DIRECT AND SEQUENTIAL REMOVAL OF PHENOLIC OXYGEN FUNCTIONS IN S-(+)-BULBOCAPNINE, S-(+)-BOLDINE AND R -(-)-APOMORPHINE†

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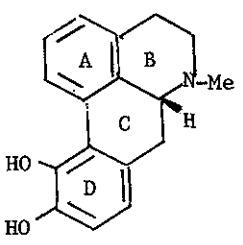
Three poly-oxygenated aporphines have been transformed into a variety of desoxy congeners. This was readily accomplished by O-dealkylation with BBr_3 and BCl_3 to cleave methoxyl and methylenedioxy groups, respectively, followed by reductive elimination of the resulting phenols as their tetrazoyl ethers or diethyl phosphate esters. The simultaneous elimination of two o-positioned hydroxy groups by these procedures was difficult to accomplish without racemization.

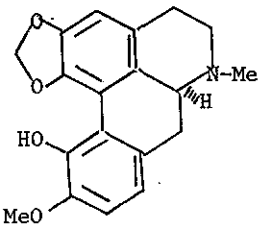
†Dedicated to Professor Robert Burns Woodard on the occasion of his sixtieth birthday.

The recent confirmation by Cotzias and co-workers[1] that apomorphine (1), a semi-synthetic dopamine agonist, was effective against Parkinsonism in man prompted the synthesis of a variety of related aporphines[2] in search for analogs with fewer side effects. In this connection, we now report the facile conversion of some poly-oxygenated aporphines by regioselective procedures into less oxygenated congeners.[3]

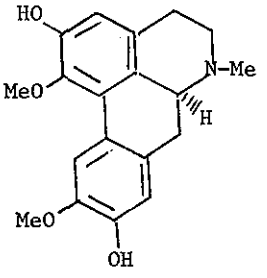
For this study, the readily available tetraoxy-substituted alkaloids bulbocapnine[4] (2) and boldine[5] (3), both possessing the S-configuration, were subjected either to O-demethylation with boron tribromide[6] or to preferential O-demethylenation with boron trichloride.[7] Elimination of the phenolic groups was accomplished either via hydrogenolysis of the corresponding tetrazoyl ethers[8] or via lithium-ammonia reduction of the corresponding diethyl phosphate esters[9] to afford, almost exclusively, the related desoxy derivatives with S-configuration. However, since S-apomorphine, the enantiomer of (1), is not an effective dopamine agonist,[10] these S-aporphines may have to be converted by standard sequences into their R-enantiomers.[11]



(1)



(2)

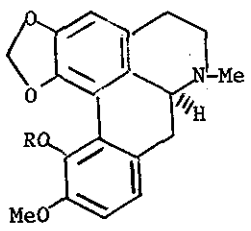


(3)

Reaction of bulbocapnine (2) with 5-chloro-1-phenyl-1H-tetrazole in refluxing acetone containing anhydrous potassium carbonate[12] provided the tetrazoyl ether (4) [mp 208-210°, $[\alpha]_D^{22}$ + 128° (c 1, $CHCl_3$)]. Hydrogenation of (4) over an almost equal amount of 10% Pd-C in acetic acid at 3 atmospheres and 40° gave a mixture which was separated by column chromatography into starting material and S-(+)-laureline (5) [33%, mp 115-117°, $[\alpha]_D^{22}$ + 97.3° (c 1, EtOH)], enantiomeric with the alkaloid isolated from Lauraceae species.[13] On the other hand, reduction of the diethyl phosphate ester (6) [184-186°, $[\alpha]_D^{22}$ + 235.7°, c 0.67, $CHCl_3$)] prepared from (2) and diethyl chlorophosphate by standard procedures,[9] with lithium in liquid ammonia at -78°, eliminated the original 1,11-positioned oxygen functions to afford the known[14] S-(+)-2-hydroxy-10-methoxyaporphine (7) [hydrobromide: 80%, mp 252-254° dec., $[\alpha]_D^{21}$ + 102.5°, (c 0.68, MeOH), M^+ 281] in more than 70% yield.

