A New Asymmetric Transformation of α-Amino-acid Esters with (+)-Tartaric Acid [1]

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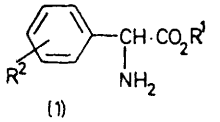
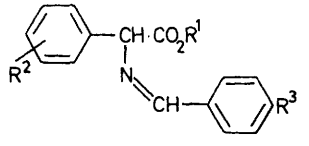
Esters of DL-phenylglycine or substituted phenylglycines, on being stirred with (+)-tartaric acid in alcohols in the presence of carbonyl compounds, give, depending on the reaction conditions, the D- or L-ester hydrogen (+)-tartrates in up to nearly 100% yield (*i.e.* almost all the racemic ester is converted into the D- or L-salt). The mechanism of this new type of asymmetric transformation is discussed. The D- or L-ester hydrogen (+)-tartrates are hydrolysed by strong acids or strong bases to give amino-acids of high optical purity.

THE preceding paper describes the second-order asymmetric transformation of ethyl DL-phenylglycinate (1b; $R^2 = H$) with (+)-tartaric acid in ethanol containing dimethyl sulphoxide or acetic acid. The racemisation was slow, resulting in inconveniently long reaction times and yields of up to only 65%.[2] We therefore sought a way of accelerating the racemisation of alkyl phenylglycinates or their hydrogen (+)-tartrate salts (2).



(1)



(3)

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

α-Amino-acids are normally optically stable,[3] but can be racemised as Schiff's bases at 100 °C by carbonyl compounds (*e.g.* pyridoxal).[4]

There are several reports [5] suggesting that Schiff's bases of optically active amino-acid esters (including ethyl D-*N*-isopropylidenephenylglycinate [6]) are optically stable. However, Schiff's bases of ethyl L-phenylalaninate [7] and ethyl D-methioninate [8] have been racemised more quickly than the free esters by bases at *ca.* 20 °C. The fact that phenylglycine is more readily racemised than most amino-acids [9] prompted us to study the racemisation of Schiff's bases of its esters.

DISCUSSION AND RESULTS

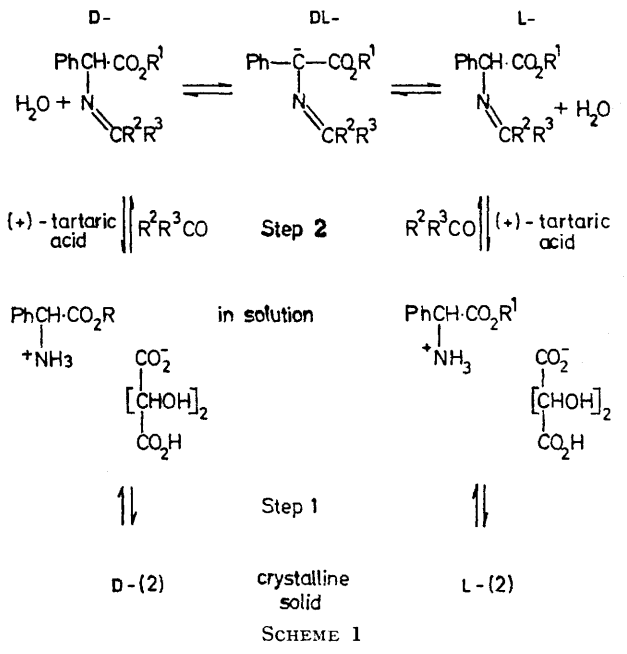
Phenylglycine.—The optically active Schiff's base (3a; $R^2 = R^3 = H$) made *in situ* from benzaldehyde and methyl D-phenylglycinate was racemised 5 times more quickly in dimethyl sulphoxide at 20 °C than was the methyl ester (1a; $R^2 = H$). Small amounts of weak bases (*e.g.* benzoate) increased the rate of racemisation. The drop in rotation of a solution of methyl D-phenylglycinate hydrogen (+)-tartrate (2a; $R^2 = H$) in methanol was about 30 times faster after the addition of 1 mol. equiv. of benzaldehyde. This result cannot be interpreted solely as racemisation because of chemical changes in solution (see below), but it did appear that the the salts (2) were optically labile in solution with benzaldehyde.

When 1 equiv. of benzaldehyde and 1 mol. equiv. of (+)-tartaric acid were stirred at 20 °C with a 10% solution of methyl DL-phenylglycinate (1a; $R^2 = H$) in ethanol for 24 h, a new type of asymmetric transformation occurred giving an 85% yield of methyl D-phenylglycinate hydrogen (+)-tartrate (2a; $R^2 = H$) (Table 1). Similar reactions, but without benzaldehyde, showed no asymmetric transformation and gave about half the yield or an optically impure product. We presumed, therefore, that the Schiff's base (3a; $R^2 = R^3 = H$) was an intermediate in the asymmetric transformation (see Scheme 1). This was confirmed by stirring methyl DL-*N*-benzylidenephenylglycinate with 1 mol. equiv. each of (+)-tartaric acid and water in ethanol: the D-salt (2a; $R^2 = H$) was obtained in 69% yield. Some other asymmetric transformations are summarised in Table 1. Ethyl L-phenylglycinate underwent complete inversion by this method.

The filtrates from the asymmetric transformation reactions contained mainly the carbonyl compound, the dissolved salt (2), and the Schiff's base (3), and could be used as solvents, for further reactions. When this re-use of filtrate was carried out 11 times in succession, with the methyl ester (1a; $R^2 = H$) and benzaldehyde, the overall yield of the salt (2a; $R^2 = H$) was raised to 95%. When filtrates from reactions in acetone–methanol (1 : 1) were re-used, the optical purity of the product sometimes

