Aust. J. Chem., 1996, **49**, 1235–1242

The Structure of a Human Metabolite of Pholcodine

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The structure of a metabolite of pholcodine produced by humans is shown, by spectroscopic and synthetic data, to be a morpholin-3-one (amide) derivative rather than the alternative morpholin-2-one (lactone) isomer. Acylation of diethanolamine leads to an *N*,*O*-diacyl product even when only 1 equiv. of acylating agent is used. A mechanism is proposed to account for this observation. The appropriately substituted diacyl product can be cyclized to give a morpholin-3-one derivative which can be coupled to morphine by using caesium carbonate to give the metabolite. Suitable morpholin-2-one systems were coupled with morphine in basic conditions to give the alternative metabolite structure whose lactone group hydrolysed on standing to form a hydroxy acid derivative.

Introduction

Pholcodine[1] [3-*O*-(2-morpholinoethyl)morphine] (1) is a widely used antitussive belonging to the opioid-like class of compounds which includes codeine (2) and morphine (3). However, unlike the last two compounds, pholcodine is non-addictive and non-analgesic.[2–4]

Recent studies[5,6] have shown that pholcodine has a mean half-life of approximately 50 h in man after oral administration and that this value is much higher than that found[5] for codeine (2–3 h). Pharmacokinetic studies[5,6] also show that morphine is not produced in man by *O*-dealkylation of (1). The effectiveness of pholcodine as an antitussive is subject to considerable variation from individual to individual,[7,8] a fact leading to the speculation that a more active metabolite, produced in the body, may be responsible for the main pharmacological properties of pholcodine.

A recent investigation[6,9] has shown the presence of several additional peaks, besides pholcodine, in the h.p.l.c. traces of urine samples from patients given oral doses of pholcodine. The compound corresponding to the major new peak was isolated[6,9] by preparative h.p.l.c. High-field ^{1}H n.m.r. and f.a.b. mass spectrometric data showed that oxidation of the morpholinoethyl side chain of pholcodine had occurred and suggested that the metabolite had structure (4). The alternative lactone stucture (5) was considered[6,9] less likely.

Fritz and Maurer[10] have published gas chromatographic/mass spectrometric data which indicate that (4) and/or (5) (obtained as their acetylated derivatives) were present in urine samples of patients after pholcodine administration. They also showed that the formation of morphine from pholcodine was only a very minor metabolic pathway and that other metabolites, in which the morpholino substituent had undergone ring opening, were also present.

We now report studies towards the synthesis of both (4) and (5) and a comparison of the spectroscopic data for these compounds with those of the metabolite isolated from the Adelaide investigation;[6,9] these results confirm that this particular metabolite has the amide structure (4).

Results and Discussion

Synthesis of 3-O-[2-(2-Oxomorpholino)ethyl]-morphine (5)

Pholcodine (1) is prepared commercially by alkylation[11] of morphine with 4-(2-chloroethyl)morpholine (6) in aqueous sodium hydroxide, and we chose a similar procedure for the synthesis of (5), utilising 4-(2-chloroethyl)morpholin-2-one (7).

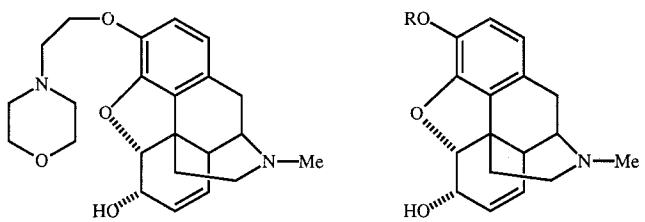
An obvious precursor to (7) was the alcohol (8) which can be synthesized by using either of two literature methods.[12,13] The more practical of these,[13] starting from glycine, gave the hydroxy acid (9) directly (Scheme 1). Distillation of (9) at 195° under reduced pressure resulted in ring closure to form the desired hydroxy lactone (8). Chlorination of (8)[14] with thionyl chloride gave a low yield of (7) and produced substantial amounts of polymeric material. The bromide (10) was more conveniently prepared, in good yield (70%), from the reaction of (8) with triphenylphosphine and carbon tetrabromide in dichloromethane.[15]

Manuscript received 2 May 1994

0004-9425/96/111235$05.00

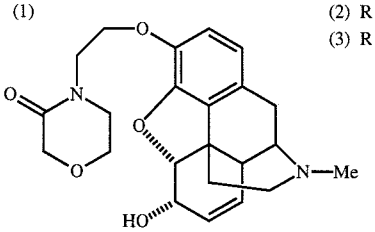
The etherification of phenol (used as a model compound) with the bromide (10), by using sodium hydride in tetrahydrofuran, gave the required product (11) in variable yield. A more reliable synthesis was the reaction of (2-bromoethoxy)benzene with 2-aminoethanol, followed by cyclization with methyl bromoacetate. An analogous etherification of (10) with a suspension of morphine hydrochloride in tetrahydrofuran and 2 equiv. of sodium hydride gave a crude product that contained the morphine ether (5), as indicated by the expected M+H peak at *m/z* 413 by using f.a.b. mass spectrometry and by ^{1}H n.m.r. data (Table 1). However, this material no longer had the *m/z* 413 peak after standing for several days and instead showed a new molecular ion at *m/z* 431. Thus, it appeared that the initial product (5) had reacted with adventitious moisture and undergone hydrolysis of the lactone moiety to form the hydroxy acid (12).

The ^{1}H n.m.r. data of (5) are not the same as those obtained for the metabolite isolated from humans (Table 1). In particular the 3′-methylene hydrogens of the lactone ring of (5) resonated as a singlet at δ 3·41 whereas the metabolite showed[6,9] a singlet resonance at 4·17. The isolated metabolite did not show any tendency to hydrolyse on standing.[6,9]



(1)

(2) R = Me
(3) R = H



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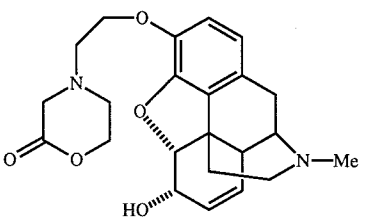

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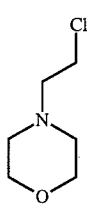

