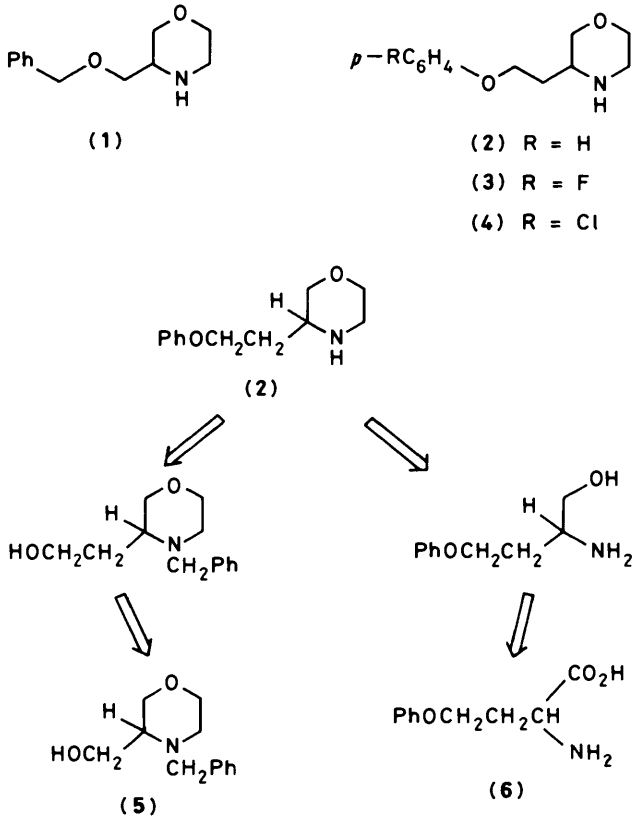
Synthesis and Resolution of 3-Substituted Morpholine Appetite Suppressants and Chiral Synthesis *via* O-Arylhomoserines

George R. Brown,* Alan J. Foubister, and Donald Stribling
Research Department II, ICI Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire

The synthesis and resolution of potential appetite suppressant 3-(2-aryloxyethyl)morpholines is described. Assignment of the absolute configuration of the resolved enantiomers is based on a chiral synthesis from *O*-phenylhomoserines of known configuration. Appetite suppressant effects in dogs are briefly reported.

We have reported[1] that the *S*-enantiomer of 3-benzyloxymethylmorpholine (**1**) has appetite suppressant activity when dosed orally to dogs. In order to explore the relationship between this appetite suppressant effect and chemical structure, the 3-phenoxyethyl isomer (**2**) of (**1**) was selected as a target for synthesis. The anorexiant activity of (**1**) in dogs was confined only to its *S*-enantiomer, the corresponding *R*-enantiomer being inactive. Thus a chiral synthesis or resolution of the morpholine (**2**) was required to determine whether its biological activity had the same stereospecific requirement. Two close halogeno substituted analogues, (**3**) and (**4**) of (**2**) were prepared to examine the effect of a *para* substituent in the phenyl ring, a potential site[2] for *in vivo* metabolism of the phenoxyethylmorpholine (**2**).



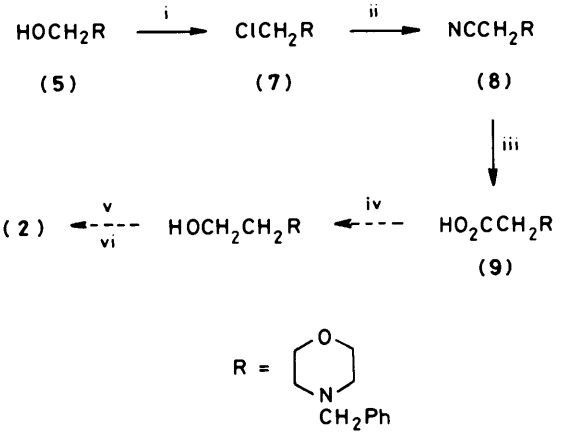
Scheme 1.

