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Note

An Efficient Procedure for the Regioselective Synthesis of 10-Methoxy-11-Hydroxyaporphine from (R,S)-10,11-Dihydroxyaporphine

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A regioselective preparation of 10-methoxy-11-hydroxyaporphine ("Apocodeine, **1b**") from (R,S)-10, 11-dihydroxyaporphine(apomorphine, **1a**) is described. The isopropylidene ketal ring of 10,11-(isopropylidenyldioxy) aporphine (**2**) obtained by the isopropylidenation of apomorphine, was regioselectively opened by the ten equivalent of trimethylaluminum to give 10-hydroxy-11-t-butyloxyaporphine (**3**). The free 10-hydroxyl position of 3 was methylated with methyl p-toluenesulfonate/NaH, and afforded 10-methoxy-11-t-butyloxyaporphine (**4**) in high yield. Selective debutylation gave the desired 10-methoxy-11-hydroxyaporphine("apocodeine", **1b**) in good yield.

Key words: Regioselective synthesis, Apocodeine, Apomorphine, Isopropylidenation, 10,11-(isopropylidenyldioxy)aporphine, 10-hydroxy-11-t-butyloxy aporphine, 10-methoxy-11-t-butyloxyaporphine, Trimethylaluminum nucleophile ring opening

INTRODUCTION

Continuing interest has been developed in delineating the portions of the apomorphine molecular structure (10,11-dihydroxy aporphine, **1a**) responsible for its medicinal application of a powerful central acting emetic (Cannon *et al.*, 1972) and the role of dopaminergic properties in the etiology and therapy of Parkinsonism (Gessa and Corsini, 1981). And the metabolic fate of apomorphine (**1a**) in mammalian systems showed that the *in vivo* methylations appeared to be one of the important pathways in this biodisposition (Cannon and Qijie, 1991) of this compound. Metabolic reactions occurred at the 10- and 11-phenolic hydroxyl positions of apomorphine molecule (**1a**) to give para-methylated product, 10-methoxy-11-hydroxyaporphine (apocodeine, **1b**) and meta-methylated product, 10-hydroxy-11-methoxy aporphine (isoapocodeine, **1c**) (Cannon *et al.*, 1983). As a result of these biological activities, coupled with the metabolic biotransformations of apomorphine molecule, the investigation of the regioselective synthesis of 10-methoxy-11-hydroxy-aporphine (apocodeine, **1b**) was required to obtain a sufficient quantity of apocodeine (**1b**) from the readily available apomorphine (**1a**) molecule. The apocodeine (**1b**) has been obtained not only by the total synthesis (Neumeyer, 1985; Cannon *et al.*, 1972), but also by the selective demethylation (Kim, 1980; Kim *et al.*, 1984) of 10,11-dimethexyaporphines (**1d**). Direct methylation of apomorphine with methylating agents such as methyl iodide, diazomethane, or methyl tosylate afforded completely 10,11-dimethoxyaporphine (**1d**) in quantitative yield, and either apocodeine (**1b**) or isoapocodeine (**1c**) was not abtained in regular synthetic methylation reactions (Kim, 1977; Kim, 1983). Very low yields of apocodeine had prepared (Cannon and Aleem, 1971); treatment of apomorphine with one equivalent of benzyl bromide afforded three spots on tlc, in addition to one spot for apomorphine itself; it was concluded that these three spots represented the two isomeric monobenzyl ethers (10-hydroxy-11-benzyloxyaporphine, **1e**, and 10-benzyloxy-11-hydroxyaporphine, **1f**) and the dibenzyl ether (10,11-dibenzyloxyaporphine, **1g**). Treatinent of **1e** with NaH and methyl tosylate induced formation of 10-methoxy-11-benzyloxyaporphine (**1h**) which was treated under catalytic reductive debenzylation conditions to afford 10-methoxy-11-hydroxy-aporphine (apocodeine, **1b**).

