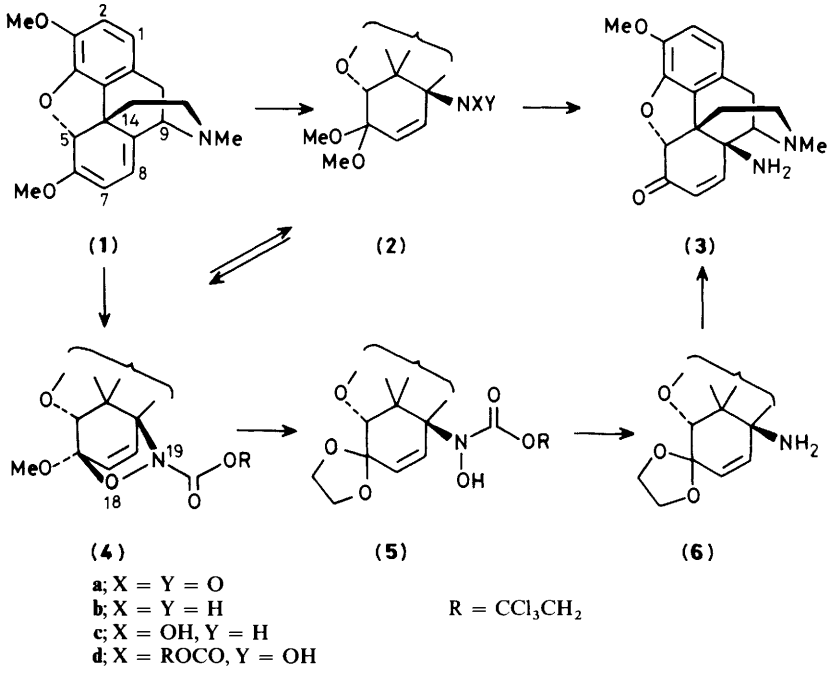
An Efficient Synthesis of 14β-Aminocodeinone from Thebaine

Gordon W. Kirby* and David McLean
Department of Chemistry, University of Glasgow, Glasgow G12 8QQ

Oxidation of 2,2,2-trichloroethyl *N*-hydroxycarbamate with sodium periodate in the presence of thebaine (**1**) gave (82%) a cycloadduct (**4**) of trichloroethyl nitrosoformate and the alkaloid. This adduct was converted with hydrogen chloride in ethylene glycol into 14β-N-(2,2,2-trichloroethoxycarbonyl)-*N*-hydroxyaminocodeinone ethylene acetal (**5**) and thence, *via* 14β-aminocodeinone ethylene acetal (**6**), into 14β-aminocodeinone (**3**) in an overall yield of 67—70%. Treatment of the adduct (**4**) with methanolic hydrogen chloride gave an equilibrium mixture (*ca.* 1 : 1) of (**4**) and the dimethyl acetal (**2d**) corresponding to (**5**).

14β-Aminocodeinone (**3**) and its dimethyl acetal (**2b**) are starting materials for the synthesis of a new family of antinociceptive 14β-acyl- and 14β-alkyl-amino-codeinones and -morphinones.[1] 14β-Aminocodeinone (**3**) was first prepared[2] (see Scheme) by a route, (**1**)→(**2a**)→(**2b**)→(**3**), starting with the nitration of thebaine (**1**) with tetranitromethane in methanol. This nitration, when conducted in the presence of ammonia[1] to ensure a high conversion of thebaine, produces, as a by-product, the ammonium salt of trinitromethane, a thermally unstable and, therefore, potentially hazardous substance. Consequently, we devised an alternative route,[3] (**1**)→(**2c**)→(**2b**)→(**3**), using 1-chloro-1-nitrosocyclohexane. The overall yield (35%) of (**3**) from thebaine was acceptable, and this method has been used recently[4] in the synthesis of 14β-(2-bromoacetamido) derivatives as ligands for the fractionation of opiate receptors. However, the large-scale preparation of 1-chloro-1-nitrosocyclohexane is also potentially hazardous and this reagent is unstable to prolonged storage at ambient temperatures. We were therefore encouraged to develop a third and more convenient route, (**1**)→(**4**)→(**5**)→(**6**)→(**3**), to 14β-aminocodeinone.

Oxidation of *N*-hydroxycarbamate esters, ROCONHOH, with periodate in the presence of thebaine (**1**) gives[5] epoxyimino derivatives of the type (**4**), presumably by cycloaddition of transient nitrosoformates, ROCONO, to the diene system of the alkaloid. For the present purposes, the trichloroethoxy derivative (**4**) was selected in the expectation that reductive cleavage of both the alkoxycarbonyl group and the N–O bond could be achieved in one preparative step. Thus, oxidation of 2,2,2-trichloroethyl *N*-hydroxycarbamate with sodium periodate in the presence of thebaine gave the adduct (**4**) (82%). This was converted at room temperature, in dry ethylene glycol containing hydrogen chloride, into the ethylene acetal (**5**) (95%). Reduction of (**5**) with zinc and ammonium chloride in methanol proceeded, as expected, with concomitant removal of the trichloroethoxycarbonyl group and cleavage of the N–O bond to give the amino acetal (**6**) (80%). This was hydrolysed in methanolic hydrochloric acid to afford 14β-aminocodeinone (**3**) (80%). The shorter version of the synthesis was readily devised.