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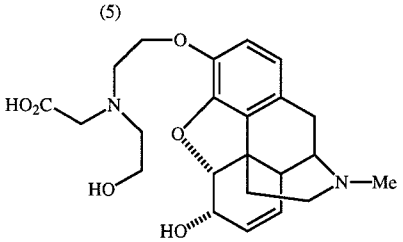
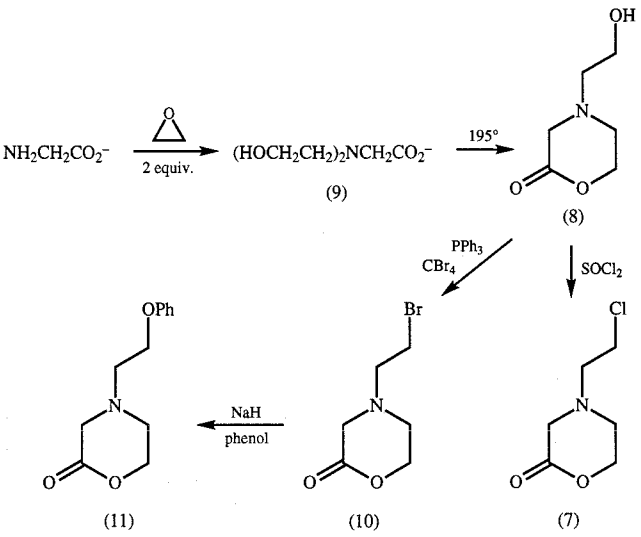


(12)



Scheme 1

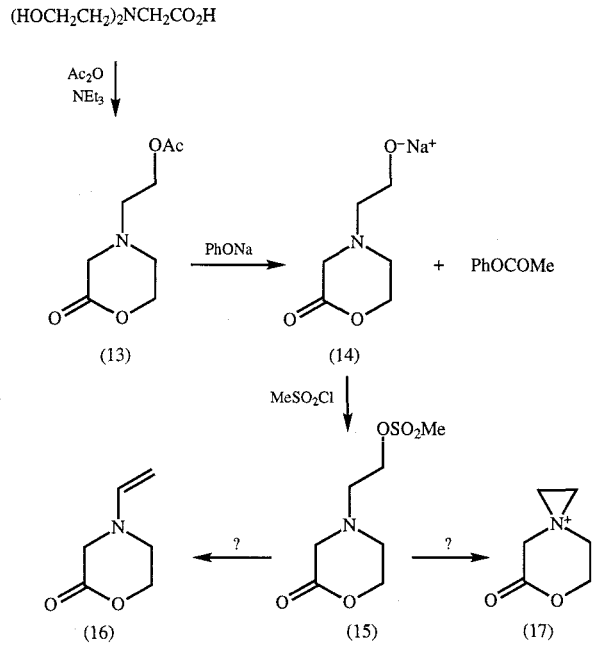
Table 1. Selected ^{1}H n.m.r. data for the pholcodine metabolite and for the synthetic materials (4) and (5)

Assignment	Metabolite	(4)	(5)
H2	6·65 (d)	6·70 (d)	6·67 (d)
H1	6·54 (d)	6·58 (d)	6·51 (d)
H7	5·70 (d)	5·75 (d)	5·73 (d)
H8	5·29 (d)	5·33 (d)	5·22 (d)
H5	4·87 (d)	4·90 (d)	4·90 (d)
H6, CH_2OAr	4·10–4·31 (m)	4·20–4·33 (m)	4·3–4·4 (m)
$(H2')_2$	4·17 (s)	4·20 (s)	
$(H3')_2$			3·41 (s)
$(H6')_2$	3·86 (t)	3·90 (t)	3·70 (t)
NCH_2CH_2OAr	3·74 (t)	3·80 (t)	2·63 or 2·80 (t)
$(H5')_2$	3·61 (t)	3·64 (t)	2·80 or 2·63 (t)
N–Me	2·44 (s)	2·49 (s)	2·35 (s)

Alternatives to the bromide (10) and chloride (7) were investigated to assess if they were more appropriate for the subsequent alkylation reaction. The acetate (13) was prepared in good yield from (9) by using acetic anhydride and triethylamine (Scheme 2). However, the reaction of (13) with sodium phenoxide led only to acyl transfer to form phenyl acetate and the sodium salt (14). This salt could be trapped by reaction with mesyl chloride to form the mesylate (15) as determined by f.a.b. mass spectrometry (molecular ion at *m/z* 223). Reaction of the crude mesylate with sodium phenoxide was unsuccessful, leading only to decomposition of (15). Since only phenyl acetate and methanesulfonic acid were recovered from the reaction mixture it is not clear whether the mesylate underwent elimination [to give (16)] or intramolecular substitution [to form (17)] or both prior to decomposition.

Synthesis of 3-O-[2-(3-Oxomorpholino)ethyl]-morphine (4)

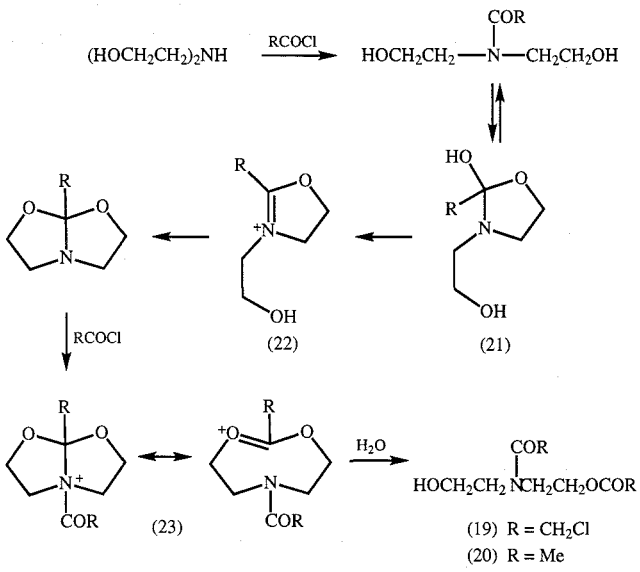
Acylation[16] of diethanolamine with 1 equiv. of chloroacetyl chloride and triethylamine was expected to form the chloroacetamide (18). However, the reaction



Scheme 2

proved to be complicated. When the reaction was conducted in tetrahydrofuran at −20° the diacetylated product (19) was obtained as a thermally unstable product. The ^{1}H n.m.r. spectrum of (19) displayed two singlet methylene resonances corresponding to the two chloroacetyl groups, and two carbonyl absorptions were evident in the infrared spectrum of this product.