[1] G.P. 2,309,180 (*Chem. Abs.*, 1973, **79**, 126791h).
[2] J. C. Clark, G. H. Phillipps, M. R. Steer, L. Stephenson, and A. R. Cooksey, preceding paper.
[3] J. P. Greenstein and M. Winitz, 'Chemistry of the Amino Acids,' Wiley, New York, 1961.
[4] J. Olivard, D. E. Metzler, and E. E. Snell, *J. Biol. Chem.*, 1952, **199**, 669; D. E. Metzler, J. B. Longenecker, and E. E. Snell, *J. Amer. Chem. Soc.*, 1954, **76**, 639.
[5] J. C. Sheehan and V. J. Grenda, *J. Amer. Chem. Soc.*, 1962, **84**, 2417; E. D. Bergmann, H. Bendas, and W. Taub, *J. Chem. Soc.*, 1951, 2673; Fr. P. 1,502,262 (*Chem. Abs.*, 1969, **70**, 29307m); F. Bergel, G. E. Lewis, S. F. D. Orr, and J. Butler, *J. Chem. Soc.*, 1959, 1431; F. Bergel and M. Peutherer, *ibid.*, 1964, 3965; R. Bonnett, N. J. David, J. Hamlin, and P. Smith, *Chem. and Ind.*, 1963, 1836.
[6] H. E. Smith, M. E. Warren, and A. W. Ingersoll, *J. Amer. Chem. Soc.*, 1962, **84**, 1513.
[7] P. Pfeiffer, W. Offermann, and H. Werner, *J. prakt. Chem.*, 1942, **159**, 313.
[8] T. Taguchi and T. Ishida, *Pharm. Bull.* (*Tokyo*), 1957, **5**, 181.
[9] J. P. Greenstein, S. M. Birnbaum, and M. C. Otey, *J. Biol. Chem.*, 1953, **204**, 307.

fell, possibly because of the formation of mesityl oxide and 4-methoxy-4-methylpentan-2-one,[10] which could be isolated.



SCHEME 1

Other Amino-Acids.—Esters of DL-*m*-methoxy-, -*p*-chloro-, and -*p*-hydroxy-phenylglycines underwent similar asymmetric transformations (Table 2). The asymmetric transformation of methyl DL-*p*-chlorophenylglycinate in ethanol did not seem to be directed solely by the solubility of the salts in ethanol. The asymmetric transformation of methyl DL-*p*-hydroxyphenylglycinate (1a; $R^2 = p$-HO) could give the D- or the L-salt (2a; $R^2 = p$-HO), depending on the solvent (Table 2). Addition of small amounts of benzene altered the reaction completely. The key to this dramatic change is the formation of a very stable methanol (1.0 mol. equiv.) and benzene (*ca.* 0.45 mol. equiv.) solvate of the D-salt (2a; $R^2 = p$-HO).

Hydrolysis.—The optically active esters (1; except R^1 = H) were liberated from their salts (2) by conventional [2] methods (Table 3). The salts (2) or the esters (1; except R^1 = H) were hydrolysed [2] by refluxing 6N-hydrochloric acid or 2N-sodium hydroxide at *ca.* 20 °C to give the optically active amino-acids (Table 4). The hydrolysis of unsubstituted phenylglycine esters and salts is described in the preceding paper.[2]

Methionine.—Amino-acids lacking a phenyl group on the α-carbon atom, such as methionine, are more optically stable than phenylglycine,[9] so we were interested to see if the foregoing asymmetric transformation could be extended to esters of methionine. This appeared possible because the racemisation of the Schiff's base (3) did not seem to be the slowest step in the asymmetric transformation of aromatic amino-acid esters (see below). Schiff's bases of ethyl methioninate have been reported [8] to be optically labile, particularly in the presence of bases. Losse [11] has partially resolved methyl DL-methioninate with (+)-tartaric acid. We have found that methyl DL-methioninate gives the L-salt in 82% yield in an asymmetric transformation with anisaldehyde and (+)-tartaric acid in methanol. Reaction times of up to 28 days at 20 °C were needed. The salt was hydrolysed to L-methionine in 58% yield.

Mechanism.—General. Our proposed pathway for the asymmetric transformation is shown in Scheme 1. A key step (step 2) is the formation of an equilibrium concentration of the Schiff's base (3) which is more readily racemised than the ester (1). We have already shown that the Schiff's base is more optically labile than the ester and that the asymmetric transformation does not work under the conditions summarised in Tables 1 and 2 except in the

TABLE 1

Asymmetric transformation of phenylglycine esters with 1 mol. equiv. of (+)-tartaric acid at 20—25 °C

Ester			Carbonyl compd.		Reaction	Product (2)			
R^1	No.	Conc. (%)	(equiv.)	Solvent	time (h)	Yield [a] (%)	Isomer	$[\alpha]_D$ [b] (°) (H_2O)	Optical purity (%)
Me	(1a)	10	PhCHO (1.0)	EtOH	24	85	D	−64	99
Me	(1a)	3.3	None	10% H_2O in EtOH	24	42	D	−63	97
Me	(1a)	10	None	EtOH	24	64	D	−12	27
Me	(1a)	10	PhCHO (1.0)	EtOH	120	90	D	−63	97
Et	(1b)	10	PhCHO (1.0)	EtOH	24	76	D	−47	95
Et	(1b)	10	MeCHO (1.0)	EtOH	19	68	D	−44.5	91
Et	(1b)	13.5	PhCHO (1.0)	MeOH	25	58	D	−48	97
Me	(1a)	10	Me_2CO (8.0)	EtOH	20	93	D	−64	99
Me	(1a)	10	$[CH_2]_5CO$ (2.0)	EtOH	141	95	D	−65	100
Me	(1a)	10	PhCOMe (2.0)	EtOH	288	90	D	−61.5	95
Et	(1b)	10	Me_2CO (50% v/v)	MeOH	24	73	D	−47.5	96
Pr^i	(1c)	10	PhCHO (0.55)	EtOH	144	62 [c]	L	+57 [c]	98

[a] The percentage yields in this and Table 2 are based on the input of DL-ester (1), so that a complete asymmetric transformation would give 100% yield of one isomer. The percentage yields are corrected for solvation (see *b*). [b] The salts (2) were dried at 20° C and 2 mmHg and were normally solvated with 1 mol. equiv. of the alcohol. The rotation figures are corrected to account for the solvation. [c] Dried at 70 °C and 2 mmHg; m.p. 148—150° (Found: C, 51.5; H, 6.1; N, 3.8. $C_{15}H_{21}NO_8,0.5H_2O$ requires C, 51.2; H, 6.3; N, 4.0%).

