An Asymmetric Synthesis of *N*-Benzyl-D-Aspartic Acid

By Y. Liwschitz and A. Singerman

An asymmetric synthesis of *N*-benzyl-D-aspartic acid was achieved by addition of benzylamine to *N*-D-α-methylbenzylmaleamic acid and hydrolysis of the resulting N^1-benzyl-N^2-D-α-methylbenzylasparagine with 48% hydrobromic acid. Attempts to carry out asymmetric syntheses from crotonic or maleic acids and asymmetric bases were unsuccessful.

THE problem of synthesising optically active molecules without resource to resolution methods, has intrigued organic chemists for a long time.[1] Marckwald[2] defined " asymmetric syntheses " as those processes which produce optically active compounds from symmetrically constituted molecules by the intermediate use of optically active reagents, but without the use of any of the methods of resolution. The asymmetric synthesis of amino-acids has been of special interest to all those speculating on the origin of life, since optically active amino-acids are required for the synthesis of the first proteins.

Methods which have been devised, so far, for the asymmetric preparation of optically active amino-acids may be classified as follows:

I. Catalytic hydrogenation of C=N bonds by means of an asymmetric catalyst, *i.e.*, palladium on silk.[3]

II. Catalytic hydrogenation of C=N bonds after incorporation of an asymmetric centre into the molecule.[4]

III. Catalytic hydrogenation of C=C bonds after incorporation of an asymmetric centre into the molecule.[5]

IV. Asymmetric Strecker synthesis with optically active α-methylbenzylamine.[6]

A recent Paper[7] dealt with the addition of optically active α-methylbenzylamine to a C=C bond, a procedure incidentally used by us in an investigation on asymmetric syntheses of amino-acids by methods we had developed for the preparation of the racemic compounds.[8] The procedure in our hands did not give the results found by the Russian workers.[7] They claimed that on treating maleic acid with two equivalents of L-α-methylbenzylamine, liberating the *N*-α-methylbenzylaspartic acid from its α-methylbenzylamine salt by acidification with hydrochloric acid, and carrying out catalytic hydrogenation, they obtained D-aspartic acid in 88% optical purity. However, a second crop of crystals treated similarly proved to be DL-aspartic acid. Whether this was an instance of a true asymmetric synthesis or merely a separation by fractional crystallisation of diasteriomers having pronouncedly different solubilities was not established.

In one experiment we treated maleic acid with three equivalents of D-α-methylbenzylamine and decomposed the resulting salt with hydrochloric acid. After a few hours *N*-α-methylbenzyl-L-aspartic acid was obtained in 34% yield. Hydrogenolysis with a palladium chloride–Norite catalyst (30%) gave optically pure L-aspartic acid. This incidentally provides an alternative method for the removal of α-methylbenzyl groups by catalytic hydrogenolysis, for which only a palladium hydroxide–charcoal catalyst had previously been found suitable.[4a] After a few days the original mother-liquor yielded a second crop of crystals (10%), which, after hydrogenolysis, afforded D-aspartic acid in 98% optical purity.

Similar experiments revealed that this was definitely not a true asymmetric synthesis, but rather an instance of formation of diasteroisomers in which the asymmetric carbon atom assisting in the resolution is incorporated into the molecule to be resolved. This recalls the work of Holmes and Adams.[9]

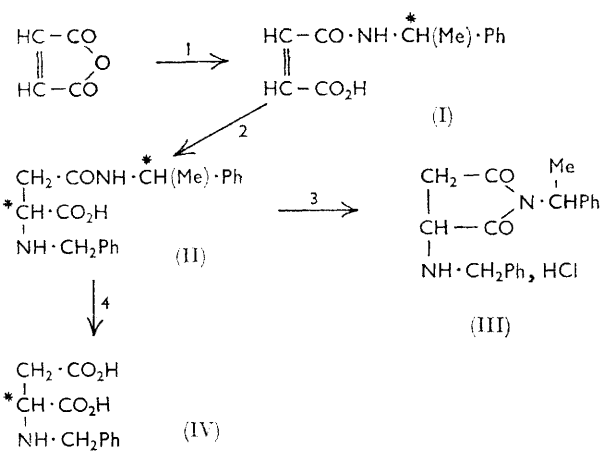
Further proof for this was obtained from the reaction of L-α-methylbenzylamine and maleic acid, when the total yield of *N*-α-methylbenzylaspartic acid was 75%, and catalytic hydrogenolysis gave optically inactive aspartic acid.