Further investigation of this reaction with acetyl chloride showed that diacetylation, forming (20), was observed irrespective of the amount of acetyl chloride used. A possible mechanism to explain the acylation is shown in Scheme 3. Assuming that *N*-acylation occurs first, the intermediate *N*-acyl product may cyclize to form (21) whose elimination product (22) cyclizes and

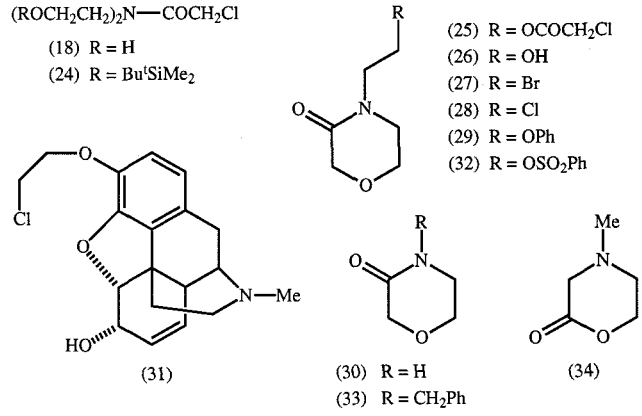


Scheme 3

then further acylates to yield (23). Workup of the reaction mixture then leads to the hydrolysis of (23), releasing the acylated product (19).

When the hydroxy groups of diethanolamine were protected by formation of the bis t-butyldimethylsilyl ether and the product was treated with chloroacetyl chloride the amide (24) was obtained. Removal of the silyl groups from (24) with tetrabutylammonium fluoride was complicated by the fact that the solubility properties of the reagent and the product were very similar. It was experimentally easier to remove the silyl groups and obtain (18) by using *p*-toluenesulfonic acid in water.

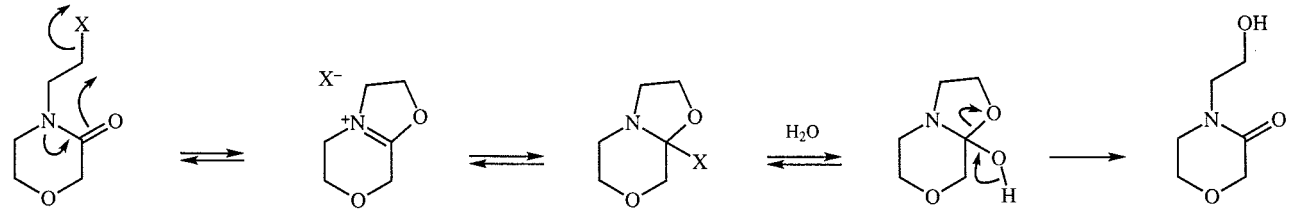
The bis(chloroacetylated) product (19) readily cyclized when treated with sodium hydride to form the morpholin-3-one derivative (25), which showed two singlet methylene resonances at δ 4·24 and 4·12 in the ^{1}H n.m.r. spectrum. The chloroacetoxy group of (25) was then hydrolysed by using potassium hydroxide in methanol at room temperature to form 4-(2-hydroxyethyl)morpholin-3-one (26) in 80% yield.



The bromo derivative (27) could not be obtained from (26) by using carbon tetrabromide and triphenylphosphine. This result, which is in contrast to that obtained in the '2-one' series, may be due to the insolubility of (26) in the usual organic solvents for this reaction. The chloro derivative (28) was readily obtained, however, when (26) was treated with neat thionyl chloride at room temperature overnight followed by careful removal of excess reagent under reduced pressure.

The alkylation of phenol with (28) could only be achieved by using potassium hydroxide in dimethyl sulfoxide and it proved impossible to find conditions where morphine could be alkylated with (28). The chloride (28) was extremely susceptible to hydrolysis but remarkably resistant to attack by other nucleophiles. For example, (28) was stable to sodium methoxide in methanol overnight but rapidly formed (26) on treatment with water. This behaviour may be explained by the equilibria shown in Scheme 4.

The phenoxy derivative (29) was also prepared by an alternative procedure involving alkylation of the sodium



Scheme 4

salt of (30) with (2-bromoethoxy)benzene.[17] However, heating 3-*O*-(2-chloroethyl)morphine[18] (31) (obtained from sodium morphinoxide and 2-chloroethyl benzenesulfonate) with morpholin-3-one (30)[19] and sodium hydride failed to yield (4), even after extended heating in dimethylformamide.

In view of the comparatively facile alkylation of morphine to form (31), the sulfonate ester (32), obtained in good yield from (26) and benzenesulfonyl chloride, was prepared as a potential alkylating agent for morphine. However, the sodium salt of morphine failed to react with this compound.

Although alkylations of morphine have been described in the literature, these utilize either unhindered or reactive alkylating agents such as benzyl chloride[20,21] and ethyl bromide.[22] The *O*-benzylation of morphine has recently been accomplished[23] by using caesium carbonate in dimethylformamide at elevated temperature. In contrast to other bases, such as potassium carbonate or sodium ethoxide, the caesium salt only gave alkylation on the phenolic oxygen with no reaction at the tertiary amine or alcohol functions. A multicoordinate transition state has been suggested to explain this selectivity.[23]

Addition of a solution of the chloride (28) to a mixture of caesium carbonate (2·5 equiv.) and morphine hydrochloride in dimethylformamide at 150° caused the slow appearance of a new product by t.l.c. This material could be separated, in poor yield, from the unreacted morphine by treatment with base followed by chromatography. The yield was eventually improved to 20% by the use of *N*-methylpyrrolidinone as solvent at 140°; however, the reaction proved unsatisfactory on a larger scale. In both cases extensive degradation of the chloro compound (28) appeared to be occurring. It is possible that intramolecular substitution of (28), involving the amide oxygen (Scheme 4), is competing with the desired alkylation.

The product (4) did not stain with ferric chloride spray on a silica plate and had ^{1}H n.m.r. and f.a.b. mass spectrometric data identical to the metabolite isolated from humans. A mass-analysed ion kinetic energy spectrum showed that the molecular ion (M+H, 413) fragments to give both morphine and *N*-ethylmorpholin-3-one species. A comparison of the relevant n.m.r. data for the metabolite and the alkylation products (4) and (5) is given in Table 1. The major distinguishing feature of the n.m.r. spectra for the two synthetic materials (4) and (5) is the chemical shift of the methylene protons adjacent to the carbonyl group of the morpholine ring (δ 4·17 and 4·20 for the amide systems and 3·41 for the lactone). The signal[24] of the methylene adjacent to the carbonyl group of the amide in (33) is at δ 4·20 which is clearly distinct from that[25] (δ 2·80) of the methylene adjacent to the carbonyl of the lactone (34).

The alkylation conditions with caesium carbonate were also extended to the reaction of morphine and (10). Unfortunately the product (5) was unstable under these conditions although its presence was detected by f.a.b. mass spectrometry (M+H, 413) and by t.l.c.