Consideration of the possible disconnections for retrosynthetic analysis of the preparation of these target molecules was influenced by the availability of two pertinent intermediates (**5**) and (**6**). These intermediates have been synthesized[3,4] in resolved and racemic forms and were thus chosen as the basis for two general synthetic routes to the target molecules (Scheme 1). In the first approach the morpholinomethanol (**5**), which can be prepared[3] from serine enantiomers in three synthetic steps, was converted (Scheme 2) into the chloro derivative (**7**)

Table 1. Aminophenoxybutanols

Compd.	M.p. (°C)	Found (%) C	H	N	Formula	Requires (%) C	H	N
(12)[a]	165—166	55.4	7.6	6.6	$C_{10}H_{16}ClNO_2$	55.2	7.4	6.4
(17)	68—69	75.1	7.7	4.8	$C_{17}H_{21}NO_2$	75.3	7.7	5.1
(17a)	64—65	75.6	7.8	5.1	$C_{17}H_{21}NO_2$	75.3	7.7	5.1
(18)	63—65	71.0	7.2	4.7	$C_{17}H_{20}FNO_2$	70.6	6.9	4.8
(19)	60—62	66.4	6.9	4.6	$C_{17}H_{20}ClNO_2$	66.8	6.5	4.6

[a] Hydrochloride salt



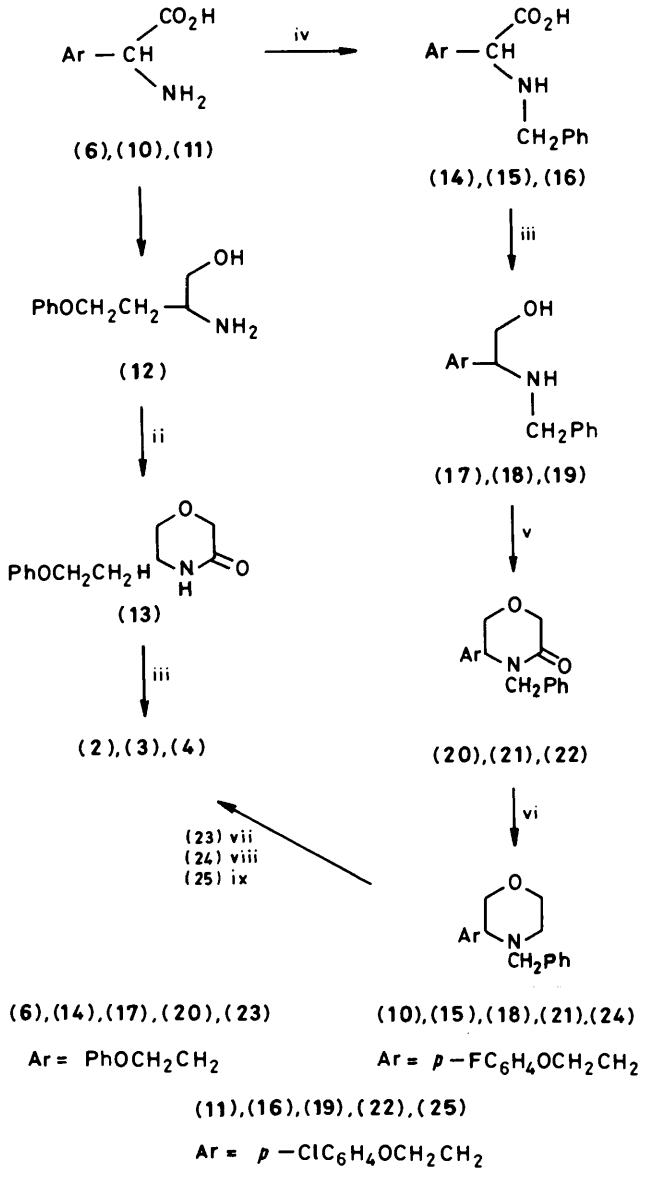
Scheme 2. *Reagents:* i, $SOCl_2$; ii, NaCN; iii, NaOH; iv, $LiAlH_4$; v, Diethyl azodicarboxylate–Ph_3P; vi, PhOH.

(Table 1) and allowed to react with sodium cyanide to obtain the nitrile (**8**). Hydrolysis of this nitrile proceeded in poor yield to give the acid (**9**). Progression of this route *via* reduction of the acid (**9**), Mitsonobu coupling with phenol, and debenzylation to give (**2**) was not attempted because accumulation of sufficient material for *in vivo* testing would be laborious. Alternative procedures to obtain (**2**) using the known[4] intermediate amino acid (**6**) were explored (Scheme 3). Reduction of the acid function of (**6**) to give the aminobutanol (**12**) (Table 1) and ring closure with chloroacetyl chloride to give the morpholinone (**13**) proceeded in good yield. Reduction of (**13**) to (**2**) proceeded in 66% yield. The second process (**14**)—(**23**) (Scheme 3) using the same reagents, but incorporating a benzyl protective group afforded (**2**) in an improved overall yield particularly in large

