Anal. Calcd for $C_{18}H_{12}N_2$: C, 84.35; H, 4.72; N, 10.93. Found: C, 83.96; H, 4.66; N, 10.66.

Photocyclization of Methyl 2-(1-Naphthyl)-3-(4-pyridyl)-acrylate.—A solution of methyl 2-(1-naphthyl)-3-(4-pyridyl)-acrylate (1.0 g, 3.46 mmol) in methanol (400 ml) was irradiated with a 100-W mercury vapor lamp through a Pyrex well for 18 hr. Air was bubbled slowly through, and the solution was stirred during the irradiation. The solvent was evaporated and the residual oil was dissolved in benzene (20 ml) and poured onto a 1.5 × 10 cm column of basic alumina. The column was washed with benzene (~100 ml) until a yellow band approached the end of the column, then eluted with chloroform (~200 ml) until no more yellow product was obtained. Evaporation of the chloroform left 0.75 g of yellow oil (7 and **8**, two spots on tlc with ethyl acetate), which was dissolved in a large volume of hot hexane. On long cooling, 0.13 g (13%) of yellow crystals of **8** formed, mp 97–100°. Recrystallization from hexane gave yellow needles: mp 110–113°; ir 5.82, 6.24, 6.99, 8.09, 8.25, 8.82, 9.42, 11.76, 12.10, and 12.98 μ; nmr ($CDCl_3$) δ 3.82 (s, 3), 7.25–8.40 (m, 8), and 8.85 (d, 2); mass spectrum *m/e* 287, 256, 227, 200, and 100; uv λ_{max} 316 nm (ϵ 7350) and 343 (9950).

Anal. Calcd for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.33; H, 4.59; N, 5.07.

Different runs gave approximately the same mixture of **7** and **8**. However, the relative amount of **8** appeared to slowly increase in solutions left exposed to air.

The photocyclizations with other solvents were run under the same experimental conditions.

2-(4-Pyridyl)acenaphthene-1-carbonylhydrazide (10a).—A chromatographed mixture of **7** and **8** (0.75 g), ethanol (20 ml), and 95% hydrazine (1.5 ml) was heated on a steam bath for 2 hr. The solution was evaporated to dryness, treated with benzene (20 ml), and again evaporated to dryness. The residual yellow oil was crystallized twice from methylene chloride–carbon tetrachloride to afford 0.21 g (28%) of **10a** as a sticky yellow powder: mp 135–138°; nmr ($CDCl_3$) δ 3.80 (s, 2), 4.32 (d, 1, J = 4 Hz), 5.25 (d, 1, J = 4 Hz), 7.00–8.00 (m, 9), and 8.47 (d, 2, J = 6 Hz); mass spectrum *m/e* 289, 230, 152, 121, 119, 117. Satisfactory elemental analyses were not obtained.

Acetone 1-(4-Pyridyl)acenaphthene-2-carbonylhydrazone (10b).—A sample of crude hydrazide **10a** (prepared from 0.5 g of ester **5b**) was crystallized from acetone–hexane to give a light yellow powder, mp 235–238°. Recrystallization from acetone–ethanol gave 0.15 g (26%) of white solid: mp 242–245°; nmr (TFA) δ 2.10 (s, 3), 2.25 (s, 3), 4.35 (m, 1), 5.15 (m, 1), and 6.65–8.35 (m, 10).

Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.35; H, 6.02; N, 12.70.

2-(4-Pyridyl)acenaphthylene-1-carboxylic Acid (9).—A crude chromatographed mixture of **7** and **8** (0.75 g) was suspended in 10% sodium hydroxide (20 ml), and potassium permanganate (1.0 g) was added. The mixture was heated on a steam bath for 2.5 hr, with occasional swirling, and then cooled and filtered. The solids were washed with water (20 ml). The combined filtrates were acidified with acetic acid and cooled to give 0.56 g (59% from **5b**) of bright yellow solid. Recrystallization from methanol–water gave an analytical sample: mp >300° dec; nmr (DMSO-d_6) δ 7.55–8.45 (m, 8) and 8.65–8.90 (m, 2).

Anal. Calcd for $C_{18}H_{11}NO_2$: C, 79.11; H, 4.06; N, 5.13. Found: C, 78.89; H, 4.06; N, 5.36.

Reesterification of **9** with methanol and HCl afforded **8**, identical with **8** obtained by photocyclization above on comparison of melting point, mixture melting point (no depression), ir, and tlc.

