Procedural Refinements in the *N*-Demethylation of Morphine and Codeine Using Phenyl Chloroformate and Hydrazine

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A refined, rapid procedure for the preparation of normorphine and norcodeine in 80-90% yields is described.

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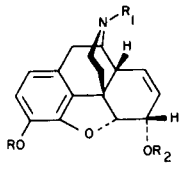
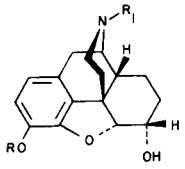
In 1975, one of us (KCR) reported an improved procedure for *N*-demethylating morphine (**1a**) and codeine (**1c**) using phenyl chloroformate and subsequent hydrazinolysis of the carbophenoxy groups (1). Very careful, thin-layer chromatography (2) later showed that the normorphine (**1b**) thus obtained contained 5-10% of dihydronormorphine (**2a**), the norcodeine (**1d**) a lesser amount of dihydronorcodeine (**2b**). As normorphine is frequently used as a standard in biopharmacological studies (3), it is desirable, in some instances crucial, to have scrupulously pure material, obtainable without the necessity for elaborate purification methods. We wish to report refined, speedier procedures which give **1b** and **1d** in 80-90% yields to the exclusion of **2a** and **2b**.



1a, R = R_2 = H, R_1 = Me
1b, R = R_1 = R_2 = H
1c, R = R_1 = Me, R_2 = H
1d, R = Me, R_1 = R_2 = H
1e, R = R_1 = CO_2Et, R_2 = H
1f, R = R_2 = H, R_1 = CO_2Et



2a, R = R_1 = H
2b, R = Me, R_1 = H

Features of the revised procedures are: 1) Shorter reaction times in both the acylation and hydrazinolysis reactions; 2) use of a steady stream of nitrogen or argon passed through the reaction mixture; 3) use of allyl alcohol (in the preparation of **1b** only) for the hydrazinolysis step to react with diimide, believed to be the active reducing species of hydrazine (4).

Allyl alcohol was not needed as an inhibitor in the hydrazinolysis leading to **1d**. Just why the olefinic bond of the methyl-ether series (**1c,1d**) is less reactive than in the phenolic (**1a,1b**) series is not clear.

During one of the early experiments (1) in the reaction of phenyl choroformate with **1a**, there was inadvertant interruption of stirring. The resultant, crude, discolored product, on hydrazinolysis, gave a 1:1 mixture of **1b** and **2a**. From this mixture, pure **1b** could be obtained *via* the sulfamate salt. The "mother liquors" yielded nearly pure **2a** (5) after treatment of an aqueous solution of the residue (from evaporation of solvent *in vacuo*) with ammonium hydroxide. It was identified by comparison (mass spectra, nmr, analytical and chromatography data) with an authentic specimen prepared by *N*-demethylation (6) of dihydromorphine.

We have also used ethyl chloroformate to prepare **1b**. The intermediate 3,*N*-dicarbethoxynormorphine (**1e**) was formed in 90% yield (7), but the hydrazinolytic cleavage to **1b** required 4-6 days. This method is not considered practical, the high yield of **1e** notwithstanding. Recently, Brine, *et al.*, (8) reported yields of 74 and 70%, respectively, for **1b** and **1d**, using methyl chloroformate. Although an inert atmosphere was not used and the time for hydrazinolysis was 65 hours, contamination with dihydro compounds was not noted. It is possible that they were lost in the "workup" procedure used by these investigators.

EXPERIMENTAL

Melting points (capillary, Hershberg apparatus) are corrected. Mass (Hitachi Perkin-Elmer RMU 6E) and nmr (Varian A-60 or HR-220) spectral and analytical data were provided by the Section on Instrumentation and Analytical Services of this Institute. Infrared measurements were made in chloroform (Perkin-Elmer 257).

Normorphine (**1b**)·1.5·H_2O.

To morphine·H_2O (2.5 g.), 12.5 g. of potassium bicarbonate and 200 ml. of chloroform was added 9.0 g. of phenyl chloroformate. The mixture was stirred vigorously and refluxed for 15-20 hours. Filtration and evaporation of the chloroform (9) at the water pump left a liquid mixture which was de-aerated with nitrogen for 3-5 minutes and treated with 9 ml. of allyl alcohol, then carefully with 31 ml. of 95% hydrazine. While continuing to pass nitrogen through the solution, it was refluxed gently for 7-8 hours. Dilution with 10-15 ml. of water, evaporation to dryness (9) at the water pump and partitioning the residue between ether and 6-8% hydrochloric acid gave, after addition of ammonium hydroxide to the acid layer to *p*H 9-11, 2.2-2.3 g. (90-93%) of **1b**·1·5H_2O, free of **2a** (1,2).

The sulfamate salt was prepared by suspending 2.2 g. of **1b** in 80 ml. of hot methanol, adding 0.7 g. of sulfamic acid in 2 ml. of hot water, filtering the solution hot and cooling to 0°; needles, m.p. 130-140° (froth).

Anal. Calcd. for $C_{16}H_{20}N_2O_6S·O·5H_2O$: C, 50.9; H, 5.6; N, 7.4. Found: C, 50.6; H, 5.6; N, 7.4.

Norcodeine (**1d**).