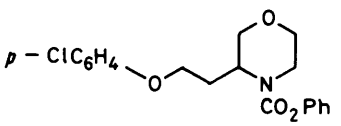
Table 2. 5-Substituted morpholin-3-ones

Compd.	M.p. (°C)	Found (%) C	H	N	Formula	Requires (%) C	H	N
(13)	79—81	65.0	6.8	6.0	$C_{12}H_{15}NO_3$	65.2	6.8	6.3
(20)	oil	73.7	6.5	4.3	$C_{19}H_{21}NO_3$	73.3	6.8	4.5
(20a)	oil	73.2	6.5	4.6	$C_{19}H_{21}NO_3$	73.3	6.8	4.5
(21)	oil	72.3	6.7	4.2	$C_{19}H_{20}FNO_3$	72.4	6.3	4.4
(22)	oil	66.0	5.9	3.9	$C_{19}H_{20}ClNO_3$	66.0	5.8	4.1

scale operation. The benzyl group was removed from (23) by catalytic hydrogenolysis. The fluoro and chloro derivatives (3) and (4) were prepared by this longer route, but the debenzylation step to give (3) was achieved by catalytic hydrogen transfer in the presence of ammonium formate. In the case of (4),



Scheme 3. *Reagents:* i, $NaBH_4$–BF_3Et_2O; ii, NaH–$ClCH_2CO_2Et$; iii, Na $(MeOEtO)_2AlH_2$; iv, PhCHO–$NaBH_4$; v, $ClCH_2COCl$–EtN_3–KOBu^t; vi, BH_3–Me_2S; vii, Pd–C–H_2; viii, Pd–C–HCO_2NH_4; ix, $ClCO_2Ph$–$NaHCO_3$; KOH–EtOH(aq.)



(26)

a phenylformate ester (**26**) was prepared and hydrolysed with potassium hydroxide in aqueous ethanol to achieve debenzylation.

Preparation of Morpholine Enantiomers.—The morpholine (**2**) was resolved by crystallisation of the salt with (+)-dibenzoyltartaric acid to give the (−)-enantiomer (**2b**). Treatment of the crystallisation solvent with the (−)-resolving acid gave the (+)-enantiomer (**2a**). The optical purity of (**2a**) and (**2b**) was shown to be >98% by h.p.l.c. examination of a derivative made from the chiral reagent methoxy(trifluoromethyl)phenylacetic acid (MPTA).[5] The fluoro analogue (**3**) was resolved in a similar manner to (**2**), to give the enantiomers (**3a**) and (**3b**). The absolute configuration of the morpholines (**2a**) and (**2b**) was determined by the synthesis of (**2a**) from the (*R,S*)-*O*-phenylhomoserine enantiomers (**6a,b**). The resolution was performed with brucine rather than the reported[4] strychnine, because of the lower toxicity of brucine. One of the resolved amino acids (**6a**) was elaborated through the intermediates (**14a**)—(**23a**) (Scheme 3) to give (**2a**) with optical rotation and melting point identical with a sample of (**2a**) prepared by direct resolution of (**2**). The known chirality of the homoserine (**6a**) enabled (**2a**) to be assigned as the *R*-enantiomer and consequently (**2b**) as the *S*-enantiomer.

The reason for carrying out these syntheses was that the 3-substituted morpholines would show appetite suppressant properties. Summary test results indicate that this rationale was supported (Table 3). In a previously reported[1] test, dogs given a 10 mg/Kg oral dose of test compound before a meat meal, ate significantly less food than control animals during the hour after food was supplied. The *R*- and *S*-enantiomers (**2a**) and (**2b**) were both potent appetite suppressants.

Experimental

M.p.s were determined with a Buchi apparatus and are uncorrected. The ^1H n.m.r spectra were determined with a Perkin-Elmer R12 (60 MHz) and a Varian EM390 (90 MHz) instrument (with $SiMe_4$ as an internal standard). Optical rotations were measured on a NDL 243 automatic polarimeter in a 2 ml cell and mass spectra on a MS 902 Kratos (AEI) instrument. Reactions were carried out under an atmosphere of nitrogen. Column chromatography was on E. Merck silica gel Kieselgel 60. Solvents were dried over $MgSO_4$ before evaporation. Ether is diethyl ether.

