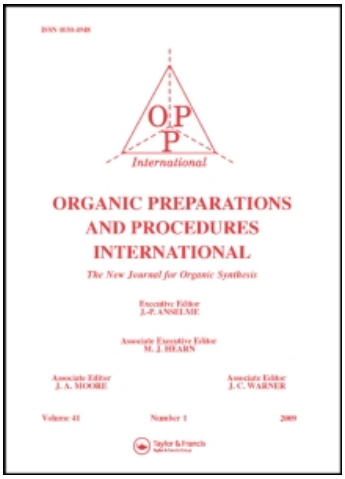

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THE N-DEMETHYLATION OF MORPHINE AND CODEINE USING METHYL CHLOROFORMATE[1]

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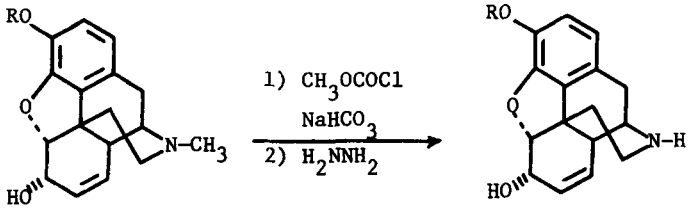
In recent years several research groups have reported the N-demethylation of morphine (1a) and codeine (1b) using various chloroformate esters. Abdel-Monem and Portoghese[2] prepared N-carbophenoxy-N-normorphine and N-carboethoxy-N-norcodeine using phenyl and ethyl chloroformate respectively. Subsequent base hydrolysis afforded N-normorphine (2a) and N-norcodeine (2b) in low overall yield. Montzka and co-workers[3] obtained 2a in 79% overall yield by treating 1a with 2,2,2-trichloroethyl chloroformate and cleaving the intermediate carbamate with zinc in 90% acetic acid. Most recently, Rice[4] reported an improved synthesis of 2a and 2b involving reaction of 1a and 1b with phenyl chloroformate followed by hydrazine cleavage of the crude carbamates. The overall yields were 85% and 89%, respectively.



1a, R = H
1b, R = CH_3

2a, R = H
2b, R = CH_3

After investigating several literature methods, we found the Rice procedure[4] to be preferable for effecting the N-demethylation reaction.

However, in the case of 1a, product isolation was complicated by the presence of the phenol by-product. In our hands, neither vacuum distillation[4] nor azeotropic distillation with water removed all of the phenol. Moreover, both procedures seemed unnecessarily time-consuming. Consequently, we studied the N-demethylation of 1a using methyl chloroformate in order to produce a volatile by-product in the second step. The intermediate carbamate (ir 1750 s, 1688 s cm^{-1}) was formed readily and was treated with hydrazine without purification. N-Normorphine (2a) precipitated from the hydrazine reaction mixture and was isolated as analytically pure white needles in 74% overall yield. Although the yield was lower than that reported by Rice,[4] the procedure was considerably simpler. Reproducible results were obtained on several runs.

We have observed that even analytically pure samples of 2a free base obtained by the above method gradually undergo some darkening and decomposition. We have not encountered this problem with the hydrochloride salt. Consequently, for storage purposes, we recommend that the free base be converted to the hydrochloride salt even though this additional manipulation further lowers the overall yield.

We also examined the conversion of codeine (1b) to N-norcodeine (2b) using the modified procedure. In this case, treatment of the crude carbamate (ir 1758 m, 1688 s cm^{-1}) with aqueous hydrazine afforded 2b contaminated with some 2a. The occurrence of some O-demethylation was attributed to the need for a longer heating time than that used[4] for the cleavage of the N-carbophenoxy compound.[5] The O-demethylation side reaction was circumvented by the use of methanolic hydrazine, which enabled the cleavage reaction to be run at lower temperature. The two-step procedure afforded pure N-norcodeine (2b) in 71% overall yield. Even though this yield was lower than the literature yield,[4] the heating and extraction steps necessary to remove the phenol were avoided.

N-DEMETHYLATION OF MORPHINE AND CODEINE

The use of ethyl chloroformate in the N-demethylation of tertiary methylamines has frequently been hampered by the difficulty encounted in hydrolizing the N-carboethoxy intermediate.[2,3,6] Our results suggest that the sequence of methyl chloroformate followed by hydrazine could allow an alkyl chloroformate ester to be used when other chloroformate esters were less desirable.

EXPERIMENTAL[7]

N-Normorphine (2a).- A mixture of morphine (20.1 g, 0.07 mol), methyl chloroformate (110 g, 1.16 mol), and $NaHCO_3$ (84 g, 1.00 mol) in $CHCl_3$ (1 ℓ) was stirred and refluxed for 20 hr. Afterwards, the reaction mixture was filtered and the inorganic solids washed with fresh $CHCl_3$. The combined filtrate and washings were then dried (Na_2SO_4) and evaporated to get 29.4 g of yellow foam. To this was slowly added 97% hydrazine (20 ml). After the ensuing exothermic reaction had subsided, additional 97% hydrazine (40 ml) and 64% hydrazine (80 ml) were added. The resulting solution was refluxed for 63 hr. Upon cooling to room temperature, 2a (11.3 g) precipitated from the red solution as white needles which were collected and washed with H_2O, Me_2CO, and $CHCl_3$. The mother liquors and H_2O wash were combined and chilled to get a second crop (2.8 g) of white needles which were collected and washed as before. Extraction of the second mother liquors with $CHCl_3$: i-PrOH (3:1) followed by trituration of the resulting residue with Me_2CO yielded additional 2a (1.0 g) as a pink solid. The first two crops totaled 14.1 g (74.2%), mp 272-274° dec (lit.[4] mp 275-277° dec).

Anal. Calcd. for $C_{16}H_{17}NO_3 \cdot 1/4\ H_2O$: C, 69.67; H, 6.40; N, 5.08. Found: C, 69.82; H, 6.44; N, 5.47.

The hydrochloride salt was prepared by treating a slurry of the free base (15.1 g) in hot MeOH (500 ml) with methanolic HCl (500 ml). The resulting crude salt (16.3 g) was redissolved in MeOH, decolorized with neutral Norit, and recrystallized as white needles by the addition of EtOAc

and concentration. After recrystallization of the smaller crops from MeOH: EtOAc, 12.0 g of 2a·HCl, mp 304° dec (lit.[8] mp 305° dec) was obtained. Anal. Calcd. for $C_{16}H_{17}ClNO_3$: C, 62.44; H, 5.89; N, 4.55. Found: C, 62.19; H, 6.14; N, 4.35.

N-Norcodeine (2b).- A mixture of codeine (5.0 g, 0.017 mol), methyl chloroformate (27.5 g, 0.29 mol), and $NaHCO_3$ (21 g, 0.25 mol) in $CHCl_3$ (250 ml) was stirred and refluxed 20.5 hr. Workup by the procedure described above afforded 6.5 g of white foam. This was dissolved in a mixture of 97% hydrazine (30 ml) and MeOH (21.5 ml), and the resulting solution was refluxed for 67 hr. Afterwards, the mixture was cooled, diluted with H_2O (50 ml), and extracted with $CHCl_3$ (x3). The combined organic extracts were dried (Na_2SO_4) and evaporated to get a yellow foam. Crystallization from Me_2CO yielded 3.4 g (70.8%) of 2b as white needles, mp 183-185° (lit.[4] 183.5-185°).

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