Scheme.

The adduct (**4**) was converted into (**5**) in glycolic hydrogen chloride, as before. The mixture was treated directly with ammonium carbonate to generate glycolic ammonium chloride. Zinc powder was then added to effect the conversion, (**5**)→(**6**), and the amino acetal (**6**) was isolated and hydrolysed, without prior purification, to give (**3**). The overall yields of 14β-aminocodeinone (**3**) from the adduct (**4**) in two separate preparations were 67 and 70%. Attempts to shorten the procedure further by carrying out the final hydrolysis without isolating (**6**) led to poor yields (42%) of (**3**), reflecting apparently the difficulty of isolating 14β-aminocodeinone from mixtures rich in zinc salts.

It was recognised from the outset that the 6-oxo group of codeinone derivatives must be in protected, acetal form during their exposure to zinc, since unprotected codeinones undergo reductive cleavage of the C(5)–O bond. Indeed, rigorously dry glycol must be used for the transformation (**4**)→(**5**), to ensure that acetal formation is not accompanied by hydrolysis to the corresponding ketone. We initially planned to convert the adduct (**4**) into the dimethyl acetal (**2d**) and thence into the intermediate (**2b**) of the earlier routes. However, the adduct (**4**) was converted in methanolic hydrogen chloride into an equilibrium mixture containing approximately equal amounts of (**4**) and the required dimethyl acetal (**2d**). The latter was isolated and cleaved with zinc to give the amino-acetal (**2b**), which was hydrolysed to afford 14β-aminocodeinone (**3**). An unsuccessful attempt was made to overcome the problem presented by the balanced equilibrium, (**4**) ⇌ (**2d**). The mixture, under equilibrating conditions in methanolic hydrogen chloride, was treated with zinc amalgam. It was hoped either that the acetal (**2d**) would be reduced faster than the adduct (**4**) and would be replenished by equilibration, or that (**4**), after reduction, would be rapidly converted into (**2b**). However, the products were the desired amino acetal (**2b**) (36%) and thebaine (**1**) (40%). The latter, unexpected product probably arose from reduction of the adduct (**4**), since treatment of (**4**) with zinc and ammonium chloride also gave thebaine as one component of a complex mixture. Very likely, the thebaine was formed from the parent epoxyimino derivative (**4**; ROCO = H) which is known[5] to decompose in this manner.

In conclusion, the foregoing synthesis of 14β-aminocodeinone from thebaine *via* the adduct (**4**) is superior in yield and convenience to our earlier methods involving the nitro acetal[2] (**2a**) or the hydroxyamino acetal[3] (**2c**). Further, the ethylene acetal (**6**) is an acceptable alternative to the dimethyl acetal (**2b**) for the synthesis of 14β-alkylaminocodeinones *via* reduction of *N*-acyl derivatives with lithium aluminium hydride.[1]

Experimental

M.p.s were determined with a Kofler hot-stage apparatus. ^{1}H N.m.r. spectra were recorded at 60 MHz for $CDCl_3$ solutions and i.r. spectra for KBr discs. Molecular ion peaks of trichloro derivatives are reported only for the [$^{35}Cl_3$] species.

Adduct (**4**) *of Thebaine and Trichloroethyl Nitrosoformate.*—2,2,2-Trichloroethyl *N*-hydroxycarbamate[5] (3.12 g, 15 mmol) was added in portions during 15 min to a vigorously stirred, ice-cold mixture of thebaine (**1**) (3.11 g, 10 mmol) in ethyl acetate (100 ml) and sodium periodate (3.12 g, 15 mmol) in aqueous 0.5M-sodium acetate (50 ml) previously adjusted to pH 6 by addition of hydrochloric acid. The mixture was stirred for 1 h at 0 °C then made alkaline by addition of saturated aqueous sodium hydrogen carbonate. The ethyl acetate layer was washed with aqueous sodium thiosulphate and then brine and was dried (Na_2SO_4) and evaporated to afford 19-(2,2,2-*trichloroethoxycarbonyl*)-6,14-*dihydro*-6β,14β-*epoxyiminothebaine* (**4**) (82%), m.p. 173—174 °C (from methanol) (Found: C, 50.9; H, 4.2; Cl, 20.8; N, 5.6. $C_{22}H_{23}Cl_3N_2O_6$ requires C, 51.0; H, 4.4; Cl, 20.8; N, 5.5%); $\nu_{max.}$ 1 720 cm^{-1}; δ 2.49 (s, NMe), 3.64 (s, 6-OMe), 3.82 (s, 3-OMe), 4.56 (d, *J* 7 Hz, 9-H), 4.59 (s, 5-H), 4.64 and 4.90 (ABq, *J* 12 Hz, OCH_2), 6.06 and 6.14 (ABq, *J* 9 Hz, 7-and 8-H), and 6.56 and 6.69 (ABq, *J* 9 Hz, 1- and 2-H); *m/z* 516.

