Chiral Synthesis of 3-Substituted Morpholines *via* Serine Enantiomers and Reductions of 5-Oxomorpholine-3-carboxylates

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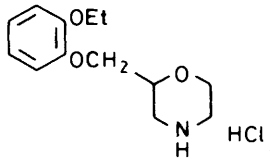
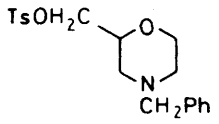
The chiral synthesis of 3-hydroxymethyl- and 3-carboxy-morpholines from serine enantiomers is described. Chemoselective and total reductions of 5-oxomorpholine-3-carboxylates are key synthetic steps.

The antidepressant drug viloxazine (**1**) has been shown to be a selective inhibitor of noradrenaline uptake into mouse heart *in vivo* and rat brain *in vitro*.[1] This noradrenaline uptake inhibiting activity of (**1**), which may be responsible for its clinical utility, resides mainly in the *S*-enantiomer of (**1**). For this reason a chiral synthesis of (**1**) was developed based on the optically active toluenesulphonate (**2**).[2] In order to make synthetic analogues of (**1**) where the morpholine ring substitutent was placed at the 3- rather than the 2-position of the morpholine ring, a chiral synthesis of 3-substituted morpholines was explored.

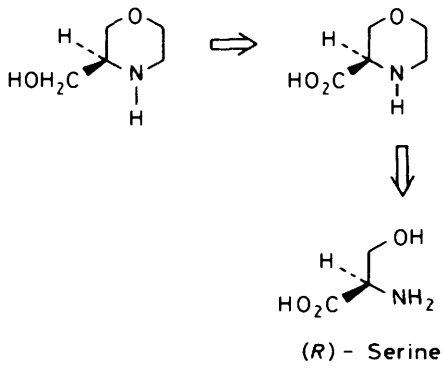


(**1**)



(**2**)

Consideration of all the possible synthetic disconnections in a retrosynthetic analysis of the 3-substituted morpholines, suggested that the ring system would be best constructed by ring closure of an ethanolamine with a two-carbon fragment. Further examination of the target molecules (Scheme 1)



Scheme 1.

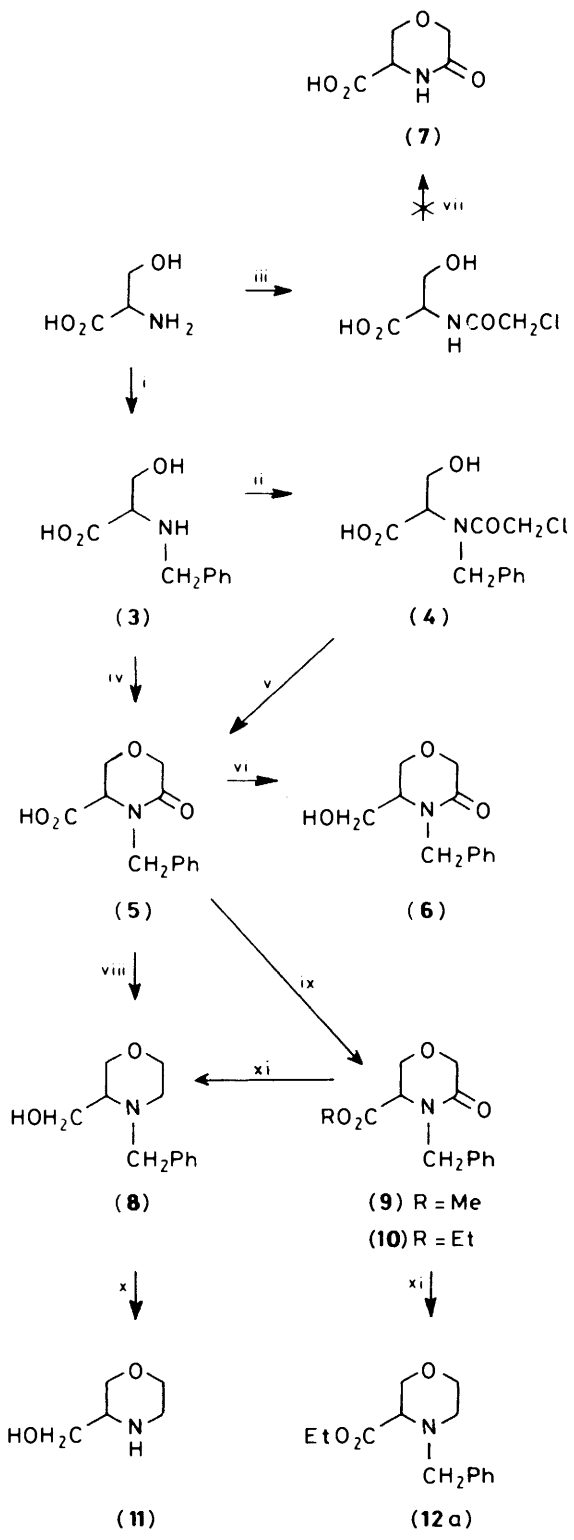
revealed that the amino acid serine would be a suitable ethanolamine for the construction of the morpholine ring. In this way serine enantiomers were employed as a 'chiral template' to obtain optically active 3-substituted morpholines. Recently this use of serine as a means of introducing chirality in the synthesis of natural products has been reported for enterobactins[3] and cerebrosides.[4]

