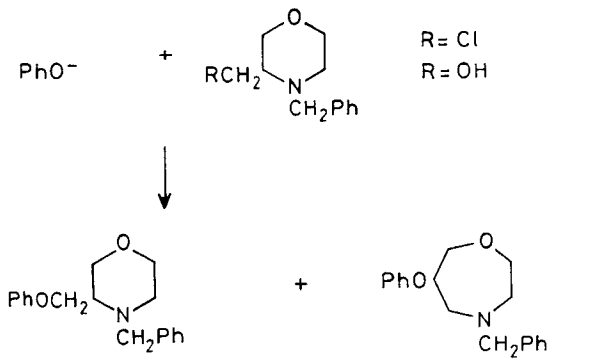
Unambiguous Synthesis of 3-Aryloxymethylmorpholine Hydrochlorides Without Ring Enlargement Side Reactions

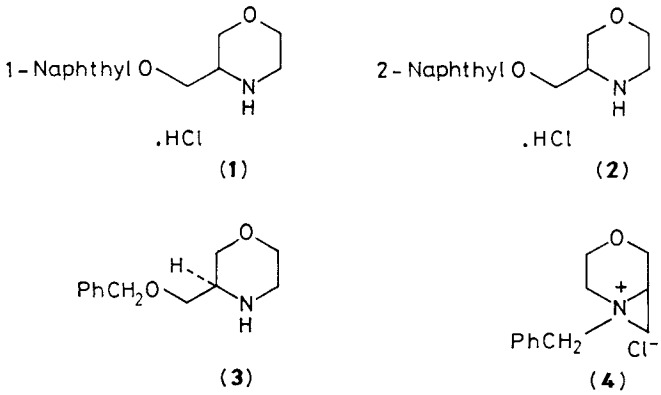
George R. Brown* and Alan J. Foubister
ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, SK10 4TG

The unambiguous synthesis of 3-naphthyloxymethylmorpholine hydrochloride appetite suppressants is reported. Chemoselective reduction of 4-benzyl-5-oxomorpholine-3-carboxylic acid and its derivatives is described under various metal hydride reducing conditions.

We have reported[1] the synthesis of 3-phenoxymethylmorpholines (Scheme 1) *via* the nucleophilic displacement by phenoxide anion of the chlorine atom of a 3-chloromethylmorpholine and by Mitsunobu coupling of phenols to 3-hydroxymethylmorpholines. These procedures led to a mixture of the desired 3-phenoxymethylmorpholine together with an isomeric hexahydro-1,4-oxazepine from which it was difficult to separate the products. We now report an improved synthetic route which avoids the ring enlargement problem and permits larger amounts of 3-aryloxymethylmorpholines to be prepared. This new method is illustrated by the synthesis of 3-(1-naphthyloxymethyl)morpholine hydrochloride (**1**) and its 2-naphthyl substituted isomer (**2**) in quantities sufficient for pharmacological testing as potential appetite suppressants. These naphthyl compounds were required as they are close analogues of the potent appetite suppressant[2] (*S*)-3-benzyloxymethylmorpholine (**3**). The naphthyl group of compounds (**1**) and (**2**) may have greater lipophilic binding at the putative receptor site than the corresponding benzyl group of compound (**3**).



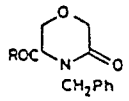
Scheme 1.



One possible explanation[1] for the formation of rearranged oxazepine products in these nucleophilic displacements of 3-substituted morpholines is the formation of an ambident aziridinium intermediate (**4**). Cleavage of this aziridine by attack of nucleophile at its carbon ring junction with the morpholine ring could be responsible for the undesired oxazepines. We postulated that if the morpholine ring nitrogen were amidic in character (rather than a tertiary base) during the substitution, the aziridine intermediate would not form and a clean substitution would result.