Conversion of the Adduct (**4**) *into the Ethylene Acetal* (**5**).—Ethylene glycol was distilled at atmospheric pressure and the middle fraction collected. This was dried (Na_2SO_4) and redistilled twice. Dry hydrogen chloride was passed into the dry glycol to produce a stock, concentrated solution, which was diluted as needed. Solutions of glycolic hydrogen chloride were transferred by syringe through rubber seals; concentrations were determined by titration. The adduct (**4**) (0.517 g, 1 mmol) in dichloromethane (*ca.* 2 ml) was added to 0.26M-glycolic hydrogen chloride (15 ml). The mixture was kept at room temperature for 2 h then made alkaline by addition of powdered sodium hydrogen carbonate. The mixture was diluted with water (20 ml) and extracted with chloroform. The extracts were washed with brine, dried, and evaporated to give 14β-[2,2,2-*trichloroethoxycarbonyl*(*hydroxy*)*amino*]*codeinone ethylene acetal* (**5**) (95%) which crystallised, with some difficulty, as needles, m.p. 137—138 °C (from dichloromethane–di-isopropyl ether) (Found: C, 50.6; H, 4.5; N, 5.0. $C_{23}H_{25}Cl_3N_2O_7$ requires C, 50.4; H, 4.6; N, 5.1%); $\nu_{max.}$ 3 420 and 1 720 cm^{-1}; δ 2.40 (s, NMe), 3.85 (s, OMe), 4.12 [m, $O(CH_2)_2O$], 4.78 (s, 5-H), 4.62 and 4.95 (ABq, *J* 12 Hz, OCH_2CCl_3), 5.38 (br s, OH, exch. with D_2O), 5.68 and 6.10 (ABq, *J* 10 Hz, 7- and 8-H), and 6.55 and 6.68 (ABq, *J* 8 Hz, 1- and 2-H); *m/z* 533.

14β-*Aminocodeinone Ethylene Acetal* (**6**).—The adduct (**4**) (1 mmol) was treated with glycolic hydrogen chloride as before. Powdered ammonium carbonate (0.192 g, 2 mmol) was stirred slowly into the mixture. Powdered zinc (0.4 g) was added with stirring and the mixture was then heated at 70 °C for 1 h. The zinc was filtered off and the filtrate made alkaline with saturated aqueous sodium hydrogen carbonate and then diluted with water (50 ml). The mixture was extracted with chloroform and the extracts were washed with brine, dried ($MgSO_4$), and evaporated to give 14β-*aminocodeinone ethylene acetal* (**6**) (87%), m.p. 203—204 °C (from ether) (Found: C, 67.2; H, 7.0; N, 7.9. $C_{20}H_{24}N_2O_4$ requires C, 67.4; H, 6.7; N, 7.9%); $\nu_{max.}$ 3 400 cm^{-1}; δ 2.35 (s, NMe), 3.40 (br s, NH_2, exch. with D_2O), 3.83 (s, OMe), 4.02 [m, $O(CH_2)_2O$], 4.50 (s, 5-H), 5.66 and 5.84 (ABq, *J* 9 Hz, 7- and 8-H), and 6.50 and 6.62 (ABq, *J* 8 Hz, 1- and 2-H); *m/z* 356. Alternatively, the ethylene acetal (**5**) (261 mg) was heated under reflux in methanol (15 ml) containing ammonium chloride (212 mg) and powdered zinc (260 mg) for 1 h. The mixture was worked up as before to give the amino acetal (**6**) (80%). Initially, the amino acetal (**6**) was obtained as an oil; crystallisation was first effected after chromatography on silica plates developed with ethyl acetate–methanol–diethylamine (74:25:1).

