In each case a considerable quantity of alcohol-soluble material, triphenyltin hydroxide, as shown by its infrared spectrum, was isolated: benzyl chloride, calcd 6.24 g; 1-bromobutane, calcd 6.50 g; and 2-bromopropane, calcd 5.10 g. No effect was made to determine whether there was any triphenyltin halide formed in these reactions.

Reaction of I with Trityl Chloride in Benzene.—A solution of 4.0 g of trityl chloride in 100 ml of benzene was added from a dropping funnel to a stirred solution of 10.0 g of I and 100 ml of benzene was maintained under an atmosphere of dry nitrogen. The reaction mixture was colorless and no changes were noted after stirring at room temperature for 1 hr. The mixture was slowly heated and gradually turned first yellow and then red. After being heated at reflux for 5 hr the mixture was transferred to a one-necked flask. No insoluble trityl peroxide was observed. The solution was evaporated to dryness and the solid residue was treated with methyl alcohol and filtered. The infrared spectrum of the precipitate, 8.90 g, indicated only the presence of phenyltin compounds. The methanolic filtrate was evaporated to dryness. The infrared spectrum of the residue did not indicate the presence of either peroxide or triphenyl carbinol. The presence of triphenyltin chloride in the residue was indicated by the infrared spectrum.

The experiment was repeated except that after the red color had developed in the solution the heat was removed and air was admitted to the flask. The red color was discharged to a pale yellow. Upon further heating under nitrogen the red color would again appear and in turn could be discharged by admitting further quantities of air. This procedure was repeated several times. After heating for a total of 12 hr the solvent was removed by evaporation. The precipitate was treated with 200 ml of methanol, filtered, and the filtrate evaporated to dryness. The solid was treated with petroleum ether, filtered, and the petroleum ether filtrate was concentrated to an oily liquid. The infrared spectrum of this material was identical with that of commercial benzophenone although further attempts at purification failed to give a sample with the correct melting point.

Stereoselective Synthesis of Optically Active Aspartic Acid from Derivatives of Fumaric Acid and Maleic Acid[1]

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Optically active aspartic acid (4.5–15.4%) was synthesized by the amination of the derivatives of fumaric acid and maleic acid with (*S*)- and (*R*)-α-methylbenzylamine. Three kinds of reactions were carried out: (a) reaction of (*S*)- and (*R*)-α-methylbenzylamine [(*S*)- and (*R*)-amine] with N,N′-di-(*S*)- and -(*R*)-α-methylbenzyl fumaramide; (b) reaction of (*S*)- and (*R*)-amine with diethyl maleate; (c) reaction of (*S*)- and (*R*)-amine with diethyl fumarate. In each case, the reaction intermediates were isolated. To avoid the fractionation of the resulting optically active aspartic acid during the isolation and recrystallization procedures, a column chromatographic method for DNP-aspartic acid was employed. Possible steric courses of the reactions a, b, and c are discussed.

The nonenzymatic asymmetric synthesis of α-amino acids and of other organic compounds has long been an attractive subject in investigations of stereochemistry. Several studies of the asymmetric synthesis of α-amino acids have already been reported.[2-15] However, most of the syntheses have been carried out by the use of a catalytic hydrogenation procedure.

In previous studies from this laboratory,[13-14] optically active alanine was synthesized in solution by the Strecker method in which optically active (−)- and (+)-α-methylbenzylamine[16] functioned as asymmetric centers in the syntheses. The absolute configuration of (−)- and (+)-amine had been determined as *S* and *R*, respectively, by Leithe.[17]

In this study, the syntheses of optically active aspartic acid by the use of both *S*(−)- and *R*(+)-α-methylbenzylamine [(*S*)-amine, (*R*)-amine] and derivatives of fumaric acid and maleic acid in solution are described. Three kinds of amination reactions were carried out to synthesize optically active aspartic acid: (a) reaction of (*S*)- and (*R*)-amine with N,N′-di-(*S*)- and -(*R*)-α-methylbenzyl fumaramide [(*S*)- and (*R*)-fumaramide]; (b) reaction of (*S*)- and (*R*)-amine with diethyl maleate; (c) reaction of (*S*)- and (*R*)-amine with diethyl fumarate.

In reaction a, (*S*)-fumaramide was heated with (*S*)-amine ($[\alpha]^{25}D$ −42.3°) in butanol at 115–120° for 3 days. The α-methylbenzyl residue of the resulting N-(α-methylbenzyl)aspartic acid was removed by hydrogenolysis, using the palladium hydroxide–charcoal system of Hiskey.[12] The isolated aspartic acid (yield 64%) showed optical activity of $[\alpha]^{25}D$ −2.6° in 5 *N* HCl [10.2% optically active (*R*)-aspartic acid]. To avoid the fractionation[15,18] of the resulting aspartic acid during the isolation and recrystallization procedure, a part of the hydrogenolyzed product was converted to DNP-aspartic acid by the use of 1-fluoro-2,4-dinitrobenzene. The resulting DNP-aspartic acid was separated chromatographically by the use of a

(1) (a) Sterically Controlled Syntheses of Optically Active Organic Compounds. II. Part I: K. Matsumoto and K. Harada, *J. Org. Chem.*, **31**, 1956 (1966). (b) Contribution No. 055 of the Institute of Molecular Evolution, University of Miami.

(2) (a) F. Knoop and C. Martius, *Z. Physiol. Chem.*, **258**, 238 (1939); (b) S. Akabori, T. Ikenaka, and K. Matsumoto, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **73**, 112 (1952).

(3) M. Nakazaki, *ibid.*, **75**, 831 (1954).

(4) G. Maeda, *ibid.*, **77**, 1011 (1956).

(5) S. Akabori, Y. Izumi, Y. Fujii, and S. Sakurai, *ibid.*, **77**, 1374 (1956).

(6) S. Akabori, Y. Izumi, S. Sakurai, and Y. Fujii, *Nature*, **178**, 323 (1956).

(7) S. Akabori, Y. Izumi, and Y. Fujii, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **78**, 168 (1957).

(8) S. Akabori and S. Sakurai, *ibid.*, **78**, 1629 (1957).

(9) A. Pedrazzoli, *Helv. Chim. Acta*, **40**, 80 (1957).

(10) M. Murakami and K. Takahashi, *Bull. Chem. Soc. Japan*, **32**, 308 (1959).

(11) J. C. Sheehan and R. E. Chandler, *J. Am. Chem. Soc.*, **83**, 4791 (1961).

(12) R. G. Hiskey and R. C. Northrop, *ibid.*, **83**, 4798 (1961); **87**, 1753 (1965).

