Resolution of Esters of Phenylglycine with (+)-Tartaric Acid [1]

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The methyl, ethyl, and isopropyl esters of DL-phenylglycine are resolved with 1 mol. equiv. of (+)-tartaric acid in aqueous alcohols to give the D-ester hydrogen (+)-tartrate salts in up to 42% yield (or 84% based on the D-content of the DL-esters). The L-salts in the filtrates from the resolutions are racemised in ethanol containing polar co-solvents. The resolution and racemisation stages may be combined so that ethyl DL-phenylglycinate undergoes a second-order asymmetric transformation to give ethyl D-phenylglycinate hydrogen (+)-tartrate in up to 65% yield. The resolved salts are hydrolysed to D-phenylglycine in up to 90% yield.

D-PHENYLGLYCINE [(2*R*)-2-amino-2-phenylacetic acid (1; R = H)] is needed for the manufacture of the antibiotics Ampicillin and Cephalexin. The isomers of Ampicillin and Cephalexin made from L-phenylglycine have very low antibacterial activity.

The resolution of DL-phenylglycine and its *N*-protected derivatives has been widely reported,[2] but attempts to resolve esters of DL-phenylglycine have failed to give optically pure phenylglycine.[3,4] Ethyl DL-phenylglycinate has been partially resolved with (−)-dibenzoyltartaric acid.[3] The L-hydrochloride (2b) was rapidly hydrolysed by barium hydroxide but with 25% racemisation.[3] Makleit [4] has also reported a partial resolution of ethyl DL-phenylglycinate but with (+)-tartaric acid in ethanol. Few details were given.[4]

DISCUSSION AND RESULTS

The availability and relatively low cost of (+)-tartaric acid persuaded us to re-investigate the resolution of ethyl DL-phenylglycinate, and to attempt to resolve the methyl (1a) and isopropyl (1c) esters.

Resolution.—Methyl DL-phenylglycinate (1a) was efficiently resolved with 1 mol. equiv. of (+)-tartaric acid in aqueous ethanol, to give methyl D-phenylglycinate hydrogen (+)-tartrate (3a), $[\alpha]_D^{20}$ −63°, in 42% yield. This and similar results for the methyl, ethyl, and isopropyl esters are shown in Table 1. The D-salts (3a and b) were characterised after recrystallisation to constant specific rotation (Table 2).

$$\begin{array}{l} \mathrm{PhCH{\cdot}CO_2R} \\ \quad\vert \\ \quad\mathrm{NH_2} \end{array} \qquad (1)$$

The methyl, ethyl, and isopropyl esters are designated a, b, and c in the text The hydrochloride and hydrogen (+)-tartrate salts of (1) are designated (2) and (3), respectively.

TABLE 1

Resolution of alkyl DL-phenylglycinates with 1 mol. equiv. of (+)-tartaric acid

Ester	R	% Ester	Solvent	Cryst. Temp. (°C)	Product D-(3) Yield (%) [b]	$[\alpha]_D$ [b] (°) (H_2O)	Optical [c] purity (%)	Solvation (product dried at 20 °C and 2 mmHg)
(1a)	Me	15	MeOH	−4	13	−37	62	Not solvated
(1a)	Me	10	EtOH	20	64	−12	27	Solvated
(1a)	Me	3.3	10% H_2O in EtOH	5	42	−63	96	Solvated
(1a)	Me	4.5	9% Me_2SO in EtOH	−4	43	−61	94	*a*
(1a)	Me	4.5	9% AcOH in EtOH	2	43	−59	92	*a*
(1a)	Me	20	MeOH–$(CH_2Cl)_2$ (1 : 1)	20	25	−61.5	95	*a*
(1b)	Et	15	10% H_2O in MeOH	24	25	−48	97	Solvated
(1b)	Et	4.5	10% H_2O in EtOH	0	36	−48	97	Solvated
(1b)	Et	9	9% Me_2SO in EtOH	3	41	−39	81	*a*
(1c)	Me_2CH	3	10% H_2O in EtOH	5	40 [d]	−31 [d]	*ca.* 100	Possibly solvated