Shortened Synthesis of 14β-Aminocodeinone (**3**) *from the Adduct* (**4**).—The adduct (**4**) (0.517 g, 1 mmol) was converted as before into the ethylene acetal (**5**). This was reduced *in situ*, as before, with zinc in glycolic ammonium chloride to give the amino acetal (**6**) which was isolated, as an oil, and hydrolysed, without prior purification, in methanol (6 ml) and water (3 ml) containing 6M-hydrochloric acid (12 drops) with heating under reflux for 30 min. The mixture was treated with an excess of saturated aqueous sodium hydrogen carbonate and extracted with chloroform. The extracts were washed with brine, dried ($MgSO_4$), and evaporated to give 14β-aminocodeinone (**3**), m.p. 189—191 °C (from methanol) (lit.,[2] 192—194 °C, lit.,[4] 188—191 °C) (Found: C, 69.0; H, 6.35; N, 8.9. Calc. for $C_{18}H_{20}N_2O_3$:

C, 69.1; H, 6.45; N, 9.0%); $\nu_{max.}$ 3 360, 3 260, and 1 680 cm^{-1}; δ 2.18 (br s, NH_2, exch. with D_2O), 2.38 (s, NMe), 3.81 (s, OMe), 4.69 (s, 5-H), 6.04 and 6.65 (ABq, *J* 10 Hz, 8- and 7-H), and 6.61 (s, 1- and 2-H); *m/z* 312. The yields of 14β-aminocodeinone from (**4**) in two separate preparations were 67 and 70%.

Conversion of the Adduct (**4**) *into the Dimethyl Acetal* (**2d**).—The adduct (**4**) (103 mg, 0.2 mmol) was treated with dry 0.2M-methanolic hydrogen chloride (4 ml) at 0 °C for 15 min. The mixture was treated with an excess of powdered sodium hydrogen carbonate and then diluted with water (10 ml) and extracted with chloroform. The extracts were dried ($MgSO_4$) and evaporated to give an oily mixture of (**4**) and (**2d**) (55:45, as judged by ^1H n.m.r. spectroscopy). The oil was dissolved in ethyl acetate and set aside at room temperature. 14β-[2,2,2-*Trichloroethoxycarbonyl(hydroxy)amino]codeinone dimethyl acetal* (**2d**) crystallised out as plates (30%), m.p. 161—162 °C (Found: C, 50.4; H, 5.1; Cl, 19.5; N, 5.4. $C_{23}H_{27}Cl_3N_2O_7$ requires C, 50.2; H, 4.9; Cl, 19.4; N, 5.1%); $\nu_{max.}$ 3 240 and 1 695 cm^{-1}; δ 2.40 (s, NMe), 3.25 (s, OMe), 3.51 (s, OMe), 3.88 (s, OMe), 4.89 (s, 5-H), 4.60 and 5.03 (ABq, *J* 12 Hz, OCH_2CCl_3), 5.68 and 6.24 (ABq, *J* 10 Hz, 7- and 8-H), and 6.55 and 6.75 (ABq, *J* 8 Hz, 1- and 2-H); *m/z* 548. The ratio of (**4**) to (**2d**) was not changed by extended reaction times. Equilibration at −15 and −78 °C gave ratios of (**4**) to (**2d**) of 45:55 and 40:60 (determined by n.m.r. spectroscopy) and yields of crystalline (**2d**) of 38 and 39%, respectively.

14β-*Aminocodeinone Dimethyl Acetal* (**2b**).—The acetal (**2d**) (103 mg) was heated under reflux for 1 h in methanol (7 ml) containing ammonium chloride (107 mg) and powdered zinc (195 mg). The zinc was filtered off and the filtrate evaporated to dryness. The residue was shaken with water and chloroform and the chloroform layer was washed with brine, dried ($MgSO_4$), and evaporated to give a brown oil. This was chromatographed on grade III, neutral alumina. Elution with chloroform gave 14β-aminocodeinone dimethyl acetal (**2b**) (85%), having spectroscopic properties identical with those reported [2] for the reduction product of (**2a**).

Reduction of the Equilibrium Mixture of (**4**) *and* (**2d**) *with Zinc Amalgam.*—The adduct (**4**) (1.03 g, 2 mmol) was dissolved in 0.7M-methanolic hydrogen chloride (100 ml) at 0 °C. After 15 min, zinc amalgam (2.5 g, 9 mmol zinc) was added in portions with stirring during 20 min, and the mixture was stirred at 0 °C for a further 1 h and then filtered. The filtrate was treated with an excess of powdered sodium hydrogen carbonate and extracted with chloroform. The extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed on grade III, neutral alumina. Elution with chloroform gave, successively, thebaine (**1**) (40%) and 14β-aminocodeinone dimethyl acetal (**2b**) (36%). The acetal (**2b**) was hydrolysed with methanolic hydrochloric acid, as described for the shortened synthesis of (**3**), to give 14β-aminocodeinone (**3**) [23% yield based on (**4**)].

Reduction of the Adduct (**4**) *with Zinc.*—The adduct (**4**) (103 mg) was heated under reflux for 1 h in methanol (20 ml) containing ammonium chloride (107 mg) and powdered zinc (195 mg). The mixture was worked up as described for the preparation of (**2b**). Chromatography gave thebaine (40%).

Acknowledgements

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