(13) K. Harada, *Nature*, **200**, 1201 (1963).

(14) K. Harada and S. W. Fox, *Naturw.*, **51**, 106 (1964).

(15) Part 1 of series; see ref 1a.

(16) W. Theilacker and H. Winkler, *Chem. Ber.*, **87**, 690 (1954).

(17) W. Leithe, *Ber.*, **64**, 2831 (1931).

(18) The recrystallization procedure resulted in fractionation of the optically active aspartic acid. The specific rotation varied upon recrystallization and finally the value reached zero after several recrystallization procedures.

TABLE I

OPTICALLY ACTIVE ASPARTIC ACID PREPARED FROM FUMARAMIDE

Fumaramide[a]	Amine[b]	Yield, g (%)	Confign of aspartic acid	Isolated[c] aspartic acid (5 *N* HCl)	Optical[d] purity, %	DNP-aspartic acid[e] (1 *N* NaOH)	Optical[f] purity, %
(*S*)	(*S*)	0.53 (64)	(*R*)	$[\alpha]^{25}D$ −2.6° α −0.108° (*c* 4.10)	10.2	$[\alpha]^{25}D$ −14.1° α −0.095° (*c* 0.67)	15.3
(*R*)	(*R*)	0.50 (61)	(*S*)	$[\alpha]^{25}D$ +3.1° α +0.143 (*c* 4.65)	12.2	$[\alpha]^{25}D$ + 14.0° α +0.133° (*c* 0.95)	15.2
(*S*)	Benzylamine	0.48 (58)	(*R*)	$[\alpha]^{25}D$ −2.0° α −0.078° (*c* 3.93)	7.9	$[\alpha]^{25}D$ −7.0° α −0.072° (*c* 1.04)	7.6
(*R*)	Benzylamine	0.50 (61)	(*S*)	$[\alpha]^{25}D$ +2.2° α +0.085° (*c* 3.80)	8.7	$[\alpha]^{25}D$ +5.0° α +0.055° (*c* 1.09)	5.6

[a] N,N'-Di-α-methylbenzyl fumaramide, 2.0 g. [b] *S*-(−)- or *R*-(+)-α-Methylbenzylamine, 1.5 g. [c] Specific rotations were measured without further purification. The recrystallization procedure resulted in fractionation and the $[\alpha]D$ values finally reached zero. [d] Defined as ($[\alpha]D$ observed/$[\alpha]D$ literature) × 100. (*S*)-Aspartic acid, $[\alpha]^{24}D$ +25.39° (5 *N* HCl). J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1961, p 1856. [e] To avoid fractionation, the hydrogenolyzed solution was directly dinitrophenylated. [f] DNP-(*S*)-aspartic acid, $[\alpha]^{25}D$ +91.9° (1 *N* NaOH). K. R. Rao, H. A. Sober, *J. Am. Chem. Soc.*, **76**, 1328 (1954).

TABLE II

OPTICALLY ACTIVE ASPARTIC ACID PREPARED FROM DIETHYL MALEATE[a]

Amine[b]	Yield g, %	Confign of aspartic acid	Isolated aspartic acid (5 *N* HCl)	Optical[d] purity, %	DNP-aspartic acid (1 *N* NaOH), deg	Optical[f] purity, %
(*S*)	1.14 (86)	(*S*)	$[\alpha]^{25}D$ +2.8° α +0.113° (*c* 4.00)	11.0	$[\alpha]^{25}D$ +12.6° α +0.093° (*c* 0.78)	13.7
(*R*)	1.13 (86)	(*R*)	$[\alpha]^{25}D$ −3.1° α −0.126° (*c* 4.10)	12.2	$[\alpha]^{25}D$ −14.2° α −0.148° (*c* 1.04)	15.4

[a] Diethyl maleate was employed in the amount of 0.01 mole (1.72 g). [b] *S*-(−)- or *R*-(+)-α-methylbenzylamine (4.30 g). [c] The specific rotations were measured without further purification. The recrystallization procedure resulted in fractionation and the $[\alpha]D$ values finally reached zero. [d] Defined as ($[\alpha]D$ observed/$[\alpha]D$ literature) × 100. (*S*)-Aspartic acid $[\alpha]^{24}D$ +25.39° (5 *N* HCl). J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1961, p 1856. [e] To avoid fractionation, the hydrolyzed solution was directly DNPylated. [f] DNP-(*S*)-aspartic acid, $[\alpha]^{25}D$ +91.9° (1 *N* NaOH). K. R. Rao, H. A. Sober, *J. Am. Chem. Soc.*, **76**, 1328 (1954).

celite column treated with pH 4 phosphate–citrate buffer.[19] The corresponding DNP-aspartic acid band was cut off, dried, and eluted. The optical rotation of the isolated pure DNP-aspartic acid was measured to obtain the accurate value of specific rotation of synthesized aspartic acid.[15] The isolated DNP-aspartic acid showed an optical rotation of $[\alpha]^{25}D$ −14.1° [15.3% optically active DNP-(*R*)-aspartic acid].

The reaction of (*R*)-fumaramide and (*R*)-amine ($[\alpha]^{25}D$ +41.5°) resulted in (*S*)-aspartic acid (yield 61%), $[\alpha]^{25}D$ +3.1° (12.2% optically active). The corresponding DNP-aspartic acid showed optical activity of $[\alpha]^{25}D$ +14.0° (15.2% optically active). Results are shown in Table I.

In reaction b, diethyl maleate was reacted with (*S*)-amine under similar conditions to reaction a, but without butanol. The resulting product was hydrolyzed with 6 *N* hydrochloric acid and then subjected to hydrogenolysis as before. The isolated (*S*)-aspartic acid showed a specific rotation of $[\alpha]^{25}D$ +2.8° (11.0% optically active), and the DNP-(*S*)-aspartic acid showed an optical activity of $[\alpha]^{25}D$ +12.6° (13.7% optically active), whereas in reaction a (*R*)-aspartic acid was obtained by the use of (*S*)-amine.

(19) J. C. Perrone, *Nature*, **167**, 513 (1951); A. Courts, *Biochem. J.*, **58**, 70 (1954).

In the same way, the reaction of diethyl maleate and (*R*)-amine resulted in (*R*)-aspartic acid, $[\alpha]^{25}D$ −3.1° (12.2% optically active). The DNP-(*R*)-aspartic acid showed an optical activity of $[\alpha]^{25}D$ −14.2° (15.4% optically active). Results are shown in Table II.