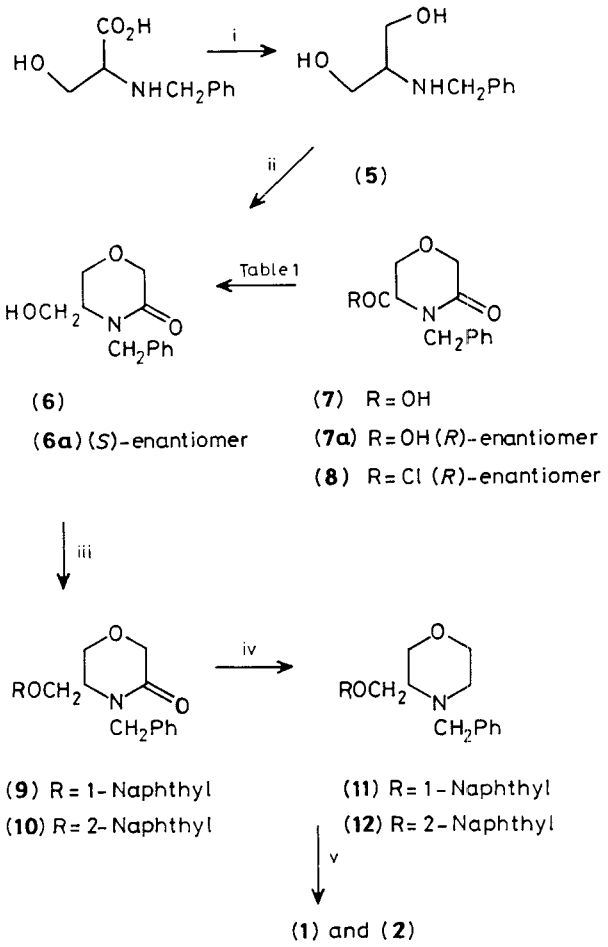
Amidic character for the morpholine ring nitrogen of 3-substituted morpholines could be achieved either in a 4-benzoylmorpholine or a 5-oxo morpholine. Following the latter approach, reduction of *N*-benzylserines (Scheme 2) with sodium bis(2-methoxyethoxy)aluminium hydride afforded 2-benzylaminopropane-1,3-diol (**5**), but a ring closure with chloroacetyl chloride gave 4-benzyl-3-hydroxymethylmorpholin-5-one (**6**) in only 3% yield. This approach to the alcohol (**6**) had a further drawback, in that if a chiral *N*-benzylserine starting material were used, asymmetry would be lost in the reduction step. Alternatively the chemoselective reduction of derivatives of the known[3] morpholine acid (**7**) afforded the desired alcohol (**6**). The reduction conditions employed are displayed in the Table. Reduction of the ethyl ester of the acid (**7**) proceeded selectively in 95% yield and represented the method of choice. Other lower yielding reduction conditions are referenced in the Table. In particular, reduction of the acid (**7**) with sodium borohydride in methanesulphonic acid gave a complex reduction product from which it was possible to isolate only the alcohol (**6**) in 10% yield. When the optically active (*R*)-acid (**7a**) was reduced *via* the acid chloride (**8a**), the product (**6a**) was not racemised, indicating that chiral 3-aryloxymethylmorpholines could be prepared. The optical purity of (**6a**) was validated by h.p.l.c. examination of a derivative made with the chiral reagent (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid.

Table. Reduction of 4-benzyl-5-oxomorpholine-3-carboxylic acid



R	Reduction conditions	Yield (%)	References
OEt	$LiBH_4$	95	4
OH	$ClCO_2Et$–$NaBH_4$	72	5
OH	$NaBH_4$–$MeSO_3H$	10	6
OH	$NaBH_4$–$AlCl_3$	32	7
Cl[a]	$NaBH_4$–Diglyme	41	8

[a] (*R*)-enantiomer.