Results and Discussion

Initially racemic serine was used as the starting material to explore the synthesis in Scheme 2. Ring closure of serine or serine methyl ester with chloroacetyl chloride in the presence of a base to give a morpholinone, *e.g.* (**7**), could not be achieved. Furthermore, the known[5] *N*-chloroacetylserine could not be ring closed to (**7**) in the presence of potassium t-butoxide, sodium hydride, or sodium hydroxide. The ring closure of ethanolamine to 1,4-oxazin-3-one has been reported[6] to proceed in modest yield but better yields have been achieved by protecting the amino group with a benzyl group[7] and removing the latter at a later stage in the synthesis. Thus, *N*-benzylserine (**3**) was prepared and in the presence of chloroacetyl chloride ring closed to give *N*-benzyl-5-oxomorpholine-3-carboxylate 5-one (**5**) (Scheme 2) in 35% yield. This transformation was also carried out, less conveniently, in two steps *via* the chloroacetyl derivative (**4**).

Reduction of 4-*Benzyl*-5-*oxomorpholine*-3-*carboxylic Acid*.—The reduction of the morpholinone (**5**) was examined using different reducing agents in order to determine the optimum conditions. Reduction of the morpholinone (**5**) with lithium aluminium hydride in tetrahydrofuran failed to proceed, as an insoluble lithium salt formed and starting material was recovered from the reaction. When the morpholinone (**5**) was allowed to react with a solution of sodium bis(2-methoxyethoxy)aluminium hydride in toluene, a 75% yield of the morpholinylmethanol (**8**) was obtained; the product gave a satisfactory elemental analysis and ^{1}H n.m.r. spectrum but was only stable for a few days. Reduction with sodium diethylaluminium hydride gave a trace of (**8**) together with a complex mixture of other products but the recently reported reagent,[8] sodium borohydride–methanesulphonic acid in dimethyl sulphoxide gave a 24% yield of (**8**). Sodium borohydride in the presence of aluminium chloride caused selective reduction of the carboxy group of (**5**) to give the methanol (**6**). Borane–dimethyl sulphide complex in tetrahydrofuran afforded (**8**) (which was colourless in this instance) in 40—90% yields and was the method of choice. Catalytic debenzylation of the morpholinylmethanol (**8**) afforded 3-hydroxymethylmorpholine (**11**).