In reaction c, a reaction of diethyl fumarate with (*S*)-amine was carried out. (*S*)-Aspartic acid, $[\alpha]^{25}D$ +2.0° (7.9% optically active), was isolated. DNP-(*S*)-aspartic acid, $[\alpha]^{25}D$ +4.3° (4.6% optically active), was obtained after DNPylation, whereas in reaction a (*S*)-fumaramide and (*S*)-amine resulted in (*R*)-aspartic acid. In the same way, diethyl fumarate and (*R*)-amine gave (*R*)-aspartic acid, $[\alpha]^{25}D$ = −1.6° (6.3% optically active), and DNP-(*R*)-aspartic acid, $[\alpha]^{25}D$ −4.2° (4.5% optically active). Results are listed in Table III.

In each reaction a, b, and c, the reaction intermediates were isolated. Using these results, possible steric courses for these reactions will be considered in the following discussion section.

Discussion

The syntheses of optically active aspartic acid described here consisted of an addition reaction of (*S*)- and (*R*)-amine to the double bond of fumaric acid and

TABLE III

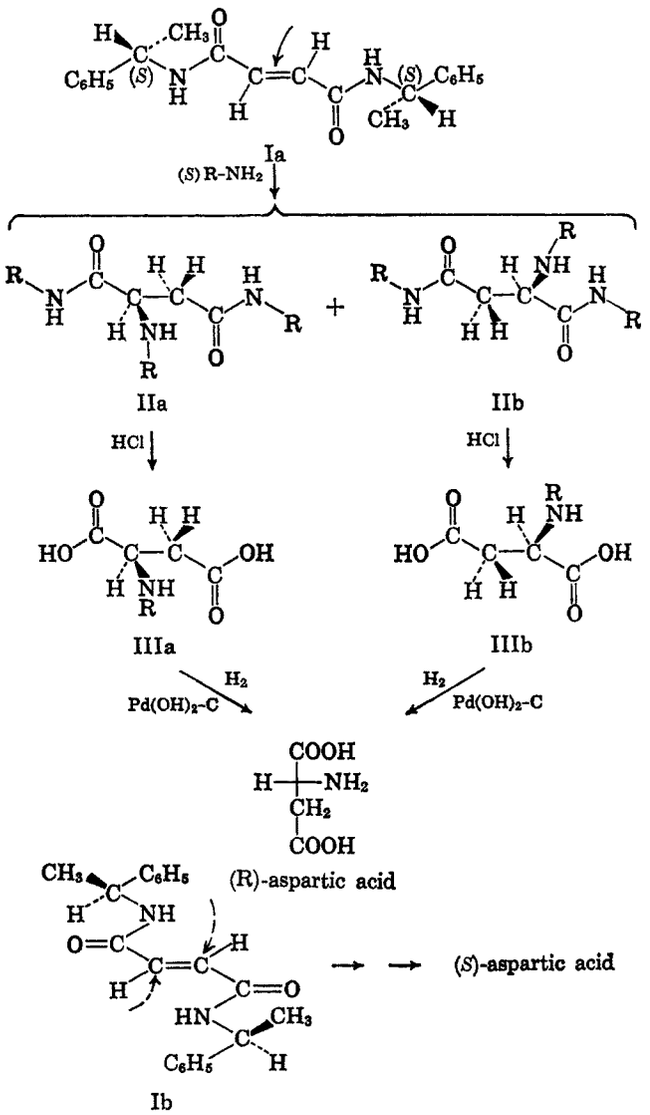
OPTICALLY ACTIVE ASPARTIC ACID PREPARED FROM DIETHYL FUMARATE[a]

Amine[b]	Yield g, %	Config of aspartic acid	Isolated[c] aspartic acid (5 *N* HCl)	Optical[d] purity, %	DNP-aspartic acid[e] (1 *N* NaOH), deg	Optical[f] purity, %
(*S*)	1.15 (87)	(*S*)	$[\alpha]^{25}D$ +2.0° α +0.076° (*c* 3.90)	7.9	$[\alpha]^{25}D$ +4.3° α + 0.046° (*c* 1.08)	4.6
(*R*)	1.11 (85)	(*R*)	$[\alpha]^{25}D$ −1.6° α −0.064° (*c*, 3.98)	6.3	$[\alpha]^{25}D$ −4.2° α −0.043° (*c* 1.03)	4.5

[a] Diethyl fumarate was employed in the amount of 0.01 mole (1.72 g). [b] *S*-(−)- or *R*-(+)-α-methylbenzylamine (4.30 g). [c] The specific rotations were measured without further purification. The recrystallization procedure resulted in fractionation and the $[\alpha]D$ values finally reached zero. [d] Defined as ($[\alpha]D$ observed/$[\alpha]D$ literature) × 100. (*S*)-Aspartic acid, $[\alpha]^{24}D$ +25.39° (5 *N* HCl). J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1961, p 1856. [e] To avoid fractionation, the hydrolyzed solution was directly DNPylated. [f] DNP-(*S*)-aspartic acid, $[\alpha]^{25}D$ +91.9° (1 *N* NaOH). K. R. Rao, H. A. Sober, *J. Am. Chem. Soc.*, **76**, 1328 (1954).

maleic acid derivatives under the influence of asymmetric induction. In these reactions, it is possible to explain the configurations of the final products by a method similar to the rules proposed by Cram[20] and Prelog.[21]

