Arch. Pharm. Res. 6(2), 137~140 (1983)

A High Yield Conversion of N-Norapomorphine from Apomorphine

Jack C. Kim

College of Natural Sciences, Busan National University, Busan 607, Korea

(Received 3 August 1983)

Abstract □ A rapid, high yield of N-norapomorphine from apomorphine was accomplished by allowing it to react with phenyl chloroformate without isolating and purifying the intermediate carbamate, and have found that the crude carbamate can be easily cleaved in situ with a 1:1 mixture of 64% and 95% hydrazine to afford analytically pure N-norapomorphine in 81% overall yields. Previously, various other methods gave an untoward ring opening reactitons and scission of the hydropyridine ring in the apomorphine series.

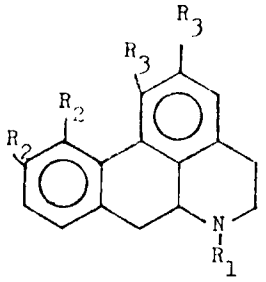
Keywords □ Amorphine, Emetics, Parkinsonism, Dopaminergic, N-Norapomorphine, N-Demethylation.

For many years, apomorphine (**Ia**) has been found medicinal application as a powerful centrally acting emetics. And more recently considerable interest has been shown in apomorphine due to its application in the treatment of Parkinsonism[1], and because of suggested relationships of this compound to dopaminergic and emetic activities[1]. The metabolic fate of apomorphine in mammalian systems has been observed that the N-demethylation of the apomorphine appears to be one of the most important pathways to give N-norapomorphine (**Ib**)[2]. As a result of these high biological activities, coupled with the metabolic biotransformation of apomorphine, the chemical N-demethylation procedures of apomorphine molecule prompted us to investigate a facile synthetic procedure to obtain significant quantities of N-norapomorphine from the more readily available apomorphine; so that one may demonstrate minor changes in substitution on the apomorphine nitrogen atom which may produce large changes in biological activities, such as Parkinsonism, emetic and dopaminergic effects, etc[1-6].

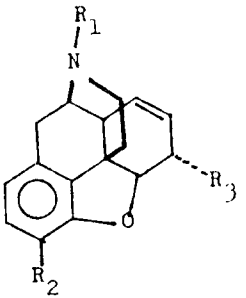
The N-demethylated, N-norapomorphines constitute an important subgroup of alkaloids to the more widely found N-methylated bases, the aporphines. The aporphines may be obtained not only by total synthesis, but also by N-methylation of N-noraporphines which are available only by isolation and by total synthesis via their N-benzyl derivatives[7].

The N-demethylation of tertiary methylamines has been accomplished in several ways. The reductive demethylation of trimethylamine N-oxide by sulfur dioxide[8] led to the preparation of nornuciferine (**Ic**) in low yields (34%). The classic von Braun reaction[9] using cyanogen bromide was improved upon for many amines by the use of benzyl or ethyl chloroformate. Further improvement[10] involved the use of ethyl and phenyl chloroformate to obtain N-carbophenoxy-N-normorphine (**IIa**) and N-carboethoxy-N-norcodeine (**IIb**), respectively. Subsequent base hydrolysis afforded N-normorphine (**IIc**) and N-norcodeine (**IId**) in low overall yield. Ethyl diazodicarboxylate[11] has been also used to de-methylate thebaine (**IIe**) and various 6-ester derivatives of morphine (**IIf**) and codeine in reasonable yield. However, this diazodicarboxylate procedure gave only ca. 40% yields of an N-nor-6, 7-benzomorphan[12]. Mon-

tzka and his co-workers[13] obtained N-normorphine in 79% overall yield by treating codeine (**IIg**) with 2, 2, 2-trichloroethyl chloroformate, and cleaving the intermediate carbamate with zinc in acetic acid or methanol. Recently, Rice[14], and Carroll and his groups[15] reported an improved synthesis of N-normorphine and N-norcodeine utilizing a modified phenyl-and methyl chloroformate procedures, followed by hydrazine cleavage of the crude carbamate intermediates. The overall yields were exceptionally good in contrast to the earlier methods[8-15]. In all methods just described, no other N-demethylation procedure of the apomorphine series was reported. Most recently, Kim[16] reported the first demonstration of an N-demethylation procedure of the apomorphine series, and yielded high yields of N-norapomorphine.



I a; R_1=CH_3, R_2=OH, R_3=H
b; R_1=H, R_2=OH, R_3=H
c; R_1=H, R_2=H, R_3=OCH_3



II a; R_1=COOPh, R=H, R_3=OH
b; R_1=$COOCH_2CH_3$, R_2=OCH_3, R_3=OH
c; R_1=H, R_2=R_3—OH
d; R_1=H, R_2=OCH_3, R_3=OH
e; R_1=CH_3, R_2=OCH_3, R_3=CH_3
f; R_1=CH_3, R_2=OH, R_3=OH
g; R_1=CH_3, R_2=OCH_3, R_3=OH

EXPERIMENTAL METHODS

Melting points were determined using a Polytemp (Polyscience Corporation) and are uncorrected. Infrared spectra were taken in KBr disks with a Shimadju 400 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian EM-60 spectrometer at 60Mc. relative to an internal standard of TMS; s signifies singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

Norapomorphine (**Ib**)