4-Benzyl-3-chloromethylmorpholine (**7**).—A solution of the morpholine (**5**) (2.0 g) in dichloromethane (15 ml) was treated with thionyl chloride (2 ml) and dimethylformamide (DMF) (2 drops) and the mixture heated under reflux for 2 h. The solvent was evaporated and the residue crystallised from ethanol–ether (1:1) to give the *hydrochloride* of (**7**) as a colourless solid, m.p. 123—126 °C (Found: C, 54.6; H, 6.9; N, 5.2. $C_{12}H_{17}Cl_2NO$ requires C, 55.0; H, 6.5; N, 5.3%). The hydrochloride was treated with an excess of saturated sodium hydrogen carbonate and extracted with ethyl acetate. The ethyl acetate was dried and evaporated and the residue chromatographed on silica gel in toluene. Elution with toluene–ethyl acetate (10:1) gave, on evaporation, (**7**) as a colourless oil (1.2 g, 65%); δ($CDCl_3$) 2.25 (m, 1 H, CH), 2.67 (m, 2 H, CH_2), 3.67 (m, 8 H, $4CH_2$) and 7.23 (m, 5 H, Ph); *m/z* 225 (M^+).

Table 3. 3-Substituted morpholines

Compd.	M.p. (°C)	Found (%) C	H	N	Formula	Requires (%) C	H	N	Reduction of food intake (%)
(2)[b]	142—143	59.0	7.6	5.6	$C_{12}H_{18}ClNO_2$	59.1	7.4	5.8	−51
(2)[c]	180—182	61.8	7.1	5.5	$C_{13}H_{18}NO_4$	61.9	7.1	5.6	
(2a)[b]	170—172	58.9	7.3	5.6	$C_{12}H_{18}ClNO_2$	59.1	7.4	5.8	−78
(2b)[b]	173—174	58.8	7.2	5.4	$C_{12}H_{18}ClNO_2$	59.1	7.4	5.8	−84
(3)[b]	147—149	55.1	6.5	5.4	$C_{12}H_{17}ClFNO_2$	55.1	6.5	5.4	−46
(3a)[b]	150—152	54.9	6.7	5.2	$C_{12}H_{17}ClFNO_2$	55.1	6.5	5.4	
(3b)[b]	150—152	55.1	6.8	5.2	$C_{12}H_{17}ClFNO_2$	55.1	6.5	5.4	
(4)[b]	159—161	51.7	6.2	4.6	$C_{12}H_{17}Cl_2NO_2$	51.8	6.2	5.0	−36
(7)	oil	63.6	7.1	5.9	$C_{12}H_{16}ClNO$	63.9	7.1	6.2	
(8)	oil	71.8	7.1	12.6	$C_{13}H_{16}NO_2$	72.2	7.4	13.0	
(9)[b]	105—108	57.1	6.7	4.8	$C_{13}H_{18}ClNO_3$	57.5	6.6	5.2	
(23)[b]	159—161	67.9	7.5	4.3	$C_{19}H_{24}ClNO_2$	68.3	7.2	4.2	
(23a)[b]	136—138	68.2	7.3	4.1	$C_{19}H_{24}ClNO_2$	68.3	7.2	4.2	
(24)[c]	103—105	62.2	6.1	3.2	$C_{21}H_{24}FNO_6$	62.2	5.7	3.5	
(25)[b]	132—134	61.5	6.3	3.6	$C_{19}H_{23}Cl_2NO_2$	61.9	6.3	3.8	
(26)	oil	63.5	5.6	3.5	$C_{19}H_{20}ClNO_4$	63.1	5.6	3.8	

[a] During 1 h after a 10 mg/kg oral dose to dogs[1]. [b] Hydrochloride salt. [c] Oxalate salt.

4-*Benzyl*-3-*cyanomethylmorpholine* (**8**).—The halide (**7**) (4.5 g) and sodium cyanide (930 mg) were heated at 70 °C for 3.5 h in dimethyl sulphoxide (DMSO) (15 ml) and the cooled mixture was diluted with water (150 ml). The mixture was extracted with ether and the ether washed with brine, dried, and evaporated to give an oil. The oil was purified by column chromatography on silica gel in toluene. Elution with ethyl acetate–toluene (1:10) gave as an oil the *nitrile* (**8**) (2.5 g, 58%); δ($CDCl_3$) 2.6 (m, 6 H, $3CH_2$), 3.6 (m, 5 H, $2CH_2$, CH) and 7.25 (m, 5 H, Ph).