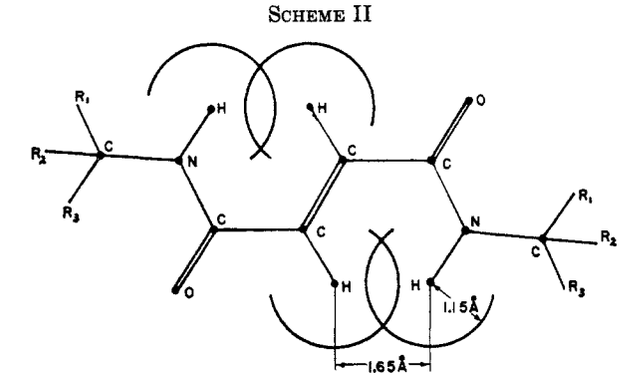
SCHEME I



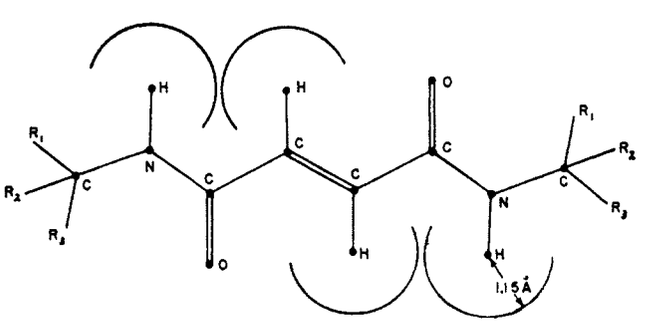
In reaction a, the reaction of (*S*)-fumaramide and (*S*)-amine resulted in (*R*)-aspartic acid. The possible conformations of the fumaramide could be shown by structures Ia (cisoidal conformation) and Ib (transoidal conformation) as in Scheme I. The addition of (*S*)-amine to the double bond of the fumaramide prefers to take place from the front side of the paper (the least hindered side), because both methyl groups are on the back side of the plane of the paper. The configurations of the two addition products IIa and IIb are identical (*R* configuration). After hydrolysis and hydrogenolysis, (*R*)-aspartic acid was obtained. The contribution of structure Ib which would produce (*S*)-aspartic acid might be smaller in this reaction because of its steric hindrance. In a similar way, (*R*)-fumaramide and (*R*)-amine resulted in (*S*)-aspartic acid.

The assumed transoidal and cisoidal conformations of fumaramide in the form of "Dreiding Stereomodels" are shown in Scheme II. In the transoidal conformation, the distance between the hydrogen of the amide

SCHEME II



transoidal conformation

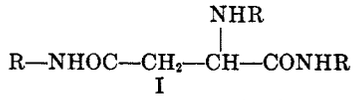


cisoidal conformation

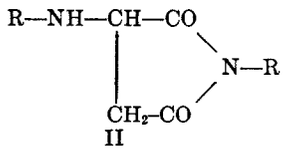
(20) D. J. Cram and F. A. Abd. Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

(21) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953).

TABLE IV
ISOLATED INTERMEDIATES I AND II AND ASPARTIC ACID



I



II

	Isolated intermediate	Isolated intermediate, wt in g	Mp, °C	$[\alpha]^{25}D$ deg (c, in abs EtOH)	Confign of aspartic acid	DNP-aspartic acid, $[\alpha]^{25}D$, deg (c, in 1 N NaOH)
Reaction a[a]	Unreacted	0.55	298–301	...	...	...
	I	1.75	119–121	−112.9 (0.79)	(R)	−7.0 (0.48)
Reaction b[a]	I	0.27	121–123	−112.1 (0.77)	(R)	c
	II	1.75	223–224[b]	−47.5 (0.75)[b]	(S)	+14.2 (0.18)
Reaction c[a]	I	0.70	121–123	−112.0 (0.87)	(R)	−4.8 (0.54)
	II	1.48	222–224[b]	−48.0 (0.79)[b]	(S)	c

[a] Reaction a: (S)-fumaramide, 2.0 g; (S)-amine, 1.5 g, were used. Reaction b: diethyl maleate, 1.72 g; (S)-amine, 4.3 g, were used. Reaction c: diethyl fumarate, 1.72 g; (S)-amine, 4.3 g, were used. [b] Measured as the intermediate II hydrochloride. [c] The sample amounts were too small to measure accurate optical purity.

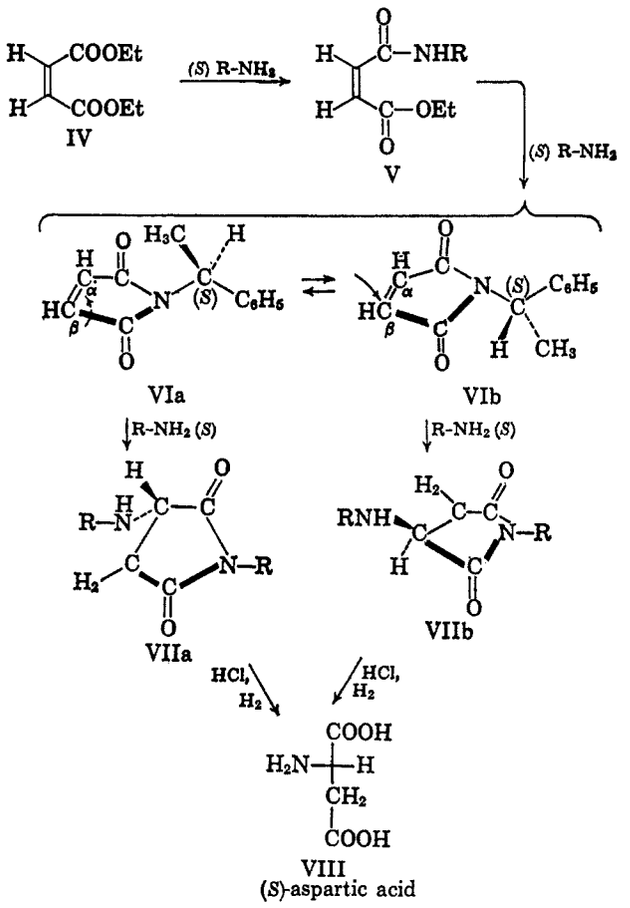
bond and the hydrogen attached to the α-carbon atom is measured to be 1.65 A. Because the Van der Waals radius of hydrogen is 1.15 A, these two hydrogens overlap each other and the transoidal conformation cannot exist as a planar molecule.[22] In the cisoidal conformation, on the other hand, there is no such steric hindrance and it can exist as a planar structure. The loss of resonance energy due to nonplanarity in the transoidal conformation suggests that the preferred conformation might be cisoidal.

The assumed cisoidal conformation of (S)-fumaramide (Ia) was also supported by the isolation of the reaction intermediate N-alkyl aspartic acid diamide (IIa, IIb) [intermediate I]. The isolated diamide was converted to (R)-aspartic acid upon hydrolysis and hydrogenolysis (Table IV).

When benzylamine was used in the addition reaction instead of (S)- or (R)-amine, similar results were obtained. (S)-Fumaramide and benzylamine gave (R)-aspartic acid and (R)-fumaramide and benzylamine resulted in (S)-aspartic acid. However, the optical activities of the isolated aspartic acid and the corresponding DNP derivative were both lower than those which were obtained by the reaction with optically active (S)- or (R)-amine. The sterically directed addition reaction of the entering optically active amine might be a reason for the higher optical activity. Another explanation is that amide exchange might have occurred during the reaction with benzylamine.