Analogously, the reaction with D-α-methylbenzylamine and α,β-unsaturated acids was applied for the production of the two enantiomorphs of β-aminobutyric acid from crotonic acid. Thus two substances could be isolated which differed in optical rotation and yielded after hydrogenolysis (−)- and (+)-β-aminobutyric acid in 29% yield (80% optical purity) and 24% (85% optical purity), respectively.

A true asymmetric synthesis of *N*-benzyl-D-aspartic acid was achieved by the series of reactions shown, which is based on the symmetric induction by means of an optically active amide toward the addition of benzylamine to a double bond. *N*-D-α-Methylbenzylmaleamic acid (I) was prepared by opening maleic anhydride with D-α-methylbenzylamine. On addition of benzylamine to the double bond N^1-benzyl-N^2-D-α-methylbenzylasparagine (II) was obtained. Theoretically both α- and β-amides could result in this reaction, but the formation of β-amides should be favoured since the nucleophilic attack of the large benzyl-

[1] " Organic Chemistry," ed. Henry Gilman, vol. I, 2nd edn., 1942, p. 308.
[2] W. Marckwald, *Ber.*, 1904, **37**, 349.
[3] S. Akabori *et al.*, *Nature*, 1956, **178**, 323.
[4] (*a*) R. Hiskey and R. Northrop, *J. Amer. Chem. Soc.*, 1961, **83**, 4798; (*b*) R. Hiskey and J. Jung, *ibid.*, 1963, **85**, 578; (*c*) R. Hiskey and R. Northrop, *ibid.*, 1965, **87**, 1753.
[5] (*a*) A. Pedrazzoli, *Helv. Chim. Acta*, 1957, **40**, 80; (*b*) J. Sheehan and R. Chandler, *J. Amer. Chem. Soc.*, 1961, **83**, 4795; (*c*) S. Yamada, T. Fujii, and T. Shioiri, *Chem. Pharm. Bull.* (*Tokyo*), 1962, **10**, 680.
[6] (*a*) K. Harada, *Nature*, 1963, **200**, 1201; (*b*) K. Harada *et al.*, *Naturwiss.*, 1964, **51**, 106.
[7] A. P. Terent'ev *et al.*, *Doklady Akad. Nauk S.S.S.R.*, 1964, **154**, 1406.
[8] (*a*) M. Frankel, Y. Liwschitz, and Y. Amiel, *J. Amer. Chem. Soc.*, 1953, **75**, 330; (*b*) Y. Liwschitz and A. Zilkha, *ibid.*, 1955, **77**, 1265.
[9] D. Holmes and R. Adams, *J. Amer. Chem. Soc.*, 1934, **56**, 2093.

amino group should occur in the vicinity of the free carboxyl group. This tendency should be enhanced by mesomeric effects of the carboxylate anion. That only one substance and not a mixture was obtained was



Reagents. 1, NH_2·*CH(Me)Ph, Et_3N, HCl; 2, $PhCH_2$·NH_2; 3, HCl; 4, HBr.

proved conclusively by thin-layer chromatography in two different solvent systems, when only one spot resulted.

Hydrolysis of the amide was attempted by heating it under reflux in a closed tube at 100° with 20% hydrochloric acid, but this only resulted in the production of the imide (III). However, reflux with 48% hydrobromic acid for six hours gave *N*-benzyl-D-aspartic acid (IV) in 60% optical purity, and this could be debenzylated with complete retention of configuration.[10] This, therefore, represents the first instance of an asymmetric synthesis achieved by addition of benzylamine to a carbon–carbon double bond and not by catalytic hydrogenation as in all previous work.

EXPERIMENTAL

Melting points were determined in a Fisher–Johns apparatus.

Reaction between Maleic Acid and D-α-*Methylbenzylamine Resulting in Isolation of Optically Pure* L- *and* D-*Aspartic Acids.*—Maleic acid (5·8 g., 0·05 mol.) was dissolved by heating in water (15 ml.) and to this was added D-α-methylbenzylamine (18·1 g., 0·15 mol.). The mixture was heated under reflux for 3 hr., and, after cooling, diluted with water to 50 ml. and brought to a pH of 3—4 by addition of concentrated hydrochloric acid. After scratching with a glass rod, *N*-α-methylbenzyl-L-aspartic acid crystallised (4 g., 34%) (Found: N, 5·4. $C_{12}H_{15}NO_4$ requires N, 5·9%).

