Hexahydro-1,4-oxazepines. Part 1. Synthesis by Morpholine Ring Expansion

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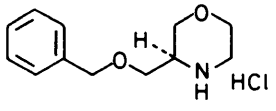
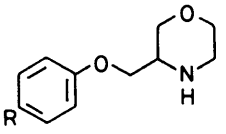
Reaction of 4-benzyl-3-chloromethylmorpholine with phenoxide anions led not only to 4-benzyl-3-phenoxymethyl morpholines, but substantial amounts of 4-benzyl-6-phenoxy-1,4-oxazepanes. The ring expansion reaction is explained in terms of neighbouring group participation, leading to an ambident aziridinium cation intermediate.

In a previous paper[1] we have reported that the 3-substituted morpholine, (*S*)-3-benzyloxymethylmorpholine hydrochloride (**1**) has significant appetite suppressant properties when dosed orally to dogs. In order to explore the relationships between this appetite suppressant activity and chemical structure, the lower homologue of (**1**),3-phenoxymethylmorpholine (**2**), was selected as a target for synthesis.

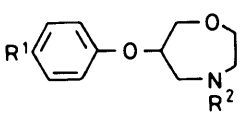


(**1**)

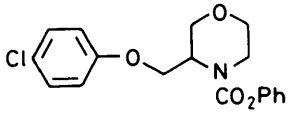


(**2**) R = H
(**3**) R = Cl

The choice of a synthetic route to (**2**) was influenced by the availability of the chloromethylmorpholine (**4**). We have previously shown[2] that nucleophilic displacement of the chlorine atom of (**4**) with the cyanide anion led to the 3-cyanomethylmorpholine (**5**) (Scheme 1). It was envisaged that a similar displacement of chlorine with phenoxide anion would, after *N*-debenzylation, afford the desired morpholine (**2**). This synthetic strategy would also facilitate the subsequent preparation of the enantiomers of (**2**), as the starting material morpholine (**6**) could be obtained[3] in both enantiomeric forms.

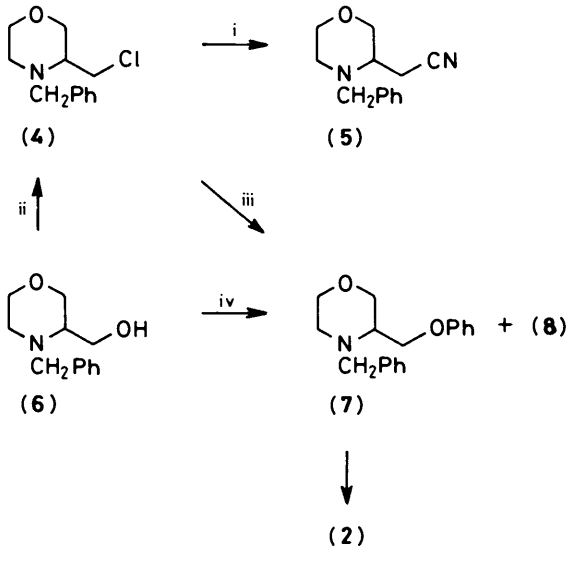


(**8**) $R^1 = H, R^2 = CH_2Ph$
(**9**) $R^1 = Cl, R^2 = CO_2Ph$
(**11**) $R^1 = Cl, R^2 = H$