[a] Dried at 60—80 °C and 2 mmHg; not solvated. [b] Yields and $[\alpha]_D$ values of all solvated products have been corrected to take into account the solvation with ethanol or methanol. The amount of solvation (usually 1.0 ± 0.1 mol. equiv.) was measured by ^{1}H n.m.r. [c] Optical purity (%) = 100 ($2F_1$ − 1) where F_1 is the mole fraction (K. Mislow and M. Raban, *Topics Stereochem.*, 1967, **2**, 199), *i.e.* a racemic mixture has 0% optical purity. [d] Calculated assuming no solvation: the degree of solvation was not determined. The sample was hydrolysed (see below) to D-phenylglycine with a specific rotation of +159°.

Preparation of D- *and* L-*Esters* (1), *Hydrochlorides* (2), *and* L-*Salts* (3).—We made the L-salts (3) and L-esters (1) to study their solubility and racemisation. The D- and L-ester hydrochlorides (2) were made conventionally [5] from commercially available D- and L-phenylglycines (Table 3). The D-esters (1a and b) were made from the

[1] G.P. 2,227,011 (*Chem. Abs.*, 1973, **78**, 725 92c).
[2] J. P. Greenstein and M. Winitz, 'Chemistry of the Amino Acids,' Wiley, New York, 1961, vol. I, pp. 722—729.
[3] G. Losse, R. Wagner, P. Neuland, and J. Rateitschak, *Chem. Ber.*, 1958, **91**, 2410.
[4] Sh. Makleit, F. Starichkai, and M. Pushkash, *Visn. Kiiv Univ. Ser. Fiz. Khim.*, 1967, No. 7, 155.
[5] C. S. Marvel and W. A. Noyes, *J. Amer. Chem. Soc.*, 1920, **42**, 2259.

TABLE 2

Properties of hydrogen (+)-tartrate salts (3)

Compd.	R	Isomer	Made by method *	$[\alpha]_D$ (°) (*c* 2.5 in H_2O)	Optical purity (%)	Solvated with	M.p. (°C)	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
(3a)	Me	D	A	−64°	99	$0.5H_2O$ [a]	141—143	47.75	5.2	4.0	$C_{13}H_{17}NO_8$, $0.5H_2O$	48.15	5.6	4.3
(3a)	Me	D	A	−65	*ca.* 100	$0.5H_2O$ $1.0EtOH$ [b]	140—144	48.55	6.0	3.8	$C_{13}H_{17}NO_8$, $0.5H_2O,C_2H_6O$	48.6	6.5	3.8
(3a)	Me	L	B	+81	*ca.* 97	$0.33H_2O$ [a]	140—144	48.7	5.4	4.4	$C_{13}H_{17}NO_8$, $0.33H_2O$	48.6	5.5	4.4
(3b)	Et	D	B	−46	94	$0.5H_2O$ [a]	13.65—137.5	49.25	5.65	4.1	$C_{14}H_{19}NO_8$, $0.5H_2O$	49.7	5.95	4.1
(3b)	Et	D	A	−50	*ca.* 100	$0.5H_2O$ [b] $1.0EtOH$	129—134	49.75	5.8 [c]	3.95	$C_{14}H_{19}NO_8$, $0.5H_2O,C_2H_6O$	50.0	6.8	3.6
(3b)	Et	D	B	−48	97	$0.5H_2O$ [b] $1.0MeOH$	136.5—137.5	48.7	6.1	3.55	$C_{14}H_{19}NO_8$, $0.5H_2O,CH_4O$	48.6	6.5	3.8
(3b)	Et	L	B	+70	*ca.* 97	$0.5H_2O$ [b]	121—123	49.9	5.7	4.05	$C_{14}H_{19}NO_8$, $0.5H_2O$	49.7	5.9	4.1

*A, resolution then recrystallisation to constant rotation; B, from the optically active ester and 1 mol. equiv. of (+)-tartaric acid.

[a] Dried at 70 °C and 1.0 mmHg. [b] Dried at 20 °C and 1.0 mmHg. [c] Mean of 3 analyses: no reason for the low figure is offered.