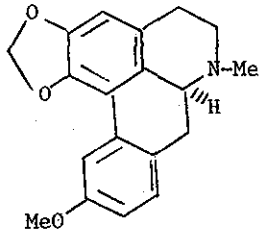
Conversion of the monophenol (7) into the "naked" aporphine (10) [hydrobromide: 43%, mp 292-294° dec. (green at 270°), $[\alpha]_D^{21}$ + 92.0° (c 0.4, MeOH); free base: $[\alpha]_D^{23}$ + 148.5° (c 0.42, $CHCl_3$)][15] could easily be accomplished by hydrolysis of (7) with 48% HBr to the diphenol (8)[16] [base: mp 187-189°, $[\alpha]_D^{21}$ + 135.2° (c 0.56, MeOH); hydrobromide: mp 250-252.5°, $[\alpha]_D^{21}$ + 94.5° (c 0.61, MeOH)], etherification to its bis-tetrazolyl ether (9) [mp 200-202°], followed by catalytic hydrogenation of the latter over an equal amount of Pd-C in acetic acid at room temperature. Further, hydrogenolysis of the mono-tetrazolyl ether (11), obtained as an oil from (7), afforded the S-(+)-10-methoxyaporphine (12) [hydrochloride: mp 282-284° dec. (green at 255°), $[\alpha]_D^{23}$ + 92.4° (c 0.50, EtOH], chromatographically and spectroscopically

identical, except for its optical behavior, with racemic material obtained by total synthesis[16,17]. Treatment of the monomethyl ether (12) with 48% HBr gave the optically active monophenol (13)[17] [hydrobromide: mp 294.5-296.5° dec.(green at 270°) $[\alpha]_D^{21}$ + 85.8°, (c 0.565, MeOH), M^+ 251]. Finally, treatment of the monophenol (7) with diazomethane in methanol readily gave S-(+)-2,10-dimethoxyaporphine[14] [hydrobromide: mp 254-256° dec.,$[\alpha]_D^{23}$ + 94.6°, (c 0.316 , EtOH), M^+ 295].



(4) R = „T"

(6) R = „P"



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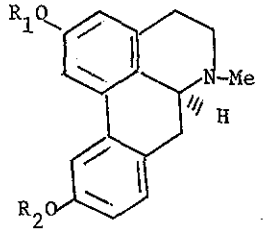
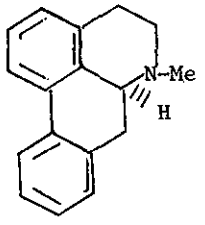


(7) R_1 = H, R_2 = Me

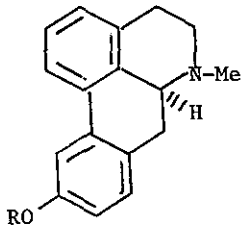
(8) R_1 = R_2 = H

(9) R_1 = R_2 = „T"

(11) R_1 = „T", R_2 = Me

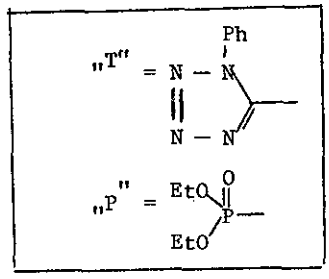


(10)



(12) R = Me

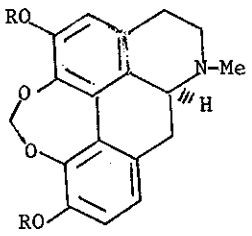
(13) R = H



In addition, the 2,10-diphenol (14), obtained from (2) with boron tribromide in dichloromethane,[18] was treated with 5-chloro-1-phenyl-1H-tetrazole and sodium hydride in DMF for 2 hr at 100° to yield the bis-tetrazoyl ether (15) [mp 178-179°] followed by hydrogenation over Pd-C in acetic acid at 40° to give a 1 : 1 mixture of starting material and the 1,11-methylenedioxyaporphine (16). The latter was obtained in pure form by column chromatography (Alox, grade III) and crystallized from benzene-isopropyl ether in 66% yield [mp 136-137°, $[\alpha]_D^{22}$ + 67.8° (c 1, $CHCl_3$)]. From the crystallization mother liquors, ca. 12% of the crude racemate (16) [mp 101-103°, $[a]_D^{22}$ + 2.0° (c 1, $CHCl_3$)] was isolated.

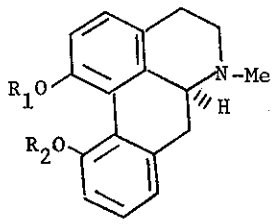
While the seven-membered dioxepin system in (16) was quite resistant to acid hydrolysis-probably due to stabilization of the protonated species-repeated treatment with boron tribromide in dichloromethane furnished 59% of the desired diphenol (17). The latter was extracted with sodium hydroxide and the crude, obtained by adjusting the aqueous solution to pH 7.5, was converted with alcoholic HCl and ether into a crystalline hydrochloride whose aqueous solution was treated with hydrobromic acid to afford, after recrystallization from water, (17) as its hydrobromide [mp > 300°, $[\alpha]_D^{22}$ + 180° (c 0.84, H_2O)]. Transformation of (17) in the usual manner furnished the bis-tetrazoyl ether (18) [amorphous, single spot on tlc] which proved resistant to catalytic hydrogenation. Forcing conditions gave rather complex mixtures which were not further investigated.