In connection with ongoing research, we had occasion to study the reaction of o-dealkylation of apomorphine molecules (Kim, 1980; Kim *et al.*, 1984; Kim,

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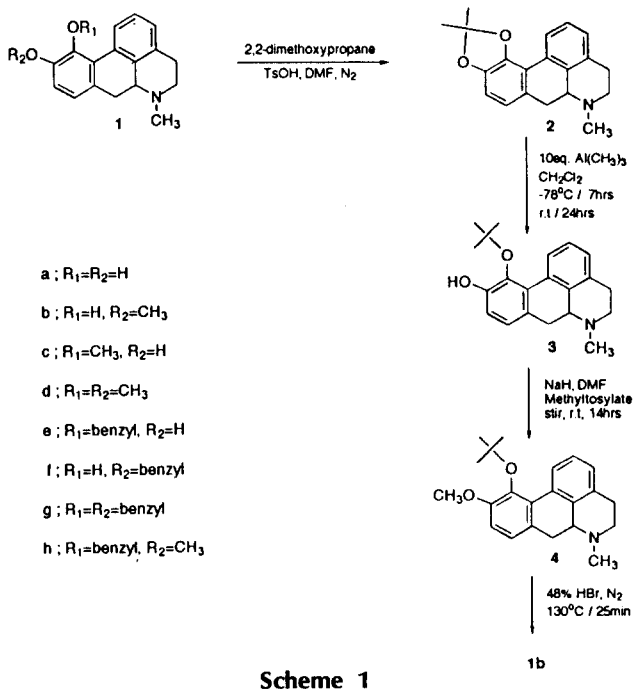

Scheme 1

1977; Kim, 1983). We describe here an efficient procedure for the regioselective synthesis of 10-methoxy-11-hydroxyaporphine (apocodeine, **1b**) from (R,S)-10,11-dihydroxyaporphine (apomorphine, **1a**) (Scheme 1).

MATERIALS AND METHODS

Column chromatogrphy was carried out on E. Merck silica gel 60 (230~400 mesh). Reagents were purified according to known procedures. Melting points were taken with a Thomas-Hoover capillary apparatus and are uncorrected. Reactions were monitored by the analytical TLC using 2×5 cm aluminum sheets precoated with silica gel 60 F_{254} (Merck) and detection by UV light and charring with H_2SO_4. ^{1}H-NMR spectra were recorded on a Brucker Am-250 spectrometer with TMS as internal standard.

(R,S)-10,11-(Isopropylidenyldioxy) aporphine (2)

To stirred solution of apomorphine (**1a**, 3.43 g, 12.79 mmol) and 2,2-dimethoxypropane (4.0 ml, 32.6 mmol) in dry DMF (50 ml) was added p-toluenesulfonic acid (49 mg, 0.284 mmol) in dry DMF (15 ml) under N_2 atmosphere, and the reaction mixture was stirred at room temperature for 10 hours, and then added Amberite 1RA-410 (OH form) ion exchange resin to remove the p-toluenesulfonic acid. The resulting resin was removed by filtration and washed with CH_3OH. The combined washings and filtrate were evaporated in vaccuo to yield sirupy residues which were chromatographed on silica gel (CH_3OH : CH_3Cl : NH_4OH=1 : 1.9 : 0.2) to yield a light brown oil (5.01 g, 79%). ^{1}H-NMR ($CDCl_3$/TMS) : δ=1.33 & 1.59 (s, 6H, $C(CH_3)_2$), 2.84 (s, 3H, -N-CH_3), 3.35 (m, 7H, aliph-H), 7.40~7.72 (m, aromat-2H, 3H, 8H, 9H), 8.23 (m, 1H, aromat-1H).

(R,S)-10-Hydroxy-11-t-Butyloxy aporphine (3)

10,11-Isopropylidenyldioxy aporphine (**2**, 3.52 g, 11.45 mmol) in freshly distilled, dry CH_2Cl_2 were introduced under N_2 atmosphere to a flame dried round-bottomed flask, and cooled to −78℃. Trimethylaluminum (10eq, 2 M solution in hexane) was then added dropwise. The reaction mixture was stirred at −78 ℃ for 7 hours and at room temperature for 24 hours. It was then quenched by addition of aq NH_4Cl, and the precipitate was filtered off. The filtrate was extracted with CH_2Cl_2 several times. The combined organic layers were washed with H_2O, brine, and dried (anhyd. $MgSO_4$), and concentrateed in vaccuo. The foamy residue was chromatographed on silica gel (hexane : EtOAc=8 : 2) to give the product (2,78 g, 78%) ^{1}H-NMR (DMSO-d_6/TMS) δ=1.16 (s, 9H, t-Bu), 2.85 (s, 3H, N-CH_3), 3.02~3.34 (m, 7H, aliph-H), 5.90 (broad, s, 1H, aromatic-OH, exchangeable with D_2O), 7.35~7.67 (m, 4H, aromat-2H, 3H, 8H, 9H), 8.25 (m, 1H, aromat-1H).