All the assigned structures in Scheme 2 were supported by satisfactory elemental analyses and ^{1}H n.m.r. spectra. A full assignment for the methanol (**8**) was obtained from a 220 MHz ^{1}H n.m.r. spectrum in $CDCl_3$. The chemical shifts and coupling constants were consistent with the expected chair form of the morpholine ring. The morpholinones (**5**), (**6**) and (**9**) showed a strong carbonyl absorption in their i.r. spectra in the range 1605—1640 cm^{-1} corresponding to an amide I band. Absorption in the i.r. region at 1 730 and 1 740 cm^{-1} found for (**5**) and (**9**) was assigned to the carboxylic acid and ester functional groups respectively.



Scheme 2. *Reagents*: i, $PhCHO–NaBH_4$; ii, $ClCH_2COCl$; iii, $ClCH_2COCl$; iv, $NaOH–ClCH_2COCl$; v, $KOBu^t$; vi, $NaBH_4–AlCl_3$; vii, NaH; viii, $BH_3–Me_2S$; ix, $NaHCO_3–MeI$ or $PhPO_2Cl_2–EtOH$; x, $Pd–C–H_2$; xi, $BH_3–Me_2S$.

Synthesis of Chiral Morpholines.—The reaction sequence in Scheme 2 from *N*-benzylserine (**3**) directly to the morpholine (**5**) followed by reduction with borane–dimethyl sulphide complex to give the methanol (**8**) was repeated starting from (*R*)- and (*S*)-*N*-benzylserine (**3a**) and (**3b**) separately. Each pair of the chiral products (**3a,b**); (**5a,b**); and (**8a,b**) showed equal and opposite rotations of the plane of polarised light at 589 μm. The melting points of each pair of enantiomers were the same and different from that of the corresponding racemates (see Table). The change in absolute configuration from *R* to *S* and *S* to *R* as the morpholinones (**5a**) and (**5b**) were reduced is due to a different priority of groups in the sequence rules for absolute configuration rather than an inversion of configuration during the reduction.

The optical purity of the chiral methanols (**8a**) and (**8b**) was determined by the use of a chiral shift reagent in the ^1H n.m.r. spectrum, which induced non-equivalence in the spectra of the enantiomers.[9,10] The shift reagent of choice was found to be tris(3-heptafluorobutyryl-D-camphorato)europium(III), [Eu(hFbc)$_3$]. The upfield half of the benzyl AB pattern in the spectrum of the racemate (**8**) separated into two doublets ($\Delta\delta_{R-S}$ = 4 Hz). The spectrum of the synthesized *R*- and *S*-enantiomers (**8a**) and (**8b**) showed no doubling of this resonance under the same conditions, but two sets of signals were again observed when the solutions of the enantiomers (**8a**) and (**8b**) were mixed. The lower level of detection of a minor enantiomer was *ca.* 5% and hence the optical purities of both the *R*- and *S*-enantiomers (**8a**) and (**8b**) were estimated to be greater than 90%. If the methanols (**8a**) and (**8b**) are pure chiral materials they should have an absolute configuration that corresponds with the chiral serine from which they were derived, unless total inversion of configuration has taken place during the synthetic sequence. Under the reaction conditions used, current knowledge of reaction mechanisms would suggest that inversion of configuration cannot occur. In addition, it has been claimed that racemisation of cyclic amino acids is more difficult than with their acyclic counterparts.[11] The enantiomers (**8a**) and (**8b**) have therefore been assigned the absolute configuration corresponding to their originating chiral serine.

Esterification of the acid (**5**) with sodium hydrogen carbonate and methyl iodide gave the ester (**9**) and with ethanol and sulphuric acid the ethyl ester (**10**) was obtained. A superior yield of the ester (**10**) and its enantiomers (**10a**) and (**10b**) was achieved by using phenyl dichlorophosphate as the esterification reagent. Reduction of the ester (**10**) with the theoretical amount of borane–dimethyl sulphide complex required to reduce the morpholinone function alone gave, after heating under reflux, the methanol (**8**). A similar reduction of the ester (**10a**) at 0 °C afforded the chemoselective reduction product (**12a**) where only the morpholinone amide function was reduced.

