (71 Gm., 63%) was removed by filtration and washed with ether after standing overnight in the refrigerator. Recrystallization from 1000 ml. of water containing 10 ml. of pyridine gave 37 Gm. (33%) of pure XI: m.p. 211.5 to 212.5° dec.; $[\alpha]_D^{25}$ + 27° (1 *N* HCl).

Anal.—Calcd. for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: C, 58.86; H, 6.01; N, 6.33.

Benzyl Esters of L-Glutamic Acid.—Under conditions similar to those described above for L-aspartic acid, the reaction of 33.0 Gm. (0.224 mole) of L-glutamic acid, 75 ml. (0.723 mole) of benzyl alcohol, and 45.0 Gm. (0.238 mole) of *p*-toluenesulfonic acid monohydrate in benzene for 13 hours afforded 98 Gm. (88%) of dibenzyl L-glutamate *p*-toluenesulfonate, m.p. 122.5 to 128.5°. On recrystallization from hot water, the m.p. was raised to 139.5 to 141.5°.

Anal.—Calcd. for $C_{26}H_{29}NO_7S$: C, 62.71; H, 5.87; N, 2.80; S, 6.41. Found: C, 62.47; H, 5.76; N, 3.05; S, 6.66.

When 14.7 Gm. (0.100 mole) of L-glutamic acid, 30 ml. of benzyl alcohol, 19.2 Gm. (0.110 mole) of *p*-toluenesulfonic acid monohydrate, and 75 ml. of benzene were allowed to react for only 4 hours, the product amounted to 43.5 Gm. of a white solid. On recrystallization from ethanol-ether, 33 Gm. of a solid, m.p. 147–153°, was obtained. A solution of 2.00 Gm. of this material in 20 ml. of 95% alcohol was stirred; 5 ml. of pyridine was added dropwise. After storage overnight in an icebox, the solid was filtered, washed with cold alcohol, and dried to give 0.68 Gm. (43%) of γ-benzyl L-glutamate (IXc), m.p. 162–164°, $[\alpha]_D^{25}$ + 19° (c = 2.62 in acetic acid). A sample of this ester prepared by following the method of Guttmann and Boissonnas (14) showed m.p. 168° and $[\alpha]_D^{25}$ + 18.6° (c = 5.855 in acetic acid).

Using the same method as for preparing IVa, 54.0 Gm. of dibenzyl L-glutamate *p*-toluenesulfonate was converted into 34.4 Gm. (97%) of the free diester IVb. This ester was characterized by its conversion in a nearly quantitative yield to its hydrochloride, m.p. 99–100°, $[\alpha]_D^{25}$ + 9° (0.1 *N* HCl) [lit. (17) m.p., 100–102°, $[\alpha]_D^{25}$ + 9.4°].

Anal.—Calcd. for $C_{19}H_{22}ClNO_4$: C, 62.71; H, 6.09; Cl, 9.74. Found: C, 62.77; H, 6.25; Cl, 9.67.

L-Leucine Benzyl Ester *p*-Toluenesulfonate.—This compound was prepared from L-leucine (26.2 Gm., 0.200 mole), benzyl alcohol (35 Gm., 0.32 mole), and *p*-toluene sulfonic acid monohydrate (40.0 Gm., 0.230 mole) by the esterification procedure described above. The yield of the crude product was 50 Gm. (62%). After recrystallization from water, the m.p. was 211.5 to 212.5° dec.

Anal.—Calcd. for $C_{20}H_{27}NO_5S$: C, 61.04; H, 6.92; N, 3.56; S, 8.15. Found: C, 61.21; H, 7.05; N, 3.84; S, 8.22.

N-(β-Carbomethoxyprepionyl)-L-aspartic Acid,

Dibenzyl Ester (VIa).—A solution of 1.9 Gm. (0.015 mole) of sodium carbonate monohydrate in 4.5 ml. of water was added to a solution of 9.4 Gm. of freshly prepared IVa in 50 ml. of ether. A solution of 3-carbomethoxypropionyl chloride (18) in 50 ml. of ether was added dropwise to this mixture in the course of 30 minutes at 15–17°. After stirring for another 30 minutes the ether layer was separated, dried over anhydrous sodium sulfate, and the solvent removed under reduced pressure. The residual oil (11.7 Gm., 91%) solidified after standing for 2 days under reduced pressure over concentrated sulfuric acid. Recrystallization from petroleum ether gave 9.1 Gm. (71%) of VIa, m.p. 57–58°.