(**10**) $R^1 = CO_2Ph$

Reaction of (**4**) with the phenoxide anion in dimethylformamide (DMF) (Scheme 1) gave a product, which although homogenous by t.l.c. examination on silica gel plates, was shown by ^1H n.m.r. to be a mixture. In particular, a distinctive multiplet of chemical shift δ 4.48 (m, 1 H) indicated that the mixture contained a compound with a single proton attached to a carbon atom, which was bonded to oxygen and flanked on either side by methylene groups. This structural feature was not present in the starting material for the reaction or in the expected product. Attempts to isolate this novel product by column chromatography on silica gel or preparative t.l.c. in a number of solvents and solvent mixtures of varying polarity, were unsuccessful. The reaction was repeated using toluene as the solvent, to determine if solvent polarity affected the product ratio, but an identical mixture was obtained. Mitsonobu coupling of phenol and the methanol (**6**) in the presence of diethyl azodicarboxylate (DEAD) also gave the same inseparable mixture. The original mixture was treated with hydrogen chloride to give a mixture of salts, fractional crystallisation of which enabled the *N*-benzylmorpholine product (**7**) to be isolated and characterised. Catalytic debenzylation of (**7**) with hydrogen in the presence of 5% palladium-on-carbon gave the morpholine (**2**).



Scheme 1. *Reagents:* 1, NaCN; ii, $SOCl_2$; iii, PhONa; iv, PhOH–Ph_3P–DEAD

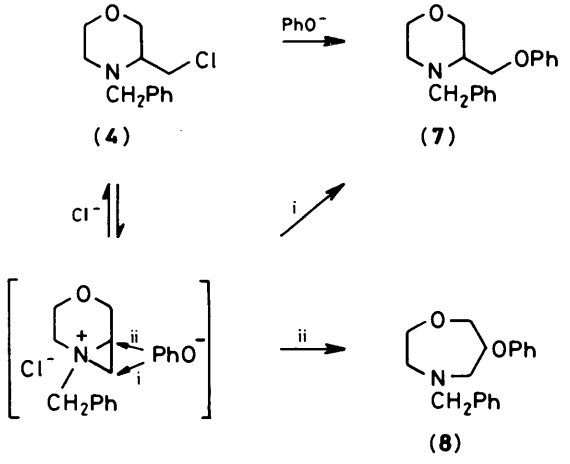
Examination of the original product mixture from the reaction of (**4**) and phenoxide anion by g.l.c.–m.s. showed that (**7**) was present in 70% yield and the novel by-product (**8**) in 30% yield. Additionally, the two products were shown to be isomers [*m/z* 283 (M^+)]. The ^{13}C n.m.r. spectrum of the mixture in the region δ 50—79 p.p.m., where carbon signals due to aliphatic carbons would be observed, showed 12 signals. Off-resonance experiments showed that 10 of these were triplets (corresponding to methylene groups) and two were doublets (corresponding to methine carbons). One methine doublet was observed at δ 58.88 which was consistent with a CH–N group and compared with a singlet of δ 60.35 found for the CH–N group in the ^{13}C n.m.r. spectrum of the methanol (**6**). This methine group was assigned as the CH–N in the major product (**7**). The second methine doublet was observed at δ 76.60 which corresponded to a CH–O group and was ascribed to the unknown product (**8**). This supported the previous observation of a multiplet at δ 4.48 in

the ^{1}H n.m.r. spectrum, which also corresponded to a CH–O group. Further examination of the ^{1}H n.m.r. spectrum of the mixture (**7**) and (**8**) after (**7**) was characterised revealed that in addition to the widely spaced AB pattern δ 3.26 and 4.02 observed for the benzyl methylene group of (**7**), a singlet was present at δ 3.64. This signal was compatible with a benzyl methylene group which was symmetrically substituted on nitrogen. In addition, at δ 2.60—3.15, signals were observed which were assigned as two non-benzylic methylene groups next to nitrogen. These n.m.r. spectroscopic observations taken together with mass spectral evidence that (**8**) was an isomer of (**7**) led to the provisional assignment of the hexahydro-1,4-oxazepine structure for the unknown reaction product (**8**).

As part of a further investigation of the reaction, 4-chlorophenol was allowed to react with the methanol (**6**) under Mitsonobu coupling conditions. A similar inseparable mixture of products was obtained. Reaction of this mixture with phenyl chloroformate in the presence of sodium hydrogen carbonate afforded a mixture of two phenoxycarbonyl derivatives. Purification of this mixture by column chromatography gave the esters (**9**) and (**10**). Alkaline hydrolysis of these esters separately, gave 3-(4-chlorophenoxy)methylmorpholine (**3**) and 6-(4-chlorophenoxy)-1,4-oxazepane (**11**). This definitive isolation of a 1,4-oxazepane confirmed that ring expansion of the morpholine ring had occurred.