After a few days, *N*-α-methylbenzyl-D-aspartic acid precipitated in the mother-liquor (1·2 g., 10%) (Found: N, 5·4. $C_{12}H_{15}NO_4$ requires N, 5·9%).

L-*Aspartic acid.* *N*-α-Methylbenzyl-L-aspartic acid (3·9 g.) was suspended in glacial acetic acid (50 ml.) and a 30% palladium chloride on Norite catalyst (0·5 g.) was added. Hydrogenolysis was carried out for 6 hr. at 70° in a Parr low pressure apparatus. After cooling, the catalyst and the substance which adhered to it were filtered off and extracted with formic acid (20 ml.). Addition of acetone to the extract gave L-aspartic acid (1·1 g., 51%), $[\alpha]_D^{25}$ +25·6° (*c*, 0·125 in 5N-hydrochloric acid); lit.,[11] $[\alpha]_D^{25}$ +25·5° (*c*, 0·2 in 5N-hydrochloric acid) [Found: N, 10·0; N (Van Slyke), 10·2. Calc. for $C_4H_7NO_4$: N, 10·5; N (Van Slyke), 10·5%].

D-*Aspartic acid.* *N*-α-Methylbenzyl-D-aspartic acid (1 g.) was catalytically hydrogenolysed in the same manner. The product had $[\alpha]_D^{25}$ −25° (*c*, 0·075 in 5N-hydrochloric acid). This corresponds to 98% purity [Found: N (Van Slyke), 10·3. Calc. for $C_4H_7NO_4$: N (Van Slyke), 10·5%].

Reaction between Maleic Acid and D-α-*Methylbenzylamine not Leading to Optical Resolution.*—Maleic acid (9 g., 0·078 mol.) and D-α-methylbenzylamine (19 g., 0·156 mol.) were treated as above for 2 hr. The precipitate of *N*-α-methylbenzyl-L-aspartic acid obtained on acidification was collected after a few hours (13 g., 70%). In order to obtain a more complete recovery, the mother-liquor was evaporated *in vacuo* and the residue redissolved in 10% sodium hydroxide solution (50 ml.); four extractions with ether and acidification of the aqueous layer with concentrated hydrochloric acid to pH 2—3 gave *N*-α-methylbenzyl-D-aspartic acid, which was filtered off after standing overnight (2 g., 11%). The two acids were catalytically hydrogenolysed, as above, and the following specific optical rotations were obtained from the products. Product from *N*-α-methylbenzyl-L-aspartic acid: $[\alpha]_D^{24}$ +4° (*c*, 0·125 in 5N-hydrochloric acid), corresponding to 16% optical purity; product from *N*-α-methylbenzyl-D-aspartic acid: $[\alpha]_D^{24}$ −20° (*c*, 0·125 in 5N-hydrochloric acid), corresponding to 79% optical purity.

Reaction between Maleic Acid and L-α-*Methylbenzylamine.*—Maleic acid (5·8 g., 0·05 mol.) and L-α-methylbenzylamine (18·1 g., 0·15 mol.) were treated as above. After acidification with concentrated hydrochloric acid to pH 3—4 and leaving overnight, the product was filtered off (8·8 g., 74%). 4 g. was catalytically hydrogenolysed, as usual, to give aspartic acid (1·5 g., 67%) [Found: N (Van Slyke), 10·1. Calc. for $C_4H_7NO_4$: N (Van Slyke), 10·5%]. No optical rotation was observed.

Reaction between Crotonic Acid and D-α-*Methylbenzylamine.*—Freshly crystallised crotonic acid (4·3 g., 0·05 mol.) was dissolved in pyridine (15 ml.) and D-α-methylbenzylamine (6·1 g., 0·05 mol.) was added. The mixture was heated under reflux for 2 hr. and, after cooling, acetone (200 ml.) was added and the mixture kept overnight. N-α-*Methylbenzyl*-(−)-β-*aminobutyric acid* was then filtered off (3 g., 29%) (Found: N, 6·7. $C_{12}H_{17}NO_2$ requires: N, 6·8%); $[\alpha]_D^{25}$ −8° (*c*, 0·125 in water). After several days a further 2·5 g. (24%) was collected from the mother-liquor (N-α-*methylbenzyl*-(+)-β-*aminobutyric acid*) (Found: N, 6·7. $C_{12}H_{17}NO_2$ requires N, 6·8%); $[\alpha]_D^{25}$ +40° (*c*, 0·125 in water).