TABLE 3

Specific rotations and melting points of hydrochlorides (2)

Compd.	R	Isomer	$[\alpha]_D$ (°) (*c* 1.0 in H_2O)	Optical purity (%)	Lit. $[\alpha]_D$ (°) (*c* 1 in H_2O)	M.p. (°C) §	Lit. m.p. (°C)	Notes
(2a)	Me	D	−118	*ca.* 97	−119 [a]	169—173	222—223 [a]	
(2a)	Me	L	+118	*ca.* 97		168—204		*
(2b)	Et	D	−91	*ca.* 97	−81.6 [b]	171—175	198 [c]	
(2b)	Et	L	+91	*ca.* 97	+89.0 [d]	171—175	197—198 [d]	
(2c)	Me_2CH	D	−69	*ca.* 97		175—177		†

[a] W. Klyne, P. M. Scopes, R. N. Thomas, and H. Dahn, *Helv. Chim. Acta*, 1971, **54**, 2420. [b] Ref. 3. Herlinger (H. Herlinger, H. Kleinmann, and I. Ugi, *Annalen*, 1967, **706**, 37) quotes −91.8° (*c* 4.5 in H_2O); McKenzie (ref. 6) quotes −89.3° (*c* 5.0 in H_2O); Fischer (ref. 12) quotes +88.95 ± 0.4° (*c* 5 in H_2O) (presumably a typographical error of sign). [c] Ref. 3. Herlinger (see footnote *b*) quotes 199—200°; Fischer [2] quotes 203° (decomp.). [d] Ref. 3.

* Found: C, 53.6; H, 6.0; Cl, 17.7; N, 7.25. $C_9H_{12}ClNO_2$ requires C, 53.6; H, 6.0; Cl, 17.6; N, 6.95%.

† Found: C, 57.3 H, 6.9; Cl, 15.5; N, 6.0. $C_{11}H_{16}ClNO_2$ requires C, 57.5; H, 7.0; Cl, 15.4; N, 6.1%. § With decomp.

TABLE 4

Preparation of optically active alkyl phenylglycinates

Compd.	R	Isomer	Made from	$[\alpha]_D$ (°) (*c* 2 in C_6H_6)	Optical purity (%)	Lit. $[\alpha]_D$ (°) (*c* 2 in C_6H_6)	M.p. (°C)
(1a)	Me	D	Tartrate (3a)	−181	*ca.* 98	−141 *	29—32 [a]
(1a)	Me	D	Hydrochloride (2a)	−180	*ca.* 98	−141 *	29—32
(1a)	Me	L	Hydrochloride (2a)	+177	*ca.* 96	+127 *	*b*
(1b)	Et	D	Tartrate (3b)	−136	*ca.* 97	−139.5 †	*c*
(1b)	Et	D	Hydrochloride (2b)	−134	*ca.* 96	−139.5 †	*c*
(1b)	Et	L	Hydrochloride (2b)	+127	*ca.* 90	+116 †	*d*

[a] Found: C, 65.4; H, 6.6; N, 8.7. $C_9H_{11}NO_2$ requires C, 65.4; H, 6.7; N, 8.5%. [b] Did not crystallise (Found: C, 64.8; H, 6.7; N, 8.35. $C_9H_{11}NO_2,0.1H_2O$ requires C, 64.7; H, 6.75; N, 8.4%). [c] Not crystalline. [d] Not crystalline (Found: C, 66.9; H, 7.4; N, 7.8. $C_{10}H_{13}NO_2$ requires C, 67.0; H, 7.3; N, 7.8%).

* L. Arpesella, A. La Manna, and M. Grassi, *Gazzetta*, 1955, **85**, 1354. † L. Arpesella, A. La Manna, and P. Pratesi, *Gazzetta*, 1954, **84**, 879; L. Arpesella and A. La Manna, *Il Farmaco* (*Pavia*) *Ed. Sci.*, 1953, **8**, 212.