[10] A. Hofmann, *J. Amer. Chem. Soc.*, 1927, **49**, 530.
[11] G. Losse, R. Wagner, P. Neuland, and J. Rateitschak, *Chem. Ber.*, 1958, **91**, 2410.

TABLE 2

Asymmetric transformation of substituted phenylglycine esters with 1 mol. equiv. of (+)-tartaric acid

Ester					Product hydrogen (+)-tartrate *			
R^2	R^1	Conc. (%)	Solvent	Carbonyl compd. (%)	Yield (%)	Isomer	$[\alpha]_D$ (°)	Optical purity (%)
m-MeO	Me	10	MeOH	None	41	D	−49.5	79
m-MeO	Me	10	MeOH	Me_2CO (50)	87 [a]	D	−62	>95
p-MeO	Pr^i	10	EtOH	None	*ca.* 71 [b]	DL	+11	0
p-MeO	Pr^i	9	EtOH	PhCHO (4.5)	50 [c]	L	+50.5	*ca.* 90
p-Cl	Me	10	MeOH	None	14 [d]	D	−53	85
p-Cl	Me	10	MeOH	Me_2CO (50)	58 [d]	D	−61	⩾96
p-Cl	Me	10	10% H_2O in EtOH	None	21	L	+42	*ca.* 40
p-Cl	Me	5	EtOH	*p*-MeO·C_6H_4·CHO (3.5)	46 [e]	D	−60	⩾96
p-HO	Et [f]	14	MeOH	Me_2CO (50)	67 [g]	D	−50	98
p-HO	Me	10	MeOH	None	38	D	−9	24
p-HO	Me	5	MeOH	Me_2CO (50)	78 [h]	L	+95	99
p-HO	Me	10	MeOH	PhCHO (6)	55	L	+93	96
p-HO	Me	10	MeOH–C_6H_6 (21 : 1)	PhCHO (6)	80	D	−68	98
p-HO	Me	12.5	MeCN	PhCHO (6)	96 [i]	D	−65	94

* The solvation with alcohols was measured by ^1H n.m.r.

[a] M.p. 157—158°, τ 2.85—3.20 and 2.62 (m and t, *J* 7 Hz, ArH), 5.11 (s, CH), 5.88 (s, [C*H*OH]$_2$), 6.21 (s, OMe), and 6.32 (s, Me) (Found: C, 46.9; H, 5.4; N, 3.8. $C_{14}H_{19}NO_9$,0.8CH_4O,0.5H_2O requires C, 46.8; H, 6.15; N, 3.7%). [b] Mixture; contained bis-ester tartrate. [c] M.p. 134—137° (Found: C, 48.95; H, 6.05; N, 3.35. $C_{16}H_{23}NO_9$,0.4C_2H_6O, H_2O requires C, 49.2; H, 6.7; N, 3.4%). [d] Solvated with methanol. [e] M.p. 150—156°, τ 2.49 (s, ArH), 5.05 (s, CH), 5.80 (s, [C*H*OH]$_2$), and 6.31 (s, Me) (Found: C, 44.2; H, 4.55; Cl, 10.05; N, 3.7. $C_{13}H_{16}ClNO_8$,0.2H_2O requires C, 44.2; H, 4.7; Cl, 10.0; N, 4.0%). [f] The salt (2b; R^2 = *p*-HO) did not crystallise from methanol. It was not resolved in ethanol, confirming Makleit's work (Sh. Makleit, F. Starichkai, and M. Pushkash, *Visn. Kiiv Univ. Ser. Fiz. Khim.*, 1967, No. 7, 155). [g] M.p. 88—90° (decomp. to give a liquid, then flat needles, m.p. 148—150°), τ 2.72 and 3.21 (ABq, *J* 8.5 Hz, ArH), 5.09 (s, CH), 5.83 (s, [C*H*OH]$_2$), and 5.83 and 8.84 (q and t, *J* 7 Hz, Et) (Found: C, 47.7; H, 6.0; N, 3.6. $C_{14}H_{19}NO_9$,CH_4O requires C, 47.75; H, 6.15; N, 3.7%). [h] M.p. 95—126°, τ 2.75 and 3.21 (ABq, *J* 8.5 Hz, ArH), 5.12 (s, CH), 5.93 (s, [C*H*OH]$_2$), and 6.34 (s, Me) (Found: C, 46.1; H, 5.8; N, 3.8. $C_{13}H_{17}NO_9$,CH_4O requires C, 46.25; H, 5.8; N, 3.85%). [i] Solvated with 1 mol. equiv. of acetonitrile.

TABLE 3

Preparation of optically active esters (1a and b) from the hydrogen (+)-tartrates (2a and b)

					Optical		Found (%)				Required (%)		
R^2	R^1	Isomer	Yield (%)	$[\alpha]_D$ (°)	purity (%)	M.p. (°C)	C	H	N	Formula	C	H	N
p-Cl	Me	D	99	−129 *	*ca.* 95	*a*	54.65	5.1	6.85	$C_9H_{10}ClNO_2$ [c]	54.2	5.05	7.0
m-MeO	Me	D	99	−135 *	>95	*a*	61.2	6.6	7.3	$C_{10}H_{13}NO_3$	61.5	6.7	7.2
p-HO	Me	L	89	+146 †	⩾98	159—173 [b]	58.9	6.05	7.6	$C_9H_{11}NO_3$,0.15H_2O	58.8	6.2	7.6
p-HO	Et	D	93	−110 †[d]	⩾98	127—130 [e]	60.8	6.7	6.95	$C_{10}H_{13}NO_3$,0.15H_2O	60.7	6.8	7.1

* In MeOH. † In N-HCl.

[a] Isolated as an oil. [b] Needles, m.p. 159—161° (decomp. to rectangular plates, m.p. 168—173°). [c] Found: Cl, 17.6. Required: Cl, 17.8%. [d] A recent patent [20] quotes $[\alpha]_D^{25}$ −109.2° (*c* 1 in HCl). [e] A recent patent [20] quotes m.p. 129—130°.