Boldine (3) was converted in 83% yield into the bis-tetrazoyl ether (19) [mp 130-132°, $[\alpha]_D^{25}$ + 125° (c 1, $CHCl_3$)] and hydrogenated in acetic acid at



(14) R = H

(15) R = „T"

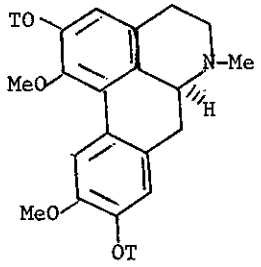


(16) $R_1 + R_2 = CH_2$

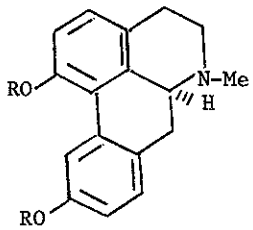
(17) $R_1 = R_2 = H$

(18) $R_1 = R_2 =$ „T"

3 atmospheres and 40° over an almost equal amount of 10% Pd-C, to give in 75% yield S-(+)-1,10-dimethoxyaporphine (20) [hydrochloride: mp 257°, $[\alpha]_D^{25}$ + 87.3° (c 1, MeOH)]. O-Demethylation of (20) with boron tribromide in dichloromethane afforded 62% of the corresponding 1, 10-diphenol (21) [hydrobromide: mp 317-318°, $[\alpha]_D^{25}$ + 41.0° (c 0.5, MeOH)] which was then transformed into the bis-tetrazoyl ether (22) [mp 186-187°, $[\alpha]_D^{25}$ -17.6° (c 0.5, DMF)]. However, removal of the oxygen functions in (22) by catalytic hydrogenation could not be accomplished without racemization.



(19)

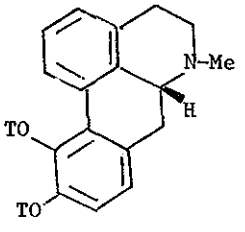


(20) R = Me

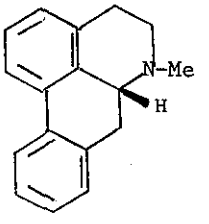
(21) R = H

(22) R = „T"

In contrast to a previous report that hydrogenolysis of S-1,2-bis-tetrazolyoxyaporphine obtained from (2) was accompanied by racemization[19], the elimination of the catechol function in (1) could however successfully be accomplished. The bis-tetrazolyl ether of apomorphine (23) was prepared from (1) by reaction with sodium hydride and 5-chloro-1-phenyl-1H-tetrazole in THF (5hr, 25°). The material obtained [mp 184-185°, $[\alpha]_D^{20}$ + 41.2° (c 0.86, MeOH)] seems identical with that prepared differently.[20] Preliminary experiments have shown that (23) under the usual conditions of catalytic hydrogenation (48 hrs, AcOH, 40°) is partially racemized while milder reaction conditions (20 hr, AcOH, 25°) afforded the free base (24), $[\alpha]_D$-133° (c 0.36, MeOH)] in 53% yield. This material could easily be further purified via its hydrobromide, to give a 40% yield of optically pure (24) HBr [mp 291-293°, $[\alpha]_D^{20}$ -92° (c 0.38, MeOH)] whose ORD was equal and opposite to that of 10.HBr prepared from bulbocapnine (2).



(23)



(24)

Our experience has shown that both methods used for the elimination of aromatic hydroxyl groups in the aporphine series have their limitations. The elimination of phosphate ester functions by an alkali metal in liquid ammonia suffers from side reactions involving the aromatic moieties while the elimination of tetrazolyl ether functions by hydrogenolysis seems to demand special steric requirements for the groups to be removed. Whether non-reactivity involves the formation of stable Pd-complexes is worthy of consideration. The removal of catechol units via their bis-tetrazolyl ethers has furthermore shown that racemization at the chiral center can be suppressed to a considerable degree by using "milder" conditions. The cause of racemization is subject to further studies.

The semi-synthetic approach to novel aporphines starting from easily available natural aporphines is nevertheless practical and thus provides an alternate to total synthesis and isolation. That this scheme is not restricted to aporphines has been recently demonstrated.[21,22,23]

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