In reaction b, diethyl maleate reacted with (S)-amine to give (S)-aspartic acid and with (R)-amine to give (R)-aspartic acid. In this reaction, formation of amide (V) might have occurred by the reaction of ester and amine. The resulting ethyl maleamate (V) may have cyclized to form N-alkyl maleimide (VIa, VIb) as shown in Scheme III. Maleimide (VIa) and

SCHEME III

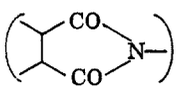


(VIb) are in equilibrium. (S)-Amine attacks the α-carbon atom of VIa from the backside of the plane of the paper and (S)-amine approaches the β-carbon of VIb from the front side. In each case the resulting amino acids have the (S) configuration as is shown in Scheme III.

From the reaction mixture of reaction b, two intermediates were isolated. Intermediate (I) is N-alkyl aspartic acid diamide (mp 121–123°) which is the same compound obtained in reaction a. Intermediate II is a derivative of succiniimide (VIIa, VIIb) (mp 223–224° as hydrochloride) (Table IV, Scheme III).

(22) The conformational problem in mesityl oxide is similar to that in the fumaramide. The transoidal structure of mesityl oxide is sterically hindered, whereas the cisoidal structure is not. If the empirical rule[a-c] of infrared spectra on the α,β-unsaturated ketone [(a) *trans* structure: intensity of C=O is stronger than C=C; (b) *cis* structure: intensity of C=O and C=C are almost equal or C=C is stronger than C=O] were applicable to the mesityl oxide, the molecule could be in the cisoidal conformation because the C=C absorption is stronger than C=O absorption. (a) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **78**, 6193 (1956). (b) D. H. R. Barton and C. R. Narayaman, *J. Chem. Soc.*, 963 (1958). (c) K. Nakanishi, "Infrared Absorption Spectroscopy—Practical—," Nankodo Press (Tokyo), Japan, 1963, p 105.

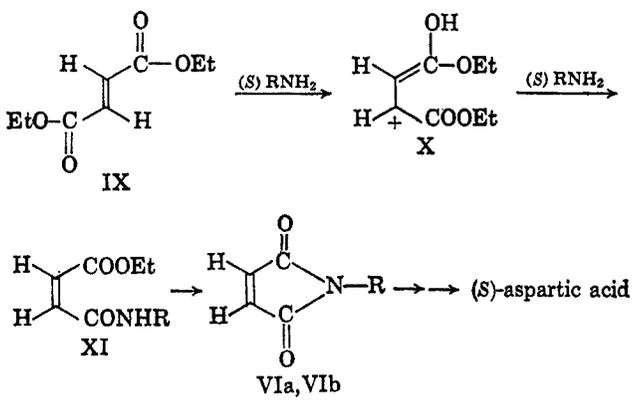
From intermediate I, (*R*)-aspartic acid was obtained as in reaction a. Intermediate II shows infrared absorption bands at 1780 and 1710 cm^{-1} characteristic of the cyclic N-substituted imide structure.



Intermediate II was converted to (*S*)-aspartic acid by hydrolysis and hydrogenolysis. The amount of the isolated intermediate I is small (0.27 g) compared with intermediate II (1.75 g as crude oil). These facts suggest that the major reaction in reaction b is the cyclic imide formation as is shown in Scheme III. Therefore reaction b would result in (*S*)-aspartic acid.

In reaction c, diethyl fumarate (IX) reacted with (*S*)-amine to give (*S*)-aspartic acid and with (*R*)-amine to give (*R*)-aspartic acid. These results are the same as those which were obtained from diethyl maleate (reaction b). This fact suggests the possibility of conversion of the *trans* fumarate to the *cis* maleate during the reaction (Scheme IV). By the

SCHEME IV



trans to the *cis* transformation, the resulting maleamic acid ester (XI) could be cyclized under the reaction conditions to the more stable five-membered N-alkyl maleimide (VIa and VIb in Scheme III). The addition reaction to the double bond of VIa and VIb proceeds as described in reaction b. Thus the reaction of diethyl fumarate and (*S*) and (*R*)-amine resulted in (*S*)- and (*R*)-aspartic acid as in reaction b.

Isolated intermediates in reaction c supported the above postulated mechanism. The isolated compounds were intermediate I, 0.70 g (mp 121–123°), and intermediate II, 1.48 g as crude oil (mp 222–224° as hydrochloride). These compounds were the same as isolated in reaction b; however, a greater amount of intermediate I was isolated. These facts suggest that (a) *trans* to *cis* transformation takes place during reaction c; (b) cyclic intermediate II (VIIa, VIIb) formation is a major reaction and intermediate I (IIa, IIb) formation is a minor reaction. The optical purity of the obtained aspartic acid in reaction c is smaller than that which was obtained in reaction b. This could be explained by the greater amount of intermediate I which would result in the lower optical purity of (*S*)-aspartic acid in reaction c.

The discussions mentioned above would suggest the relationship between reaction a, b, and c as is shown in Scheme V. Under the reaction conditions, conversion of maleate to fumarate could be possible[23] in reaction b. In reaction c, the conversion of fumarate to maleate is also possible, because the resulting maleate could be converted to the stable five-membered cyclic maleimide.[24] The isolated reaction intermediates confirm the possibility of *trans* to *cis* and *cis* to *trans* conversion in reactions b and c. In each case, however, cyclic imide (intermediate II) was found to be a major product and fumaramide (intermediate I) was a minor product in both reaction b and c.

Experimental Section[25]

N,N′-Di-(*S*)-α-methylbenzyl Fumaramide.—(*S*)-α-Methylbenzylamine [(*S*)-amine], ($[\alpha]^{25}D$ −42.3° in benzene), 12.0 g, in tetrahydrofuran (50 ml) was added to a solution of fumaryl chloride (24.0 g) and tetrahydrofuran (50 ml) with stirring at a temperature below 20°. The evolving hydrogen chloride gas was removed under moderately reduced pressure. The mixture was stirred for 2 hr at room temperature until the evolution of hydrogen chloride ceased. The precipitated crystals were collected by filtration and the crude product was washed with ethanol (19.4 g). After recrystallization from tetrahydrofuran, 16.6 g (65%) of pure (*S*)-diamide was obtained, mp 297–300° dec, $[\alpha]^{25}D$ −156.4° (*c* 0.372, N,N′-dimethylformamide).

Anal. Calcd for $C_{20}H_{22}O_2N_2$: N, 8.69. Found: N, 8.71.

N,N′-Di-(*R*)-α-methylbenzyl Fumaramide.—The compound was prepared in the same way as that described above, by the use of (*R*)-amine ($[\alpha]^{25}D$ +41.5° in benzene): yield 68%, mp 296–300° dec, $[\alpha]^{25}D$ +159.2° (*c* 0.277, N,N′-dimethylformamide).