Discussion

This type of ring expansion of morpholines has not been previously described and in addition ring expansion of a six-membered to a seven-membered nitrogen containing ring under these reaction conditions is novel. We propose that it represents a further example in saturated heterocyclic chemistry, of the known[4] formation of rearrangement products during the nucleophilic substitution of β-chloroethylamines. Initially nucleophilic displacement of chlorine by nitrogen (Scheme 2)



Scheme 2.

leads to the formation of an ambident aziridinium cation. This postulated intermediate may react either with chloride anion to regenerate the starting reagent (**4**), or undergo nucleophilic displacements to afford the morpholine (**7**) and the ring expanded oxazepane product (**8**).

The finding that, in contrast with phenoxide anion, the cyanide anion does not lead to a ring enlarged product, parallels work reported[5,6] on chloromethyl pyrrolidines. Strong nucleophiles such as the cyanide anion, give normal substitution products, whereas weak nucleophiles, such as the phenoxide anion afford mixtures containing ring-enlarged products.

In summary, spectroscopic evidence showed that morpholine ring expansion had occurred. Consideration of the reaction mechanism indicated that the reaction may proceed by a known process of ring enlargement.

Experimental

M.p.s are uncorrected. ^{1}H N.m.r. spectra were recorded on a Varian HA100 (100 MHz) and ^{13}C n.m.r. on a JEOL FX90Q (22.5 MHz) instrument. G.l.c.–m.s. investigations were made on a methyl silicone gum (OV1) column linked to a Vacuum Generator mass spectrometer (VG 70/70). Reactions were carried out under an atmosphere of nitrogen. Solvents were dried over magnesium sulphate prior to evaporation. Column chromatography was on Merck silica gel 'Kieselgel 60'. Ether was diethyl ether.

4-Benzyl-3-phenoxymethylmorpholine (**7**).—Sodium hydride (50% dispersion in mineral oil; 660 mg) was added to a solution of phenol (1.3 g) in DMF (10 ml) and the mixture heated to 40 °C. A solution of the chloromethylmorpholine (**4**) (3.1 g) in DMF (15 ml) was added and the reaction heated at 90 °C for 4 h. The DMF was evaporated off and the residue shaken with toluene and 2M-aqueous sodium hydroxide. The toluene layer was washed with saturated brine and extracted with 2M-hydrochloric acid. The acid was basified with sodium hydroxide solution (40%, v/v) and extracted with ethyl acetate. The ethyl acetate extract was dried and evaporated and the residue purified by column chromatography on silica gel in toluene–ethyl acetate (4:1) to give, as a colourless oil an isomeric mixture of (**7**) and (**8**) (2.2 g, 57%); δ_H ($CDCl_3$) 2.16 (m, 1 H), 3.26 (d, 1 H), 3.64 (s, 2 H), 4.02 (d, 1 H) and 4.48 (m, 1 H); δ_C 58.88 (CH–N) and 76.60 (CH–O); *m/z* 283 (M^+). The oil was dissolved in ether and an excess of ethanolic hydrogen chloride added. Crystallisation of the precipitated hydrochloride salts from isopropyl-alcohol–ether gave as a colourless *hydrochloride* (**7**) (250 mg, 6%), m.p. 175—177 °C (Found: C, 67.2; H, 7.0; N, 4.4. $C_{18}H_{22}ClNO_2$ requires C, 67.6; H, 6.9; N, 4.4%); δ($CDCl_3$) 2.16 (m, 1 H), 2.82 (m, 2 H), 3.26 (d, 1 H), 3.95 (m, 6 H), 4.02 (d, 1 H), 6.95 (m, 2 H), and 7.30 (m, 8 H).