TABLE 5

Hydrolysis of phenylglycine ester derivatives

Starting material: Compd.	R	$[\alpha]_D$ (°) (H_2O)	Optical purity (%)	Reagent (equiv.)	Hydrolysis time (min)	Product D-phenylglycine: Yield (%)	$[\alpha]_D$ (°) (*c* 1.0 in N-HCl)	Optical purity (%)
(3a)	Me	−63	97	6N-HCl (4)	85	90	−154	97
(3a)	Me	−64.5	99	6N-HCl (4)	75	77 [a]	−157	99
(3b)	Et	−46.5	94	6N-HCl (4)	60	91	−151.5	96
(3c)	Pr^i	−31 [b]	*ca.* 100	6N-HCl (15)	60	74 [a]	−159	*ca.* 100
(1a)	Me	−136 [c]	95	6N-HCl (4)	30	71 [a]	−154	97
(3a)	Me	−63	97	2.2N-NaOH (3.3)	90	86	−156	98
(3a)	Me	−64	98	2.0N-KOH (4.0)	15	85	−157	99
(1b)	Et	+117 [d]	*ca.* 97	Sat. $Ba(OH)_2$ (1.9)	5	66	+155	97
(2b)	Et	+91	*ca.* 97	Sat. $Ba(OH)_2$ (2.3)	5	52	+156	98

[a] Diluted with an equal volume of water before precipitation of D-phenylglycine. The other acid hydrolysates were diluted with a half volume of water. The base hydrolysates were not diluted before neutralisation. [b] Unknown solvation (see Table 1). [c] In benzene. [d] In methanol.

hydrochlorides (2) and the resolved salts (3) by extracting them into ethyl acetate at pH 7.0 (Table 4). Care was needed during and after neutralisation: too high a pH or temperature caused racemisation (see also below). The L-esters (1a and b) were made similarly from the hydrochlorides (Table 4). The L-ester salts (3a and b) were made conventionally (Table 2) and were less strongly solvated than the D-ester salts (3a and b). The differing solvation is probably a contributory reason for the D- and L-salts (3) having different solubilities in aqueous ethanol.

Hydrolysis.—The D-ester hydrogen (+)-tartrates (3a—c) and the esters (1) were hydrolysed without racemisation by refluxing 6N-hydrochloric acid or by strong bases in water at ambient temperature (Table 5). The basic hydrolysis was rapid and efficient at pH 11.0 or greater. It was slow and gave partially racemised phenylglycine at pH 10.0 or less.

The basic hydrolysis is effective only because under these conditions it is faster than racemisation of the ester. The esters (1a—c) were optically labile to base (see below), but sodium D-phenylglycinate was relatively stable: the rotation of a solution in N-sodium hydroxide at 22 °C dropped by 1% per day. Previously reported [4,6] basic hydrolyses of optically active phenylglycine esters in aqueous alcohol gave partially racemised phenylglycine. We repeated Losse's hydrolysis [3] (see above) of ethyl L-phenylglycinate hydrochloride, but found no detectable racemisation (Table 5).

Racemisation and Asymmetric Transformation.—Only the D-isomer of phenylglycine is required for making the antibiotics Ampicillin and Cephalexin, so we sought a way of racemising the L-esters (1) and L-salts (3). In particular we wanted a convenient way of racemising the filtrates from the resolution either as they stood or after concentration, so that an increased yield of D-salt could be obtained by further crystallisation.

The optically active esters (1) were racemised slowly on storage at 5 °C, but rapidly with sodium methoxide in methanol at 20 °C, or in hot alcohols. Surprisingly, the hydrogen tartrates (3) were also racemised in hot alcohols, usually faster than the free esters (1). However, when the filtrate from the resolution of methyl DL-phenylglycinate in aqueous ethanol was racemised (*ca.* 10 h at reflux), there were problems with hydrolysis and transesterification. These were avoided by using ethanol containing 10% dimethyl sulphoxide, which was a satisfactory solvent for the resolution of ethyl DL-phenylglycinate and for the racemisation of the L-salt (3b). Thus, when a 10% solution of the DL-ethyl ester (1b) was stirred with (+)-tartaric acid in ethanol containing dimethyl sulphoxide, it underwent a second-order [7] asymmetric transformation giving a 65% yield of the D-salt (3b) in two crops. Similar results were obtained by using acetic acid instead of dimethyl sulphoxide. After our work was completed [1] the second-order asymmetric transformation of 2-amino-2-phenylacetonitrile with (+)-tartaric acid in solvents containing carboxylic acids was reported.[8] Our asymmetric transformation has now been superseded by the more convenient Schiff's base method described in the following paper.[9]