Anal. Found: N, 8.86.

N,N′-Di(±)α-methylbenzyl Fumaramide (Racemic).—Yield was 67%, mp 285–290° dec.

Reaction a. (*R*)-(−)-Aspartic Acid from (*S*)-Fumaramide and (*S*)-Amine.—A mixture of (*S*)-fumaramide, 2.0 g, (*S*)-amine, 1.5 g, and 1-butanol, 25 ml, in a 100-ml round flask with a reflux condenser was heated at 115–120° in an oil bath for 3 days under a nitrogen atmosphere. After the reaction was over, 1-butanol and the excess amine were removed under reduced pressure. The residue was hydrolyzed with 6 *N* hydrochloric acid, 80 ml, for 8 hr under refluxing. Water-insoluble material was removed by filtration and by ether extraction. The solution was evaporated to dryness *in vacuo*. Water was added and the water was evaporated to minimize the remaining hydrogen chloride. The procedure was repeated three times. The residue was dissolved in 100 ml of water and the pH was adjusted to about 5. Palladium hydroxide on charcoal,[12] 1.5 g, was added to the solution and hydrogenolysis was carried out at room temperature for 8 hr. After the hydrogen uptake ceased, the catalyst was removed by filtration. To the filtrate, hydrochloric acid was added to bring the pH to about 1. The solution was evaporated to dryness under reduced pressure, and the dried residue was extracted with absolute ethanol (50 ml) and filtered. The alcoholic solution was kept overnight in a freezer, and the precipitated salt was separated by filtration. Pyridine was added to the filtrate to precipitate aspartic acid. After standing overnight in a refrigerator, 530 mg (64%) of aspartic acid was obtained, $[\alpha]^{25}D$ −2.6° (5 *N* HCl, *c* 4.1). The material showed a single spot when subjected to paper chromatography, R_f 0.20 (*n*-BuOH–AcOH–H_2O = 4:1:2).

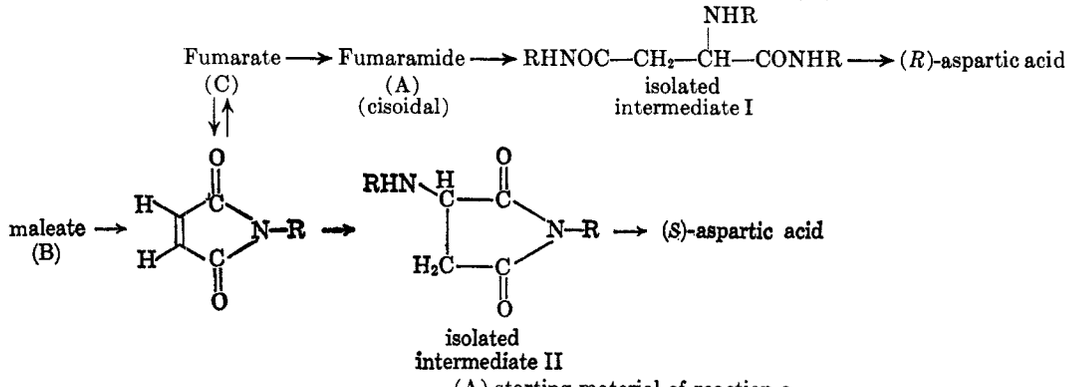
The aspartic acid was recrystallized from water and ethanol: $[\alpha]^{25}D$ −3.1° (*c* 3.22, 5 *N* HCl).

(23) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., New York, N. Y., 1962, p 345. G. R. Clemo and S. B. Graham, *J. Chem. Soc.*, 213 (1930).

(24) Maleimide and other similar five-membered compounds have been prepared under thermal conditions.[a-d] (a) H. T. Clarke and L. D. Behr, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 562; (b) A. Piutti, *Gazz. Chim. Ital.*, **12**, 169 (1882); (c) A. Piutti, *ibid.*, **26**, 435 (1896); (d) K. Harada, *J. Org. Chem.*, **24**, 1662 (1959). Maleic anhydride was prepared from fumaric acid by heating: J. Wislicenus, *Ann. Chem.*, **246**, 93 (1888).

(25) All temperature measurements were uncorrected. All optical rotation measurements were carried out by the use of the Rudolph Model 80 polarimeter with PEC-101 photometer. All elemental analyses were carried out by Micro-Tech Laboratories, Inc., Skokie, Ill. Infrared absorption spectra were recorded by the use of the Perkin-Elmer Model 137 B Infracord spectrophotometer.

SCHEME V
SCHEMATIC RELATIONSHIP OF REACTIONS a, b, AND c



(A) starting material of reaction a
(B) starting material of reaction b
(C) starting material of reaction c

Anal.[26] Calcd for $C_4H_7NO_4$: N, 10.52. Found: N, 10.64.

DNP-Aspartic acid from Synthesized Aspartic Acid.—A part of the hydrogenolyzed solution (containing about 150 mg of aspartic acid) was treated with 1-fluoro-2,4-dinitrobenzene, 0.50 g, and sodium hydrogen carbonate, 0.50 g, by the usual method.[27] DNP-aspartic acid was separated by celite column chromatography.[19] The celite, 45 g, was treated with 22.5 ml of pH 4.0 phosphate–citrate buffer (0.2 *M*). The charged DNP derivative was developed with a mixture of chloroform and ether (4:1). The DNP-aspartic acid band was cut off, dried, and dissolved in 1.5% sodium hydrogen carbonate. The solution was acidified and the DNP-aspartic acid was extracted with ethyl acetate. The ethyl acetate solution was evaporated and the optical rotation of the remaining DNP-aspartic acid measured: $[\alpha]^{25}D$ −14.1° (*c* 0.67, 1 *N* NaOH), mp 184–186° dec.

(*S*)-Aspartic acid was prepared from (*R*)-fumaramide, 2.0 g, (*R*)-amine, 1.5 g, and 25 ml of *n*-butanol as described above: yield, 500 mg (61%); $[\alpha]^{25}D$ +3.1° (*c* 4.65, 5 *N* HCl).

Anal. Found: N, 10.54.

DNP-(*S*)-aspartic acid had $[\alpha]^{25}D$ +14.0° (*c* 0.95, 1 *N* NaOH), mp 185–187° dec.

(±)-Aspartic acid was prepared from (±)-fumaramide, 1.5 g, (±)-amine, 1.5 g, and 1-butanol, 25 ml, yield 400 mg (65%).