Conclusion

In conclusion, although neither of the two possible structures (4) and (5) for the metabolite were obtained completely pure both were obtained in sufficient purity for their spectroscopic data to indicate unambiguously that the metabolite isolated from human urine has the amide structure (4).

Experimental

General

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Microanalyses were performed by the Canadian Microanalytical Service, Vancouver. Flash chromatography[26] was performed by using Amicon Matrix silica, pore diameter 60 Å. Squat column chromatography was carried out with Merck Kieselgel PF_{254} silica and refers to 'dry column' chromatography assisted by vacuum.[27] Analytical thin-layer chromatography (t.l.c.) was carried out with Merck Kieselgel $60F_{254}$ on alumina-backed plates. Drying and other purification of organic solvents were accomplished by standard laboratory procedures.[28,29] All organic extracts were dried over anhydrous magnesium sulfate unless otherwise stated.

Infrared spectra were recorded on a Jasco IRA-1 grating spectrometer or a Hitachi 270–30 data processor spectrometer as Nujol mulls or as solutions in chloroform. Proton nuclear magnetic resonance (^{1}H n.m.r.) spectra were recorded on Varian T60 and Jeol JNM-PMX 60 spectrometers operating at 60 MHz, or a Brucker ACP-300 operating at 300 MHz. All spectra were recorded as $CDCl_3$ solutions with $SiMe_4$ as internal standard unless otherwise stated. Multiplicities are abbreviated: s, singlet; d, doublet; t, triplet; m, multiplet; dt, doublet of triplets; br s, broad singlet. Mass spectra were recorded by using electron impact (e.i.) conditions on an AEI MS3074 spectrometer operating at 70 eV or on a VG ZAB 2HF spectrometer. The morphine derivatives did not show molecular ions with e.i. conditions and their mass spectra were obtained by using fast atom bombardment (f.a.b.) conditions. F.a.b. mass spectra and mass-analysed ion kinetic energy spectra

(MIKES) were recorded on the VG ZAB 2HF spectrometer. Only the major fragments are given.

Sodium [Bis(2-hydroxyethyl)amino]acetate (9)

This compound was prepared (100%) from glycine and ethylene oxide according to the procedure of Pascal[13] and was used directly in the next step.

4-(2-Hydroxyethyl)morpholin-2-one (8)

The sodium salt of [bis(2-hydroxyethyl)amino]acetic acid (2·00 g) was placed in a Kugelrohr apparatus and heated under reduced pressure until a clear viscous liquid (1·42 g, 91%) distilled, block temperature 200°/0·05 mm, (lit.[13] 180–182°/0·05 mm). The material solidified on cooling and was recrystallized from ethanol to yield pure 4-(2-hydroxyethyl)morpholin-2-one (8) as white crystals, m.p. 138–139° (lit.[14] 138–139°). ν_{max} 3410, 1760, 1105 cm^{-1}. ^1H n.m.r. δ 4·44, t, J 5 Hz, CH_2OCO; 3·70, t, J 6 Hz, CH_2OH; 3·40, s, NCH_2CO; 3·05, s, OH; 2·80, t, J 5 Hz, CH_2N; 2·64, t, J 6 Hz, CH_2N. Mass spectrum m/z 145 (M), 128, 114, 100.

4-(2-Chloroethyl)morpholin-2-one (7)

The alcohol (8) (100 mg, 0·61 mmol) in thionyl chloride (5 ml) was refluxed for 2·5 h, the excess thionyl chloride removed under reduced pressure, then triethylamine added to neutralize the cooled solution. The mixture was filtered, excess amine removed under reduced pressure and the residue distilled to afford the chloride (7) (20%), b.p. 67°/0·1 mm (lit.[14] 148–150°/5 mm). ν_{max} 1750, 1240 cm^{-1}. ^1H n.m.r. δ 4·40, t, J 5 Hz, CH_2OCO; 3·60, t, J 5 Hz, CH_2Cl; 3·40, s, NCH_2CO; 2·85, t, J 5 Hz, CH_2N; 2·27, t, J 6 Hz, CH_2N. Mass spectrum m/z 163/165 (M), 128, 100.

4-(2-Bromoethyl)morpholin-2-one (10)

The hydroxy lactone (8) (500 mg, 3·45 mmol) was dissolved in dichloromethane and the solution added to one of triphenylphosphine (900 mg, 3·45 mmol) in dichloromethane (10 ml) under an atmosphere of nitrogen. The solution was cooled to approx. 0–5° and carbon tetrabromide (1·36 g, 4·14 mmol) was added in small portions to maintain the temperature. After the addition was complete the mixture was left to stir at room temperature for 12 h, then filtered and evaporated to dryness. Purification by flash column chromatography (ethyl acetate/hexane, 3:1) gave the *bromide* (10) as a colourless oil (500 mg, 70%) which decomposed on standing and hence was used immediately (Found: $M^{+\bullet}$, 206·988. $C_6H_{10}{}^{79}BrNO_2$ requires $M^{+\bullet}$, 206·990). ν_{max} 1752, 1194 cm^{-1}. ^1H n.m.r. δ 4·38, t, J 5 Hz, CH_2OCO; 3·37, t, J 7 Hz, CH_2Br; 3·36, s, NCH_2CO; 2·81, t, J 7 Hz, CH_2N; 2·74, t, J 5 Hz, CH_2N. Mass spectrum m/z 207/209 (M), 114.

4-(2-Phenoxyethyl)morpholin-2-one (11)

(A) A mixture of 2-[(2-phenoxyethyl)amino]ethanol[30] (500 mg, 2·76 mmol) and triethylamine (280 mg, 2·76 mmol) in benzene (3 ml) was stirred at room temperature while methyl bromoacetate (422 mg, 2·76 mmol) was added dropwise. The mixture was stirred overnight then washed with dilute hydrochloric acid and water, dried and the solvent concentrated to yield a colourless oil (103 mg) which ran as two spots on thin-layer chromatography. ^1H n.m.r. analysis indicated the presence of the non-cyclized product (ester methyl at δ 3·82) as a minor component in a ratio of 1:5. A pure sample of the major, less polar, component was obtained by precipitating the more polar material from a solution in dichloromethane by the addition of light petroleum. The concentrated filtrate solidified on standing and was recrystallized from dichloromethane/light petroleum to yield the *ether* (11), m.p. 88–91° (Found: $M^{+\bullet}$, 221·104. $C_{12}H_{15}NO_3$ requires $M^{+\bullet}$, 221·105). ^1H n.m.r. δ 7·28–7·35, m, 2×ArH; 6·91–7·02, m, 3×ArH; 4·45, t, J 5 Hz, CH_2OCO; 4·15, t, J 5 Hz, CH_2OAr; 3·52, s, NCH_2CO; 2·92, t, J 5 Hz, CH_2N; 2·90, t, J 5 Hz, CH_2N. ^{13}C n.m.r. δ 167·2, 158·2, 129·5, 121·2, 114·4, 68·5, 65·6, 56·0, 55·9, 49·4. Mass spectrum m/z 221 (M), 128, 114, 94, 86.