Anal.—Calcd. for $C_{23}H_{25}NO_7$: C, 64.62; H, 5.89; N, 3.28. Found: C, 64.73; H, 5.99; N, 3.19.

β-Carbobenzyloxypropionyl Chloride.—A mixture of benzyl hydrogen succinate (19) (6.24 Gm., 0.040 mole) and thionyl chloride (9.5 Gm., 0.080 mole) was heated in a bath at 35–40° for 100 minutes. The excess thionyl chloride was removed under reduced pressure at room temperature. The colorless oil could not be purified by distillation under reduced pressure and was, therefore, used directly for the preparation of VIb.

N-(β-Carbobenzyloxypropionyl)-L-aspartic Acid, Dibenzyl Ester (VIb).—A solution of 2.0 Gm. (0.016 mole) of sodium carbonate monohydrate in 4.5 ml. of water was added to a solution of 9.4 Gm. of freshly prepared IVa in 50 ml. of methylene chloride. A methylene chloride solution of 3-carbobenzoxypropionyl chloride (prepared freshly from 6.24 Gm. (0.040 mole) of the corresponding acid) was added dropwise to this mixture in the course of 30 minutes at 10–15°. Proceeding in a similar manner as described above for compound VIa, 13.6 Gm. (90%) of VIb, m.p. 70 to 71.5°, was obtained.

Anal.—Calcd. for $C_{29}H_{29}NO_7$: C, 69.17; H, 5.81; N, 2.78. Found: C, 69.08; H, 5.49; N, 2.74.

N-(β-Carboxypropionyl)-L-aspartic Acid, Dibenzyl Ester (VIc).—A solution of 28.8 Gm. of freshly prepared IVa and 9.0 Gm. (0.090 mole) of succinic anhydride in 300 ml. chloroform was heated under reflux for 30 minutes. After removing the solvent by distillation, an oil (36.6 Gm.) was obtained which crystallized on scratching with a glass rod and adding some petroleum ether. Recrystallization from carbon tetrachloride gave 34.9 Gm. (96%) of a white solid, m.p. 97–98°.

Anal.—Calcd. for $C_{22}H_{23}NO_7$: C, 63.91; H, 5.61; N, 3.39. Found: C, 63.76; H, 5.63; N, 3.36.

N-(β-Carboxypropionyl)-L-aspartic Acid (I).—(*a*) Compound VIb (0.5 Gm., 0.001 mole), dissolved in 150 ml. of absolute methanol, was catalytically hydrogenated in the presence of 2.0 Gm. of 10% palladium-on-charcoal and at an initial pressure of 50 lbs./sq. in. The hydrogenation was complete in 5–10 minutes. The catalyst was removed by filtration and the solvent was distilled under reduced pressure over phosphorus pentoxide. Attempts to crystallize the oil were unsuccessful even after several months of storage.

Anal.—Calcd. for $C_8H_{11}NO_7$: C, 41.20; H, 4.76; N, 6.01. Found: C, 41.70; H, 4.91; N, 5.67.

(*b*) Compound VIa was hydrogenated as described above and the product was isolated as an amorphous solid.

Anal.—Calcd. for $C_8H_{11}NO_7$: C, 41.20; H, 4.76; N, 6.01. Found: C, 41.40; H, 5.12; N, 5.53.

N-(β-Carboxypropionyl)-L-aspartic Acid, Trimethyl Ester (VIIa).—Compound VIc (1.0 Gm.) was hydrogenated as described above; to the methanol solution of the product (*ca.* 3 ml.) was added dropwise with stirring at 0–5° a cold solution of diazomethane in ether until a yellow color remained. After standing for 10 minutes, dilute 1:4 hydrochloric acid was added until the yellow color of the excess diazomethane had disappeared. The ether layer was washed with water and dried over anhydrous sodium sulfate. After removing the solvent by distillation a colorless oil was obtained, the infrared spectrum of which indicated that no free carboxyl group was present. The product was used directly for preparing compound VIIb.