1-(4-Pyridyl)acenaphthylene (11) Picrate.—A finely powdered mixture of 1-(4-pyridyl)acenaphthylene-2-carboxylic acid (0.2 g, 0.7 mmol) in a small sublimation apparatus (no vacuum) was placed in an oil bath preheated to 260°. After 20 min, the mixture was cooled and the entire apparatus was washed out with benzene (50 ml). The benzene was filtered and evaporated to leave a yellow oil. The oil was dissolved in ethanol (20 ml), and a saturated picric acid solution in ethanol (20 ml) was added. The suspension was heated to boiling on a steam bath and cooled. The yellow solid was collected. Recrystallization from ethanol gave tiny yellow needles (0.04 g, 12%): mp 266–268° dec[16] (lit.[11] mp 264–265°); nmr (DMSO-d_6) δ 6.80–9.10 (m).

Anal. Calcd for $C_{23}H_{14}N_4O_7$: C, 60.26; H, 3.08; N, 12.22. Found: C, 60.45; H, 3.43; N, 12.03.

Acknowledgments.—We thank Mr. R. B. Bicknell and his staff for the large-scale preparations of intermediates, as well as those already named in the Experimental Section.

Registry No.—**5a**, 42245-94-3; **5b**, 42245-95-4; **5c**, 42245-96-5; **7**, 42245-97-6; **8**, 42245-98-7; **9**, 42245-99-8; **10a**, 42246-00-4; **10b**, 42246-01-5; **11** picrate, 42246-02-6; 1-naphthylacetic acid, 86-87-3; pyridine-4-carboxaldehyde, 872-85-5; 1-naphthylacetonitrile, 132-75-2.

(16) Corrected melting point.

Optical Resolution of DL-Amino Acids by Preferential Crystallization Procedure

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To make preferential crystallization procedure more generally applicable for optical resolution of racemic amino acids, the resolution was carried out in the form of aromatic sulfonates of amino acids. Aromatic sulfonic acids were chosen because they vary greatly in properties and easily form salts with any kind of amino acids. Moreover it seemed very likely that some of these salts would form racemic mixtures suitable for preferential crystallization procedure. As a result of extensive studies, a method was developed for the resolution of amino acids in high yields such as DL-alanine, DL-leucine, DL-lysine, DL-serine, DL-3,4-dihydroxyphenylalanine, DL-tryptophan, and DL-3-(3,4-methylenedioxyphenyl)-2-methylalanine through the use of different aromatic sulfonic acids. These results indicate that the present method can be applied more generally for resolution of amino acids.

Although a number of methods for optical resolution of DL-amino acids have been reported, most of them have employed chemical or enzymatic procedures and only a few reports on preferential crystallization procedure have appeared.[1] If successfully applied, preferential crystallization procedure is a very advantageous method for the production of optically active amino acids, since the procedure can be easily accomplished by providing seed crystals of one antipode in a supersaturated solution of the racemic modification.[2] However, in nearly a century since the first example of this type of resolution was reported, satisfactory application of this simple procedure has been restricted to several amino acids such as asparagine,[3] histidine,[4]

(1) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 1, Wiley, New York, N. Y., 1961, pp 715–716.

(2) R. M. Secor, *Chem. Rev.*, **63**, 297 (1963).

(3) A. Piutti, *C. R. Acad. Sci.*, **103**, 134 (1886).

(4) R. Duschinsky, *Chem. Ind. (London)*, **53**, 10 (1934); "Festschrift Emil Barell," Friedrich Reinhardt A. G., Basel, 1936, p 375.

