COMMUNICATIONS

LETTERS

A Regioselective O-Demethylation of 10,11-Dimethoxyaporphine

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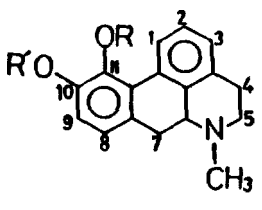
Considerable interest has been demonstrated in Apomorphine (1), due to its medicinal application of a powerful central acting emetic[1], and the treatment of parkinsonism[2], and because of suggested structural relationships of this compound to dopamine.[3,4] The metabolic fate of apomorphine in mammalian systems has been studied that the methylation[5] appears to be one of important pathways in this biodisposition[6] of this compound. Metabolic reactions occur at the 10- and 11-phenolic hydroxyl positions of apomorphine to give 10-methoxy-11-hydroxyaporphine (2, apocodeine) and 10-hydroxy-11-methoxyaporphine (3, isoapocodeine), respectively.

As a result of these biological activities, coupled with the metabolic biotransformations of apomorphine, the regioselective O-demethylation of 10, 11-dimethoxyaporphine (4) prompted us to investigate a facile synthetic procedure to obtain a sufficient quantity of isoapocodeine (3) from the more readily available apomorphine.

Cannon and his associates[7] had prepared 5% yields of isoapocodeine; treatment of apomorphine with 1 equiv of benzyl bromide afforded three spots on tlc, in addition to one spot for apomorphine itself; it was concluded that these three spots



1: R = R′ = H
2: R = H, R′ = CH_3
3: R = CH_3, R′ = H
4: R = R′ = CH_3
5: R = $C_6H_5CH_2$-, R′ = H
6: R = H, R′ = C_6H_5-CH_2-
7: R = R′ = $C_6H_5CH_2$-
8: R = CH_3, R′ = $C_6H_5CH_2$-

represented the two isomeric monobenzyl ethers, (10-hydroxy-11-benzyloxyaporphine, 5 and 10-benzyloxy-11-hydroxyaporphine, 6) and the dibenzyl ether (10, 11-dibenzyloxyaporphine, 7). Treatment of 6 with NaH and methyl tosylate induced formation of 10-benzyloxy-11-methoxy-aporphine (8) which was treated under catalytic reductive debenzylation conditions to afford compound 3. And from the earlier reports, we obtained the complete O-demethylation product, apomorphine and incomplete isomeric products, apocodeine and isoapocodeine from the reactions of 4 with 48% HBr[8] and with sodium thioethoxide anion[9] respectively. Under the conclusion of X-ray analysis that the 11-hydroxyl group of the biphenyl portion in the apomorphine system is apparently strained due to the steric repulsion with the 1-peri hydrogen,[10] we underwent the isolation and characterization of isoapocodeine by the regioselective O-demethylation of 4 using the sterically bulkier reagent, sodium t-thiobutoxide anion. Due to the sterically hindered nature of the 11-methoxy position of apomorphine, the bulky sodium *t*-thiobutoxide anion as a nucleophile resulted in greater inaccessibility to the sterically hindered 11-methoxy position and controlled the O-demethylation reaction such that nucleophilic attack by the bulky anionic base occurred regioselectively on the 10-methoxy position, forming the isoapocodeine in 74% yields.

A typical experimental procedure is as follows: To a stirred suspension of 0.9 g (0.0214 mole) of 57 % oil suspension of NaH in 40 m*l* of dry DMF was added 1.7 g (0.00301 mole) of *t*-butyl mercaptan in 15 m*l* of dry DMF under N_2 atmosphee, followed by the addition of 2.77 g (0.0086 mole) of 10, 11-dimethoxyaporphine.[9] The resulting mixture was then heated with vigorous stirring under N_2 in an oil bath temperature of 100°C for 3.5 hours. The thin layer chromatogram of the reaction mixture showed an isoapocodeine as a sole product and no apomorphine was detected. After addition of 50 m*l* of 10 % aq. HCl to the chilled reaction mixture, it was extracted with three 50 ml portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed with two 40 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.[11] To the oily residue were added 4 m*l* of conc. HCl and 5 m*l* of H_2O; this solution was extracted with three 20 m*l* portions of $CHCl_3$ and the combined extracts were dried ($MgSO_4$). Filtration and evaporation under reduced pressure afforded a semi-solid which was recrystallized from ethanol (charcoal treatment) to give 1.71 g (74%) of isoapocodeine hydrochloride which was identical with an authentic sample of isoapocodeine hydrochloride as determined by mixed tlc and mixed mp. mp, 244-248° dec. nmr ($CDCl_3$); δ 2.55 (*s*, 4, Ar), Me), 5.90 (*s*, 1, Ar-OH), 3.61 (s, 3, O-Me), 6.96 (*m*, 4, Ar-8.20 (*q*, 1, 1-H). ms, *m/e* (% relative abundance); 281 (99), 280 (100), 265 (33), 238 (25), 236 (16), 223 (26), 221 (12), 205 (12), 178 (23), 165 (38).