N-(β-Carboxypropionyl)-L-aspartic Acid, Triamide (VIIb).—Compound VIIa was dissolved in 3 ml. of absolute ethanol and 10 ml. of ethanol saturated with ammonia was added. The flask was stoppered and left at room temperature for 1 week. The precipitate formed was removed by filtration, washed with absolute ethanol, and recrystallized from water. The yield was 0.47 Gm. (82% based on compound VIc), m.p. 220.5 to 221.0° dec.

Anal.—Calcd. for $C_8H_{14}N_4O_4$: C, 41.73; H, 6.13. Found: C, 41.55; H, 6.05.

N-(β-Carboxypropionyl)-L-aspartic Acid, Tri-(*p*-bromophenacyl) Ester (VIIc).—Compound VIb (1.0 Gm.) was hydrogenated as mentioned before; after removing the solvent, the acid was neutralized with 0.1 *N* sodium hydroxide and then lyophilized. Water (10 ml.) and a solution of 2.98 Gm. (0.01 mole) of *p*-bromophenacylbromide in 100 ml. of absolute ethanol were added. The solution was heated on the steam bath for 3 hours, filtered, and cooled in the refrigerator for several hours. The crystalline product formed was recrystallized from absolute ethanol, m.p. 138–139° dec.

Anal.—Calcd. for $C_{32}H_{26}Br_3NO_{10}$: C, 46.62; H, 3.68; Br, 29.08; N, 1.69. Found: C, 46.58; H, 3.50; Br, 29.40; N, 1.78.

N-Phthaloyl-L-aspartic Acid.—(*a*) A mixture of 4.85 Gm. of dibenzyl L-aspartate (IVa), 2.3 Gm. (0.015 mole) of phthalic anhydride, 0.5 ml. of triethylamine, and 100 ml. of toluene was heated under reflux for 3.5 hours in a flask fitted with a Dean-Stark water separator. On working up the reaction product as described in (*b*), 6.3 Gm. of an oil was obtained which on hydrogenation gave 3.7 Gm. of a solid. Crystallization from hot water following decolorization with Darco charcoal gave a solid, m.p. 223–226°, $[\alpha]_D^{25} - 39°$ (c = 0.639 in ethanol) [lit. (10) m.p., 197°, $[\alpha]_D^{25} - 58°$ (methanol)]. The infrared spectrum of this material was identical with that of phthaloyl aspartic acid.

(*b*) Finely powdered phthalic anhydride (1.48 Gm., 0.0100 mole) was dissolved with shaking in a mixture of 250 ml. of toluene and 10 ml. of triethylamine. A 4.85-Gm. (0.0100 mole) quantity of dibenzyl L-aspartate *p*-toluenesulfonate, was added to this solution; the mixture was heated under reflux for 2.5 hours in a flask fitted with a Dean-Stark water separator. Within a few minutes of heating all suspended solid dissolved. At the end

of the reaction a small second layer of liquid below the toluene layer dissolved in water.

The upper toluene layer was washed, dried, and evaporated to give 3.9 Gm. of a viscous, yellow oil which had a satisfactory infrared spectrum [$\nu_{max.}^{Nujol}$ in cm.$^{-1}$ 1780, 1730 (phthalimido carbonyls); 1710 (ester carbonyl)]. On hydrogenation of this oil in methanol solution in the presence of 0.8 Gm. of 10% palladium-on-charcoal catalyst, nearly two moles of hydrogen were absorbed. After filtration the reaction mixture was evaporated and 2.5 Gm. of a white solid was obtained. After one crystallization from hot water, the m.p. of this product was 221–223° (softens at 180°) and $[\alpha]_D^{25}$ − 40°.

After two more recrystallizations from hot water the melting point changed to 228 to 229.5° and $[\alpha]_D^{25}$ became −9° (c = 0.627 in 95% ethyl alcohol).

Evidently DL-phthaloylaspartic acid is less soluble in water than L-phthaloylaspartic acid and recrystallization from water has resulted in the enrichment of the proportion of the DL-acid. This is in keeping with the findings of Schilling and Strong (20) concerning the comparative solubility of DL- and L-phthaloylglutamic acids.