(B) A solution of the bromo compound (10) (100 mg, 4·83 mmol) in dry tetrahydrofuran (2 ml) was added to a mixture of phenol (45 mg, 4·83 mmol) and sodium hydride (12 mg, 4·83 mmol) suspended in tetrahydrofuran (5 ml) and the resultant solution was left to stir at room temperature overnight. The sodium bromide which had formed was removed by filtration and the filtrate concentrated under reduced pressure to give a solid which was recrystallized from ethyl acetate/hexane to afford the ether (11), identical with the material above.

3-O-[2-(2′-Oxomorpholino)ethyl]morphine (5)

A solution of morphine hydrochloride (50 mg, 0·156 mmol) in tetrahydrofuran (2 ml) was added to a suspension of sodium hydride (7·5 mg, 0·312 mmol) in tetrahydrofuran (1 ml) and the mixture allowed to stir at room temperature for 1 h. The bromide (10) (32 mg, 0·156 mmol) in tetrahydrofuran was added all at once to the morphinoxide solution and the mixture stirred for 4 h at room temperature. The sodium bromide which had precipitated was removed by filtration and the solvent was removed under reduced pressure, leaving a solid which was recrystallized from ethyl acetate to yield the morphine derivative (5) as white crystals, m.p. 142–145°. ^1H n.m.r. ($CD_3SOCD_3/CDCl_3$) δ 6·67, d, J 8·1 Hz, H2; 6·51, d, J 8·6 Hz, H1; 5·73, d, J 10·8 Hz, H7; 5·22, d, J 10·8 Hz, H8; 4·90, d, J 6·5 Hz, H5; 4·44, t, J 3·4 Hz, CH_2OAr; 3·70, t, J 5·3 Hz, 2×H6′; 3·41, s, 2×H3′; 2·80 and 2·62, t, $2\times NCH_2$; 2·30, br s, NMe. Mass spectrum m/z 413 (M+H). Another mass spectrum taken 24 h later showed no peak at m/z 413; instead a new peak at m/z 431 (M+H) had appeared which was consistent with the structure *N*-(2-hydroxyethyl)-*N*-(2-morphinoxyethyl)aminoacetic acid (12), a result indicating hydrolysis of the lactone moiety of (5).

4-(2-Acetoxyethyl)morpholin-2-one (13)

[Bis(2-hydroxyethyl)amino]acetic acid[14] (9) (1·00 g, 6·2 mmol) was refluxed with acetic anhydride (1·9 g, 18·6 mmol) and triethylamine (2·02 g, 20·0 mmol) for 1 h. The cooled reaction mixture was filtered and excess acetic anhydride and triethylamine were removed under reduced pressure. The residue was dissolved in dichloromethane, the solution washed with water, dried, filtered and the solvent removed to give an oily residue. Distillation gave the *title ester* (13) (950 mg, 83%) as a colourless oil, b.p. 103°/0·1 mm (Found: C, 51·3; H, 6·9. $C_8H_{13}NO_4$ requires C, 51·3; H, 7·0%). ν_{max} 1746, 1732, 1150, 1070 cm^{-1}. ^1H n.m.r. δ 4·40, t, J 5 Hz, CH_2OCO; 4·30, t, J 6 Hz, CH_2OCO; 3·45, s, NCH_2CO; 2·75, t, J 5 Hz, NCH_2; 2·70, t, J 6 Hz, NCH_2; 2·10, s, CH_3CO_2. Mass spectrum m/z 187 (M), 128, 114.

Attempted Formation of 4-(2-Methylsulfonyloxyethyl)-morpholin-2-one (15)

The acetate (13) (200 mg, 1·1 mmol) was added to a solution formed from phenol (110 mg, 1·1 mmol) and sodium hydride (26 mg, 1·1 mmol) in dry tetrahydrofuran and the mixture refluxed for 1 h. Methanesulfonyl chloride (125 mg, 1·1 mmol) was added to the cooled solution which was then stirred at room temperature overnight. The mixture was filtered and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane, washed with water, dried and the solvent removed under vacuum. Chromatography on silica and elution with dichloromethane/ethanol (85:15) gave only phenyl acetate. The crude reaction product exhibited the following spectroscopic data consistent with the presence of the mesylate

(15): ^{1}H n.m.r. δ 4·40, t, J 7 Hz, CH_2OSO_2Me; 4·30, t, J 4 Hz, CH_2OCO; 3·43, s, NCH_2CO; 3·20, s, SO_2Me; 2·80, t, J 7 Hz, NCH_2; 2·70, t, J 4 Hz, NCH_2. Mass spectrum no M, m/z 127 (M − $MeSO_3H$).

2-{[N-(Chloroacetyl)-N-(2-hydroxyethyl)]amino}ethyl Chloroacetate (19)

A solution of 2 equiv. of chloroacetyl chloride (5·37 g, 47·55 mmol) in tetrahydrofuran (10 ml) was added slowly to a mixture of diethanolamine (2·50 g, 23·78 mmol) and triethylamine (4·80 g, 47·55 mmol) in tetrahydrofuran (30 ml) at −20° and the reaction mixture stirred overnight at room temperature. The solution was filtered and the solvent evaporated under reduced pressure to give an oil (3·40 g, 55%) which was mainly the ester (19) by ^{1}H n.m.r. This material was purified by chromatography on silica with chloroform/ethanol (9:1) and was used directly as attempted distillation led to decomposition. ν_{max} 3400, 1752, 1650 cm^{-1}. ^{1}H n.m.r. δ 4·42, t, CH_2OCO; 4·33, 4·17, both s, 2×CH_2Cl; 4·25, s, OH; 3·54–3·93, m, 2×CH_2N and CH_2OH. Mass spectrum no M, m/z 164/166 (M − $OCOCH_2Cl$).