Experimental

Melting points are uncorrected. The i.r. spectra were recorded for Nujol mulls on a Perkin-Elmer 177 spectrophotometer. The ^1H n.m.r. spectra were determined using the following instruments: Perkin-Elmer R 12 (60 MHz), Varian EM 390 (90 MHz), Varian HA 100D (100 MHz) and Perkin-Elmer R34 (220 MHz) (with $SiMe_4$ as an internal standard). Optical rotations were measured on a NDL 243 automatic polarimeter, in a 2 ml cell. Ether refers to diethyl ether.

(RS)-N-*Benzylserine* (**3**).—Benzaldehyde (140 ml) was added with vigorous stirring to a solution of (*RS*)-serine (147.0 g) in 2*M*-sodium hydroxide (700 ml). Stirring was continued for 30 min and the mixture cooled to 6 °C. Sodium borohydride (15.0 g) was added during 1 h and the reaction temperature was maintained at 6—10 °C. The mixture was stirred for 1 h without cooling and benzaldehyde (140 ml) added. Sodium borohydride (15.0 g) was added during 1 h while the reaction temperature was maintained at 6—10 °C by external cooling. The mixture was stirred for 2 h and washed with ether. Concentrated hydro-

Table. Comparison of morpholine enantiomers and racemates

Compd.	M.p. (°C)	Configuration	$[\alpha]_D^{22}$* (°)	Found (%)			Formula	Requires (%)		
				C	H	N		C	H	N
(3)	214—215	*R* + *S*		61.4	6.6	7.1	$C_{10}H_{13}NO_3$	61.5	6.7	7.2
(3a)	235—237	*R*	−5.5	61.3	6.6	7.1	$C_{10}H_{13}NO_3$	61.5	6.7	7.2
(3b)	235—236	*S*	+4.9	61.9	6.8	7.0	$C_{10}H_{13}NO_3$	61.5	6.7	7.2
(5)	189—190	*R* + *S*		60.9	5.5	6.0	$C_{12}H_{13}NO_4$	61.3	5.5	6.0
(5a)	177—178	*R*	−99.6	61.4	5.7	5.8	$C_{12}H_{13}NO_4$	61.3	5.5	6.0
(5b)	179—180	*S*	+100.3	61.0	5.6	5.8	$C_{12}H_{13}NO_4$	61.3	5.5	6.0
(8)	198—199	*R* + *S*		59.0	7.5	5.5	$C_{12}H_{17}ClNO_2$	59.1	7.4	5.7
(8a)	230—231	*S*	+97.9	59.0	7.6	5.6	$C_{12}H_{17}ClNO_2$	59.1	7.4	5.7
(8b)	229—230	*R*	−98.1	59.2	7.7	5.5	$C_{12}H_{17}ClNO_2$	59.1	7.4	5.7
(10)	52—54	*R* + *S*		63.6	6.6	5.5	$C_{14}H_{17}NO_4$	63.9	6.3	5.2
(10a)	77—78	*R*	−13.7	63.7	6.6	5.2	$C_{14}H_{17}NO_4$	63.9	6.3	5.2
(10b)	77—78	*S*	+11.8	63.5	6.5	5.3	$C_{14}H_{17}NO_4$	63.9	6.3	5.2

* Rotation solvents given in the Experimental section.

chloric acid was added to pH = 6.5 and the product collected. Crystallisation from water gave the serine (163 g, 60%).

(R) *and* (S) -N-*Benzylserine* (**3a**) *and* (**3b**).—These materials were made as for (**3**). (*R*)-Isomer (**3a**) (65%), $[\alpha]_D^{22}$ − 5.5° (*c* 1.0 in 6M − HCl). (*S*)-Isomer (**3b**) (70%), m.p. 235—236 °C (lit.,[12] 240 °C), $[\alpha]_D^{22}$ + 4.9° (*c* 1.0 in 6M-HCl) (lit.,[12] + 5.1°).