(−)-β-*Aminobutyric Acid.*— *N*-α-Methylbenzyl-(−)-β-aminobutyric acid (2·5 g.) was dissolved in glacial acetic acid (50 ml.) and catalyst (0·3 g.) was added. Hydrogenolysis was carried out for 7 hr. at 70°. After separation of the catalyst by filtration, the solvent was evaporated *in vacuo*. In order to eliminate traces of acetic acid completely, the residue was taken up in a few mls. of ethanol which were evaporated *in vacuo*. This was repeated three times. Finally, the residue was dissolved in ethanol (5 ml.) and the product precipitated by addition of acetone

[10] Y. Liwschitz, A. Vincze, and E. Nemes, *Bull. Res. Council Israel*, 1960, **9***A*, 49.

[11] E. Fischer, *Ber.*, 1899, **32**, 2463.

(1 g., 80%) (Found: N, 12·3. Calc. for $C_4H_9NO_2$: N, 13·6%); $[\alpha]_D^{25}$ −28° (*c*, 0·125 in water). This corresponds to 80% optical purity.[12]

(+)-β-*Aminobutyric Acid*.— *N*-α-Methylbenzyl-(+)-β-aminobutyric acid (2 g.) was catalytically hydrogenolysed according to the above procedure to give the product (0·8 g., 80%) (Found: N, 13·6. Calc. for $C_4H_9NO_2$: N, 13·6); $[\alpha]_D^{25}$ +30° (*c*, 0·125 in water). This corresponds to 85% optical purity. Identity of our products with β-aminobutyric acid was proved by thin-layer chromatography n-butanol–acetic acid–water (4 : 1 : 5) as mobile phase.

N-D-α-*Methylbenzylmaleamic Acid* (I).—Maleic anhydride (16 g., 0·163 mol.) in dry ether (400 ml.) was cooled in an ice-bath, and a solution of D-α-methylbenzylamine (19·8 g., 0·163 mol.) in dry ether (100 ml.) containing triethylamine (16·5 g., 0·163 mol.) was added during 20 min. with stirring, to give an immediate amorphous precipitate. Stirring was continued for 30 min. after addition was complete; ether was then evaporated *in vacuo* and the oily residue dissolved in water (100 ml.). On acidification with concentrated hydrochloric acid to pH 2, the *product* precipitated, was filtered off, and recrystallised from ethanol (20 g., 56%), m. p. 115° (Found: N, 6·7. $C_{12}H_{13}NO_3$ requires N, 6·4%).

N^1-*Benzyl*-N^2-D-α-*methylbenzyl*-D-*asparagine* (II).— To compound (I) (5 g.) in water (7 ml.) was added benzylamine (5 g.) and the mixture was heated under reflux for 3 hr. Acetone was added to the cooled mixture which was left overnight; the *product* was then filtered off (4 g., 54%). A sample was recrystallised from aqueous ethanol, m. p. 193° (Found: N, 9·1. $C_{19}H_{22}N_2O_3$ requires N, 8·6%).

N^1-*Benzyl*-N^2-α-*methylbenzyl*-D-*aspartimide Hydrochloride* (III).—A solution of compound (II) (0·5 g.) in 20% hydrochloric acid (5 ml.) was heated at 100° in a closed glass tube for 16 hr. On cooling the *product* crystallised, and was collected by filtration. After recrystallisation from aqueous ethanol it had m. p. 197° (Found: Cl, 10·2; N, 8·6. $C_{19}H_{21}ClN_2O_2$ requires Cl, 10·3; N, 8·1%).

N-*Benzyl*-D-*aspartic Acid* (IV).—A solution of compound (II) (2 g.) in 48% hydrobromic acid (20 ml.) was heated under reflux for 6 hr. After evaporation to dryness *in vacuo* the oily residue was dissolved in aqueous 5% sodium hydrogen carbonate solution (10 ml.) and extracted three times with ether. On acidification of the aqueous layer with concentrated hydrochloric acid to pH 3—4, the *product* crystallised (0·85 g., 62%), m. p. 208° (Found: N, 6·4. Calc. for $C_{11}H_{13}NO_4$: N, 6·3%); $[\alpha]_D^{25}$ +20° (*c*, 0·125 in 5% sodium hydrogen carbonate). This corresponds to 60% optical purity. The i.r. spectrum of this substance was identical with that of an authentic sample of *N*-benzyl-D-aspartic acid.

Department of Organic Chemistry,
The Hebrew University, Jerusalem,
Israel. [6/034 *Received*, *January* 10*th*, 1966]

[12] E. Fischer and H. Scheibler, *Annalen*, 1911, **383**, 443.