EXPERIMENTAL

(+)-Tartaric acid and DL- and D-phenylglycines were obtained from R. Emanuel and Co.; L-phenylglycine was obtained from the Ott Chemical Co. Inc. Solutions were routinely dried with magnesium sulphate, and were evaporated at *ca.* 40 °C and water-pump pressure. The DL-esters (1a—c) were made by standard methods.[5,10]

The rotation measurements were made at between 17 and 27 °C by using a 1 dm polarimeter tube, 10 ml grade B volumetric flasks, and a Hilger–Watts M 511.2 polarimeter with modified PCE 23A electronics. ^{1}H N.m.r. spectra were determined with a Varian A60D instrument. M.p.s were determined with a Kofler hot-stage apparatus.

Optically Pure Phenylglycine.—The specific rotation of D-phenylglycine is reported as −152° in 0.133N-hydrochloric acid,[11] but −165.43 ± 0.4° in 2.74N-hydrochloric acid; [12] the optical purities were not known. Greenstein [13] has reported that the specific rotations of 99.9% optically pure D- and L-phenylglycines are −169 and +168° respectively in 5.00N-hydrochloric acid (we have therefore taken ±168.5 ±0.5° as representing the optically pure value in this concentration of hydrochloric acid). The specific rotations of the same samples were −114 and +114°, respectively, in water.[13] We have routinely used 1.00N-hydrochloric acid as solvent for determining the rotation of phenylglycine and wished to determine the optically pure value for this normality. This was done by determining the rotation of a sample of D-phenylglycine four times in 5.00N-hydrochloric acid and four times in 1.00N-hydrochloric acid. The ratio of these values (1 : 0.9426 ± 0.0017), Greenstein's values in 5N-hydrochloric acid, and a calculation of the standard error [14] gave a value of ±158.6 ± 0.8° as the extrapolated value for optically pure phenylglycine in 1.00N-hydrochloric acid. Schawartz [15] has reported −161° as the specific rotation of D-phenylglycine in N-hydrochloric acid.

The optical purity of phenylglycine can be measured [16] by g.l.c. of the isopropyl ester of its *N*-trifluoroacetyl derivative on the optically active stationary phase *N*-trifluoroacetyl-D-phenylalanyl-DL-leucine cyclohexyl ester.[17] The optical purity of a sample of D-phenylglycine with a specific rotation of −157 ± 1° was shown to be greater than 99.7% by this method.[16]

Resolution of Methyl DL-Phenylglycinate.—A solution of methyl DL-phenylglycinate (3.30 g, 20.0 mmol) and (+)-tartaric acid (3 00 g, 20 mmol) in ethanol–H_2O (9 : 1 v/v)

[6] A. McKenzie and G. O. Wills, *J. Chem. Soc.*, 1925, **127**, 283.
[7] E. E. Turner and M. M. Harris, *Quart. Rev.*, 1947, **1**, 299.
[8] Fr. P. 2,141,354 (*Chem. Abs.*, 1973, **79**, 42210e).
[9] J. C. Clark, G. H. Phillips, and M. R. Steer, following paper; G.P. 2,309,180 (*Chem. Abs.*, 1973, **79**, 126791h).
[10] A. Kossel, *Ber.*, 1891, **24**, 4145.
[11] G. L. Clark and G. R. Yohe, *J. Amer. Chem. Soc.*, 1929, **51**, 2797.
[12] E. Fischer and O. Weichhold, *Ber.*, 1908, **41**, 1286.
[13] D. Rudman, A. Meister, and J. P. Greenstein, *J. Amer. Chem. Soc.*, 1952, **74**, 551.
[14] W. J. Reichmann, ' Use and Abuse of Statistics,' Penguin, Harmondsworth, 1971, p. 231.
[15] Hung. P. 154410; J. Schawartz and G. Eibel, *Chem. and Ind.*, 1968, 1698.
[16] F. K. Butcher, personal communication.
[17] W. A. Koenig, W. Parr, H. A. Lichtenstein, and J. Oro, *J. Chromatog. Sci.*, 1970, **8**, 183.