(RS)-N-*Benzyl*-N-*chloroacetylserine* (**4**).—Chloroacetyl chloride (0.85 ml) was added during 15 min to a stirred mixture of (*RS*)-*N*-benzylserine (2.7 g), sodium hydroxide pellets (1.2 g), water 15 ml) and dichloromethane (40 ml) cooled to 0 °C. Stirring was continued for 2 h at room temperature and the dichloromethane separated. The aqueous phase was acidified with 2M-hydrochloric acid. The solid was collected and crystallised from isopropyl alcohol–light petroleum (b.p. 60—80 °C) to give the *chloroacetate* (930 mg, 24%), m.p. 143—145 °C (Found: C, 52.8; H, 5.1; Cl, 13.4; N, 4.9. $C_{12}H_{14}ClNO_4$ requires C, 53.0; H, 5.2; Cl, 13.1; N, 5.2%); δ (CD_3OD) 3.95 (d, 2 H, CH_2O), 4.20 (s, 2 H, $COCH_2Cl$), 4.36 (m, H, CH), 4.80 (s, 2 H, $PhCH_2$), and 7.38 (s, 5 H, Ph).

(RS)-4-*Benzyl*-5-*oxomorpholine*-3-*carboxylic Acid* (**5**).—(*a*) Chloroacetyl chloride (44 ml) was added dropwise with stirring during 1 h to a solution of the acid (**3**) (89.6 g), sodium hydroxide pellets (23.0 g), and water (450 ml) cooled to 0 °C. After 30 min 30% (w/w) sodium hydroxide solution (120 ml) was added and the mixture heated at 30—33 °C for 2 h. Concentrated hydrochloric acid was added to pH = 1.0 and the product was collected. Crystallisation from isopropyl alcohol gave the acid (38.0 g, 35%), δ [$(CD_3)_2SO$] 3.75—4.25 (m, 3 H, OCH_2CHN), 4.17 (s, 2 H, OCH_2CO), 3.80 (d, H, *J* 15.0 Hz, PhCH), 5.28 (d, 1 H, *J* 15.0 Hz, PhCH) and 7.30 (s, 5 H, Ph); $\nu_{max.}$ 1 605 (amide) and 1 730 cm^{-1} (acid).

(*b*) The chloroacetate (**4**) (272 mg) and potassium t-butoxide (224 mg) were heated under reflux for 3 h in t-butyl alcohol (10 ml) after which time the t-butyl alcohol was evaporated. The residue was acidified with 2M-hydrochloric acid and evaporated to dryness. Extraction with ethanol and evaporation gave, on crystallisation from ethyl acetate–light petroleum (b.p. 60—80 °C), an acid (110 mg, 47%) which was identical in all respects with the product in (*a*) above.

(R)- *and* (S)-4-*Benzyl*-5-*oxomorpholine*-3-*carboxylic Acid* (**5a**) *and* (**5b**).—These acids were made as for (**5**) method (*a*). (*R*)-Isomer (**5a**) (23%) $[\alpha]_D^{22}$ − 99.6° (*c* 1.0 in 1M-sodium hydroxide solution; (*S*) -isomer (**5b**) (28%) $[\alpha]_D^{22}$ + 100.3 (*c* 1.0 in 1M-sodium hydroxide solution).