TABLE 4

Hydrolysis of the esters (1a—c) and the salt (2a)

Starting material				Product					
	R^2	R^1	Method	Yield (%)	Isomer	$[\alpha]_D$ (°) (H_2O)	$[\alpha]_D$ (°) (N-HCl)	Lit. $[\alpha]_D$ (°) (H_2O)	Lit. $[\alpha]_D$ (°) (N-HCl)
(1a)	*p*-Cl	Me	*a*	77 [c]	D		−129		
(1a)	*m*-MeO	Me	*a*	71	D		−137		−136 [d]
(2a)	*p*-HO	Me	*b*	78	D		−159		−154 [e]; −161.2 [f]
(1a)	*p*-HO	Me	*b*	76	L		+157	+107.7 [g]	
(1b)	*p*-HO	Et	*b*	88	D	−108	−158	−108 [g]	−154 [e]; −161.2 [f]
(1c)	H	Pr^i	*a*	71	L		+156		+158.5 [h]

[a] 6N-HCl at reflux.[2] [b] 2N-NaOH at *ca.* 20° C.[2] [c] M.p. 233—237° (decomp.), τ(F_3C·CO_2H) *ca.* 2.2br (s, CO_2H and NH_3^+), 2.48 (s, ArH), and 4.54 (ABq, CH) (Found: C, 51.8; H, 4.4; Cl, 18.8; N, 7.6. $C_8H_8ClNO_2$ requires C, 51.8; H, 4.3; Cl, 19.1; N, 7.55%). [d] U.S.P. 3 479 339 (*Chem. Abs.*, 1970, **72**, 55442n). [e] Ref. 23. [f] Ref. 22. [g] Ref. 21. [h] Ref. 2.

presence of a carbonyl compound. ^1H N.m.r. studies in deuteriomethanol (see below and Table 6) showed that the carbonyl compound rapidly formed the Schiff's base (3) from the salt (2) in solution. This was supported by the experiment starting with the DL-Schiff's base (3a; $R^2 = R^3 = H$), water, and (+)-tartaric acid.

Racemisation of Schiff's base. We have considered two mechanisms for the racemisation of the Schiff's base (3) (top of Scheme 1 and Scheme 2). The rates of racemisation and deuteriation of the D-Schiff's bases in [$^2H_6$]-dimethyl sulphoxide were nearly the same, suggesting that deuteriation and racemisation proceeded by the same mechanism. Only one proton (τ 4.58; the benzylic proton) was exchanged for deuterium. The azomethine proton (τ 1.43) was not exchanged. This supports the mechanism in Scheme 1. The carbanion would be

stabilised by the C=N bond and the ester group. Auld and Davison [12] have previously reached a similar conclusion in their study of deuteriation of chelates of glycine esters.

SCHEME 2

Electron-withdrawing groups on either aromatic ring of the Schiff's base (3) increase the rate of racemisation or deuteriation (Table 5). This result also favours the mechanism in Scheme 1. Taguchi and Ishida [8] have reached a similar conclusion about the mechanism of racemisation of Schiff's bases of ethyl D-methioninate.

TABLE 5

Relative rates of deuteriation and racemisation of Schiff's bases (3a)

Substituent R^2	Substituent R^3			
		p-NO_2	H	p-MeO
	σ:	+0.78	0.0	−0.2
p-Cl	+0.226		2.0 [a]	
H	0.0	30.0 [a,b]	1.0 [a,b]	0.3 [b]
p-HO	−0.35	30.0 [b]	0.8 [b]	0.15 [b]

[a] Calculated from the time for 50% racemisation. [b] Calculated from the time for 50% deuteriation.

Racemisation or deuteriation of the Schiff's bases was relatively slow in the absence of anions, confirming reports [5,6] on the optical stability of Schiff's bases. Sodium 3-(trimethylsilyl)propanesulphonate, the internal standard for ^{1}H n.m.r. usually added (0.14%) to [$^2H_6$]dimethyl sulphoxide, was a strong enough base to accelerate the racemisation and deuteriation. The hydrogen (+)-tartrate anion was an even more effective base.

Solution equilibria and crystallisation. In order to find out more about the solution equilibria in a solvent resembling those used for the asymmetric transformation, the protons of the OH and NH groups of the salt (2a; R^2 = H) were exchanged for deuterium. The hexadeuteriated salt (2a; R^2 = H) was dissolved in deuteriomethanol (thereby avoiding crystallisation, which would disturb equilibria), and treated with 1 equiv. of anisaldehyde, benzaldehyde, or p-nitrobenzaldehyde. The reaction was studied by ^{1}H n.m.r. (Tables 6 and 8). The results show that the equilibria in step 2 (Scheme 1) must be fast (less than 16 min) and that the deuteriation and therefore racemisation of the Schiff's base is rapid in the presence of hydrogen tartrate anion.

TABLE 6

Formation and deuteriation of Schiff's bases in deuteriomethanol

Ar	Time to equilibrium (min)	% Schiff's base at equilibrium	Time for H–D exchange of benzylic protons
p-NO_2·C_6H_4	<11	50	<11 min
Ph	<16	50	4 h
p-MeO·C_6H_4	<11	35	6 h

When 1 equiv. of benzaldehyde was added to a solution of racemic methyl phenylglycinate hydrogen (+)-tartrate in methanol, there was only a small change in rotation. This indicated that there was little, if any, asymmetry induced in solution (*i.e.* no first-order asymmetric transformation [13]) and that the equilibria in solution did not therefore determine the course of the asymmetric transformation. The product from the asymmetric transformation is therefore settled at step 1 (Scheme 1), which gives presumably the most thermodynamically stable product.