Its nmr ($CDCl_3$) spectra of the regioselective 0-demethylated isoapocodeine demonstrared 11-methoxy singlet at 3.61 and the quartet of 1-peri hydrogen at 8.20. The hydroxy proton broad singlet appeared at 5.90 which caused D_2O exchange to disappear. Four aromatic protons (2, 3, 8 and 9 H) appeared as a multiplet centered at 6.96 and the N-methyl singlet at 2.55. This assignment is corroborated in the work of Baarschers, *et al*,[12] and with an authentic sample of the natural origin of isoapocodeine. The observed regioselectivity of the ether cleavage in the aporphine systems represent, to the best of our knowledge, the first demonstration of this action, although a number of enzyme systems have been noted.[13]

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Stereospecific Coordination of *trans*-1,2-Diaminocyclohexane in the Reaction with Dichloro Platinum (II) Complexes of Optically Active 2,2′-Diamino-1,1′-binaphthyl

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Stereospecific coordination has been observed when the racemic mixture of bidentates coordinated to the dichloro platinum (II) complexes of optically active diamino skewed biaryls.[1-3] While the stereospecific coordination of racemic mixtures has long been known,[4-6] such behavior by a diamino skewed biaryl is known only recently.[1-3,6] In the present work the stereoselective behavior of another skewed biaryl, 2,2′-diamino-1,1′binaphthyl (dabn), is studied. The racemic mixture of *trans*-1,2-diaminocyclohexane is chosen for this purpose.

Experimental

2,2′-Diamino-1,1′-binaphthyl (dabn) was prepared and resolved by known method.[7,8] *Trans*-1,2-diaminocyclohexane was resolved by the method of Asperger and Liu.[9]

[Pt (R-dabn)Cl_2]·H_2O. 0.40 g of R-dabn was dissolved in 50 ml of warm aqueous ethanol, which was then added dropwise to a solution of 0.58 g of K_2PtCl_4 in 50 ml of water. The mixture was heated and stirred at a temperature of 60-70°C for one hour. The mixture was cooled and the golden product was collcted in a sintered glass filter. The product was washed wite water and ethanol, and air dried. Anal. Colcd. for Pt Found : C, 43.30 ; H, 3.27 ; N, 2.59 ; Cl, 12.76.

[Pt (R-dabn) (R,R-chxn)] Cl_2·H_2O. 0.23 g of unresolved chxn and 1.11 g of [pt(R-dabn)Cl_2]·H_2O were dissolved in 350 ml of water. The mixture was stirred and heated at a temperatue of 50-60°C for 9 hrs. The solution was cooled and filtered to remove any unreacted reactants. It was then concentrated on a rotary evaporator until crystallization. The mixture was stored in a refrigerator overnight. The product was collected, washed with ice-cold water and ethanol, and air dried. The product was recrystallized once from 0.02 *M* HCl. Yield : 0.36 g (27 %). *Anal.* Calcd. for Pt $C_{26}H_{30}N_4Cl_2$·H_2O : C, 46.71 ; H, 4.82 ; N, 8.38 ; Cl, 10.60 Found : C, 46.67 ; H, 4.84 ; N, 8.43 : Cl, 10.54.

[Pt(S-dabn) (S,S-chxn)] Cl_2·H_2O. This was made by a similar method described above using [Pt(S-dabn)Cl_2]·H_2O in place of [Pt(R-dabn)Cl_2]·H_2O. Yield : 0.28 g (26%). *Anal.* Calcd. for Pt $C_{26}H_{30}N_4Cl_2$·H_2O : C, 46.71 ; H, 4.82 ; N, 8.38 ; Cl, 10.60