Scheme 2. *Reagents:* i, $NaAl(MeOCH_2CH_2O)_2H_2$; ii, $ClCH_2COCl$; iii, ArOH–Mitsunobu; iv, BH_3–Me_2S; v, H_2, Pd/C

Alkylation of the alcohol (**6**) with 1- and 2-naphthols in the presence of triphenylphosphine and diethyl azodicarboxylate under Mitsunobu reaction conditions, gave the naphthyl ethers (**9**) and (**10**) in 61 and 71% yields respectively without the detection of any ring enlarged products. Reduction of the ring amide function of the morpholines (**9**) and (**10**) with borane–dimethyl sulphide complex gave the benzylmorpholines (**11**) and (**12**). The benzyl groups were removed by catalytic hydrogenolysis to give compounds (**1**) and (**2**).

In a previously reported [2] test, dogs were given an oral dose of 10 mg/kg of compounds (**1**) and (**2**) 1 h before access to a meat meal. Compound (**1**) had no effect on the amount of food consumed, but with compound (**2**) there was a 90% reduction in the amount of meat that was eaten compared to control conditions. This result compared with a 51% reduction found for (**3**) in a similar test, but both (**1**) and (**2**) caused slight emesis in treated dogs at the 10 mg/kg dose, in contrast to (**3**).

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. All compounds were racemic except for (**6a**), (**7a**), and (**8a**).

2-Benzylaminopropane-1,3-diol (**5**).—A 70% solution of sodium bis(2-methoxyethoxy)aluminium hydride in toluene (10 ml) was added dropwise during 10 min to a stirred suspension of *N*-benzylserine (3.9 g) in toluene (12 ml). The mixture was heated under reflux for 4 h, cooled, and made alkaline with 2M aqueous sodium hydroxide. Extraction with ether and evaporation of the dried organic phase gave a colourless oil. The oil was heated under reflux for 5 min with oxalic acid (310 mg) and cooled to give a precipitate which crystallised from isopropyl alcohol as the *oxalate* (500 mg, 9%), m.p. 143—145 °C (Found: C, 53.3; H, 6.3; N, 5.3. $C_{12}H_{17}NO_6$ requires C, 53.1; H, 6.3; N, 5.2%); $\delta_H(CD_3OD)$ 3.30 (1 H, d), 3.78 (4 H, d), 4.60 (2 H, s), and 6.90 (5 H, m).

4-Benzyl-3-hydroxymethylmorpholin-5-one (**6**).—(*a*) Chloroacetyl chloride (2.2 ml) was added during 30 min to a stirred mixture of (**5**) (4.9 g), sodium hydroxide pellets (1.1 g), water (40 ml), and 1,2-dichloroethane (20 ml) cooled to 0 °C. Stirring was continued for 2 h at room temperature and the dichloroethane phase separated. The dichloroethane solution was washed with saturated aqueous sodium hydrogen carbonate, 2M hydrochloric acid, and brine, dried, and evaporated to give a colourless oil (750 mg). Powdered potassium hydroxide (150 mg) was added to a solution of the oil in ethanol (17 ml) and the mixture stirred for 18 h. The mixture was filtered and the solvent evaporated to give an oil. The oil was purified by column chromatography on silica gel in ethyl acetate; elution with ethanol gave the *morpholinone* (**6**) (190 mg, 3%) (Found: C, 65.2; H, 7.0; N, 6.3. $C_{12}H_{15}NO_3$ requires C, 64.9; H, 6.8; N, 6.3%); $\delta_H(CDCl_3)$ 2.30 (1 H, br), 3.25 (1 H, m), 3.55—4.20 (4 H, m), 4.08 (1 H, d), 4.22 (2 H, s), 5.30 (1 H, d), and 7.28 (5 H, s); *m/z* 220 ($M^+ - 1$).

(*b*) Lithium borohydride (100 mg) was added to a stirred solution of ethyl 4-benzyl-5-oxomorpholine-3-carboxylate (1.0 g) in tetrahydrofuran (THF) (10 ml) at 5 °C. The mixture was stirred at 25 °C for 19 h and cooled to 10 °C before the cautious addition of water (10 ml) and acidification with 2M hydrochloric acid. An ethyl acetate extract was washed with brine, dried, and evaporated to give a colourless oil (**6**) (800 mg, 95%) which was identical with the product derived from the procedure (*a*) above.