(*R*)-(−)-Aspartic Acid from (*S*)-Fumaramide and Benzylamine.—A mixture of (*S*)-fumaramide, 2.0 g, and benzylamine, 6.0 g, was heated at 115–120° for 3 days in an oil bath. The reaction mixture was treated in a similar way as described earlier. A weight of 480 mg (58%) of aspartic acid was obtained: $[\alpha]^{25}D$ −2.0° (*c* 3.93, 5 *N* HCl).

Anal. Found: N, 10.80.

DNP-(*R*)-aspartic acid had $[\alpha]^{25}D$ −7.0° (1 *N* NaOH, *c* 1.04), mp 195–198° dec.

(*S*)-Aspartic acid was obtained from (*R*)-fumaramide, 2.0 g, and benzylamine, 6.0 g, as above: yield 500 mg (61%), $[\alpha]^{25}D$ +2.2° (5*N* HCl, c 3.80).

Anal. Found: N, 10.54.

DNP-(*S*)-aspartic acid had $[\alpha]^{25}D$ + 5.0° (*c* 1.09, 1 *N* NaOH), mp 196–197° dec.

Isolation of Intermediates in Reaction a.—A mixture of 2.0 g of (*S*)-fumaramide and 1.5 g of (*S*)-amine in 25 ml of 1-butanol was heated at 115–120° for 3 days. The reaction mixture was evaporated under reduced pressure to remove excess amine and butanol. The crystallized residue was fractionated into two components by the use of ethanol. One fraction, 0.55 g, melted at 298–301° and was slightly soluble in alcohol. The compound was confirmed as the unreacted (*S*)-fumaramide by a mixture melting point test and infrared absorption spectrum. The other fraction, 1.75 g, melted at 110–118°. The melting point rose to 119–121° by further recrystallization with alcohol. The compound was confirmed as *S*-(−)-N-(α-methylbenzyl) aspartic acid diamide (IIa, IIb) (intermediate I): $[\alpha]^{25}D$ −119.2° (*c* 0.79, absolute alcohol); infrared absorption bands, 1630 cm^{-1} (amide I), 1540 cm^{-1} (amide II).

Anal. Calcd for $C_{28}H_{33}N_3O_2$: C, 75.82; H, 7.50; N, 9.47. Found: C, 76.05; H, 7.52; N, 9.35.

Intermediate I, 0.89 g, was hydrolyzed with 16 ml of 6 *N* hydrochloric acid and then hydrogenolyzed by the use of palladium hydroxide on charcoal. The resulting aspartic acid showed a single spot when subjected to paper chromatography. The aspartic acid was converted to DNP-aspartic acid and this was isolated by celite column chromatography: DNP-(*R*)-aspartic acid, $[\alpha]^{25}D$ −7.0° (*c* 0.48, 1 *N* NaOH), mp 195–198° dec.

Reaction b. (*S*)-(+)-Aspartic acid from Ethyl Maleate and (*S*)-Amine.—A mixture of ethyl maleate, 1.72 g, and (*S*)-amine, 4.3 g, was heated at 115–120° for 3 days. The reaction mixture was hydrolyzed and hydrogenolyzed as described in reaction a. (*R*)-Aspartic acid, 1.14 g (86%), was obtained: $[\alpha]^{25}D$ +2.8° (*c* 4.0, 5 *N* HCl).

Anal. Calcd for $C_4H_7NO_4$: C, 36.10; H, 5.30; N, 10.52. Found: C, 36.02; H, 5.54; N, 10.34.

DNP-(*S*)-aspartic acid had $[\alpha]^{25}D$ +12.6° (*c* 0.78, 1 *N* NaOH), mp 186–188° dec.

(*R*)-Aspartic acid was prepared as above: yield 1.13 g (86%); $[\alpha]^{25}D$ −3.1° (*c* 4.1, 5 *N* HCl).

Anal. Found: N, 10.44.

DNP-(*R*)-aspartic acid had $[\alpha]^{25}D$ −14.2° (*c* 1.04, 1 *N* NaOH), mp 195–197° dec.

(±)-Aspartic acid was also prepared from ethyl maleate, 1.79 g, and (±)-amine, 4.3 g: yield, 1.15 g (87%).

Anal. Found: N, 10.38.

Isolation of Intermediates in Reaction b.—A mixture of ethyl maleate, 1.72 g, and (*S*)-amine, 4.30 g, was heated at 115–120° for 3 days. The reaction mixture was dissolved in 100 ml of ether. The solution was washed with water ten times (10-ml portions) to remove the unreacted amine. The ether solution was dried with anhydrous sodium sulfate and the solvent was evaporated to dryness *in vacuo*. The residue crystallized after drying for 3 days in an evacuated desiccator over sodium hydroxide and sulfuric acid. The crystals and the oil were separated by the use of unglazed pottery. The crude crystals, 0.29 g, were collected. These were recrystallized from ethanol and pure intermediate I was obtained: mp 121–123°; yield, 0.27 g; $[\alpha]^{25}D$ −112.1° (*c* 0.77, absolute ethanol); infrared absorption bands, 1630 (amide I), 1540 cm^{-1} (amide II).

Anal. Calcd for $C_{28}H_{33}N_3O_2$: C, 75.82; H, 7.50; N, 9.47. Found: C, 75.62; H, 7.73; N, 9.44.

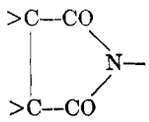
A part of the intermediate I was hydrolyzed and hydrogenolyzed as described above. The resulting aspartic acid showed a single spot when subjected to paper chromatography.

The crude oil absorbed in the unglazed pottery was extracted with petroleum ether (total 300 ml). The solvent was evaporated and 1.75 g of crude oil was obtained. Infrared absorption bands of the material showed at 1740 cm^{-1} in addition to the characteristic bands of N-substituted succinimide at 1780 and 1710 cm^{-1}. A part of the oil (300 mg) was dissolved in ether and washed with 5% aqueous sodium hydrogen carbonate and water. After the ether solution was dried with anhydrous sodium sulfate, dry hydrogen chloride gas was introduced to the

(26) Elemental analyses of isolated aspartic acid were carried out after one recrystallization of the first isolated aspartic acid.

(27) F. Sanger, *Biochem. J.*, **39**, 507 (1945). F. C. Green and L. M. Kay, *Anal. Chem.*, **24**, 726 (1952). K. R. Rao and H. A. Sober, *J. Am. Chem. Soc.*, **76**, 1328 (1954).

solution. The amine hydrochloride was precipitated. The crystals were collected and washed with ether. Intermediate II hydrochloride was obtained: yield, 88 mg; mp 223–224°; $[\alpha]^{25}D$ −47.5° (*c* 0.75, absolute ethanol). Infrared absorption bands at 1785 and 1710 cm^{-1} showed that the compound has a N-substituted succinimide structure, below. A band at 1745 cm^{-1} disappeared after the purification procedure.