threonine,[5] glutamic acids,[6,7] and aspartic acid.[8,9] The reason for this limited applicability is that most amino acids form racemic compounds instead of racemic mixtures and have no properties suitable for this resolution procedure. Although it was suggested[10] that resolution is possible when the solubility of each of the pure optical isomers is less than that of the racemic modification, resolution by preferential crystallization is more easily accomplished when the racemic modification forms a racemic mixture. Therefore, if it becomes possible to find out the conditions under which respective amino acid crystallizes as a racemic mixture, this convenient method is expected to be applied for all synthetic amino acids as a general method. To realize this expectation, the optical resolution of amino acids was carried out in the form of their aromatic sulfonates. Aromatic sulfonic acids were chosen because they vary greatly in properties and easily form salts with any kinds of amino acids, so that it is very likely that some of their salts will form racemic mixtures and can be resolved by preferential crystallization procedure. Previously, it was found that DL-lysine, as an example of basic amino acids, was resolved in the form of the salt with *p*-aminobenzenesulfonic acid.[11] Subsequently, under this idea, optical resolution of other amino acids was investigated, and it became possible to resolve many amino acids, for example, DL-alanine and DL-leucine as typical aliphatic amino acids, DL-serine as a hydroxy amino acid, DL-3,4-dihydroxyphenylalanine as an aromatic amino acid, DL-tryptophan as a heterocyclic amino acid, and DL-3-(3,4-methylenedioxyphenyl)-2-methylalanine as an α-alkyl amino acid. The optically active forms of these amino acids are important in nutritional and pharmaceutical fields. Especially, L-3,4-dihydroxyphenylalanine (L-DOPA) has been in large commercial demand as a specific drug for treatment of Parkinson's disease and L-3-(3,4-methylenedioxyphenyl)-2-methylalanine (L-MDPMA) is useful for an intermediate of the antihypertensive drug, L-3,4-dihydroxyphenyl-2-methylalanine (L-α-methyl DOPA).

Generally it is well recognized that the solid state infrared spectra of respective optical isomers are identical but different from that of the corresponding racemic compound.[12] However, in the case where racemic amino acids exist as a racemic mixture, the infrared spectrum of a racemic modification should be identical with that of the respective optical isomers. Thus the above amino acids were converted to the wide variety of the salts with aromatic sulfonic acids and the spectra of their optically active salts were compared with those of the respective racemic modifications. This method was very useful for screening the salts which form racemic mixtures. As a result, the spectra of DL-alanine *p*-chlorobenzenesulfonate (DL-Ala-*p*-ClBS), DL-leucine benzenesulfonate (DL-Leu-BS), DL-serine *m*-xylene-4-sulfonate (DL-Ser-*m*-XS), DL-3,4-dihydroxyphenylalanine 2-naphthol-6-sulfonate (DL-DOPA-NS·$^3/_2H_2O$), DL-tryptophan benzenesulfonate (DL-Trp-BS), and DL-3-(3,4-methylenedioxyphenyl)-2-methylalanine *p*-phenolsulfonate (DL-MDPMA-*p*-PS·H_2O), were found to be exactly identical with those of the corresponding optical isomers. The result suggests that these racemic modifications exist as racemic mixtures. This was also supported by the melting point–composition diagram. In each case, the melting point of the racemic modification was identical with that of the mechanical mixture of equal amount of the two antipodes, and admixture of one of the pure isomers to the racemic modification increased the melting point. Also, the solubility of the racemic modifications was much higher than that of the corresponding isomers. The saturated solution of the racemic modifications no longer dissolved the optically active isomers. Thus, DL-Ala-*p*-ClBS, DL-Leu-BS, DL-Ser-*m*-XS, DL-DOPA-NS·$^3/_2H_2O$, DL-Trp-BS, and DL-MDPMA-*p*-PS·H_2O could be easily screened as the simple salts forming the racemic mixtures.

The resolutions of these salts were accomplished in the usual manner. Seeding a supersaturated solution of each racemic modification with the crystals of the desired isomer (for example, L isomer) brought about preferential crystallization of the L isomer, while the nonseeded D isomer remained in the mother liquor as supersaturation. The resolutions were also carried out without seeding by spontaneous crystallization of an excess isomer (L isomer) from a supersaturated solution containing an excess of one isomer (L isomer). This procedure of using an excess of one isomer in the initial solution was equivalent, in principle, to adding seed crystals because the L isomer present in higher concentration began to crystallize initially and it played a role of seed crystals. However, the most favorable resolution procedure in a practical purpose was that described in the Experimental Section. This was started with a supersaturated solution containing an excess of one isomer (L isomer). Furthermore, the solution was nucleated with the isomer (L isomer) present in excess. In this case, preferential crystallization of L isomer occurred more rapidly and smoothly without crystallization of D isomer. The presence in the initial solution of an excess of the isomer being crystallized seemed to be important for the successful functioning of the resolution procedure. It was also desirable that the amount of an excess isomer (L isomer) dissolved initially in a supersaturated solution of racemic modification was adjusted to almost the same amount of L isomer resolved in a single cycle, and that the amount of crystallization was controlled to about twofold of the excess of L isomer employed initially. In that case, almost the same conditions as the first, except that the solution contained D isomer in excess, could be obtained by adding the same amount of the racemic modification as that of the L isomer previously separated into the mother liquor. Then D isomer was separated in the same way. Thus, the entire cycle could be repeated and both L and D isomers were obtained reciprocally. However, the amount of a desired isomer resolved in a single cycle should be limited in order to avoid crystallization of the antipode. As shown in Table IV, optimal conditions for resolution were dependent on the properties of the individual racemic modification. The iso-