(R,S)-10-Methoxy-11-t-Butyloxy aporphine (4)

To a stirred solution of 57% oil suspension of NaH (0.30 g, 12, 44 mmol) in dry DMF (100 ml) was added 10-hydroxy-11-t-butyloxyaporphine (**3**, 3.135 g, 9.69 mmol), then methyl p-toluenesulfonate (2.079 g, 11.808 mmol) in anhydrous Et_2O (60 ml) was slowly added. The reaction mixture was stirred at room temperature for 14 hours and was permitted to stand at room temperature for additional 10 hours. After addition of water (150 ml) to the reaction mixture, it was concentrated, and taken up in EtOAc (150 ml), which was washed with three portions of brine (100 ml×3) and then dried (MgSO4). Filtration and evaporation of the filtrate under reduced pressure gave an oily residue which was chromatographed on silica gel (hexane : EtOAc=8 : 2) to yield a product (3.45 g, 83%). ^{1}H-NMR (DMSO-d_6/TMS) : δ=1.16 (s, 9H, t-Bu), 2.91 (s, 3H, N-CH_3), 3.02~3.44 (m, 7H, aliph-H), 3.90 (s, 3H, O-CH_3), 7. 35~7.67 (m, 4H, aromat-2H, 3H, 8H, 9H), 8.25 (m, 1H, aromat-1H).

(R,S)-10-Methoxy-11-Hydroxyaporphine (Apocodeine, 1b)

10-Methoxy-11-t-butyloxyaporphine (**4**, 2.5g, 5.24 mmol) was heated under N2 with 40 ml of 48% HBr in an oil bath at 130℃ for 25 min. Removal of the volatiles under reduced pressure left a solid residue which was recrystallized from ethanol (charcool treat-

ment) to give 0.98g (66%) of apocodeine hydrobromide. mp>280℃ ^{1}H-NMR (DMSO-d_6/TMS) : δ 2.95-3.1 (m, 7H, aliph-H), 2.89 (s, 3H, -N-CH_3), 3.81 (s, 3H, -OCH_3), 5.91 (s, 1H, aromal-OH, exchangeable with D_2O), 7.25-7.60 (m, 4H, aromat-2H, 3H, 8H, 9H), 8.20 (q, 1H, aromat-1H).

RESULTS AND DISCUSSION

Under the understanding of X-ray analysis of apomorphine (Sharma and Slusurchyk, 1964) that the phenolic 11-hydroxyl group of the biphenyl portion in the 10,11-dihydroxyaporphine (apomorphine, **1a**) system is apparently strained due to its steric repulsion with the 1-peri hydrogen, we have developed the most simple and efficient regioselective monomethylation reaction method for converting apomorphine (**1a**) into apocodecine (**1h**) in excellent yield. Due to the sterically hindered nature of 11-hydroxyl position of the 10,11-(isopropylidenyldioxy)aporphine molecule (**2**) prepared readily from the isopropylidenation (Kim *et al.*, 1988) of apomorphine, the bulky trimethylaluminum Lewis acid resulted in greater inaccessibility to the sterically hindered 11-ketal oxygen atom and controlled the association of the Lewis acid with the ketal oxygen (Fujiwara *et al.*, 1984) such that the bulky trimethylaluminnm Lewis acid group coordinated regioselectively to the less hindered 10-ketal oxygen atom (Alexabis and Mangeney, 1990) only forming the 10-hydroxy-11-t-butyloxy aporphine (**3**), where the 10-hydroxyl group was intact. The regioselectivity of the reaction is clearly demonstrated the more sterically demanding 11-hydroxyl group was selectively protected as the t-butyl ether in this transformation. The 10 hydroxyl group of the compound **3** was then freely methylated with methyl p-toluenesulfonate under NaH condition to give (RS)-10-methoxy-11-t-butyloxyaporphine (**4**). Selective ether cleavage of the 10-methoxy-11-t-butyloxyaporphine (**4**) molecule, with 48% HBr/130℃ /N_2/25 min afforded the desired 10-methoxy-11-hydroxy aporphine (apocodeine, **1b**) in good yield. Because of the stability of the t-butyl carbonium ion, cleavage of the O-t-butyl linkage occurred more readily than the O-CH_3 ether linkage so that the t-butyl group can be removed.

In conclusion, this simple synthetic procedure is the most practical one for converting apomorphine to apocodeine, and to the best of our knowledge, it is the first demonstration in the apomorphine series, since various other methods failed to effect the direct methylation of apomorphine.

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