TABLE 7

Preparation of Schiff's bases (3a)

R^2	R^3	Isomer	Yield * (%)	M.p. (°C)	$[\alpha]_D$ (°)	Found (%) C	H	N	Formula	Required (%) C	H	N
H	H	D	S	49—60	+57							
H	NO_2	D	S		+14							
H	MeO	D	S		+38							
p-Cl	H	L	S		−26							
H	H	DL	60	67—69		75.7	6.15	5.15	$C_{16}H_{15}NO_2$	75.9	6.0	5.5
H	NO_2	DL [a]	17	134—140		64.6	4.8	9.05	$C_{16}H_{14}N_2O_4$	64.4	4.7	9.4
H	MeO	DL [b]	14	106—108		72.25	6.1	4.7	$C_{17}H_{17}NO_3$	72.1	6.05	4.95
p-HO	H	DL [c]	62	129—133		71.45	5.7	4.8	$C_{16}H_{15}NO_3$	71.4	5.6	5.2
p-HO	NO_2	DL [d]	38	175—182		61.0	4.55	8.7	$C_{16}H_{14}N_2O_5$	61.15	4.5	8.9
p-HO	MeO	DL [e]	51	96—107		67.2	5.9	3.7	$C_{17}H_{17}NO_4$,0.5H_2O, 0.35 $C_8H_8O_2$	66.8	5.9	3.9

* S, made in benzene from the ester and 1 mol. equiv. of aldehyde. The Schiff's base was not isolated nor characterised. The specific rotation was calculated from the maximum rotation of the solution (a *ca.* 6% solution), on the assumption of complete conversion into the Schiff's base.

[a] τ 1.28 (s, CH=), 1.61 and 1.89 (ABq, J 8.5 Hz, p-NO_2·C_6H_4), 2.30—2.70 (m, Ph), 4.49 (s, removed by D_2O, PhC*H*), and 6.29 (s, Me). [b] τ 1.54 (s, CH=), 2.18 and 2.93 (ABq, J 8.5 Hz, p-MeO·C_6H_4), 2.35—2.75 (m, Ph), 4.66 (s, removed by D_2O, PhC*H*), 6.16 (s, OMe), 6.31 (s, Me). [c] τ 0.60br (s, OH), 1.55 (s, CH=), 2.00—2.70 (m, *Ph*CH=), 2.68 and 3.20 (ABq, J 8.5 Hz, p-HO·C_6H_4), 4.73 (s, removed by D_2O, CH), 6.32 (s, Me). [d] τ 0.50br (s, OH), 1.36 (s, CH=), 1.62 and 1.92 (ABq, J 9 Hz, p-NO_2·C_6H_4), 2.65 and 3.18 (ABq, J 8.5 Hz, p-HO·C_6H_4), 4.62 (s, removed by D_2O, CH), and 6.31 (s, Me). [e] τ 0.58br (s, OH), 1.65 (s, CH=), 2.22 and 2.96 (ABq, J 8.5 Hz, p-MeO·C_6H_4), 2.70 and 3.21 (ABq, J 8.5 Hz, p-HO·C_6H_4), 4.80 (s, removed by D_2O, CH), 6.18 (s, OMe), and 6.33 (s, Me), and resonances indicating the presence of 0.35 mol. equiv. of anisaldehyde.

[12] G. A. Auld and A. Davison, *Inorg. Chem.*, 1968, **7**, 306.
[13] E. E. Turner and M. M. Harris, *Quart. Rev.*, 1947, 299.

The principle of the asymmetric transformation can apply to any asymmetric amine ($R^1R^2CH{\cdot}NH_2$) provided that the amino-group is sufficiently basic to form a salt with the optically active acid. In practice at least one of the groups attached to the asymmetric carbon atom should be electron-withdrawing, in order to get sufficiently fast racemisation.

There are many asymmetric transformations in which the optical lability is caused by rotation about single bonds.[13,14] Some asymmetric transformations involve tautomerism [15] or formation of a planar carbocation, [14] but ours is apparently the first involving an optically and chemically labile intermediate.

TABLE 8

^{1}H N.m.r. data for the ester (1a; R^2 = H), the hydrogen (+)-tartrate (2a; R^2 = H), and the Schiff's bases (3a; R^2 = H) in deuteriomethanol

			τ Values (singlets unless otherwise stated)						
	R^1	R^3	Ph	CH	$[CHOH]_2$	R^1	R^3	*Ar*CH=	CH=
(1a)	Me		2.72	5.47		6.38			
(2a)	Me		2.65	4.82	5.61	6.20			
(3a)	Me	H	*ca.* 2.7	4.77 *		6.29		2.15—2.90 (m)	1.77
(3a)	Me	*p*-MeO	2.78 (m)	4.82 *		6.27	6.19	2.37 and 3.15 (ABq, *J* 9 Hz)	1.86
(3a)	Me	*p*-NO_2	*ca.* 2.6	4.63 *		6.26		1.70 and 1.97 (ABq, *J* 9 Hz)	1.46

* Removed by exchange with deuterium from the solvent.

EXPERIMENTAL

The general procedures are those described previously.[2] *p*-Methoxyphenylglycine [16] was made by the method of Steiger.[17] *m*-Methoxy-,[18] *p*-chloro-, and *p*-hydroxy-phenylglycines were made by the method of Harvill and Herbst.[19] ^{1}H N.m.r. spectra were measured for solutions in [$^2H_6$]-dimethyl sulphoxide unless otherwise stated. Integrals are in agreement with the proposed structures.

Methyl DL-p-*Hydroxyphenylglycinate* (1a; R^2 = *p*-OH). —A solution of DL-*p*-hydroxyphenylglycine (4.96 g, 29.6 mmol) and concentrated sulphuric acid (3.95 ml, 7.26 g, 74.1 mmol) in dry methanol (20 ml) was refluxed for 2 h. Ammonium hydroxide solution (*d* 0.880) was added to neutralise the solution (pH 7), giving a solid, which was washed and dried to give the *ester* (4.80 g, 90%) as white needles, m.p. 178—180°, τ 2.81 and 3.28 (ABq, *J* 8.5 Hz, ArH), 5.58(s, CH), and 6.41(s, Me) (Found: C, 58.65; H, 6.2; N, 7.75. $C_9H_{11}NO_3$,0.15 H_2O requires C, 58.8; H, 6.2; N, 7.6%).

