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NOTE

높은 온도에서 DMF에 용해시킨 Na-Thioethoxide를 사용한 10, 11-Dimethoxy- 및 10, 11-Diethoxy-apomorphine의 *O*-Dealklylation 반응

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O-Dealkylation of 10, 11-Dimethoxy-, and 10, 11-Diethoxy-apomorphine Using Sodium Thioethoxide in Dimethylformamide at Elevated Temperature

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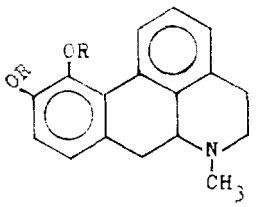
Considerable interest has been demonstrated in apomorphine(I) due to its application in the treatment of Prakinsonism[1] and because of suggested relationships of this compound to dopamine.[2,3] The apomorphine may be obtained not only by total sythesis, but also by N-methylation of N-norapomorphine which are available only by isolation and by total synthesis *via* their N-benzyl derivatives.[4] During multistage syntheses or derivatizations of apomorphine, the phenolic hydroxyl groups are usually protected by their facile and effcient conversion in the much less reactive alkyl ethers (usually methyl ethers), firstly because of the ease of preparation in a high yield and secondly, because of the comparative inertness of these ethers to a wide variety of reagents and conditions. Because of their stability, however, aryl methyl (or alkyl) ethers present some difficulties when the regeneration of the parent phenol is desired. Although many reagents have been developed for this purpose, only few are completely specific to apporphine compounds. Exposure of aporphines to oxidizing agents as well as to acylating agents at higher temperatures, is known to promote a substantial decomposition of this alkaloid.[5]

Rapoport, *et al.*[6] reported the *O*-demethylation product (morphine) in 22% yield when codeine was treated with pyridine hydrochloride at elevated temperature. Practical difficulties were also encountered in isolation and purification of morphine by obtaining a 24% yield by a slight modification of the work-up phase by Gates and Tschudi.[7] Takeda and Kugita[8] in a patent claim have reported the use of lithium diphenyl-phosphide to effect the *O*-demethylation of a compound related to codeine in 61% yield, but this procedure appears to lack practicability for a large scale preparation. Most recently, Rice,[9] and Lawson and DeGraw[10] reported an improved *O*-demethylation of codeine, utilizing boron tribromide in chloroform, and potasium *t*-butoxide and *n*-propanethiol in dimethylformamide at elevated teperature, respectively. The yields were good in contrast to the earlier methods.[6,7]

In this note, we wish to report an efficient

preparation of apomorphine (I) from the *O*-dealkylation of 10, 11-dimethoxy-(IIa), and 10, 11-diethoxy-apomorphine(IIb). Feutrill and Mirrington's[11] successful utilization of aromatic methyl ethers cleavage with sodium alkyl mercaptide in dimethylformamide at elevated temperatures, prompted the use of this system for the *O*-dealkylation of phenolic group-protected apomorphine derivatives. Previously strongly acidic 48 % HBr (or 57 % HI) has been used to cleave methyl ethers of aporphine derivatives to give moderate yields.[12] However, our high yielding *O*-dealkylation method seems remarkable in view of the labile nature of the aporphine chemistry toward strongly basic nuleophilic thioethoxide anion at 135 °C for 1.5 hours.



I : R=H
IIa: R=CH_3
b: R=$-CH_2CH_3$

Thioethoxide ion was chosen as the nucleophile because of its ready preparation from ethanethiol and sodium hydride, and the ease of separating the volatile thioethers (RSC_2H_5) and the diphenolic apomorphine from the excess reagent. The cleavage of methyl- or ethyl ether linkages by SN_2 dispalcement proceeded smoothly in dipolar aprotic solvent.[13] N, N-Dimethylformamide was chosen as a solvent in the present study because it is an efficient solvent for nucleophilic thioethoxide ion, it is stable to strong bases at reflux temperatures,[14] and it is water-soluble, allowing for easy recovery of the deblocked phenolic products.

EXPERIMENT

Apomorphine(I). In a typical run; To a stirred suspension of 1.8 g (0.0428 mole) of 57 % oil suspension of NaH in 50 m*l* of dry DMF was added 3.4 g(0.0.0602 mole) of ethanethiol in 20 m*l* of dry DMF under nitrogen atomsphere, followed by the addition of 5.53 g (0.0171 mole) of 10, 11-diethoxy-apomorphine.[4] The resulting mixture was then heated with vigorous stirring under N_2 in an oil bath temperature of 135 °C for 1.5 hours. After addition of 70 m*l* of10% aq. HCl to the chilled reaction mixture (sodium thioethoxide instantly hydrolyzes), it was extracted with three 80 m*l* portions of $CHCHl_3$. The combined $CHCl_3$ extracts were washed with two 70 m*l* portions of H_2O and dried ($MgSO_4$). Filtration and evaporation of the filtrate under reduced pressure gave an oily residue which was subjected to ion-pair extraction.[15] To the oily residue were added 7 m*l* of conc. HCl and 8 m*l* of H_2O; this solution was extracted with three 30 m*l* portions of $CHCl_3$, and the combined extracst were dried ($MgSO_4$). Filtration and evaporation of the filtrate under reduced pressure afforded a semi-solid which was recrystallized from EtOH(charcoal) to give 3.29 g (72 %) of a grey solid. The meterial was homogeneous on tlc and identical (m.p, ir, nmr) with an authetic sample.

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정 정 : 본지 제24권 (1호) 48면 8행

誤	正
$T_2=1/W_{\frac{1}{2}}$	$T_2=1/\pi W_{\frac{1}{2}}$