2-{[N-Acetyl-N-(2-hydroxyethyl)]amino}ethyl Acetate (20)

Acetyl chloride (1·9 g, 23·8 mmol) in tetrahydrofuran (10 ml) was added slowly to a solution of diethanolamine (2·5 g, 23·8 mmol) and potassium carbonate (5·0 g) in tetrahydrofuran (40 ml) at −20° and the mixture stirred overnight at room temperature. The precipitated solid was filtered off, the solvent removed under reduced pressure and the residue distilled to afford the *ester* (20) as a colourless oil (2·7 g, 60%), b.p. 51°/0·02 mm [Found: $(M-H_2O)^{+\bullet}$, 171·090. $C_8H_{15}NO_4$ requires $(M-H_2O)^{+\bullet}$, 171·090]. ν_{max} 3370, 1740, 1670, 1120 cm^{-1}. ^{1}H n.m.r. δ 4·80, s, OH; 4·20, t, J 6 Hz, CH_2OCO; 3·67, t, J 4 Hz, overlapping with 3·57, t, J 6 Hz, and 3·13, m, 2×CH_2N and CH_2OH; 2·20 and 2·10, both s, 2×MeCO. Mass spectrum m/z 189 (M), 171, 158, 129, 116.

Bis[2-(t-butyldimethylsilyloxy)ethyl]amine

A solution of t-butyldimethylsilyl chloride (7·8 g, 52·3 mmol) in tetrahydrofuran was added to a mixture of diethanolamine (2·5 g, 23·8 mmol), triethylamine (5·8 g, 57·1 mmol) and 4-dimethylaminopyridine (300 mg, 2·4 mmol) in tetrahydrofuran (50 ml) and the mixture stirred at room temperature overnight. The solution was then diluted with water and extracted with dichloromethane. The organic layers were combined, washed with sodium bicarbonate solution, dried and evaporated under reduced pressure. The residual material was distilled (block temperature 165°/0·02 mm) to give the *title amine* (6·35 g, 80%) (Found: $M^{+\bullet}$, 333·246. $C_{16}H_{39}NO_2Si_2$ requires $M^{+\bullet}$, 333·252). ^{1}H n.m.r. δ 3·67, t, J 5 Hz, 2×CH_2OSi; 2·66, t, J 5 Hz, 2×CH_2N; 0·83, s, 2×Me_3C; −0·01, s, 4×MeSi. Mass spectrum m/z 333 (M), 318, 277, 202.

N,N-*Bis[2-(t-butyldimethylsilyloxy)ethyl]chloroacetamide (24)*

Chloroacetyl chloride (1·70 g, 15·0 mmol) was dissolved in tetrahydrofuran (10 ml) and the solution added slowly to a mixture of *N,N*-bis[2-(t-butyldimethylsilyloxy)ethyl]amine (5·00 g, 15 mmol) and triethylamine (1·52 g, 15·0 mmol) in tetrahydrofuran (20 ml) at −20° and the mixture was stirred at room temperature overnight. The solution was then diluted with water (30 ml) and extracted with dichloromethane. The organic layers were washed with a saturated sodium bicarbonate solution then dried, and the solvent was removed under reduced pressure. The residue was distilled (block temperature 225°/0·025 mm) to give the *chloroacetamide* (24) as a colourless oil (5·54 g, 90%) [Found: $(M-CH_3)^{+\bullet}$, 394·202. $C_{18}H_{40}ClNO_3Si_2$ requires $(M-CH_3)^{+\bullet}$, 394·200]. ν_{max} (film) 1650 cm^{-1}. ^{1}H n.m.r. δ 4·18, s, CH_2Cl; 3·73, t, J 5 Hz, CH_2O; 3·69, t, J 5 Hz, CH_2O; 3·56, t, J 5 Hz, CH_2N; 3·42, t, J 5 Hz, CH_2N; 0·83 and 0·82, both s, 2×Me_3C; −0·009 and −0·013, both s, 2×Me_2Si. ^{13}C n.m.r. δ 167·4, 61·2, 60·6, 51·5, 48·6, 41·5, 25·8, 18·1, −5·5, −5·6. Mass spectrum m/z 410/412 (M+H, 5), 394/396 (M − Me, 6), 352/354 (M − Bu^t, 100), 278/280.

N,N-*Bis(2-hydroxyethyl)chloroacetamide (18)*

A catalytic amount of *p*-toluenesulfonic acid (8 mg) was added to a solution of the chloroacetamide (24) (100 mg, 0·24 mmol) in a mixture of tetrahydrofuran/water (20:1, 10 ml) and the solution was stirred overnight at room temperature. The mixture was then heated at 55° for 1·5 h and concentrated almost to dryness under reduced pressure. The residue was extracted with ethyl acetate (3×20 ml). The extract was neutralized with solid anhydrous potassium carbonate, filtered and dried with magnesium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica by using a gradient of ethyl acetate and methanol to yield the amide (18) as a pale yellow mobile liquid (37 mg, 83%). Attempts to distill this material resulted in some decomposition. ν_{max} (Nujol) 3380, 1632 cm^{-1}. ^{1}H n.m.r. (CD_3OD) δ 4·31, s, CH_2Cl; 3·63, m, 2×CH_2O; 3·50, t, J 5 Hz, CH_2N; 3·44, t, J 5 Hz, CH_2N. ^{13}C n.m.r. δ 170·1, 60·4, 52·5, 50·3, 42·7. Mass spectrum no M, m/z 150/152 (M − OCH_3, 17), 114, 86, 74, 56 (100), 43, 42.

2-(3-Oxomorpholino)ethyl Chloroacetate (25)

The amido ester (19) (5·98 g, 23·3 mmol) was dissolved in tetrahydrofuran (25 ml) and added slowly to a suspension of sodium hydride (800 mg, 33·3 mmol) in tetrahydrofuran (25 ml) and the mixture allowed to stir at room temperature overnight. The solution was filtered and the filtrate evaporated. The residue was dissolved in dichloromethane, washed with water, dried, and the solvent removed to give a brown oil. The crude ester (25) (2·93 g, 57%) was used directly in the next step. ν_{max} 1754, 1656 cm^{-1}. ^{1}H n.m.r. δ 4·51–4·12, m, 2×CH_2O; 4·25, s, OCH_2CO; 4·05, s, CH_2Cl; 3·95–3·33, m, 2×CH_2N. Mass spectrum no M, m/z 145 [(M+H) − $COCH_2Cl$].