(RS)-4-*Benzyl*-3-*hydroxymethylmorpholin*-5-*one* (**6**).—Anhydrous aluminium chloride (2.2 g) in diethylene glycol dimethyl ether (20 ml) was added during 15 min to a stirred solution of sodium borohydride (1.9 g) and the acid (**5**) (2.4 g) in diethylene glycol dimethyl ether (25 ml). The mixture was stirred for 18 h and poured onto ice (100 g) and acidified with concentrated hydrochloric acid (5 ml). The mixture was extracted with ethyl acetate and the extract washed with saturated aqueous sodium hydrogen carbonate and brine. The dried ($MgSO_4$) extract was evaporated to give as a colourless oil the alcohol (700 mg, 32%), δ ($CDCl_3$) 2.30 (br, 1 H, OH), 3.25 (m, 1 H, CHN), 3.55—4.20 (m, 4 H, CH_2OH, OCH_2CH), 4.08 (d, 1 H, *J* 15.0 Hz, PhC*H*), 5.30 (d, 1 H, *J* 15.0, PhC*H*), 4.22 (s, 2 H, OCH_2CO), and 7.28 (s, 5 H, Ph); *m*/*z* 220, (M^+ − 1).

(RS)-1-*Benzyl*-3-*hydroxymethylmorpholine* (**8**).—(*a*) Sodium bis(2-methoxyethoxy)aluminium hydride (3.4M solution in toluene; 50 ml) was added under nitrogen during 20 min to a stirred suspension of the acid (**5**) (7.8 g) in toluene (80 ml). After 24 h the mixture was cooled to below 10 °C and ethanol slowly added until gas evolution ceased. The mixture was made alkaline with 2M-sodium hydroxide solution and the toluene phase was separated. The toluene was extracted with 2M-hydrochloric acid and the acid solution was made alkaline with 2M-aqueous sodium hydroxide. Extraction with ethyl acetate and evaporation of the organic phase gave an oil which was dissolved in ethanol. Addition of saturated ethereal hydrogen chloride afforded a precipitate which crystallised from ethanol–ether as a pink solid identified as the *methanol* (**8**) (6.1 g, 75%); δ ($CDCl_3$; 220 MHz) 2.33 (ddd, 1 H, 5-H_{ax}, *J* 12.2, 10.0, 3.3), 2.57 (m, 1 H, 3-H_{ax}), 2.73 (dt, 1 H, 5-H_{eq}, *J* 12.2, 2.7), 3.55, (ddd, 1 H, 6-H_{ax}, *J* 11.7, 10.0, 2.7), 3.67 (dd, 1 H, 2-H_{ax}, *J* 11.7, 9.0), 3.75 (ddd, 1 H, 6-H_{eq}, *J* 11.7, 3.3, 2.7), 3.95 (dd, 1 H, 2-H_{eq}, *J* 11.7, 4.7), 3.52 (d, 1 H of C*H*OH, *J* 11.3), 3.85 (d, 1 H, C*H*OH, *J* 11.3), 3.26 (d, 1 H, PhC*H*, *J* 13.2), and 4.14 (d, 1 H, PhC*H*, *J* 13.2).

(*b*) Sodium borohydride (2.9 g) was added to a stirred solution of the acid (**5**) (3.5 g) in dimethyl sulphoxide (20 ml). After 15 min. methanesulphonic acid (6.3 ml) in dimethyl sulphoxide (20 ml) was added dropwise during 1 h. The mixture was heated to 70 °C for 2 h, cooled to 20 °C, and treated with aqueous sodium hydroxide (10% w/v; 40 ml). Water (250 ml) was added and the mixture was extracted with dichloromethane (150 ml). The dichloromethane phase was washed with 2M-

aqueous sodium hydroxide and extracted with 2M-hydrochloric acid. The acid solution was treated as in (*a*) to give the *methanol* (900 mg, 24%) which was identical in all respects with the product in (*a*) above.

(*c*) Borane–dimethyl sulphide complex (6 ml; 10M) was added under nitrogen to a stirred solution of the morpholinone (**5**) (2.4 g) and triethylamine (1.0 g) in anhydrous tetrahydrofuran (40 ml) maintained at 0 °C. After 15 min the mixture was heated under reflux for 6 h and allowed to cool. Water was added to the ice-cooled mixture until gas evolution ceased and the tetrahydrofuran was evaporated. The residue was made alkaline with 2M-aqueous sodium hydroxide and extracted with ethyl acetate. The ethyl acetate was extracted with 2M-hydrochloric acid and the acid solution treated as in (*a*) to give the *methanol* (**8**) (1.1 g, 45%) which was identical to the product in (*a*) and (*b*) above.