A mixture of 3.0 g. of **1c** (Merck), 11.5 g. of potassium bicarbonate, 175 ml. of chloroform and 10.0 g. of phenyl chloroformate was refluxed (vigorous magnetic stirring) for 15-20 hours. Filtration and evaporation of solvent at the water pump

left a liquid mixture (9) which was de-aerated with nitrogen for 3-5 minutes and treated carefully with 11 ml. of 65% hydrazine, then 15 ml. of 95% hydrazine. While continuing to pass nitrogen through the soluiton, it was refluxed for 7-8 hours and treated with 5-10 ml. of water. Evaporation to dryness (9) at the water pump, partitioning the residue between an excess of 8-10% hydrochloric acid and ethyl acetate (warming), cooling (to 0°) and filtering gave 3.5 g. (90%) of **1d**·HCl·$3H_2O$ (10). This was suspended in chloroform and shaken with dilute potassium hydroxide. The water-washed, dried, chloroform layer, on evaporation to dryness, yielded 2.3 g. (80%) of pure **1d** (2), m.p. 186-188° (11).

Compound **2a**, M^+ 273, was similarly made or was prepared *via* ethyl chloroformate and subsequent hydrazinolysis, to be described later (6). The *hydrobromide salt* of **2a** (from acetone-33% hydrogen bromide in acetic acid) melted at 275-280° dec.

Anal. Calcd. for $C_{16}H_{20}BrNO_3$: C, 54.2; H, 5.7; N, 4.0. Found: C, 54.1; H, 6.0; N, 4.1.

3,*N*-Dicarbethoxynormorphine (**1e**).

Morphine·H_2O (6.0 g.), 30 g. of potassium bicarbonate, 20 g. of ethyl chloroformate and 300 ml. of chloroform were refluxed and stirred vigorously for 24 hours, filtered and evaporated to dryness *in vacuo*. The residue was triturated in 12-15 ml. of ether to give, after cooling to 0°, 7.7 g. (90%) of **1e** (7), m.p. 153-154° before and after recrystallization from ethyl acetate; M^+ 415, ir 3500 (allylic OH), 1760 (3-OCO_2Et), 1645 (N-CO_2Et) cm^{-1}. The material was insoluble in aqueous caustic unless heated to 100° for a few minutes.

Anal. Calcd. for $C_{22}H_{25}NO_7$: C, 63.6; H, 6.1; N, 3.4. Found: C, 63.4; H, 6.3; N, 3.2.

N-Carbethoxynormorphine (**1f**).

A mixture of 2.0 g. of **1e**, 15 ml. of 95% hydrazine and 5 ml. of allyl alcohol was refluxed with continuous nitrogen or argon de-aeration for 48 hours, diluted with 5-10 ml. of water and evaporated to dryness *in vacuo*. The residue was treated with 5-8% hydrochloric acid in slight excess and 5-10 ml. of ethyl acetate. Treatment of the acidic layer with ammonium hydroxide to *p*H 9-11 gave 0.85 g. (60%) of **1b** essentially free of **2a**. Drying and evaporation of the ethyl acetate gave a residue which crystallized from ether; yield of **1f**, m.p. 171-172°, M^+ 343, ir 1645 (N-CO_2Et) cm^{-1}, 0.6 g. (36%).

Anal. Calcd. for $C_{19}H_{21}NO_5$: C, 66.5; H, 6.2; N, 4.1. Found: C, 66.5; H, 6.2; N, 3.9.

Acknowledgments.

We are grateful to Herman Yeh and Noel Whittaker for nmr data, to William Landis for mass spectra and to Paula Parisius, Alice Wong and Byron Baer for elemental analyses; all are in the Section on Instrumentation and Analytical Services of this Institute. Helpful suggestions came from Arthur Jacobson also of this Institute.

REFERENCES AND NOTES

(1) K. C. Rice, *J. Org. Chem.*, **40**, 1850 (1975).

(2) Solvent system, chloroform-methanol-concentrated ammonium hydroxide (74:24:2). After two "passes" in this system (Silica Gel GF) the Rf of **1b** is about 0.22, that of **2a** about 0.16.

(3) H. W. Kosterlitz and A. A. Waterfield, *Ann. Rev. Pharmacol.*, **15**, 29 (1975).

(4) U. Eppenberger, M. W. Warren and H. Rapoport, *Helv. Chim. Acta*, **51**, 381 (1968); E. J. Corey, D. J. Pasto and W. L. Mock, *J. Am. Chem. Soc.*, **83**, 2957 (1961).

(5) We reason that the hydrogen ions necessary for the reduction in this instance arose from oxidation of the phenol (from phenyl chloroformate) to quinones.

(6) Either phenyl or ethyl chloroformate was used. In the latter case a period of 7 days was required for the hydrazinolysis. This information will be published by A. E. Jacobson and J. Minamikawa (Visiting Fellow) of this laboratory.

(7) It is surprising that only traces of 3,6,*N*-tricarbethoxynormorphine (M^+ of unpurified product) was formed under these conditions (large excess of ethyl chloroformate, potassium bicarbonate, refluxing chloroform).

(8) G. A. Brine, K. G. Boldt, C. K. Hart and F. I. Carroll, *Organic Prep. Proced. Int.*, **8**, 103 (1976).

(9) It is not necessary to remove phenol (see reference 1).

(10) This material contains 1-3% of normorphine and traces of morphine hydrochlorides resulting from *O*-demethylation by hydrazine. The isolation procedure described in reference 1 (aqueous-caustic extraction of a chloroform solution of the product from hydrazinolysis) eliminates these phenolic compounds.

(11) Occasionally, a higher-melting modification of **1d** was encountered.