TABLE 6

^{1}H N.m.r. data of esters (1), hydrochlorides (2), and salts (3) (τ values; J in Hz) *

Compd.	Solvent	R	Ph	CH	R	Other
(1a)	$CDCl_3$	Me	2.62	5.37	6.30	8.02 [a]
(1b)	$CDCl_3$	Et	2.64	5.42	5.42 (q, J 7), 8.81 (t, J 7)	8.10 [a]
(2a)	D_2O	Me	2.45	4.65	6.16	
(2b)	D_2O	Et	2.43	4.68	5.67 (q, J 7), 8.76 (t, J 7)	
(2c)	D_2O	Pr^i	2.41	4.71	4.79 (sept, J 6), 8.68 (d, J 6), 8.79 (d, J 6)	
(3a)	$(D_3C)_2SO$	Me	2.58	5.05	6.33	5.87 [b]
(3b)	$(D_3C)_2SO$	Et	2.71	5.05	5.82 (q, J 7), 8.88 (t, J 7)	5.89 [b]
(3c)	$(D_3C)_2SO$	Pr^i	2.56	5.12	5.0 (sept, J 6), 8.72 (d, J 6), 8.84 (d, J 6)	5.88 [b]

[a] NH_2. [b] $(CHOH)_2$.

* Integrals are in agreement with the proposed structures.

(100 ml) at 50 °C was seeded with the solvated D-salt (3a), allowed to cool to 20 °C during 3 h, then kept at 5 °C for 16 h. The mixture was filtered, and the product was washed and dried at 20 °C and 1 mmHg to give *methyl* D-*phenylglycinate hydrogen* (+)-*tartrate* (3a) *monoethanolate* as white needles (3.00 g, 42%), $[\alpha]_D^{20}$ −63° (*c* 1.00 in H_2O). The salt was recrystallised from IMS–H_2O (9 : 1 v v) and dried at 20 °C and 1 mmHg to give the optically pure monoethanolate (3a), $[\alpha]_D^{25}$ −65° * (*c* 2.51 in H_2O). The rotation was unchanged by further recrystallisation. The final sample was re-dried at 70 °C and 1.0 mmHg for 15 h to give the *hemi-hydrated salt* (3a), $[\alpha]_D^{22}$ − 64° (*c* 1.010 in H_2O).† Karl Fischer titration and microanalysis indicated the presence of water (0.5 mol. equiv.). Similar resolutions are recorded in Table 1. The properties of the salts (3) are recorded in Tables 2 and 6. The solvated salts (3) were sometimes racemised when dried at 70 °C and 1—2 mmHg. Once desolvated the D-salt (3a) was optically stable at 70 °C and 2 mmHg during 20 h.

Methyl D-*Phenylglycinate* (1a).—(a) *From the hydrogen tartrate* (3a). The pH of a solution of methyl D-phenylglycinate hydrogen (+)-tartrate (3a; monoethanolate; $[\alpha]_D$ −64°; 5.277 g, 14.6 mmol) in water at 20 °C was adjusted to 7.0 with 10N-ammonium hydroxide. The mixture was extracted into methylene chloride, and the extract was washed, dried, and evaporated to give the *ester* as white prisms (2.075 g, 86%). The properties of this and the D-ethyl ester (1b) are summarised in Tables 4 and 6.

(b) *From the ester hydrochloride* (2a). The pH of a solution of methyl D-phenylglycinate hydrochloride [made from D-phenylglycine ($[\alpha]_D$ −156°; 50.24 g, 0.332 mol) by the method of Marvel and Noyes [5]] was adjusted to 7.0 with 10N-ammonium hydroxide to give the free base, which was extracted into ethyl acetate. The organic layer was washed, dried, and evaporated to give the *ester* as a pale yellow liquid, which crystallised on cooling to give prisms (43.3 g, 79%). The L-esters (1a and b) and the D-ester (1b) were made similarly: their properties are summarised in Tables 4 and 6.