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(6) F. Kögl, H. Erxleben, and G. J. van Veersen, *Z. Physiol. Chem.*, **277**, 260 (1943).
(7) T. Akashi, *Nippon Kagaku Zasshi*, **83**, 417 (1962).
(8) T. Haga, M. Sato, and K. Miura, Japanese Patent 42-3290 (1967).
(9) K. Harada, *Bull. Chem. Soc. Jap.*, **38**, 1552 (1965).
(10) A. Werner, *Ber.*, **47**, 2171 (1914).
(11) S. Yamada, M. Yamamoto, and I. Chibata, *J. Agr. Food Chem.*, **21**, 889 (1973).
(12) R. J. Koegel, R. A. McCallum, J. P. Greenstein, M. Winitz, and S. M. Birnbaum, *Ann. N. Y. Acad. Sci.*, **69**, 94 (1957).

mers obtained by this procedure were almost optically pure. If the optical purity is not satisfactory and further purification is required, the crude products can be easily purified by recrystallization without loss of the optically active isomer. The optically active enantiomorph no longer dissolves in the saturated solution of the racemic modification. Therefore, this purification can be performed by dissolving the mixture in a minimum amount of water required to dissolve the racemic modification in the crude crystals, and allowing the pure crystals to crystallize out. However, the operation is not so easy because the amount of water required to dissolve the racemic impurity is very small. So it was convenient to carry out the above operation by adding an appropriate amount of the solution saturated with the racemic modification. Thus, obtained optically pure sulfonates were easily converted to optically pure amino acids by neutralization with alkali or by use of ion exchange resin.

In the present work we cannot establish a theory to predict what kind of racemic modification forms a racemic mixture suitable for the resolution by preferential crystallization. By the use of aromatic sulfonates, however, it becomes easy to find out the simple salts which form racemic mixtures and can be resolved by the preferential crystallization procedure. Consequently, it is very likely that the present simple method using aromatic sulfonates may be applied more generally for resolution of synthetic amino acids.

Experimental Section

Materials.—Analytical standard grade amino acids manufactured by our company, Tanabe Seiyaku Co., Ltd., were used, except MDPMA.[13] All aromatic sulfonic acids were obtained from Tokyo Kasei Kogyo Co., Ltd., and E. Merck AG. These were used without further purification.

Analyses.—All samples for analyses were dried overnight *in vacuo* at 45–50° unless otherwise noted. Melting points were measured with a Yamato MP-21 melting point apparatus in an unsealed capillary tube and were uncorrected. Infrared spectra of samples were determined in KBr disks using a Shimazu infrared spectrophotometer, Model IR-27G. Optical rotations were measured with a Perkin-Elmer 141 automatic polarimeter. Elemental analyses were performed by a Perkin-Elmer 240 elemental analyzer. Solubility was determined by approaching saturation equilibrium from both sides of undersaturation and supersaturation. Concentration of solutes was measured by a Karl Zeiss immersion refractometer.

Preparation of Aromatic Sulfonates of Amino Acids.—DL-Alanine *p*-chlorobenzenesulfonate (DL-Ala-*p*-ClBS), DL-3,4-dihydroxyphenylalanine 2-naphthol-6-sulfonate (DL-DOPA-NS·$^3/_2H_2O$), DL-leucine benzenesulfonate (DL-Leu-BS), DL-lysine *p*-aminobenzenesulfonate (DL-Lys-*p*-ABS), DL-3-(3,4-methylenedioxyphenyl)-2-methylalanine *p*-phenolsulfonate (DL-MDPMA-*p*-PS·H_2O), DL-serine *m*-xylenesulfonate (DL-Ser-*m*-XS), and DL-tryptophan benzenesulfonate (DL-Trp-BS) were easily prepared from amino acids and the corresponding aromatic sulfonic acids.

A mixture of 1 mol of amino acids and 1.03 mol of aromatic sulfonic acids was dissolved in water by heating, treated with charcoal, concentrated *in vacuo*, and cooled in a refrigerator. The resulting precipitates and further crops obtained by successive concentrations of the combined filtrate were collected, washed with cold water, and dried *in vacuo* at 45°. The products were almost pure and could be used for optical resolution without further purification. The optically active isomers were prepared in the same way. The total yields based on the amino acids were from 95 to 98%. The elemental analyses are summarized in Table I.