4-(2-Hydroxyethyl)morpholin-3-one (26)

The chloroacetate (25) (2·50 g, 11·3 mmol) was added to a solution of potassium hydroxide (1·25 g, 22·3 mmol) in methanol (125 ml) and the mixture stirred for 3 h. The solution was filtered and then chromatographed through a squat column with methanol/chloroform (1:9). The solvent was removed and the product distilled under reduced pressure (block temperature 165°/0·08 mm) to give the *alcohol* (26) (0·80 g, 49%) as a colourless, viscous oil [Found: C, 49·7; H, 8·1; N, 9·5%; $(M+H)^{+\bullet}$, 146·083. $C_6H_{11}NO_3$ requires C, 49·7; H, 7·6; N, 9·7%; $(M+H)^{+\bullet}$, 146·082]. ν_{max} 3394, 1654 cm^{-1}. ^{1}H n.m.r. δ 4·20, s, OCH_2CO; 3·91, t, J 5 Hz, CH_2O; 3·83, t, J 5 Hz, CH_2O; 3·57, t, J 5 Hz, CH_2N; 3·51, t, J 5 Hz, CH_2N; 1·25, br s, OH. Mass spectrum m/z 145 (M), 128 (M − OH).

4-(2-Chloroethyl)morpholin-3-one (28)

Thionyl chloride (5·0 ml) was added to the alcohol (26) (300 mg, 2·07 mmol) under a nitrogen atmosphere and after the initial exothermic reaction the clear solution was stirred at room temperature overnight. The excess thionyl chloride was removed under reduced pressure and the pale yellow oil placed under high vacuum for 30 min to remove traces of hydrogen chloride and thionyl chloride. The crude *chloride* (28) (300 mg, 89%), which decomposed on attempted distillation, was used immediately in the next step (Found: $M^{+\bullet}$, 163·040. $C_6H_{10}ClNO_2$ requires $M^{+\bullet}$, 163·040). ν_{max} 1655 cm^{-1}. ^{1}H n.m.r. δ 4·20, s, OCH_2CO; 3·91, t, J 5 Hz, CH_2O; 3·74, m, CH_2N and CH_2Cl; 3·56, t, J 5 Hz, CH_2N. Mass spectrum m/z 163/165 (M), 128, 114, 86, 42.

The reaction could also be conducted under reflux but often these conditions led to extensive decomposition.

Morpholin-3-one (30)

This compound was prepared according to the procedure of Vieles and Seguin[19] in 7% yield and recrystallized from ethanol as colourless needles, m.p. 105–106° (lit.[19] 106°). ν_{max} 3190, 1660 cm^{-1}. ^1H n.m.r. δ 4·20, s, OCH_2CO; 3·87, t, CH_2O; 3·09, m, CH_2N.

4-(2-Phenoxyethyl)morpholin-3-one (29)

Sodium hydride (23·0 mg, 0·96 mmol) was added to dry dimethylformamide and to this suspension was added morpholin-3-one (30) (50 mg, 0·53 mmol) and the mixture stirred for 10 min. (2-Bromoethoxy)benzene[17] (150 mg, 0·75 mmol) was then added dropwise and the mixture stirred for 24 h. The dimethylformamide was removed under reduced pressure and the residue dissolved in chloroform (10 ml), filtered to remove inorganic salts and the solvent evaporated. Purification of the residue by dry column (squat) chromatography with ethyl acetate/petroleum spirits gave the *ether* (29) as a colourless, viscous oil (98 mg, 84%) [Found: $M^{+\bullet}$, 221·104; $(M - OC_6H_5)^{+\bullet}$, 128·072. $C_{12}H_{15}NO_3$ requires $M^{+\bullet}$, 221·105; $C_6H_{10}NO_2$ requires *m/z*, 128·072]. ν_{max} 1635, 1605, 1505 cm^{-1}. ^1H n.m.r. δ 6·86–7·31, m, ArH; 4·19, t, *J* 5·5 Hz, CH_2O; 4·16, s, CH_2O; 3·85, t, *J* 4·6 Hz, CH_2O; 3·78, t, *J* 5 Hz, CH_2N; 3·60, t, *J* 4·6 Hz, CH_2N. Mass spectrum *m/z* 221 (M), 128, 120.

Attempted Reaction of 4-(2-Chloroethyl)morpholin-3-one (28) with Sodium Methoxide

To a solution of sodium methoxide [from sodium (25 mg, 1·10 mmol) and dry methanol (1·0 ml)] was added the ketone (28) (165 mg, 1·0 mmol) and the mixture stirred at room temperature overnight. T.l.c. (methanol/chloroform, 1:4) indicated only the starting material to be present. The solution was evaporated to dryness and the residue treated with water (5 ml). Extraction of the aqueous phase with chloroform (3×5 ml), followed by drying and evaporation of the solvent gave a colourless oil (100 mg, 69%), identical by ^1H n.m.r. and t.l.c. to 4-(2-hydroxyethyl)morpholin-3-one (26).

4-(2-Phenylsulfonyloxyethyl)morpholin-3-one (32)

The alcohol (26) (300 mg, 2·07 mmol) and triethylamine (0·43 ml, 3·11 mmol) were dissolved in dry dichloromethane (10·0 ml) under a nitrogen atmosphere and to the solution was added benzenesulfonyl chloride (0·3 ml) in dichloromethane (1·0 ml) dropwise over a few minutes. The mixture was allowed to stir at room temperature overnight, then water was added and the organic phase separated, washed thoroughly with water, followed by cold 3% hydrochloric acid and finally with saturated sodium bicarbonate. The solution was then dried, filtered and the solvent evaporated to give the *sulfonate ester* (32) (220 mg, 37%) as a yellow oil. Attempted distillation resulted in decomposition [Found: $(M - C_2H_2O_2)^{+\bullet}$, 227·060. $C_{12}H_{15}NO_5S$ requires $(M - C_2H_2O_2)^{+\bullet}$, 227·062]. ν_{max} 1655, 1380, 1180 cm^{-1}. ^1H n.m.r. δ 8·08–7·29, m, 5H, ArH; 4·19, s, OCH_2CO; 3·91, t, CH_2O; 3·74, m, CH_2N and CH_2OSO_2; 3·57, t, CH_2N. Doubling of the non-aromatic signals was obvious at room temperature, possibly due to restricted rotation of the phenylsulfonyloxy group. Mass spectrum no M, *m/z* 141, 114, 101 $[(M+H) - CH_2CH_2OSO_2C_6H_5]$.