The following DL-esters were prepared similarly: *ethyl* DL-p-*hydroxyphenylglycinate* (1b; R^2 = *p*-HO) as white needles (88%), m.p. 145—155°,* τ 2.79 and 3.25 (ABq, *J* 9 Hz, ArH), 5.59 (s, CH), and 5.91 and 8.88 (q and t, *J* 7 Hz, Et) (Found: C,61.2; H, 6.65; N, 7.05. $C_{10}H_{13}NO_3$ requires C, 61.5; H, 6.7; N, 7.2%); *methyl* DL-*p-chlorophenylglycinate* (1a; R^2 = *p*-Cl), which was extracted with methylene chloride to give pale yellow needles (76%), m.p. 43—44°, τ ($CDCl_3$) 2.66 (s, ArH), 5.40 (s, CH), 6.30 (s, Me), and 8.12 (s, NH_2) (Found: C, 54.5; H, 5.0; Cl, 17.6; N, 6.7. $C_9H_{10}ClNO_2$ requires C, 54.2; H, 5.0; Cl, 17.8; N, 7.0%); *methyl* DL-m-*methoxyphenylglycinate* (1a; R^2 = *m*-MeO) was extracted with methylene chloride to give an oil (99%) contaminated with methylene chloride (*ca.* 0.02 mol. equiv.), τ 2.90—3.25 and 2.68 (m and t, *J* 7.5 Hz, ArH), 5.45 (s, CH), 6.21 (s, OMe), 6.36 (s, Me) and 7.73 (s, NH_2) (Found: C, 60.6; H, 6.6; Cl, 0.7; N, 7.1. $C_{10}H_{13}NO_3$ containing 0.02 mol. equiv. of CH_2Cl_2 requires C, 61.1; H, 6.7; Cl, 0.7; N, 7.1%); *isopropyl* DL-p-*methoxyphenylglycinate* (1c; R^2 = *p*-MeO) was extracted with methylene chloride to give a tan oil (90%), τ ($CDCl_3$) 2.68 and 3.13 (ABq, *J* 9Hz, ArH), 4.96 (sept, *J* 7 Hz, C*H*Me_2), 5.99 (s, C*H*Ar), 6.20 (s, OMe), 8.01 (s, NH_2), and 8.75 and 8.90 (two d, *J* 7 Hz, CH*Me*$_2$) (Found: C, 63.75; H, 7.35; N, 5.85. $C_{12}H_{17}NO_3$,0.15H_2O requires C, 63.8; H, 7.7; N, 6.2%).

Preparation and Racemisation of Methyl N-*Benzylidene*-D-*Phenylglycinate*.—A solution of methyl D-phenylglycinate (186 mg, 1.13 mmol) in dimethyl sulphoxide (2.5 ml) was treated with benzaldehyde (0.12 ml, 125 mg, 1.18 mmol, 1.05 equiv.) at 20 °C. The rotation (α) changed from −7.60 to +5.24° during 6 h, indicating formation of the D-Schiff's base (3a; R^2 = R^3 = H). The rotation had fallen half-way to the racemic value after 4 days at 20 °C.

In a similar experiment but without benzaldehyde, the rotation of a solution of methyl D-phenylglycinate in dimethyl sulphoxide had fallen by 50% after 22 days at 20 °C.

Other optically active Schiff's bases were similarly made *in situ* (Table 7) and their racemisation was recorded. The relative rates of racemisation are shown in Table 5.

Asymmetric Transformation of Methyl DL-*Phenylglycinate*. —A solution of methyl DL-phenylglycinate (4.934 g, 29.8 mmol), (+)-tartaric acid (4.497 g, 29.8 mmol, 1.0 equiv.), and benzaldehyde (3.0 ml, 3.14 g, 29.6 mmol, 1 equiv.) in ethanol (46 ml) was stirred at 70 °C. A solid crystallised at *ca.* 60 °C. The mixture cooled to 21 °C during 30 min, and was stirred at 21 °C for a total of 24 h. The solid was filtered off, washed with ethanol (3 × 12 ml), and dried at 20 °C and 2 mmHg for 4 h to give the salt (2a; R^2 = H) as a monoethanolate (9.177 g, 85%), m.p. 142—144° (lit.,[2] 140—144°), $[\alpha]_D^{21}$ −64° (*c* 2.500 in H_2O) (lit.,[2] $[\alpha]_D$ −65°).

Methyl DL-N-*Benzylidenephenylglycinate*.—A solution of methyl DL-phenylglycinate (2.073 g, 12.5 mmol) and benzaldehyde (1.33 g, 12.9 mmol, 1.03 equiv.) in benzene (50 ml) was refluxed for 2½ h under a Dean–Stark head. The clear pale yellow solution was evaporated to give a semicrystalline mass (3.40 g, 100%). A sample was crystallised from ethanol to give the DL-*Schiff's base* (3a; R^2 = R^3 = H) as prisms, m.p. 67—69°, τ 1.43 (s, CH=), 1.95—2.70 (m, *Ph*CH=), *ca.* 2.6 (s, *Ph*CH), 4.58 (s, removed by D_2O, PhC*H*),

* A recent patent [20] gives m.p. 160—161° (from ethanol).

[14] M. M. Harris, *Progr. Stereochem.*, 1958, **2**, 157.
[15] M. K. Hargreaves and M. A. Khan, *J.C.S. Perkin II*, 1973, 1204.
[16] F. Tiemann and K. Köhler, *Ber.*, 1881, **14**, 1979.
[17] R. E. Steiger, *Org. Synth.*, Coll. vol. III, 1967, p. 84.
[18] A. H. Neims, D. C. De Luca, and L. Hellerman, *Biochemistry*, 1966, **5**, 203.
[19] E. K. Harvill and R. M. Herbst, *J. Org. Chem.*, 1944, **9**, 21.
[20] G.P. 2,345,302 (*Chem. Abs.*, 1974, **80**, 133823w).

and 6.30 (s, Me). Other constants of this and other similarly made Schiff's bases are summarised in Table 7.

Methyl D-*Phenylglycinate Hydrogen* (+)-*Tartrate from Methyl* DL-N-*Benzylidenephenylglycinate.*—A solution of the DL-Schiff's base (3a; $R^2 = R^3 = H$) (8.132 g, 32.1 mmol), (+)-tartaric acid (4.947 g, 32.9 mmol, 1.02 equiv.), and water (0.55 ml, 30.5 mmol, 0.95 equiv.) in ethanol was cooled from 50 to 22 °C during 1 h. A solid had crystallised after 2 min. The thick suspension was stirred at 22 °C for a further 20 h. The product was filtered off, washed, and dried to give the D-salt (2a; $R^2 = H$) as a monoethanolate (8.054 g, 69%), $[\alpha]_D^{24}$ −65° (*c* 1.011 in H_2O).