(*c*) Ethyl chloroformate (12 ml) was added dropwise during 20 min to a stirred solution of (**7**) (27.0 g) and triethylamine (16.8 ml) in THF (900 ml) at −10 °C. After 30 min at 0 °C the mixture was filtered. The filtrate was added during 1 h to a solution of sodium borohydride (12.0 g) in water (900 ml) at 0 °C. The mixture was stirred at 25 °C for 4 h before being cooled to 10 °C and acidified with 2M hydrochloric acid. THF was evaporated under reduced pressure and the aqueous residue extracted with dichloromethane. The extracts were washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated to give an oil. The oil was purified by column chromatography on silica gel, with 7% ethanol in dichloromethane as eluant, to give the morpholinone (**6**) (18.3 g, 75%) which was identical with the product from (*a*) above.

(*d*) Aluminium chloride (2.2 g) in diethylene glycol dimethyl ether (digol) (20 ml) was added during 15 min to a stirred solution of sodium borohydride (1.9 g) and the acid (**7**) (2.4 g) dimethyl digol (25 ml) and the mixture stirred for 18 h before decomposition on ice (1 kg). Acidification with hydrochloric acid (5 ml), extraction with ethyl acetate and evaporation of the extract gave the alcohol (**6**) (700 mg, 32%). This material was identical to that from (*a*).

(R)-*4-Benzyl-5-oxomorpholine-3-carbonyl Chloride* (**8a**).—(*R*)-4-Benzyl-5-oxomorpholine-3-carboxylic acid (**7a**) (18.8 g)

and thionyl chloride (20 ml) were heated under reflux in dichloromethane (200 ml) for 45 min and the dichloromethane evaporated. Crystallisation of the residue from light petroleum (b.p. 60—80 °C) gave the *acid chloride* (**8a**) (11.1 g, 55%), m.p. 72—74 °C (Found: C, 56.9; H, 4.9; N, 5.5. $C_{12}H_{12}ClNO_3$ requires C, 56.8; H, 4.7; N, 5.5%).

(S)-4-*Benzyl*-3-*hydroxymethylmorpholin*-5-*one* (**6a**).—The acid chloride (**8a**) (10.8 g) was added during 30 min to a stirred suspension of sodium borohydride (1.1 g) in dimethyl digol (100 ml) at 10 °C. The mixture was stirred for 16 h at 25 °C and excess of reagent destroyed with 2M hydrochloric acid. The solvent was evaporated and the residue chromatographed on silica gel, with 7% ethanol in dichloromethane as eluant, to give the *morpholinone* (**6a**) (6.5 g, 69%), $[\alpha]_D^{22}$ −76° (*c* 4.6 in dichloromethane). Other properties were identical with those of (**6**) above.

4-*Benzyl*-3-(1-*naphthyloxymethyl*)*morpholin*-5-*one* (**9**).—Diethyl azodicarboxylate (8 ml) was added during 5 min to a stirred mixture of the methanol (**6**) (10.75 g), 1-naphthol (7.0 g), and triphenylphosphine (12.1 g) in THF (200 ml) at 15 °C and stirring continued for 18 h at 25 °C. The solvent was evaporated and the residue triturated with ether and filtered. Evaporation of the ether gave a solid which was purified by column chromatography on silica gel, with 15% ethyl acetate in toluene as eluant, to give the *morpholinone* (**9**) (10.3 g, 61%) (Found: C, 75.8; H, 6.4; N, 3.6. $C_{22}H_{21}NO_3$ requires C, 76.1; H, 6.1; N, 4.0); $\delta_H(CDCl_3)$ 3.77 (2 H, m), 4.27 (6 H, m), 5.42 (1 H, d), 6.75 (1 H, m), 7.40 (9 H, m), 7.79 (1 H, m), and 8.17 (1 H, m); *m/z* 347 (M^+).