4-*Benzylmorpholin*-3-*ylacetic Acid* (**9**).—The nitrile (**8**) (2.3 g) was stirred and heated under reflux in 40% (v/v) aqueous sodium hydroxide (6 ml) and water (6 ml) for 16 h and the cooled mixture extracted with dichloromethane. The aqueous phase was acidified with glacial acetic acid to pH 5.0 and evaporated. The residue was extracted with acetone (50 ml), filtered, and evaporated to give an oil. A solution of the oil in ether was treated with an excess of ethanol which was saturated with hydrogen chloride and the precipitate collected and crystallised from ethanol–ether to give the *hydrochloride* (**9**) (230 mg, 9%), m.p. 105—108 °C; δ($CDCl_3$) 2.7 (m, 5 H, $2CH_2$, CH), 3.8 (m, 6 H, $3CH_2$), 7.35 (m, 5 H, Ph) and 10.3 (s, 1 H, CO_2H).

2-*Amino*-4-*phenoxybutanol* (**12**).—Sodium borohydride (5.7 g) was added during 1 h to a stirred suspension of (**6**) (9.8 g) in tetrahydrofuran (180 ml) at 0 °C. The mixture was stirred at room temperature for 30 min and cooled to 0 °C before addition of boron trifluoride–diethyl ether (26 ml) during 1 h. Stirring was continued for 30 h and ethanol added until frothing ceased when the mixture was acidified to pH 1.0 with 6M hydrochloric acid. Water and solvent were evaporated and the residue heated in ethanolic hydrogen chloride for 5 min and cooled. The precipitate was crystallised from ethanol to give (**12**) as a colourless *hydrochloride* (5.7 g, 52%), m.p. 165—166 °C.

5-(2-*Phenoxyethyl*)*morpholin*-3-*one* (**13**).—The aminobutanol (**12**) (2.3 g) in toluene (50 ml) was added to a stirred suspension of sodium hydride [50% (w/w) dispersion in oil; 720 mg] in toluene (15 ml) at 0 °C. The mixture was allowed to reach room temperature and ethyl chloroacetate (1.5 ml) in toluene (15 ml) was added. The mixture was heated under reflux for 18 h and cooled. The toluene was washed with 2M hydrochloric acid, brine, and water prior to drying and evaporation to an oil. The oil was purified by column chromatography in chloroform on silica gel. Elution with methanol–chloroform (1:19) and crystallisation of the product from hexane–toluene afforded the *morpholinone* (**13**) (1.9 g, 68%), m.p. 79—81 °C; δ($CDCl_3$) 2.0 (q, 2 H, OCH_2CH), 3.5 (m, 1 H, CH), 3.9 (m, 6 H, $3CH_2$), 6.9 (m, 3 H, C_6H_3) and 7.3 (m, 2 H, C_6H_2).

3-(2-*Phenoxyethyl*)*morpholine* (**2**).—(a) Sodium bis(2-methoxyethoxy)aluminium hydride (3.4M solution in toluene; 4 ml) was added to a suspension of (**11**) (1.1 g) in toluene (15 ml) and the mixture stirred for 18 h. Ethanol was added until gas evolution ceased and the mixture was then made alkaline with 2M aqueous sodium hydroxide. The toluene layer was extracted with 2M hydrochloric acid and the acid extract made basic with 10M aqueous sodium hydroxide. The liberated oil was extracted with toluene and the extract then washed with saturated brine, dried, and evaporated to give an oil. The oil was treated with ethanolic hydrogen chloride and the hydrochloride precipitated with ether. Crystallisation gave (**2**) as a colourless crystalline *hydrochloride* (780 mg, 66%), m.p. 142—143 °C; δ [$(CD_3)_2SO$] 2.1 (m, 2 H, OCH_2CH_2CH), 3.4 (m, 7 H, CH, 3 CH_2), 4.2 (t, 2 H, $PhOCH_2$), 6.9 (m, 3 H, C_6H_3), 7.25 (m, 2 H, C_6H_2), and 9.7 (m, 2 H, NH_2^+); *m/z* 207 (M^+).

(b) A solution of the oxalate of the morpholine (**23**) (400 mg) in ethanol (20 ml) and water (0.5 ml) was hydrogenated at atmospheric pressure over palladium-on-carbon catalyst (150 mg, 5%) for 1 h. The catalyst was filtered off, the filtrate evaporated, and the residue crystallised from ethanol to give as a colourless solid the *oxalate* of (**2**) (150 mg, 58%), m.p. 165—166 °C.