Inversion of Ethyl L-*Phenylglycinate.*—A solution of ethyl L-phenylglycinate hydrogen (+)-tartrate (9.878 g; containing 0.5 mol. equiv. of ethanol; 28.1 mmol) and benzaldehyde (2.85 ml, 2.98 g, 28.1 mmol 1 equiv.) in ethanol (47 ml) at 50 °C was cooled with stirring to 22 °C during 50 min. A solid crystallised, and the suspension was stirred at 22 °C for 47 h. The product was filtered off, washed with ethanol (2 × 8 ml), and dried at 22 °C and 2 mmHg to give ethyl D-phenylglycinate hydrogen (+)-tartrate as a monoethanolate (7.449 g, 71%), $[\alpha]_D^{22}$ −47° (*c* 2.504 in H_2O) (lit.,[2] $[\alpha]_D$ −50°).

Asymmetric Transformation of Methyl DL-p-*Hydroxyphenylglycinate.*—A solution of the ester (1a; $R^2 = p$-HO) (4.984 g, 27.0 mmol), (+)-tartaric acid (4.053 g, 27.0 mmol, 1 equiv.), and benzaldehyde (3.0 ml, 3.14 g, 29.6 mmol, 1 equiv.) in methanol (50 ml) at 56 °C was diluted with benzene (2.4 ml, 2.1 g, 27 mmol, 1 equiv.), seeded with the D-salt (2a; $R^2 = p$-HO) [solvated with methanol (*ca.* 1.0 mol) and benzene (*ca.* 0.45 mol)], and when crystallisation had started, cooled to 30 °C during 6 h. The mixture was then stirred at 23 °C for a further 42 h, and the product was filtered off, washed with methanol (1 × 15 ml, 1 × 10 ml), and dried at 22 °C and 1 mmHg to give the D-*salt* (2a; $R^2 = p$-HO) solvated with methanol (*ca.* 1 mol. equiv.) and benzene (*ca.* 0.45 mol. equiv.), as white needles (8.682 g, 80%), m.p. 96—118° with partial resolidification at 105°, $[\alpha]_D^{20}$ −68° (*c* 1.039 in H_2O).

A sample of the D-salt (2a; $R^2 = p$-OH) [solvated with methanol (*ca.* 1.0 mol. equiv.) and benzene (*ca.* 0.45 mol. equiv.); 154.1 g; prepared as described above] was added with stirring to refluxing dry methanol (950 ml). The clear solution was cooled to 0 °C and the solid was filtered off, washed with methanol (4 × 100 ml), and dried at 20 °C and 1mmHg for 6 h to give the D-salt (2a; $R^2 = p$-HO) [solvated with methanol (*ca.* 1.0 mol. equiv.) and benzene (*ca.* 0.45 mol. equiv.)] as white needles (147 g, 95%), $[\alpha]_D^{22}$ −70°, (*c* 1.043 in H_2O).

A sample of the D-salt (2a; $R^2 = p$-HO) [solvated with methanol (*ca.* 1.0 mol. equiv.) and benzene (*ca.* 0.45 mol. equiv.); $[\alpha]_D$ −65°; 536 mg] was kept at 70—90 °C and 0.3 mmHg for 46 h. The weight dropped to 460 mg (*i.e.* 14% weight loss) and the sample then had m.p. 95—110°, $[\alpha]_D^{21}$ −55° (*c* 1.026 in H_2O), and was solvated with benzene (*ca.* 0.4 mol. equiv.) and methanol (*ca.* 0.1 mol. equiv.).

D- *and* L-*Esters* (1).—*Methyl* L-*p-hydroxyphenylglycinate.* The pH of a solution of methyl L-*p*-hydroxyphenylglycinate hydrogen (+)-tartrate (2a; $R^2 = p$-HO) (monomethanolate; $[\alpha]_D$ +94.5°; 4.105 g, 11.3 mmol) in water (17.5 ml) was adjusted to 7.0 with 5N-sodium hydroxide solution (4.5 ml, 22.5 mmol, 1 equiv.) to give a white precipitate. The stirred mixture was cooled and filtered, and the solid was washed and dried to give the *ester* (1a; $R^2 = p$-HO; 1.814 g, 89%) as white needles, m.p. 159—161° (decomp. to give rectangular plates m.p. 168—173°), $[\alpha]_D^{21}$ +146° (*c* 1.022 in N-HCl). Other constants are summarised in Table 3. The D-ethyl ester (1b; $R^2 = p$-HO) was made similarly; the methyl esters (1a; $R^2 = p$-Cl or *m*-MeO) were also made similarly but were extracted into methylene chloride. The constants for these esters are also summarised in Table 3.

Basic Hydrolysis of the Esters (1).—D-*p-Hydroxyphenylglycine.* A solution of ethyl D-*p-hydroxyphenylglycinate* (1.281 g, 6.56 mmol) was stirred at 20 °C in 2.22N-sodium hydroxide (6 ml; 13.3 mmol, 2.0 equiv.) for 15 min. The pH was adjusted from 11.8 to 6.6 with 2N-hydrochloric acid (6.2 ml, 12.4 mmol) giving a gel at pH 8.5. The mixture was warmed briefly to 30 °C to convert the gel into dense crystals, then cooled to 0 °C and filtered to give a solid which was washed and dried to yield the D-amino-acid (1; $R^1 = H$, $R^2 = p$-HO) (796 mg, 73%), m.p. 223—225° (decomp) [lit.,[21] 225° (decomp)], $[\alpha]_D^{22}$ −158° (*c* 1.015 in N-HCl), $[\alpha]_D^{23}$ −108° (*c* 1.011 in H_2O) [lit.,[22] $[\alpha]_D$ −161.2°; lit.,[23] −154° (in N-HCl); lit.,[21] −108° (H_2O)].