4-*Benzyl*-3-(2-*naphthyloxymethyl*)*morpholine*-5-*one* (**10**).—This morpholinone was made by the method described for (**9**). Crystallisation from ethyl acetate–light petroleum (b.p. 60—80 °C) gave the *morpholinone* (**10**) (71%), m.p. 117—118 °C (Found: C, 75.9; H, 6.2; N, 4.0. $C_{22}H_{21}NO_3$ requires C, 76.1; H, 6.1; N, 4.0%); $\delta_H(CDCl_3)$ 3.60 (1 H, m), 3.80 (1 H, d), 4.20 (6 H, m), 5.50 (1 H, d), and 7.45 (12 H, m).

4-*Benzyl*-3-(1-*naphthyloxymethyl*)*morpholine Hydrochloride* (**11**).—Borane–dimethyl sulphide complex (5 ml) was added during 5 min to a stirred solution of the morpholinone (**9**) (10.2 g) in THF (250 ml) and the mixture heated under reflux for 4 h. The mixture was cooled and excess of reducing agent destroyed by addition of ethanol. Solvent was evaporated and the residue treated with an excess of ethanol which was saturated with hydrogen chloride. The ethanol was evaporated and the residue crystallised from isopropyl alcohol–methanol to give the *hydrochloride* (**11**) (8.0 g, 74%), m.p. 230—233 °C (Found: C, 71.8; H, 6.6; N, 4.2. $C_{22}H_{24}ClNO_2$ requires C, 71.4; H, 6.5; N, 3.8%); $\delta_H[(CD_3)_2SO]$ 3.18 (1 H, m), 3.59 (1 H, m), 3.98 (3 H, m), 4.15 (2 H, m), 4.60 (2 H, m), 4.86 (2 H, m), 7.11 (1 H, m), 7.58 (10 H, m), 8.35 (1 H, m), and 11.24 (1 H, m).

4-*Benzyl*-3-(2-*naphthyloxymethyl*)*morpholine Hydrochloride* (**12**).—This morpholine was made by the method described for (**11**) as a colourless solid hydrochloride (**12**) (89%), m.p. 207—209 °C (Found: C, 71.2; H, 6.5; N, 3.7. $C_{22}H_{24}ClNO_2$ requires C, 71.4; H, 6.5; N, 3.8%); $\delta_H[(CD_3)_2SO]$ 3.42 (2 H, m), 4.4 (9 H, m), 7.60 (12 H, m), and 11.42 (1 H, m).

3-(1-*Naphthyloxymethyl*)*morpholine* (**1**).—The morpholine hydrochloride (**11**) (7.7 g) in ethanol (200 ml) and water (50 ml) was hydrogenated at atmospheric pressure over palladium-on-carbon catalyst (5%, 500 mg) for 5.5 h. The catalyst was filtered off and the solvents evaporated to give a solid which crystallised from isopropyl alcohol as a *hydrochloride* (**1**) (4.9 g, 84%), m.p. 206—209 °C (Found: C, 64.1; H, 6.6; N, 4.9. $C_{15}H_{18}ClNO_2$ requires C, 64.4; H, 6.4; N, 5.0%); $\delta_H[(CD_3)_2SO]$ 3.26 (2 H, m), 4.00 (5 H, m), 4.45 (2 H, d), 6.83 (1 H, dd), 7.34 (4 H, m), 7.72 (1 H, m), 8.28 (1 H, m), and 9.91 (2 H, m).

3-(2-*Naphthyloxymethyl*)*morpholine* (**2**).—The morpholine hydrochloride (**12**) was hydrogenated following the method used for the preparation of (**1**) to give the *hydrochloride* (83%), m.p. 236—239 °C (Found: C, 64.2; H, 6.4; N, 5.0. $C_{15}H_{18}ClNO_2$ requires C, 64.4; H, 6.4; N, 5.0%); $\delta_H[(CD_3)_2SO]$ 3.24 (2 H, m), 4.03 (5 H, m), 4.44 (2 H, d), 7.32 (4 H, m), 7.91 (3 H, m), and 10.12 (2 H, m).

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Received 27*th October* 1988; *Paper* 8/04283G