TABLE I

AROMATIC SULFONATES OF AMINO ACIDS

Aromatic sulfonate of amino acids (elemental composition)		Elemental analysis, % Calcd	Found DL	Found L
	C	38.37	38.48	38.23
Ala-*p*-ClBS	H	4.29	4.40	4.42
($C_9H_{12}ClNO_5S$)	N	4.97	4.87	4.80
	S	11.38	11.52	11.20
	C	50.89	50.83	50.95
DOPA-NS·$^3/_2H_2O$	H	4.97	4.70	4.97
($C_{19}H_{19}NO_8S·^3/_2H_2O$)	N	3.12	3.03	3.13
	S	7.15	7.27	7.29
	C	49.81	50.04	50.06
Leu-BS	H	6.62	6.65	6.64
($C_{12}H_{19}NO_5S$)	N	4.84	4.97	4.82
	S	11.08	10.93	11.20
	C	45.12	45.20	45.00
Lys-*p*-ABS	H	6.63	6.73	6.74
($C_{12}H_{21}N_3O_5S$)	N	13.16	13.09	13.14
	S	10.04	10.01	10.06
	C	49.15	49.27	49.27
MDPMA-*p*-PS·H_2O[a]	H	5.10	5.21	5.10
($C_{17}H_{19}NO_8S·H_2O$)	N	3.37	3.32	3.32
	S	7.72	7.70	7.66
	C	45.35	45.38	45.43
Ser-*m*-XS	H	5.88	5.91	5.92
($C_{11}H_{17}NO_6S$)	N	4.81	4.70	4.76
	S	11.01	11.06	10.93
	C	40.36	40.25	40.55
Ser-*m*-XS·$2H_2O$[b]	H	6.47	6.32	6.47
($C_{11}H_{17}NO_6S·2H_2O$)	N	4.28	4.33	4.23
	S	9.80	9.78	9.75
	C	56.34	56.63	56.53
Trp-BS	H	5.01	5.04	5.07
($C_{17}H_{18}N_2O_5S$)	N	7.73	7.88	7.80
	S	8.85	8.57	8.82

[a] Recrystallized from 0.25 mol of an aqueous solution of *p*-phenolsulfonic acid. [b] Dried in air at room temperature.

The samples for elemental analysis were recrystallized from water except for MDPMA-*p*-PS·H_2O. Recrystallization of DL-MDPMA-*p*-PS·H_2O from water gave DL-MDPMA-$^1/_2$*p*-PS (hemisulfonate) as colorless prisms, mp 237–238° dec. *Anal.* Calcd for $C_{11}H_{13}O_4N·^1/_2(C_6H_6O_4S)$: C, 54.19; H, 5.20; N, 4.51; S, 5.17. Found: C, 53.99; H, 5.28; N, 4.45; S, 4.96. On the other hand, recrystallization from 0.25 mol of an aqueous solution of *p*-phenolsulfonic acid gave a monosulfonate as needles. It was stable as a hydrate and melted at 110–120, 184–186, and 192–193° with decomposition. For the optically active MDPMA-*p*-PS·H_2O, the hemisulfonates were not obtained. The optically active and racemic Ser-*m*-XS·$2H_2O$ crystallized from water as dihydrate. Elemental analyses of the samples dried in air at room temperature corresponded to $C_{11}H_{17}NO_6S·2H_2O$. Drying the samples *in vacuo* over P_2O_5 or at elevated temperatures yielded their anhydrates.

The properties of the aromatic sulfonates of amino acids thus obtained are shown in Table II.

Optical Resolution.—A typical experiment for the resolution was carried out as follows. DL-Ser-*m*-XS (94.00 g) and L-Ser-*m*-XS (6.00 g) were dissolved in 100 ml of water at elevated temperature. The mixture was cooled to 25°, seeded with L-Ser-*m*-XS·$2H_2O$ (0.10 g), and stirred for 50 min at the same temperature. The precipitated crystals were collected by filtration, washed with small amount of cold water, and dried. The crystals thus obtained were optically pure, yield 12.66 g, $[\alpha]^{25}D$ +4.1° (*c* 4, H_2O), mp 172–173°. *Anal.* Found: C, 45.37; H, 5.87; N, 4.85; S, 11.14. After the separation of the L isomer, DL-Ser-*m*-XS (13.88 g) and a small amount of water were added to the mother liquor. The amounts of the addition were adjusted by refractometric measurement and weighing

(13) DL-MDPMA was prepared from 3,4-methylenedioxyphenylacetone according to the method of G. A. Stein, H. A. Bronner, and K. Pfister, III, *J. Amer. Chem. Soc.*, **77**, 700 (1955). Optically pure L- and D-MDPMA were prepared by the optical resolution of the *N*-acetyl menthyl ester according to the method of S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.*, **18**, 1399 (1965).

