Hexahydro-1,4-oxazepines. Part 2. Unambiguous Synthesis

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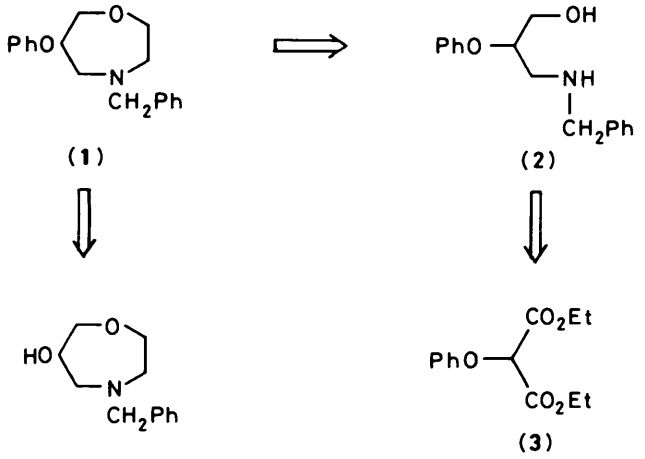
The unambiguous synthesis of 6-phenoxy-1,4-oxazepane from diethyl phenoxymalonate *via* a modified Hellmann Haas β-amino acid synthesis is described.

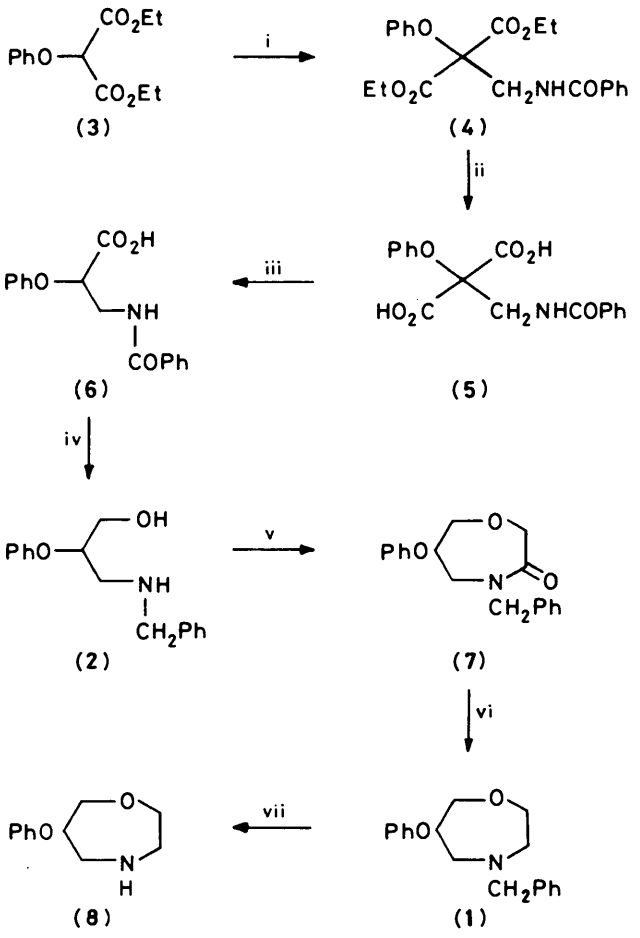
In an accompanying paper[1] we have reported that, during synthetic work on appetite suppressant morpholine derivatives, a morpholine ring expansion reaction took place. Assignment of the ring enlarged products as 1,4-oxazepanes was based on detailed spectroscopic evidence and in one case microanalysis. We now describe an unambiguous synthesis of the appropriately substituted 1,4-oxazepane ring system which further confirms the structure assigned to the ring expanded products and enables larger quantities to be made.



Scheme 1.

Choice of the synthetic route to the 6-phenoxy-1,4-oxazepane ring system was based on a consideration of all the possible synthetic disconnections in a retrosynthetic analysis. Two disconnections, in particular (Scheme 1), represented the most favourable synthetic options. As the synthesis was intended to further substantiate the morpholine ring expansion reaction, the aminopropanol precursor was preferred over the hydroxy-oxazepane. In this route the crucial bond from phenoxy to disubstituted carbon, could be formed in a known[2] compound (**3**) (Scheme 1) of unambiguous structure. Additionally ring closure of the aminopropanol starting material (**2**) could be pursued using methods previously described[3] for morpholine ring closure.