2-*Benzylamino*-4-*phenoxybutanoic Acid* (**14**).—Benzaldehyde (4 ml) was added with vigorous stirring to a solution of (**6**)[4] (7.8 g) and sodium hydroxide (1.6 g) in water (50 ml) and was stirred continuously for 15 min. The mixture was cooled to 0 °C and sodium borohydride (480 mg) added during 30 min. Stirring was continued for 30 min with the reaction temperature maintained at 10—20 °C and the mixture cooled to 16 °C. A second portion of benzaldehyde (4 ml) was added as before, followed by sodium borohydride (480 mg) at 0 °C. The mixture was stirred for 2 h without cooling, filtered, and washed with ether. The aqueous phase was acidified to pH 6 with 6M

hydrochloric acid and the precipitate collected and washed with boiling water to give as a colourless solid the acid (**14**) (9.0 g, 79%), m.p. 213—215 °C (Found: C, 71.2; H, 6.4; N, 5.0 $C_{17}H_{19}NO_3$ requires C, 71.6; H, 6.6; N, 4.9%); δ[$(CD_3)_2SO$] 2.08 (m, 2 H, $PhOCH_2CH_2$), 3.54 (m, 3 H, $CHCH_2$), 4.1 (m, 2 H, $PhOCH_2$), 6.9 (m, 4 H, C_6H_4), and 7.3 (m, 6 H, C_6H_6).

2-*Benzylamino*-4-*phenoxybutanol* (**17**).—Sodium bis(2-methoxyethoxy)aluminium hydride (3.4M solution in toluene; 3 ml) was added to a stirred suspension of the acid (**14**) (1.47 g) in toluene (12 ml) and the mixture heated under reflux for 6 h. The mixture was allowed to cool and ethanol added until gas evolution ceased. The toluene was washed with M sodium hydroxide solution and saturated brine, dried, and evaporated. The residue was crystallised from toluene to give the *alcohol* (**17**) (800 mg, 57%), m.p. 68—69 °C; δ($CDCl_3$) 2.05 (m, 4 H, CH_2, OH, NH), 3.0 (m, 1 H, $CHNH$), 3.56 (O, 2 H, CH_2OH) 3.83 (s, 2 H, $NHCH_2Ph$), 4.1 (t, 2 H, $PhOCH_2$), 6.9 (m, 3 H, C_6H_3) and 7.25 (m, 7 H, ArH).

4-*Benzyl*-5-(2-*phenoxyethyl*)*morpholin*-3-*one* (**20**).—Chloroacetyl chloride (1 ml) was added during 5 min to a stirred solution of the alcohol (**17**) (3.3 g) and triethylamine (1.66 ml) in toluene (50 ml) maintained at −3 °C. The mixture was stirred at −3 °C for 1 h and at 22 °C for 18 h. The toluene was washed with 2M hydrochloric acid and saturated brine, dried, and evaporated to give an oil. The oil (4.2 g) and potassium t-butoxide (1.12 g) were heated under reflux for 6 h in t-butyl alcohol (20 ml), after which the latter was evaporated. The residue was dissolved in ether and the ether washed with 2M hydrochloric acid and saturated brine before evaporation. The residue was purified by column chromatography on silica gel in toluene when elution with ethyl acetate–toluene (1:9) afforded as a colourless oil the *morpholinone* (**20**) (2.5 g, 66%); δ($CDCl_3$) 2.2 (m, 2 H, OCH_2CH_2CH), 3.7 (m, 6 H, 2 CH_2, 2 CH), 4.25 (2 H, NCH_2Ph), 5.45 (d, 1 H, CHCON), 6.93 (m, 3 H, C_6H_3), and 7.25 (m, 7 H, ArH); *m/z* 311 (M^+).

4-*Benzyl*-3-(2-*phenoxyethyl*)*morpholine* (**23**).—Borane–dimethyl sulphide complex (10M; 2 ml) was added to a stirred solution of the morpholinone (**20**) (2.35 g in tetrahydrofuran (50 ml) at 0 °C and the mixture stirred for 18 h at room temperature. Water was added to destroy the excess of borane and the tetrahydrofuran evaporated. The residue was treated with ethyl acetate and 2M aqueous sodium hydroxide and the ethyl acetate extracted with 2M hydrochloric acid. The acid was made basic with 10M aqueous sodium hydroxide and extracted with ethyl acetate. The extract was washed with saturated brine, dried, and evaporated to give an oil. The oil was dissolved in ether and treatment with an excess of ethanolic hydrogen chloride afforded a precipitate. Filtration and crystallisation of the precipitate from ethanol gave as a colourless solid, the hydrochloride of (**23**) (1.2 g, 49%), m.p. 159—161 °C; δ[$(CD_3)_2SO$] 2.3 (m, 2 H, OCH_2CH_2CH), 2.8 (m, 2 H, CH_2), 3.7 (m, 9 H, 4 CH_2CH), 6.6 (m, 2 H, 2 CO_2H), 6.9 (m, 3 H, C_6H_3) and 7.5 (m, 7 H, ArH); *m/z* 297 (M^+).