TABLE II

PROPERTIES OF AROMATIC SULFONATES OF AMINO ACIDS

Aromatic sulfonate of amino acids	Isomer	Mp, °C	$[\alpha]^{25}D$, deg (c 2, water)	$[\alpha]^{25}_{365}$, deg (c 2, water)	Solubility in water, g/100 ml (°C)		
Ala-*p*-ClBS	DL	190–192			50.2 (15)	86.3 (30)	139.2 (45)
	L	222–223	+3.6	+15.4	24.2 (15)	37.2 (30)	67.5 (45)
DOPA-NS·$^3/_2H_2O$	DL	152–154			1.6 (10)	3.3 (30)	9.0 (50)
	L	162–164	−8.6	−19.7	1.1 (10)	2.0 (30)	5.3 (50)
Leu-BS	DL	152–154			39.4 (15)	58.0 (25)	
	L	172–173	+3.2	+18.6	17.0 (15)	22.9 (25)	
Lys-*p*-ABS	DL	238–239			54.0 (15)	66.1 (25)	90.6 (45)
	L	250–251	+6.2	+23.0	33.8 (15)	42.7 (25)	63.1 (45)
MDPMA-*p*-PS·H_2O[c]	DL	192–193			10.8 (10)	18.6 (25)	76.3 (45)
	L	212–213	+0.8[a]	+14.0[a]	5.0 (10)	8.3 (25)	25.0 (45)
Ser-*m*-XS	DL	157–158			45.1 (15)	80.9 (25)	175.4 (40)
	L	172–173	+4.1[b]	+19.6[b]	23.5 (15)	39.5 (25)	86.8 (40)
Trp-BS	DL	210–211			5.7 (15)	10.7 (35)	20.9 (50)
	L	234–235	−2.9	+16.8	3.5 (15)	5.6 (35)	8.9 (50)

[a] 1% in 1 *N* HCl. [b] 4%. [c] Solubility was determined in 0.25 mol of *p*-phenolsulfonic acid aqueous solution.

TABLE III

SUCCESSIVE RESOLUTION OF DL-Ser-*m*-XS[a]

Expt	Amount of addition: DL form, g	Amount of addition: Active form, g	Composition of solution: DL form, g	Composition of solution: Active form, g	Crystals separated: Yield, g	Crystals separated: Optical purity, %
1 (L)	94.00	6.00	94.00	6.00	12.66	100
2 (D)	13.88		93.84[b]	6.16[b]	12.52	98
3 (L)	13.08		94.02[b]	5.98[b]	11.34	100
4 (D)	13.34		94.74[b]	5.26[b]	13.24	98
5 (L)	14.24		92.36[b]	7.64[b]	12.20	97
6 (D)	12.20		95.92[b]	4.08[b]	12.42	98
7 (L)	14.40		92.04[b]	7.96[b]	13.10	97
8 (D)	14.84		95.36[b]	4.64[b]	13.54	97
9 (L)	15.32		91.62[b]	8.38[b]	12.56	98
10 (D)	14.42		96.14[b]	3.86[b]	12.18	96
Mean	13.97		94.00	6.00	12.58	98

[a] Resolution was carried out on a 100-ml scale. Crystallization time was 50 min in every case. [b] Values calculated theoretically from analysis of separated crystals.