Anal.—Calcd. for $C_{12}H_9NO_6$: C, 54.76; H, 3.45; N, 5.32. Found: C, 54.81; H, 3.71; N, 5.19.

In a second experiment starting with 10 Gm. of dibenzyl L-aspartate *p*-toluenesulfonate, 3.7 Gm. (67%) of phthaloylaspartic acid, m.p. 223–225°, $[\alpha]_D^{25} \backsim 0°$, was obtained.

(*c*) A mixture of 3.87 Gm. of dibenzyl L-aspartate (IVa), 1.75 Gm. (0.0118 mole) of phthalic anhydride, and 50 ml. of N,N-dimethylformamide was heated to boiling for 45 minutes and then poured on cracked ice. This mixture was extracted with methylene chloride. On evaporating the methylene chloride, a dark material was extracted with ether. The ether solution was thoroughly washed with water, dried, and evaporated to give 4.4 Gm. of a yellow viscous oil which was hydrogenated. The product (2.65 Gm.), m.p. 223–225°, was optically inactive.

(*d*) A mixture of 4.63 Gm. of dibenzyl L-aspartate (IVa), 3.00 Gm. (0.0203 mole) of phthalic anhydride, and 30 ml. of acetic acid was heated under reflux for 8 hours and then poured into 250 ml. of water. The mixture was extracted with methylene chloride and the extract washed with dilute sodium bicarbonate solution and then with water, dried, and evaporated to give 5.5 Gm. of a colorless, viscous oil. On hydrogenation, 3.0 Gm. of a solid, m.p. 225–227°, $[\alpha]_D^{25} \sim 0°$, was obtained.

Diethyl N-Phthaloyl-L-aspartate.—A suspension of 11.3 Gm. (0.050 mole) of diethyl L-aspartate hydrochloride and 7.5 Gm. (0.051 mole) of phthalic anhydride in 150 ml. of toluene and 10 ml. of triethylamine was refluxed for 2.5 hours in a flask fitted with a water separator. Nearly the calculated amount of water separated. The reaction mixture was filtered and the solid so obtained was washed with benzene and dried to give 6.5 Gm. (95%) of triethylamine hydrochloride. The filtrate was washed with dilute hydrochloric acid and with water, dried over anhydrous magnesium sulfate, and evaporated to give 14.0 Gm. (92.5%) of a slightly yellow, heavy oil. On distillation a colorless oil was obtained (nearly quantitative recovery) which had a satisfactory infrared spectrum and $[\alpha]_D^{25}$ −45° (c = 0.7 in ethanol, [lit. (10), $[\alpha]_D^{?}$ −40° (ethanol)].

N-Phthaloyl-L-glutamic Acid.—(*a*) Using the general procedure described above, L-glutamic acid *γ*-benzyl ester (IIc) was converted to an oily phthaloylation product which on hydrogenation gave a colorless oil. This oil was dissolved in hot water; on seeding, a white solid (68.5% overall yield), m.p. 156–159°, was obtained. On evaporation the mother liquor gave an oil that refused to crystallize. The solid after recrystallization from hot water had a m.p. 158–160° and $[\alpha]_D^{25}$ − 45° (c = 0.773 in ethanol) [lit. (8), m.p. 160–161°; $[\alpha]_D$ − 43° (95% ethyl alcohol)].

Anal.—Calcd. for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05. Found: C, 56.56; H, 4.18; N, 4.85.

$\nu_{max.}$ in cm.$^{-1}$: 3200–2500 (bonded hydroxy), 1771 (CO), and 1742 (SH) (carbonyl).

(*b*) To the clear solution obtained on shaking 1.48 Gm. (0.0100 mole) of phthalic anhydride with 150 ml. of toluene and 5 ml. of triethylamine, 5.13 Gm. (0.0103 mole) of dibenzyl L-glutamate *p*-toluenesulfonate was added. After heating for a few minutes all solid disappeared and a two-phase liquid mixture was obtained; this was heated under reflux for 3 hours in a flask fitted with a Dean-Stark water separator. After cooling, the reaction mixture was successively washed with water, dilute hydrochloric acid and water, dried, and evaporated. A 3.5 Gm. quantity of a colorless viscous oil with the infrared spectrum expected for N-phthaloyl-glutamic acid dibenzyl ester (VIIId) was obtained. This oil was hydrogenated in methanol solution in the presence of 0.5 Gm. of 10% palladium-on-charcoal catalyst and the product was purified by crystallization from hot water. The yield of N-phthaloyl L-glutamic acid (VIIIc), m.p. 158–160°, $[\alpha]_D^{25}$ − 44° (c = 0.833 in ethanol), was 1.4 Gm. (50%). The infrared spectrum of the product was satisfactory.