(R)- *and* (S)-4-*Benzyl*-3-*hydroxymethylmorpholine Hydrochlorides* (**8a**) and (**8b**).—These methanols were made as for (**8**) method (*c*). (*R*)-Isomer (**8b**) (68%), $[\alpha]_D^{22}$ − 98.1° (*c* 1.0 in anhydrous ethanol). (*S*)-Isomer (**8a**) (67%), $[\alpha]_D^{22}$ + 97.90° (*c* 1.0 in anhydrous ethanol).

Methyl (RS)-N-*Benzyl*-5-*oxomorpholine*-3-*carboxylate* (**9**).—A mixture of methyl iodide (0.9 ml), sodium hydrogen carbonate (1.2 g), and the acid (**5**) (1.5 g) were stirred in dimethylformamide (12 ml) for 24 h and the solvent evaporated. Water (100 ml) was added and the mixture was extracted with ethyl acetate. The ethyl acetate was dried ($MgSO_4$) and evaporated to an oily solid (1.8 g). The solid was purified by preparative silica gel t.l.c. (toluene–ethyl acetate; 9:1) to give the *ester* (775 mg, 49%), m.p. 105—107 °C, δ ($CDCl_3$) 3.78 (s, 3 H, CO_2Me), 3.80—4.50 (m, 6 H, OCH_2CO, OCH_2CHN, PhC*H*), 5.58 (d, H, *J* 15.0 Hz, PhC*H*) and 7.20—7.40 (m, 5 H, Ph) (Found: C, 62.2; H, 6.1; N, 5.4. $C_{13}H_{15}NO_4$ requires C, 62.6; H, 6.1; N, 5.6%).

Ethyl (RS)-4-*Benzyl*-5-*oxomorpholine*-3-*carboxylate* (**10**).—(*a*). The acid (**5**) (1.2 g), anhydrous ethanol (0.8 ml) and concentrated sulphuric acid (0.02 ml) were stirred and heated under reflux for 18 h in benzene (4 ml). This mixture was cooled, diluted with chloroform, and washed with saturated aqueous sodium hydrogen carbonate. The organic phase was dried ($MgSO_4$) and evaporated. The residue was crystallised from light petroleum (b.p. 60—80 °C) to give the ester (400 mg, 30%), δ ($CDCl_3$) 1.25 (t, 3 H, CO_2CH_2Me), 3.70—4.45 (m, 6 H, OCH_2 CHN, CO_2CH_2 and PhC*H*), 4.25 (s, 2 H, OCH_2CO), 5.56 (d, 1 H, *J* 15.0 Hz, PhC*H*), and 7.27 (s, 5 H, Ph).

(*b*) A solution of the acid (**5**) (470 mg), pyridine (0.5 ml), phenyl dichlorophosphate (630 mg) and anhydrous ethanol (0.24 ml) in dimethoxyethane (10 ml) was stirred under nitrogen for 18 h. The mixture was acidified with 2M hydrochloric acid and extracted with chloroform. The chloroform extract was washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated. The residue was crystallised from light petroleum (b.p. 60—80 °C) to give the ester (**10**) (200 mg, 38%) which was identical in all respects with the material in (*a*) above.

Ethyl (R)- *and* (S)-4-*Benzyl*-5-*oxomorpholine*-3-*carboxylate* (**10a**) *and* (**10b**). These materials were made as for (**10**), method (*b*), above. (*R*)-Isomer (**10a**) (65%), $[\alpha]_D^{22}$ − 13.7° (*c* = 1.0 in dichloromethane). (*S*)-Isomer (**10b**) (16%), $[\alpha]_D^{22}$ + 11.8° (*c* 1.0 in dichloromethane).