To a suspension of apomorphine (0.75g, 0.0031mole) and 6.44g (0.077mole) of $NaHCO_3$ in 65ml of $CHCl_3$ was added phenyl chloroformate (0.283g, 0.0383mole) and the heterogeneous mixture was refluxed for 55hours with vigorous stirring. Afterwards, the reaction mixture was cooled, filtered and the remaining inorganic residue was thoroughly washed with 25ml of $CHCl_3$. The combined filtrate and washings were washed with H_2O (2×25ml). The whole $CHCl_3$ solution was dried ($MgSO_4$), filtered and evaporated in vaccuo to the residue. The residual phenol was continuously evaporated by adding H_2O (azeotropic distillation) under vacuum (bath temperature of about 100°C). To this residue was slowly and carefully added 64% hydrazine (7ml). After the ensuing exothermic reaction had subsided, additional 64% hydrazine (7ml) and 95% hydrazine (17ml) were added, and the resulting solution was refluxed under nitrogen atmosphere for 48hours. Upon cooling and adding H_2O (25ml), **Ib** precipitated from the bluish-red solution as a white solid which was collected and washed with H_2O (3×50ml). The mother liquor and H_2O washings were combined and chilled overnight (ca. 15hours)

to get a second crop of white solid which was collected and washed as described previously. The first two crops totaled 0.57g (81%). mp 280~282° (lit.[19] 230~250°dec.). UVλ_{max} (MeOH): 216nm (e 39,000), 271nm (e 17,500), and 312nm (e 2,700). NMR ($CDCl_3$): τ6.97 (7H, m), 3.09 and 2.82 (3H, m), 1.78 (1H, d, J=2.0Hz) and 1.65 (1H, d, J=2.0Hz). The N-methyl resonance signal at τ7.43 (3H, s) in apomorphine has disappeared.

RESULTS AND DISCUSSION

We utilized a modified phenyl chloroformate procedure for the preparation of N-norapomorphine (**Ib**) from apomorphine (**Ia**). To the best of our knowledge, this procedure is the second demonstration of an N-demethylation of the apomorphine series, since various other methods failed to effect the N-demethylation of apomorphine[17]. Chloroformate reactions of apomorphine, followed by the base hydrolysis of the intermediated carbamate gave an untoward ring opening reaction. When the apomorphine was treated with an acyl chloride, oxidation of the apomorphine molecule and scission of the hydropyridine ring was observed[18].

After surveying the literature methods[8-15], we thought a chloroformate procedure[14,15] to be preferable for the preparation of N-norapomorphine (**Ib**) from apomorphine (**Ia**). The procedure of Abdel-Monem and Portoghese[10] for the preparation of N-normorphine involved the hydrolysis of N,3,6-tricarbophenoxynormorphine to N-carbophenoxy-normorphine, its chromatography and crystallization, followed by its cleavage with ethanolic KOH in overall yield of ca. 40%; these procedures were unneccessarily time-consuming and gave an undesirable by products. We found it unneccessary in our procedure to isolate and purify the intermediate carbamate (intermediate carbamate was readily identified with the presence of ir peaks at 1750 and 1684cm^{-1}), and, with the apomorphine, the N-norapomorphine precipitated from the hydrazine reaction mixture (1:1 mixture of 64 and 95% hydrazine); washing followed by drying gave analytically pure product in 81% overall yield. The above result strongly suggests this modified procedure as the most practical one for converting apomorphine to N-norapomorphine.

Care should be exercised in the use of 64% hydrazine in the hydrazine mixture which ensued the presence of hydrazine hydrate in the vapor of the refluxing mixture, rather than the air-sensitive (explosive) anhydrous hydrazine; safety shields should be employed.

LITERATURE CITED

1) Rekker, R.F., Engel, D.J.C. and Nyes, G.G.: *J. Pharm. Pharmacol.* **24**, 589 (1972).
2) Abdel-Moneim, M.M.: *J. Med. Chem.* **18**, 427 (1975).
3) Kim, J.C., Cannon, J.G., Long, J.P. and Heintz, S.: *ASPET Meeting*, East Lansing, Mich., 1973, Abstract No. 129.
4) Long, J.P., Heintz, S., Cannon, J.G. and Kim, J.C.: *J. Pharmacol. Exp. Ther.* **129**, 336 (1975).
5) Cannon, J.G. and Kim, J.C.: *U.S. Patent*, 347, 170 (June 27, 1974).
6) Cannon, J.G., Kim, J.C., Aleem, A.M. and Long, J.P.: *J. Med. Chem.* **15**, 348 (1972).
7) Cannon, J.G., Kim, J.C. and Aleem, A.M.: *J. Heterocyclic Chem.* **9**, 731 (1972).
8) Cava, M.P. and Srinivasan, M.: *J. Org. Chem.* **37**, 330 (1972).
9) Hobson, J.D. and McCluskey, J.G.: *J. Chem. Soc.* 2015 (1967).
10) Abdel-Moneim, M.M. and Portoghese, P.S.: *J. Med. Chem.* **15**, 208 (1972).

11) Kanematsu, K., Takeda, M., Jacobsen, A.F. and King, E.L.: *J. Med. Chem.* **12**, 495 (1974).
12) Pohland, A. and Sullivan, H.R., Jr.: *U.S. Patent*, 3,342,827 (Sept. 19, 1967).
13) Montzka, T.A., Matiskella, J.D. andPartyke, R.A.: *Tetrahedron Lett.* 1325 (1974).
14) Rice, K.C.: *J. Org. Chem.* **40**, 1850 (1975).
15) Brine, G.A., Boldt, K.G., Hart, C.K. and Carroll, F.I.: *Org. Perp. Procedures Intern.* **8**, 103 (1976).
16) Kim, J.C.: *Org. Prep. Procedures Intern.* **9**, 1 (1977).
17) Borgman, R.G., Smith, R.V. and Keiser, J.E.: *Synthesis* **249** (1975).
18) Shamm, M.: *Chemistry of Alkaloids*, S.W. Pelletier, Ed., Van Norstrand-Reinhold, New York, 1970, p. 42.
19) Hensiak, J.H., Cannon, J.G. and Burkman, A.M.: *J. Med. Chem.* 8, 557 (1965).