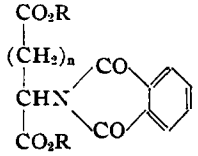
N-Phthaloyl-L-leucine.—Using the one-step phthaloylation method described above, L-leucine benzyl ester *p*-toluenesulfonate was converted to the oily N-phthaloyl-L-leucine benzyl ester which was used without purification for hydrogenation. After crystallization from aqueous methanol, the product, m.p. 119–121°, $[\alpha]_D^{25}$ − 24° (c = 0.5 in ethanol) [lit. (21) m.p., 118.5 to 119.5°, $[\alpha]_D^{26.5}$ − 24°], was obtained in 38% overall yield.

DISCUSSION

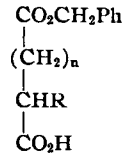
Sachs and Brand (22) have described a procedure for the preparation of dibenzyl L-glutamate hydro chloride. In our hands this method led only to the hydrochloride of L-glutamic acid. The *p*-toluenesulfonate of dibenzyl L-glutamate, which is easily prepared in good yield, can be converted into the hydrochloride or directly used in place of the hydrochloride.

The reaction of dibenzyl L-glutamate *p*-toluenesulfonate (IVb) [or *γ*-benzyl L-glutamate (IXc)] with an acid anhydride followed by hydrogenolysis appears to be a convenient synthesis of optically active pure N-acyl L-glutamic acid. It is noteworthy, however, that the same sequence of reactions with dibenzyl L-aspartate *p*-toluenesulfonate led to a racemized product. When the *β*-benzyl ester of L-aspartic acid was employed as the starting material, the extent of racemization was much reduced. It is interesting to note that when diethyl L-aspartate

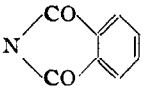
hydrochloride was substituted for the dibenzyl ester, the N-phthaloylaspartic acid diethyl ester (VIIIc) was formed without any racemization



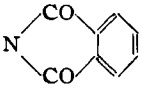
VIIIa n = 1, R = CH_2Ph
VIIIb n = 1, R = H
VIIIc n = 1, R = C_2H_5
VIIId n = 2, R = CH_2Ph
VIIIe n = 2, R = H



IXa n = 1, R = NH_2

IXb n = 1, R = 

IXc n = 2, R = NH_2

IXd n = 2, R = 

To examine the possibility that benzyl esters of amino acids may be prone to racemization, the *p*-toluenesulfonate of L-leucine benzyl ester was phthaloylated using the procedure of Bose, Greer, and Price (11) and the product hydrogenated. The N-phthaloyl-L-leucine so obtained was optically pure.

In the light of the results with benzyl esters of L-leucine and L-glutamic acid, the behavior of the benzyl esters of L-aspartic acid during phthaloylation is anomalous. In particular, it is difficult to see why β-benzyl L-aspartate should racemize to a limited extent during the phthaloylation and hydrogenation sequence.

After the completion of this work the preparation of N-phthaloyl L-glutamic acid (23) and N-phthaloyl L-aspartic acid (24) has been reported using a new method (25).

SUMMARY

L-Aspartic acid failed to condense with succinic or maleic anhydride, but the desired N-(β-carboxypropionyl)-aspartic acid could be prepared by the reaction of succinic anhydride with dibenzyl L-aspartate, followed by hydrogenolysis of the ester group.

The preparation of mono and dibenzyl esters of L-aspartic and L-glutamic acids and the benzyl esters of L-leucine is described. N-Phthaloyl derivatives of glutamic acid and aspartic acid were prepared under mild conditions *via* their benzyl esters. Optically pure N-phthaloyl L-glutamic acid was obtained this way, but anomalous racemization was observed with some aspartic acid derivatives.

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