(RS)-3-*Hydroxymethylmorpholine* (**11**).—This compound was characterised as its oxalate derivative. A solution of the methanol (**8**) (1.03 g) in anhydrous ethanol (25 ml) was hydrogenated at atmospheric pressure over palladium-on-carbon catalyst (10%; 200 mg) for 3.5 h. The catalyst was filtered off and the ethanol evaporated to give an oil. The oil was dissolved in ethanol (10 ml) and oxalic acid (630 mg) added. The solution was cooled and the *methanol oxalate* (220 mg, 28%) collected, m.p. 173—175 °C, δ [$(CD_3)_2SO$] 2.70—3.15 (m, 3 H, CH_2NHCH), and 3.24—3.90 (m, 3 × CH_2O) (Found: C, 44.2; H, 7.5; N, 8.5. $C_6H_{12}NO_4$ requires C, 44.4; H, 7.4; N, 8.6%).

Ethyl (R)-4-*Benzylmorpholine*-3-*carboxylate* (**12a**).—Borane–dimethyl sulphide complex (1.33 ml; 10M) was added to a stirred ice-cooled solution of the morpholinone (**10a**) (2.63 g) in anhydrous tetrahydrofuran (50 ml) under nitrogen. The mixture was allowed to reach room temperature during 18 h and water was added until gas evolution ceased. The tetrahydrofuran was evaporated and the residue was made alkaline with 2M- sodium hydroxide solution. The liberated oil was extracted with diethyl ether and the ether layer extracted with 2M-hydrochloric acid. The acid solution was made alkaline with 2M-aqueous sodium hydroxide and extracted with ether. The ether was dried ($MgSO_4$) and evaporated to give the *morpholine* (**12a**) as an oil (1.5 g, 60%), δ ($CDCl_3$) 1.30 (t, 3 H, CO_2CH_2Me), 2.35 (m, 1 H, CHN), 2.90—4.85 (m, 8 H, NCH, CH_2OCH_2, CHN,$PhCH_2$), 4.20 (q, 2 H, CO_2CH_2), and 7.30 (s, 5 H, Ph) (Found: C, 67.4; H, 7.9; N, 5.8. $C_{14}H_{19}NO_3$ requires C, 67.5; H, 7.6; N, 5.6%); $[\alpha]_D^{22}$ + 83° (*c* 1.0 in dichloromethane).

References

1 T. P. Blackburn, G. A. Foster, D. T. Greenwood, and R. Howe, *Eur. J. Pharmacol.*, 1978, **52**, 367.
2 R. Howe, T. Leigh, B. S. Rao, and A. H. Todd, *J. Med. Chem.*, 1976, **19**, 1074.
3 W. H. Rasteller, T. J. Erickson, and M. C. Venuti, *J. Org. Chem.*, 1981, **46**, 3579.
4 P. Tkaczuk and E. R. Thornton, *J. Org. Chem.*, 1981, **46**, 4393.
5 E. Fisher and H. Roesner, *Justus Liebigs Ann. Chem.*, 1910, **375**, 199.
6 J-M. Lehn and F. Montavon, *Helv. Chim. Acta*, 1976, **59**, 1566.
7 A. R. Surrey, M. K. Rukwid, B. F. Fullar, and S. O. Winthrop, *J. Am. Chem. Soc.*, 1955, **77**, 633.
8 P. T. Thorsen, M. M. Kreevoy, and S. R. Wann, *J. Org. Chem.*, 1981, **46**, 2579.
9 M. D. McCreary, P. W. Lewis, D. L. Wernwick, and G. M. Whitesides, *J. Am. Chem. Soc.*, 1974, **96**, 1038.
10 J. N. Eikenberry, H. L. Goering, G. S. Koermer, and C. J. Laitimer, *J. Am. Chem. Soc.*, 1974, **96**, 1493.
11 M. Barber, J. H. Jones, and M. J. Witty, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2425.
12 J. Hellerbach, P. Quitt, and K. Vogler, *Helv. Chim. Acta*, 1963, **46**, 327.

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