Phenyl 6-(4-Chlorophenoxy)-1,4-oxazepane-4-carboxylate (**9**) and *Phenyl 3-(4-Chlorophenoxy)methylmorpholine-4-carboxylate* (**10**).—DEAD (7.8 ml) was added dropwise during 5 min to a solution of the methanol (**6**) (9.7 g), 4-chlorophenol (6.0 g) and triphenyl phosphine (12.3 g) in tetrahydrofuran (110 ml) and the mixture stirred for 18 h. The solvent was evaporated off and the residue extracted with ether. The extract was evaporated and the resulting oil dissolved in ethyl acetate. The ethyl acetate solution was washed with 2M-sodium hydroxide solution and brine, dried, and evaporated to leave an oil. This was distilled to give a mixture of 4-benzyl derivatives (7.0 g), b.p. 174—176 °C/0.1 mmHg. The oil (7.0 g), phenyl chloroformate (10.3 g) and sodium hydrogen carbonate (5.7 g) were stirred in methylene dichloride (85 ml) for 18 h. The mixture was filtered and the solvent evaporated off to give an oil. The oil was chromatographed on silica gel in toluene when elution of the column with ethanol–toluene (1:9) gave two pure products as colourless oils: the *phenylcarboxylate* (**10**) (4.4 g, 27%) (Found: C, 62.0; H, 5.1; N, 4.2. $C_{18}H_{18}ClNO_4$ requires C, 62.2; H, 5.2; N, 4.0%); ($CDCl_3$) 3.9 (m, 9 H) and 7.2 (m, 9 H), the *phenyl carboxylate* (**9**) (875 mg, 5%) (Found: C, 61.9; H, 5.0; N, 3.9. $C_{18}H_{18}ClNO_4$ requires C, 62.2; H, 5.2; N, 4.0%); δ($CDCl_3$) 3.85 (m, 8 H), 4.65 (m, 1 H), and 7.15 (m, 9 H).

3-(4-Chlorophenoxy)methylmorpholine (**3**) *Hydrochloride*.—The phenyl carboxylate (**10**) (975 mg) and potassium hydroxide

pellets (700 mg) were heated under reflux for 18 h in ethanol–water [(3:1); 27 ml]. The solvent was evaporated off and the residue shaken with ethyl acetate–water. The ethyl acetate extract was dried and evaporated to an oil which was dissolved in ether and acidified with an excess of ethanolic hydrogen chloride. Crystallisation of the precipitated hydrochloride from ethanol–ether gave as a *colourless solid* (**3**) (350 mg, 47%), m.p. 166—168 °C (Found: C, 50.2; H, 5.9; N, 5.1. $C_{11}H_{15}Cl_2NO_2$ requires C, 50.0; H, 5.7; N, 5.3%); δ[$(CD_3)_2SO$] 3.18 (m, 3 H), 3.70 (m, 4 H), 4.15 (d, 2H), 7.20 (q, 4 H) and 9.85 (br s, 2 H).

6-(4-*Chlorophenoxy*)-1,4-*oxazepane* (**11**) *Oxalate*.—The phenyl carboxylate (**9**) (300 mg) and potassium hydroxide pellets (200 mg) were heated under reflux for 18 h in 3:1 ethanol–water (10 ml). The reaction mixture was treated as for (**10**) above to give (**11**) as an oil, which was allowed to react with an excess of oxalic acid. Crystallisation of the precipitated oxalate salt from isopropyl alcohol gave the *oxalate salt* of (**11**) (110 mg, 45%), m.p. 129—132 °C (Found: C, 49.1; H, 5.1; N, 4.4. $C_{13}H_{16}ClNO_6$ requires C, 49.1; H, 5.0; N, 4.4%); δ[$(CD_3)_2SO$] 3.55 (m, 4 H), 3.90 (m, 4 H), 4.90 (m, 1 H), 7.10 (d, 2 H), and 7.40 (d, 2 H).

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