TABLE IV

OPTICAL RESOLUTION OF AROMATIC SULFONATES OF AMINO ACIDS[a]

Aromatic sulfonate of amino acids	Resoln no.	Registry no.	Amount of addition: DL form, g	Amount of addition: Registry no.	Amount of addition: Active form, g	Composition of solution: DL form, g	Composition of solution: Active form, g	Crystn: Temp, °C	Crystn: Time, min	Separated crystals: Yield, g	Separated crystals: Optical purity, %
Ala-*p*-ClBS	1 (L)	36760-85-7	97.00	42334-78-1	5.00	97.00	5.00	30	40	10.56	98
	2 (D)	36760-86-8	11.00			96.71[b]	5.29[b]	30	40	10.34	98
DOPA-NS·$^3/_2H_2O$	1 (L)	42334-82-7	16.00	42334-81-6	3.00	16.00	3.00	50	25	6.44	100
	2 (D)	42334-83-8	6.50			15.66[b]	3.34[b]	50	25	6.52	100
Leu-BS	1 (L)	42398-40-3	66.50	42398-39-0	1.00	66.50	1.00	25	50	2.23	93
	2 (D)	42398-41-4	2.32			66.53[b]	0.97[b]	25	50	2.12	93
Lys-*p*-ABS	1 (L)	27168-73-6	77.00	42719-79-9	5.00	77.00	5.00	25	65	11.04	98
	2 (D)	42398-44-7	11.54			76.26[b]	5.74[b]	25	65	11.72	98
MDPMA-*p*-PS·H_2O[c]	1 (L)	42334-84-9	50.00	42398-45-8	7.50	50.00	7.50	25	120	17.83	95
	2 (D)	42398-46-9	18.40			48.36[b]	9.14[b]	25	120	17.92	97
Ser-*m*-XS[d]	1 (L)	27168-77-0	94.00	27168-75-8	6.00	94.00	6.00	25	50	12.66	100
	2 (D)	27168-76-9	13.88			93.84[b]	6.16[b]	25	50	12.52	98
Try-BS	1 (L)	42719-78-8	16.00	42719-79-9	1.20	16.00	1.20	35	50	2.84	92
	2 (D)	42746-61-2	2.93			15.88[b]	1.32[b]	35	50	2.78	92

[a] Resolution was carried out on a 100-ml scale by use of 0.10 g of seed crystals. [b] Values calculated theoretically from analysis of separated crystals. [c] Resolution was carried out in 0.25 mol of *p*-phenolsulfonic acid aqueous solution. [d] Dihydrates of this compound were used as seed crystals.

according to a standard curve previously constructed. Thus, almost the same composition as in the previous resolution was obtained, except that the predominant enantiomorph was D isomer. This supersaturated solution was seeded with D-Ser-*m*-XS·$2H_2O$ (0.10 g) at 25° and stirred for 50 min. Drying the precipitated crystals yielded D-Ser-*m*-XS (12.52 g) which had 98% optical purity. By repeating these procedures, L and D isomers were successively obtained as shown in Table III.

Other sulfonates of amino acids could also be resolved in the same manner as described above. Conditions for the resolution and the analyses for separated crystals are summarized in Table IV.

Optical Purification of Optically Impure Isomers.—The isomers obtained by the above procedure were practically pure. If the optical purification is, however, required, it can be performed as follows. Crude L-Ser-*m*-XS (10.00 g, optical purity 87.7%) was mixed with 1.5 ml of water and an appropriate amount (30 ml) of the solution saturated with DL-Ser-*m*-XS at 25° and dissolved at elevated temperature. The mixture was then stirred for 2 hr at 25°. The resulting crystals were collected

TABLE V
OPTICALLY ACTIVE AMINO ACIDS PREPARED FROM THEIR AROMATIC SULFONATES

Amino acid	Registry no. D	Registry no. L	Method	Yield, %	N analysis, % Calcd	N analysis, % Found L	N analysis, % Found D	$[\alpha]^{25}D$, deg (c 2, 5 N HCl) L	$[\alpha]^{25}D$, deg (c 2, 5 N HCl) D
Alanine	338-69-2	56-41-7	Ion exchange	96	15.72	15.72	15.73	+14.6	−14.6
DOPA	5796-17-8	59-92-7	LiOH	96	7.10	7.08	7.11	−12.2[a]	+12.3[a]
Leucine	328-38-1	61-90-5	Ion exchange	95	10.68	10.63	10.64	+15.9	−16.0
Lysine HCl	42334-88-3	10098-89-2	Ion exchange	96	15.34	15.41	15.45	+20.8	−20.8
MDPMA	42334-90-7	42334-89-4	NH_4OH	96	6.28	6.27	6.27	+25.4[b]	−25.4[b]
Serine	312-84-5	56-45-1	Ion exchange	98	13.33	13.37	13.35	+15.0[c]	−15.1[c]
Tryptophan	153-94-6	73-22-3	NH_4OH	95	13.72	13.74	13.73	−32.4[d]	+32.5[d]

[a] 4%, in 1 N HCl, at 20°. [b] $[\alpha]^{25}_{365}$, 1% in 1 N HCl. [c] In 1 N HCl. [d] 1% in H_2O.

by filtration, washed with a small amount of cold water, and dried. By this operation, optically pure crystals of L-Ser-*m*-XS were obtained, yield 8.62 g, $[\alpha]^{25}D$ +4.1° (*c* 4, H_2O).