Anal. Calcd for $C_{20}H_{23}N_2O_2Cl$: C, 66.93; H, 6.46; N, 7.81. Found: C, 66.71; H, 6.58; N, 7.79.

Intermediate II hydrochloride was liberated with aqueous sodium hydrogen carbonate. The free amine was extracted with ether. The solution was dried and the solvent was evaporated. Infrared absorption bands of the free intermediate II were recorded. The compound showed the same characteristic bands of N-substituted succiniimide at 1780 and 1710 cm^{-1}. Intermediate II did not crystallize.

The crude oil, 0.8 g, was hydrolyzed with 6 *N* hydrochloric acid, 15 ml, in the same way as above. The resulting aspartic acid was treated with 1-fluoro-2,4-dinitrobenzene. DNP-aspartic acid was separated by column chromatography. DNP-(*S*)-aspartic acid was obtained: $[\alpha]^{25}D$ +14.2° (*c* 0.18 1 *N* NaOH).

Reaction c. (*S*)-Aspartic acid from Diethyl fumarate and (*S*)-amine.—A mixture of ethyl fumarate, 1.72 g, and (*S*)-amine, 4.3 g, was heated at 115–120° for 3 days. The reaction mixture was hydrolyzed and then hydrogenolyzed in a similar way as described above. (*S*)-Aspartic acid, 1.15 g (87%), was obtained: $[\alpha]^{25}D$ +2.0° (*c* 3.90, 5 *N* HCl).

Anal. Found: C, 35.89; H, 5.47; N, 10.31.

DNP-(*S*)-aspartic acid had $[\alpha]^{25}D$ +4.3° (*c* 1.08, 1 *N* NaOH), mp 195–197° dec.

(*R*)-Aspartic acid was prepared as above from diethyl fumarate, 1.7 g, and (*R*)-amine, 4.3 g: yield, 1.11 g (85%); $[\alpha]^{25}D$ −1.6° (*c* 3.98, 5 *N* HCl).

DNP-(*R*)-aspartic acid had $[\alpha]^{25}D$ −4.2° (*c* 1.03, 1 *N* NaOH), mp 191–193° dec.

(±)-Aspartic acid was prepared by the use of (±)-amine under the same reaction conditions: yield, 1.13 g (86%).

Anal. Found: N, 10.28.

Isolation of Intermediates in Reaction c.—Isolation of intermediates in reaction c was carried out in a similar way as described in reaction b. The crude crystals, 0.92 g, were obtained. The crystals were recrystallized from ethanol. Pure intermediate I, 0.70 g, was obtained: mp 121–123°; $[\alpha]^{25}D$ −112.0° (*c* 0.87, absolute ethanol); infrared absorption bands, 1645 (amide I), 1555 cm^{-1} (amide II).

Anal. Found: C, 75.65; H, 7.59; N, 9.45.

A part of the crude intermediate II was hydrolyzed and then hydrogenolyzed in a similar way as described above. The resulting aspartic acid was dinitrophenylated and the DNP-aspartic acid was separated by column chromatography. The sample amounts were too small to accurately measure optical rotation.

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Application of the Hammett Equation to Substituent Effects on π Donors in Charge-Transfer Complex Formation. I. Singly Substituted Donors

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The effect of substituents in π donors on charge-transfer complex formation equilibrium was studied by correlation of the equilibrium constants with the extended form of the Hammett equation. Twelve sets of substituted benzene donors (two of which have constant substituents on the ring), four sets of substituted naphthalene donors, and one set of 1-substituted propene donors were studied. The results of the correlations are generally very good. The composition of the electrical effect appears to depend on donor type but seems to be independent of the acceptor with the exception of silver(I) ion complexes. For the benzene sets the average value of ε is about 1.3 [excluding the silver(I) ion complexes for which ε is 0.37]. The magnitude of the electrical effect is a function of acceptor strength. Electrical effects on complex formation are much smaller than on such reactions as electrophilic aromatic substitution and deuterium exchange in liquid ammonia. Steric effects are observed in some complexes.

We have for some time been interested in the application of the Hammett equation[1] to the effect of sub-

$$Q_X = \rho\sigma_X + Q_H \quad (1)$$

stituents in nonaromatic unsaturated systems.[2] It seemed of interest to extend these studies to substituent effects on charge-transfer complex formation[3] between substituted olefin donors and various acceptors. For comparison, we need to know the nature of substituent effects in complex formation by substituted aromatic donors. Although sporadic attempts have been made to correlate equilibrium constants for charge-transfer complex formation with the Hammett equation,[4] no comprehensive study of the available data is extant. We have, therefore, correlated equilibrium constants taken from the literature with the extended form of the Hammett equation by means of

$$Q_X = \alpha\sigma_I + \beta\sigma_R + Q_H \quad (2)$$

(1) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953); R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons Inc., New York, N. Y., 1956, p 565; V. A. Palm, *Russ. Chem. Rev.*, **31**, 471 (1961); R. R. Wells, *Chem. Rev.*, **63**, 171 (1963); C. D. Ritchie and W. F. Sager, Jr., *Progr. Phys. Org. Chem.*, **2**, 323 (1963).

(2) M. Charton, *J. Am. Chem. Soc.*, **80**, 5940 (1958); *J. Org. Chem.*, **26**, 735 (1961); *ibid.*, **30**, 552, 557, 969, 974 (1965).

(3) L. J. Andrews and R. M. Keefer, "Molecular Complexes in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964.

(4) Of the previous applications of the Hammett equation to charge-transfer complex equilibria, only that of L. J. Andrews and R. M. Keefer [*J. Am. Chem. Soc.*, **72**, 3113 (1950)] is concerned with the type of system discussed in this paper, monosubstituted benzenes in which the benzene ring itself is a π donor. Papers have recently appeared in which equilibrium constants for substituted benzenes bearing an *n*- or π-donor reaction site external to the benzene ring were correlated with the Hammett equation: J. vander Veen and W. Stevens, *Rec. Trav. Chim.*, **82**, 287 (1963); T. Fueno, T. Okuyama, T. Deguchi, and J. Furukawa, *J. Am. Chem. Soc.*, **87**, 170 (1965). M. Tamres [*J. Phys. Chem.*, **68**, 2621 (1964)] has reported the correlation of multiply substituted benzene formation constants with the σ* constants.