O-4-*Fluorophenylhomoserine* (**10**)[4].—2-(4-Fluorophenoxy)-ethyl bromide (62%) 66—77 °C/0.1 mmHg was allowed to react with diethyl acetamidomalonate to give, as a colourless solid, (**10**) (41%), m.p. 216—219 °C (Found: C, 56.4; H, 5.8; N, 6.2. Calc. for $C_{10}H_{12}NO_3$: C, 56.3; H, 5.6; N, 6.6%).

O-4-*Chlorophenylhomoserine* (**11**).—Prepared in a similar manner to (**10**) above, via 2-(4-chlorophenoxy)ethyl bromide (54%), m.p. 37—40 °C, compound (**11**) was obtained as a colourless solid (40%), m.p. 235—237 °C (Found: C, 52.2; H, 5.4; N, 5.8. $C_{10}H_{12}ClNO_3$ requires C, 52.3; H, 5.2; N, 6.15%).

2-*Benzylamino*-4-(4-*chloro and* 4-*fluorophenoxy*)*butanoic Acid* (**15**) *and* (**16**).—These compounds, prepared in a manner identical with that described for (**14**), were obtained as colourless solids: (**15**) (81%), m.p. 210—211 °C (Found: C, 67.5; H, 6.2; N, 4.4. $C_{17}H_{18}FNO_3$ requires C, 67.3; H, 5.9; N, 4.6%) and (**16**) (90%), m.p. 216—218 °C (Found: C, 63.7; H, 5.3; N, 4.0 $C_{17}H_{18}ClNO_3$ requires C, 63.8; H, 5.6; N, 4.4%).

3-[2-(4-*Fluorophenoxy*)*ethyl*]*morpholine*(**3**).—Palladium-on-carbon catalyst (10%; 1.7 g) and ammonium formate (5.4 g) were added to a stirred solution of (**24**) (6.7 g) in ethanol (150 ml) under argon. After 30 min the catalyst was filtered off and the ethanol evaporated. The residue was dissolved in ethyl acetate and washed with 2M sodium hydroxide solution and brine. Evaporation of the ethyl acetate gave an oil which after treatment with ethanolic hydrogen chloride and crystallisation from ethanol–ether, gave as a colourless solid the hydrochloride (**3**) (4.5 g, 94%), m.p. 127—129 °C. δ[$(CD_3)_2SO$] 2.05 (m, 2 H), 3.5 (m, 9 H), 7.1 (m, 4 H) and 9.85 (m, 2 H).

3-[2-(4-*Chlorophenoxy*)*ethyl*]-4-*phenoxycarbonyl-morpholine* (**26**).—A mixture of (**25**) (10.7 g), sodium hydrogen carbonate (8.36 g), and phenyl chloroformate (15.0 g) were stirred for 18 h in dichloromethane (250 ml). The mixture was filtered and the filtrate washed with 2M hydrochloric acid, dried, and evaporated to give an oil. The oil was purified by column chromatography in ethyl acetate–toluene (1:9, v/v) to give as a colourless oil (**26**) (10.6 g, 91%) $\nu_{max.}$ 1 720 cm^{-1}(CO).

3-[2-(4-*Chlorophenoxy*)*ethyl*]*morpholine* (**4**).—A solution of potassium hydroxide (10.0 g) and (**26**) (10.5 g) in water–ethanol (1:3, v/v; 180 ml) was heated under reflux for 18 h after which the ethanol was evaporated. The aqueous residue was extracted with toluene and the toluene extracted with 2M hydrochloric acid. The acid was made basic to pH 10 with 10M sodium hydroxide and the liberated oil extracted with ethyl acetate. The ethyl acetate was evaporated and the residue treated with an excess of ethanolic hydrogen chloride to give after crystallisation from isopropyl alcohol (**4**) as a colourless hydrochloride (4.7 g, 58%), m.p. 159—161 °C.