Preparation of Optically Active Amino Acids.—From optically pure aromatic sulfonates of amino acids, the free amino acids were easily obtained either by neutralization with alkali or by use of an ion exchange resin. In the former, an aqueous solution of aromatic sulfonates was adjusted with alkali to the isoelectric point of the amino acids and cooled in a refrigerator overnight. The crystallized free amino acids were filtered off, washed with cold water, and dried. This method was convenient for sparingly soluble amino acids. For readily soluble amino acids, the latter method was employed. Aromatic sulfonates were taken up in a tenfold amount of water. The solution was passed through an ion exchange column of Amberlite IR-120 (in H form). The column was washed with water and the amino acid was eluted with 2 *N* NH_4OH. The eluate was concentrated, treated with charcoal, and concentrated again until the crystalline precipitate appeared. To the residue MeOH was added and the mixture was allowed to stand in a refrigerator overnight to give the colorless amino acid.

Table V indicates the yields and the specific rotations of optically active amino acids obtained by this process.

For the preparation of L-α-methyl DOPA, the L-MDPMA (50.0 g) obtained above was hydrolyzed with 20% hydrochloric acid (930 ml) and phenol (47 g) for 17 hr. After evaporation, the residue was dissolved in 120 ml of water and adjusted to pH 5.8 with 5 *N* NH_4OH containing a small amount of sodium bisulfite. The precipitate was collected, and further crops were obtained by successive concentrations of the filtrate. The total yield of L-α-methyl DOPA·$^3/_2H_2O$ was 43.6 g (81.6%). Recrystallization from sulfurous acid solution (0.5%) gave a white powder of L-α-methyl DOPA·$^3/_2H_2O$, and drying of the sesquihydrate *in vacuo* at 100° gave the anhydrous form, mp 306–307° dec, $[\alpha]^{25}D$ −5.2°, $[\alpha]^{25}_{578}$ −5.5° (*c* 2, 0.1 *N* HCl). *Anal.* Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.63; H, 6.24; N, 6.59.

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Registry No.—DL-MDPMA·$^1/_2$ *p*-PS, 42398-50-5; L-α-methyl DOPA, 555-30-6.

Total Synthesis of *dl*-Prostaglandin E_1

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dl-Prostaglandin E_1 (PGE_1) (**61**) has been synthesized in 14 steps from 2-carboxy-5-oxo-1-cyclopentenehe ptanoic acid (**15**). The synthesis required the development of two mild procedures and a new protecting group. A Moffatt oxidation using a water-soluble carbodiimide converted the carbinol **52** to aldehyde **53**. The Wittig reaction of aldehyde **53** with the tributylphosphorane **36** was used to obtain the enone **54**. Protection of the cyclopentanone carbonyl group was achieved *via* the phenylthiomethyl oxime **48**. This derivative is unaffected by mild oxidative (Moffatt or Collins) or reductive (borohydride) procedures and yet can be readily cleaved back to the unsubstituted oxime with mercury ion catalysis and hence in turn to the ketone.

The prostaglandins have, during the past decade, become a major area of biological[1] and clinical investigation.[2] As a consequence of their limited accessibility from natural sources, and the desire to explore the structural requirements for their biological activity, the prostaglandins have become the synthetic targets of many groups.[3] Several of these groups have reported specific syntheses of prostaglandin E_1 (PGE_1)[4] (**61**). We now describe the details of our synthesis of PGE_1.[5]

At the time our efforts commenced there was no significant clinical work published on the prostaglandins which would indicate any important differences between PGE_1 and PGE_2. PGE_1 seemed to be the most appropriate target compound, as it had been converted to PGA_1 and $PGF_1\alpha$[3] and the additional double bond in the carboxylic acid side chain of PGE_2 seemed to pose additional synthetic limitations.

The preparation of an appropriate starting material, **15**, was anticipated as being possible by a process analogous to one of those used to synthesize isosarkomycin, 2-methyl-3-carboxycyclopentenone. The synthesis of Shemyakin[6] was briefly investigated but discarded in favor of the procedure used by Newman.[7]

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