The appropriate intermediates required for the formation of the 1,4-oxazepane ring system were prepared by employing part of the Hellmann and Haas β-amino acid synthesis[4] (Scheme 2). The known[2] diester (**3**) was allowed to react with *N*-diethylamino ethylbenzamide and the resulting diester (**4**) hydrolysed with sodium hydroxide, before thermal decarboxylation to give (**6**). Completion of the Hellmann and Haas procedure involves hydrolysis of the benzamide group to yield the β-amino acid. Instead the benzamide and carboxyl groups were simultaneously reduced with borane dimethylsulphide complex to give the intermediate (**2**). This deviation from the established process was made because of the improvement found previously[3] in the ring closure reactions of *N*-benzyl aminoethanol, compared with simple aminoethanol. Formation of the hexahydro-1,4-oxazepine ring with chloroacetyl chloride followed by reduction, afforded 4-benzyl-6-phenoxy-1,4-oxazepane (**1**). The spectroscopic and chromatographic properties of (**1**) were entirely consistent with the same material[1] from the morpholine ring expansion reaction. Catalytic debenzylation of (**1**) gave a 65% yield of the 1,4-oxazepane (**8**).



Scheme 2. *Reagents:* i, $Et_2NCH_2NHCOPh$; ii, NaOH; iii, Heat 140 °C; iv, BH_3–Me_2S; v, $ClCH_2COCl$–Et_3N–KOH; vi, NaAl $(MeOCH_2CH_2O)_2$ H_2; vii, Pd–C–H_2.

Experimental

M.p.s are uncorrected. ^1H N.m.r. spectra were recorded on a Varian EM390 (90 MHz) instrument and i.r. spectra on a Perkin-Elmer 157 spectrophotometer. M.s. determinations were made on a MS 902 Kratos (AEI) instrument. Reactions were

carried out under an atmosphere of nitrogen and solvents were dried over magnesium sulphate before evaporation. Ether was diethyl ether.

Diethyl Phenoxymalonate (**3**).—The preparation was carried out as described[2] to give (**3**) (50%), m.p. 53—54 °C (lit.,[2] m.p. 52—53 °C); δ($CDCl_3$) 1.19 (t, 6 H), 4.17 (q, 4 H), 5.03 (s, 1 H), and 6.97 (m, 5 H).

Diethyl Benzamidomethyl(phenoxy)malonate (**4**).—The malonate (**3**) (50.4 g), *N*-diethylaminomethylbenzamide (41.2 g) and powdered sodium hydroxide (200 mg) were heated under reflux in toluene (600 ml) for 8 h. The mixture was concentrated under reduced pressure and diluted with hexane. The solvent was decanted from the oil which separated and the residue crystallised from hexane to give, as a *colourless solid*, (**4**) (65 g, 85%), m.p. 87—88 °C (Found: C, 65.6; H, 6.1; N, 3.5. $C_{21}H_{23}NO_6$ requires C, 65.5; H, 6.0; N, 3.6%); δ($CDCl_3$) 1.15 (t, 6 H), 4.15 (m, 6 H), and 7.35 (m, 10 H).

4-*Benzoyl*-2-*phenoxy*-β-*alanine* (**6**).—The diester (**4**) (3.8 g) and a solution of sodium hydroxide (800 mg) in water (3.2 ml) were vigorously stirred for 3 h when ethanol (5 ml) was added. The mixture was stirred for 18 h and then evaporated. The residue was dissolved in water and acidified with 2M-hydrochloric acid to pH 3.0. The oil which separated was extracted with ethyl acetate and the ethyl acetate washed with brine, dried, and evaporated to give an oil. The oil was crystallised from ethyl acetate to give, as a colourless solid, (**5**) (2.0 g 58%), m.p. 129—131 °C; δ[$(CD_3)_2SO$] 4.21 (d, 2 H), and 7.42 (m, 10 H); $\nu_{max.}$ CO 1 660, 1 740, and 1 765 cm^{-1}.

The diacid (**5**) (600 mg) was heated at 140 °C for 10 min and cooled. The residue was crystallised from aqueous isopropyl alcohol to give, as a *colourless solid*, (**6**) (420 mg, 80%), m.p. 137—138 °C (Found: C, 67.8; H, 5.4; N, 5.0. $C_{16}H_{15}NO_4$ requires C, 67.4; H, 5.3; N, 5.9%); $\nu_{max.}$ CO 1 640, 1 688, and 1 735 cm^{-1}.

