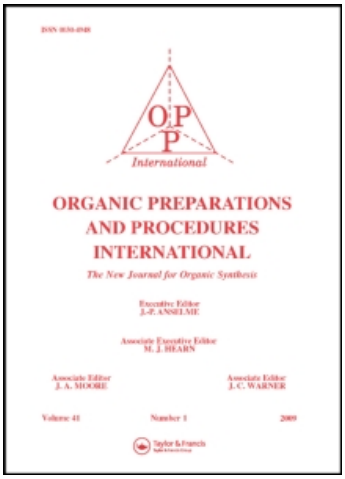

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N-DEMETHYLATION OF APOMORPHINE USING METHYL CHLOROFORMATE

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N-DEMETHYLATION OF APOMORPHINE USING METHYL CHLOROFORMATE

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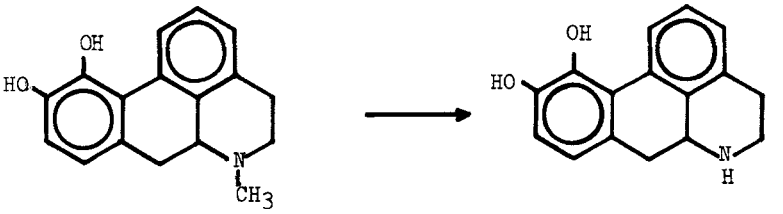
N-Noraporphines constitute an important subgroup of alkaloids to the more widely found N-methylated bases, the aporphines.[1] The aporphines may be obtained not only by total synthesis, but also by N-methylation of N-noraporphines which are available only by isolation and by total synthesis via their N-benzyl derivatives.[2] The N-demethylation of tertiary amines has been accomplished in several ways. The classical von Braun reaction,[3] using cyanogen bromide was improved upon for many amines by the use of phenyl or ethyl chloroformate[4] to obtain N-carbophenoxy-N-normorphine and N-carboethoxy-N-carbophenoxy-N-normorphine and N-carboethoxy-N-norcodeine, respectively. Subsequent base hydrolysis afforded N-normorphine



and N-norcodeine in low overall yield. Ethyl diazodicarboxylate has been used[5] to demethylate thebaine and various 6-ester derivatives of morphine and codeine in reasonable yield. However, this procedure gave only about 40% yield of an N-nor-

6,7-benzomorphan.[6] Recently Montzka and coworkers[7] have obtained N-norcodeine in 79% overall yield by treating codeine with 2,2,2-trichloroethyl chloroformate and cleaving the intermediate carbamate with zinc in acetic acid or methanol. More recently, Rice[8] and Carroll and his group[9] reported an improved synthesis of N-normorphine and N-norcodeine utilizing a modified phenyl chloroformate and methyl chloroformate procedures, followed by hydrazine cleavage of the crude carbamate. The overall yields were exceptionally good in contrast to the earlier methods.[3-7]

We utilized a methyl chloroformate procedure[8,9] for the preparation of N-norapomorphine (I) from apomorphine (II). To the best of our knowledge, this procedure is the first demonstration in the apomorphine series, since various other methods failed to effect the N-demethylation of apomorphine (II).[10] Chloroformate reactions of apomorphine followed by base hydrolysis of the intermediate carbamate gave an undesired ring opening reaction. When the apomorphine was treated with acyl chloride, oxidation of the apomorphine and scission of the hydropyridine ring was observed.[11]

The procedure of Abdel-Monem and Portoghese[4] for the preparation of N-normorphine involved the hydrolysis of N,3,6,-tricarbophenoxy normorphine to N-carbophenoxy normorphine, its chromatography and crystallization, followed by cleavage with ethanolic KOH. We found it unnecessary in our procedure to isolate and purify the intermediate carbamate; with apomorphine, N-norapomorphine precipitated from the hydrazine reaction mixture. Washing followed by drying gave analytically pure product in 87% overall yield.

The above result strongly suggests this modified method as the most practical one for converting apomorphine to N-norapomorphine.

EXPERIMENTAL[13]

Norapomorphine(I).- To a suspension of apomorphine (2.24 g, 0.0092 mol) and $NaHOC_3$ (19.32 g, 0.23 mol) in $CHCl_3$ (200 ml) was added methyl chloroformate (10.849 g, 0.1148 mol) and the mixture was heated to reflux for 52 hrs. with vigorous stirring. The reaction mixture was then filtered and the inorganic solids were thoroughly washed with $CHCl_3$ (5 x 75 ml). The combined filtrate and washings were dried ($MgSO_4$), filtered and evaporated in vacuo. To this residue was slowly added 64% hydrazine (20 ml). After the ensuing exothermic reaction had subsided, additional 64% hydrazine (20 ml) and 95% hydrazine (40 ml) were added and the resulting solution was heated to reflux under nitrogen atmosphere for 57 hrs. Upon cooling to room temperature, I (1.56 g) precipitated from the bluish-red solution as a white solid which was collected and washed with H_2O (3 x 50 ml). The mother liquors and H_2O washings were combined and chilled overnight (ca. 15 hr) to get a second crop (0.27 g) of white solid which was collected and washed as described previously. The first two crops totaled 1.83 g (87%), mp. 280-282°, lit.[12] mp. 230-250° (dec.).

UV λ_{max}(MeOH): 216 nm (ε 39,00), 271 nm (ε 17,500) and 312 nm (ε 2700); nmr ($CDCl_3$); τ6.97 (7H, m), 3.09 and 2.82 (3H, m), 1.78 (1H, d, J = 2.0 Hz) and 1.65 (1H, d, J = 2.0 Hz). The signal of II at τ7.43 (-N-Me, s) had disappeared.

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13. Melting Points were determined on a Kofler hot stage and are uncorrected. Safety shields and good ventilation hood were used during the reactions.

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