D-*Phenylglycine*.—(a) *Basic hydrolysis*. A solution of methyl D-phenylglycinate hydrogen (+)-tartrate (3a) (solvated with 0.8 mol. equiv. of ethanol; $[\alpha]_D$ −64°; 3.944 g, 11.2 mmol) in 2.0N-potassium hydroxide (22.4 ml, 44.8 mmol, 4.0 equiv.) was stirred for 15 min (t.l.c. showed that hydrolysis was complete after 1 min). The pH was adjusted from *ca.* 13.0 to 6.5 with 2N-hydrochloric acid to precipitate a solid, which was filtered off, washed, and dried to give D-phenylglycine (1.443 g, 85%) as white plates, subliming at 245—249 °C (lit.,[11] 245—248°), $[\alpha]_D^{23}$ −157° (*c* 1.002 in N-HCl). The ^{1}H n.m.r. and i.r. spectra resembled those of an authentic sample. Other similar hydrolyses are summarised in Table 5.

(b) *Acidic hydrolysis*. A solution of methyl D-phenylglycinate hydrogen (+)-tartrate (3a) (solvated with 0.8 mol. equiv. of ethanol; $[\alpha]_D$ −63°; 20.43 g, 59 mmol) in 6N-hydrochloric acid (38 ml, 228 mmol, 3.9 equiv.) was refluxed for 70 min, then distilled for 15 min. The solution was diluted with water (19 ml) and neutralised to pH 7.0 with ammonium hydroxide solution (*d* 0.880) while warm. The mixture was cooled in ice and filtered, and the solid was washed and dried to give D-phenylglycine (8.06 g, 90%), $[\alpha]_D^{25}$ −154° (*c* 1.02 in N-HCl).

Hydrolysis of Ethyl L-*Phenylglycinate Hydrochloride with Saturated Barium Hydroxide Solution*.[3]—A solution of ethyl L-phenylglycinate hydrochloride ($[\alpha]_D$ +91°; 2.010 g, 9.32 mmol) in saturated barium hydroxide solution (*ca.* 0.36N; 60 ml, *ca.* 21.6 mmol, 2.3 equiv.) was stirred at 23 °C for 5 min. The solution was neutralised to pH 7.0 with 0.7N-hydrochloric acid to give a solid which was washed and dried to give L-phenylglycine (0.731 g, 52%) as white plates subliming at 245—250° (Clark [11] quotes 242—244° as the m.p. of needles), $[\alpha]_D^{23}$ +155° (*c* 1.004 in N-HCl). The i.r. and ^{1}H n.m.r. spectra resembled those of an authentic sample.

Racemisation of Ethyl L-*Phenylglycinate Hydrogen* (+)-*Tartrate*.—A solution of ethyl L-phenylglycinate hydrogen (+)-tartrate (498 mg) in ethanol (9.0 ml) containing dimethyl sulphoxide (1.0 ml) had $[\alpha]_D$ +85°. The solution was kept at 40 °C for 54 h and polarimetric readings were taken at intervals. The time taken for the rotation to fall to 55° (half-way to the racemic value) was 20 h.

Similarly methyl D-phenylglycinate was 50% racemised after 5 h in refluxing methanol; the L-salt (3a) was 50% racemised in 2.8 h under the same conditions.

Second-order Asymmetric Transformation of Ethyl DL-*Phenylglycinate*.—A mixture of ethyl DL-phenylglycinate (1b) (4.85 g, 27.1 mmol) and (+)-tartaric acid (4.065 g, 27.1 mmol, 1 equiv.) was stirred in ethanol containing 10% v/v dimethyl sulphoxide (50 ml) at 20 °C for 10 days to give the D-salt (4.886 g, 48%), $[\alpha]_D^{21}$ −47° (*c* 2.504 in H_2O). The filtrate was concentrated to 21 ml, kept at 40 °C for 8 days, then diluted with ethanol and cooled to 4 °C to give a second crop (1.739 g, 17%), $[\alpha]_D^{21}$ −45.5° (*c* 2.483 in H_2O).

In a similar experiment using acetic acid instead of dimethyl sulphoxide, two crops of the D-salt were obtained in 55 and 9% yield ($[\alpha]_D$ −42.5 and −42°, respectively).

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* Mean of two determinations corrected to account for solvation with ethanol.

† Mean of two determinations; the drop in rotation is probably real (see below).