The filtrate was concentrated to give a second crop (164 mg, 15%), $[\alpha]_D^{21}$ −157° (*c* 1.002 in N-HCl).

Basic Hydrolysis of the Salts (2)—.D-p-*Hydroxyphenylglycine.* Powdered methyl D-*p*-hydroxyphenylglycinate hydrogen (+)-tartrate [solvated with methanol (*ca.* 1 mol. equiv.) and benzene (*ca.* 0.45 mol. equiv.); 41.59 g, 0.104 mol] was added during 10 min with stirring to a solution of sodium hydroxide (15.0 g, 0.375 mol, 3.6 equiv.) in water (75 ml) initially at 30 °C with cooling. The suspension was warmed to 50 °C and diluted with water (20 ml) to dissolve the solid. The solution was stirred at *ca.* 40 °C for 10 min and neutralised as before to give D-*p*-hydroxyphenylglycine (13.71 g, 79%), $[\alpha]_D^{22}$ −159° (*c* 1.053, N-HCl). Other similar hydrolyses are summarised in Table 4.

Asymmetric Transformation of Methyl DL-*Methioninate.*—A solution of methyl DL-methioninate[11] (10.033 g, 61.5 mmol) and (+)-tartaric acid (9.506 g, 63.5 mmol, 1.03 equiv.) in methanol (50 ml) was seeded with methyl L-methioninate hydrogen (+)-tartrate ($[\alpha]_D$ +29.6°) at 24 °C. Crystallisation occurred slowly and after 50 min anisaldehyde (7.5 ml, 8.43 g, 62 mmol, 1 equiv.) was added with stirring. The crystallising mixture was stirred for 44 h at 24 °C then filtered. The product was washed with methanol (2 × 10 ml) and dried at 25 °C and 2 mmHg for 3 h to give the L-salt (11.208 g, 58%), m.p. 142—145°, $[\alpha]_D^{24}$ +28.8° (*c* 3.038 in H_2O). Losse[11] quotes m.p. 137—140°, $[\alpha]_D$ +26.5° (*c* 3.17 in H_2O) for an 80% optically pure sample.

The filtrate from the asymmetric transformation (65 ml) was stirred with methyl DL-methioninate (13.031 g, 79.9 mmol) and (+)-tartaric acid (12.336 g, 82.3 mmol, 1.03 equiv.) for 28 days at 22 °C. It was filtered and dried as before to give the L-salt (25.335 g, 101%), $[\alpha]_D^{24}$ +29.7° (*c* 3.032 in H_2O).

Thus the combined yield for the two experiments was 82%. Similar results were obtained with benzaldehyde.

L-*Methionine.*—Methyl L-methioninate hydrogen (+)-tartrate ($[\alpha]_D$ +29.6°; 5.845 g, 18.7 mmol) was stirred at 22 °C with a solution of sodium hydroxide (2.466 g, 61.6 mmol, 3.30 equiv.) in water (12.5 ml). After 2 min the solid had dissolved, and t.l.c. showed that the reaction was

[21] A. A. W. Long, J. H. C. Nayler, H. Smith, T. Taylor, and N. Ward, *J. Chem. Soc.* (*C*), 1971, 1920.

[22] S.A.P. 68 05,703 (*Chem. Abs.*, 1970, **72**, 21684c).

[23] J. Eagles, W. M. Laird, S. Matai, R. Self, R. L. M. Synge, and A. F. Drake, *Biochem. J.*, 1971, **121**, 425.

complete. After 4 min a solid began to crystallise, and after 15 min it was filtered off [disodium tartrate (0.600 g, 16.5%)]. The pH of the filtrate was adjusted to 5.9 with concentrated hydrochloric acid. The mixture was cooled in ice and filtered, and the white solid was washed with water (2 × 3ml) and dried to give L-methionine (1.628 g, 58%), $[\alpha]_D^{22}$ +22.8° (*c* 1.004 in N-HCl) (lit.,[24] $[\alpha]_D$ +22.5°), which closely resembled an authentic sample.

Racemisation and Deuteriation of the D-*Schiff's Base* (3a; $R^2 = R^3 = H$).—A solution of the D-Schiff's base (3a; $R^2 = R^3 = H$) (0.385 g) in [$^2H_6$]dimethyl sulphoxide (5.5 ml) was treated with 10 drops of deuterium oxide. The rotation (α 1.600°) and the ^1H n.m.r. spectrum were measured immediately, then at intervals. After 11 h at 20 °C the rotation had dropped by 50% (α 0.800°). After 16 h the resonance at τ 4.58 (benzylic CH) had dropped in intensity by 50%; the resonance at τ 1.43 (azomethine CH) was unchanged. Racemisation (%) and deuteriation (%) were plotted against time. The two curves were very similar but not identical: the racemisation was always greater than the deuteriation.

The DL-Schiff's bases (3a; R^1 = H or *p*-HO, R^2 = MeO, NO_2, or H) were similarly deuteriated in [$^2H_6$]dimethyl sulphoxide. The results are summarised in Table 5.

Reaction between Methyl Phenylglycinate Hydrogen (+)-*Tartrate and Benzaldehyde.*—A solution of methyl phenylglycinate hydrogen (+)-tartrate (50 mg, 0.159 mmol) in deuterium oxide (2.5 ml) was left at 20 °C for 90 min then evaporated. The deuteriated salt was dissolved in deuteriomethanol (0.5 ml) and the ^1H n.m.r. spectrum was measured (Table 8). Benzaldehyde (17 mg, 0.160 mmol, 1 equiv.) was added and the spectrum of the solution was measured at intervals. The percentage Schiff's base (50%; from the resonances at τ 1.77, 4.77, and 6.29) was calculated after 16 min and found not to increase with time, indicating that the equilibration was rapid. After 4 h, complete exchange of the benzylic protons was indicated by the disappearance of the resonances at τ 4.77 and 4.82. Other similar results are summarised in Tables 6 and 8.

[5/1031 *Received*, 29*th May*, 1975]

[24] 'Dictionary of Organic Compounds,' eds. J. R. A. Pollock and R. Stevens, 4th edn., Eyre and Spottiswoode, London, 1965, p. 2100.