3-*Benzylamino*-2-*phenoxypropan*-1-*ol* (**2**).—Triethylamine (2.27 ml) and borane dimethylsulphide complex (9 ml) were added to a stirred solution of the acid (**6**) (4.7 g) in tetrahydrofuran (100 ml) cooled by ice–water. After the vigorous initial reaction subsided, the mixture was heated under reflux for 10 h. Water was added to the ice-cooled mixture until gas evolution ceased and the solvent evaporated off. The residue was treated with 2M-aqueous sodium hydroxide (40 ml) and extracted with ethyl acetate. The ethyl acetate was washed with 2M-hydrochloric acid and the acid made alkaline with aqueous sodium hydroxide (40%, v/v) below 10 °C. The oil obtained was extracted with ethyl acetate and the extract washed with brine, dried, and evaporated to leave an oil. The oil was crystallised from hexane to give, as a *colourless solid*, (**2**) (3.8 g, 90%), m.p. 51—52 °C (Found: C, 74.6; H, 7.4; N, 5.3. $C_{16}H_{19}NO_2$ requires C, 74.7; H, 7.4; N, 5.4%); δ($CDCl_3$) 2.75 (s, 2 H), 3.01 (d, 2 H), 3.83 (t, 4 H), 4.38 (m, 1 H), and 7.1 (m, 10 H).

4-*Benzyl*-6-*phenoxy*-1,4-*oxazepan*-3-*one* (**7**).—Chloroacetyl chloride (0.8 ml) was added dropwise during 5 min to a stirred solution of the amine (**2**) (2.57 g) and triethylamine (1.4 ml) in toluene (35 ml) at −3 °C. The mixture was stirred for 2 h at 25 °C and the toluene washed with 2M-hydrochloric acid and 2M-aqueous sodium hydroxide, dried, and evaporated. The residual oil was stirred for 5 h in a solution of potassium hydroxide (540 mg) in ethanol (30 ml). The mixture was diluted with water (300 ml) and the precipitated solid collected. Crystallisation from ethanol gave (**7**) as a colourless solid (1.8 g, 61%), m.p. 98—99 °C (Found: C, 72.9; H, 6.4; N, 4.6. $C_{18}H_{19}NO_3$ requires C, 72.7; H, 6.4; N, 4.7%); δ($CDCl_3$) 4.35 (m, 1 H), 4.4 (s, 2 H) and 7.1 (m, 10 H); *m*/*z* 297 (M^+).

4-*Benzyl*-6-*phenoxy*-1,4-*oxazepane* (1) *Oxalate*.—Sodium bis(2-methoxyethoxy)aluminium hydride (3.4M solution in toluene; 4 ml) was added during 5 min to a solution of (**7**) (500 mg) in toluene (15 ml) and the mixture stirred for 18 h. The mixture was cooled below 10 °C and ethanol slowly added until gas evolution ceased. The mixture was made alkaline with 2M-aqueous sodium hydroxide and the toluene phase was separated. The toluene was extracted with 2M-hycrochloric acid and the acid solution made alkaline with 2M-aqueous sodium hydroxide. Extraction with ethyl acetate and evaporation of the dried organic phase gave an oil. The oil in ether was stirred with an excess of an ethereal solution of oxalic acid and the precipitated salt crystallised from isopropyl alcohol–ether to give the colourless *oxalate* (**1**) (300 mg, 54%), m.p. 134 °C (Found: C, 64.2; H, 6.2; N, 3.5. $C_{20}H_{23}NO_6$ requires C, 64.3; H, 6.2; N, 3.8%); δ($CDCl_3$, free base) 2.90 (m, 4 H), 3.64 (s, 2 H), 3.80 (m, 4 H), 4.48 (m, 1 H), and 7.0 (m, 10 H); *m*/*z* 283 (M^+).

6-*Phenoxy*-1,4-*oxazepane* (**8**) *Oxalate*.—A solution of the hydrochloride salt of (**1**) (1.0 g, prepared by treating the free base of the benzyloxazepane (**1**) with an excess of ethereal hydrogen chloride and evaporating the ether to give an oil) in ethanol (30 ml) was hydrogenated at atmospheric pressure over palladium-on-carbon catalyst (5%; 100 mg) for 2 h. The catalyst was filtered off and the ethanol evaporated. The residue was shaken with an excess of 2M-sodium hydroxide–ether and the ether phase stirred with an excess of ethereal oxalic acid solution. The solid which separated was collected and crystallised from isopropyl alcohol to give the oxalate (**8**) as a colourless solid (600 mg, 65%), m.p. 136—138 °C (Found: C, 55.2; H, 6.2; N, 4.6. $C_{13}H_{17}NO_6$ requires C, 55.1; H, 6.0; N, 4.9%); δ[$(CD_3)_2SO$] 3.30 (m, 4 H), 3.87 (m, 4 H), 4.84 (m, 1 H), and 7.20 (m, 5 H).

References

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