3-O-(2-Chloroethyl)morphine (31)

Morphine hydrochloride (100 mg, 0·31 mmol) was added to a solution of sodium methoxide (from 23 mg sodium in 2·0 ml dry methanol) and after 15 min a solution of chlorohydrin benzenesulfonate ester[18] (150 mg, 0·68 mmol) in methanol (1 ml) was added all at once. The mixture was stirred at room temperature for 1 h then heated at reflux, under nitrogen, until product formation was complete by t.l.c. (approx. 2 h). The solution was evaporated to dryness, the residue was treated with water and then extracted with ether (3×5 ml). The organic extracts were dried, filtered and concentrated to give the ether (31) as a pale brown oil (110 mg, 93%) which could not be induced to crystallize [Found: $(M - H)^{+\bullet}$, 346·119. $C_{19}H_{21}ClNO_3$ requires $(M - H)^{+\bullet}$, 346·121]. Mass spectrum *m/z* 347/349 (M).

3-O-[2-(3'-Oxomorpholino)ethyl]morphine (4)

Caesium carbonate (127 mg, 0·39 mmol) and morphine hydrochloride (50 mg, 0·156 mmol) were dissolved in water (1·0 ml) and the solution was then evaporated to dryness and the residue dried thoroughly under a high vacuum. The residue was dissolved in dry dimethylformamide (1·0 ml) and to the refluxing solution was added a solution of the chloride (28) (28 mg, 0·17 mmol) in dimethylformamide (0·5 ml) all at once under a nitrogen atmosphere. After 2 h at reflux the dark mixture was cooled, poured into water (10 ml), basified with sodium hydroxide solution (2 M) then extracted with chloroform (3×5 ml). The organic extract was dried, filtered and evaporated to give a brown oil (5 mg). Purification by flash chromatography on silica (methanol/chloroform, 1:9) gave the ether (4) as a pale brown oil which could not be induced to crystallize. ^1H n.m.r. δ 6·70, d, *J* 8·0 Hz, H2; 6·58, d, *J* 8·0 Hz, H1; 5·75, d, *J* 6·5 Hz, H7; 5·33, d, *J* 6·5 Hz, H8; 4·90, d, *J* 6·5 Hz, H5; 4·20–4·33, m, H6 and CH_2OAr; 4·20, s, 2×H2'; 3·90, t, *J* 5 Hz, 2×H6'; 3·80, t, *J* 5 Hz, NCH_2CH_2OAr; 3·64, t, *J* 5 Hz, 2×H5'; 2·49, s, NMe. Mass spectrum (f.a.b.) *m/z* 413 (M+H), 128, 114. MIKES *m/z* 413 fragments to 395 $(M - H_2O)$, 286, 128.

Acknowledgments

We thank Dr Andrew Somogyi (Department of Clinical and Experimental Pharmacology, University of Adelaide) for helpful advice, and a referee for helpful comments concerning Scheme 3.

References

[1] Cahen, R., *Bull. Narc.*, 1961, **13**, 19.
[2] Jaffe, J. H., and Martin, W. R., in 'The Pharmacological Basis of Therapeutics' 7th Edn (Eds A. G. Gilman, L. S. Goodman, T. W. Rall and F. Murod) (MacMillan: New York 1985).
[3] Eddy, N. B., Friebel, H., Hahn, K. J., Halbach, H., *Bull. WHO*, 1969, **40**, 639.
[4] Findlay, J. W. A., *J. Clin. Pharm. Ther.*, 1988, **13**, 5.
[5] Findlay, J. W. A., Fowle, A. S. E., Butz, R. F., Jones, E. L., Weatherly, B. C., Welch, R. M., and Prosner, J., *Br. J. Clin. Pharmacol.*, 1986, **22**, 61.
[6] Chen, Z. R., Bochner, F., and Somogyi, A., *Br. J. Clin. Pharmacol.*, 1988, **26**, 445.
[7] Snell, E. S., and Armitage, P., *Lancet*, 1957, **272**, 860.
[8] Jaffe, G., and Grimshaw, J. J., *Curr. Med. Res. Opin.*, 1983, **8**, 594.
[9] Chen, Z. R., Siebert, D. M., Somogyi, A. A., and Bochner, F., *J. Chromatogr.*, 1988, **424**, 170.
[10] Maurer, H. H., and Fritz, Ch. F., *J. Drug Res.*, 1990, **40**(I), 563.
[11] Chabrier, P., Giudicelli, R., and Thuillier, J., *Ann. Pharm. Fr.*, 1950, **8**, 261.
[12] Khromov-Borisov, N. V., and Remizov, A. L., *Zh. Obshch. Khim.*, 1953, **23**, 598 (*Chem. Abstr.*, 1954, **48**, 7550).
[13] Pascal, M., *C. R. Seances Acad. Sci., Ser. 2*, 1957, **245**, 1318.

[14] Izumi, M., *Pharm. Bull.*, 1954, **2**, 275.
[15] Beckwith, A. L. J., Easton, C. J., Lawrence, T., and Serelis, A. K., *Aust. J. Chem.*, 1983, **36**, 545.
[16] Kashima, C., and Harada, K., *J. Chem. Soc., Perkin Trans. 1*, 1988, 1521.
[17] Marvell, C. S., and Tanenbaum, A. L., *Org. Synth.*, Collect. Vol. 1, 2nd Edn, p. 436 (John Wiley: New York 1941).
[18] Foldi, Z., *Ber. Dtsch. Chem. Ges. B*, 1920, **53**, 1839.
[19] Vieles, P., and Seguin, J., *Bull. Soc. Chim. Fr.*, 1953, 287.
[20] Merck, E., *Chem. Zentralbl.*, 1897, **II**, 158.
[21] Rodionow, W. M., *Bull. Soc. Chim. Fr.*, 1929, **45**, 109.
[22] Baizer, M. M., and Ellner, K. S., *J. Am. Pharm. Assoc.*, 1950, **39**, 581.
[23] Brands, K. M. J., Lie, T. S., and Maat, L., *Recl Trav. Chim. Pays-Bas*, 1986, **105**, 544.
[24] Perrone, R., Bettoni, G., and Tortorella, V., *Synthesis*, 1976, 598.
[25] Laurent, P. A., and Bearn, L., *Bull. Soc. Chim. Fr.*, 1978, 83.
[26] Still, W. C., Kahn, M., and Mitra, A., *J. Org. Chem.*, 1978, **43**, 2923.
[27] Harwood, L. M., *Aldrichimica Acta*, 1985, **18**, 25.
[28] Vogel, A. I., 'A Textbook of Practical Organic Chemistry Including Qualitative Organic Analysis' 4th Edn (Longman: New York 1978).
[29] Perrin, D. D., Armarego, W. L. F., and Perrin, D. R., 'Purification of Laboratory Chemicals' 2nd Edn (Pergamon: Oxford 1980).
[30] Gump, W. S., and Nikawitz, E. J., *J. Am. Chem. Soc.*, 1950, **72**, 3846.