(*R*) *and* (S)-3-(2-*Phenoxyethyl*)*morpholine* (**2a,b**).—A boiling solution of (+)-dibenzoyl-D-tartaric acid (6.8 g) in isopropyl alcohol (80 ml) was added to (**2**) (15.0 g) in isopropyl alcohol (40 ml). The solution was allowed to cool to room temperature and filtered. The filtrate was retained (see below). The collected precipitate was crystallised from methanol–water (1:1) to give (**2b**) as a tartrate salt, m.p. 183—185 °C. The salt was made alkaline with 2M sodium hydroxide and the base extracted with dichloromethane. The solvent was dried and evaporated and the residue treated with ethanolic hydrogen chloride to give, after crystallisation from isopropyl alcohol, as a colourless solid (**2b**) *hydrochloride* (3.4 g, 39%), m.p. 173—174 °C $[\alpha]_D^{22}$ −12° (*c* = 2.0 in water). The filtrate above, was treated with a hot solution of (−)-dibenzoyl-L-tartaric acid (6.8 g) in isopropyl alcohol (40 ml) as described above, to give a second tartrate salt, m.p. 183—185 °C. This salt gave in a similar manner a *hydrochloride* (**2a**) (2.4 g, 28%), m.p. 174—175 °C, $[\alpha]_D^{22}$ +12°5′ (*c* = 2.2 in water).

(+)- *and* (−)-3-[2-(4-*Fluorophenoxy*)*ethyl*]*morpholine* (**3a,b**).—The resolution of (**3**) was carried out in a manner identical with that of (**2**) to give a (−)-tartrate salt, m.p. 182—183 °C which afforded as a colourless crystalline *hydrochloride* (**3b**) (32%), m.p. 150—152 °C, $[\alpha]_D^{22}$ −10°40′ (*c* = 1.4 in 2M hydrochloric acid). Treatment of the filtrate gave a (+)-tartrate salt, m.p. 181—183 °C which afforded as a colourless crystalline

hydrochloride (**3a**) (35%), m.p. 150—152 °C, $[\alpha]_D^{22}$ +10°30′ (c = 1.6 in 2M hydrochloric acid).

Chiral Synthesis of (*R*)-3-(2-*Phenoxyethyl*)*morpholine* (**2a**).—The synthesis of (**2a**) was carried out in a manner identical with that of (**2**) (Scheme 3) from the known chiral acid (**6a**). There was thus obtained: after crystallisation from water and as a colourless solid (*R*)-2-benzylamino-4-phenoxybutanoic acid (**14a**) (80%), m.p. 223—224 °C (Found: C, 71.1; H, 6.6; N, 4.7. $C_{17}H_{19}NO_3$ requires C, 71.5; H, 6.7; N, 4.9%), $[\alpha]_D^{22}$ −14° (c = 1.0 in 2M hydrochloric acid), after crystallisation from hexane and as a colourless solid (*R*)-2-benzylamino-4-phenoxybutanol (**17a**) (85%), m.p. 64–65 °C, $[\alpha]_D^{22}$ −6° (c = 1.0 in dichloromethane), after column chromatography on silica gel and as a colourless oil (*R*)-4-benzyl-5-(2-phenoxyethyl)oxomorpholin-3-one (**20a**) (80%), $[\alpha]_D^{22}$ −37°5′ (c = 1.0 in ethyl acetate), after crystallisation from isopropyl alcohol–ether (*R*)-4-benzyl-3-(2-phenoxyethyl)morpholine hydrochloride (**23a**) (56%), m.p. 136—138 °C, $[\alpha]_D^{22}$ −30°5′ (c = 1.34 in water) and after crystallisation from isopropyl alcohol–ether (*R*)-3-(2-phenoxyethyl)morpholine hydrochloride (**2a**) (85%), m.p. 170—172 °C $[\alpha]_D^{22}$ +12°15′ (c = 1.74 in water).

References

1 G. R. Brown, G. Forster, A. J. Foubister, and D. Stribling *J. Med. Chem.*, 1986, **29**, 1288.
2 D. E. Case and P. R. Reeves, *Xenobiotica*, 1975, **5**, 113.
3 G. R. Brown, A. J. Foubister, and B. Wright, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2577.
4 M. D. Armstrong, *J. Am. Chem. Soc.*, 1948, **70**, 1756.
5 J. A. Dale, D. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

Received 14*th March* 1986; *Paper* 6/507