TETRAHYDROPROTOBERBERINES DERIVED FROM R- and S-1-(3,4-DIHYDROXYBENZYL)-1,2,3,4-TETRAHYDROISOQUINOLINE

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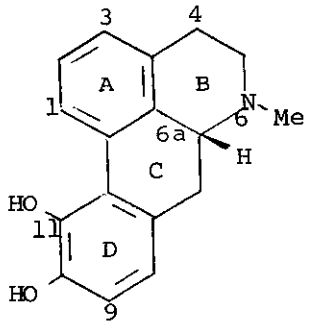
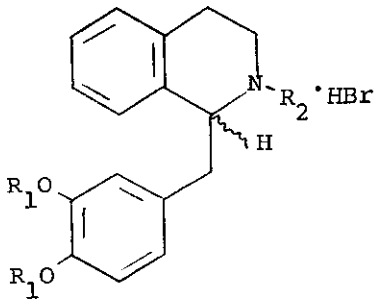
The syntheses of the optically-active diphenolic-substituted tetrahydroisoquinolines (5a,b), tetrahydropseudoberberines (7a,b), and tetrahydroprotoberberines (8a,b), all related to the anti-Parkinson agent apomorphine (1), are described. None exhibited dopamimetic activity.

The clinical utility of apomorphine (1) in the treatment of Parkinson's disease has prompted numerous investigators to prepare a variety of related compounds.[1] In this connection, we now report the synthesis of the "flexible" tetrahydroisoquinoline (5a), derivable from apomorphine (1) by cleavage of the bond between the A and D rings, and its conversion into the "rigid" tetrahydroprotoberberine (8a) wherein the dopamine moiety is now locked into a fixed conformation. In addition, since the studies

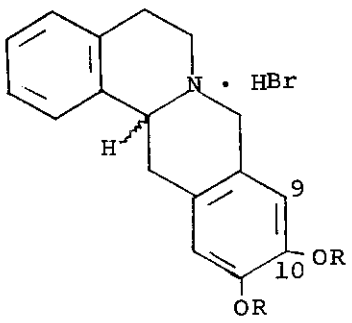


(1)

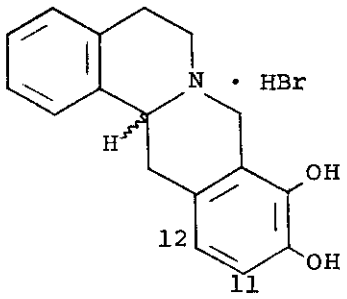


(2a,b) R_1=Me, R_2=H
(3a,b) R_1=R_2=H
(4a,b) R_1=R_2=Me
(5a,b) R_1=H, R_2=Me

a, ~~~ H = ▬ H
b, ~~~ H = |||| H



(6a,b) R=Me
(7a,b) R=H



(8a,b)

of Cannon and coworkers[2] suggested that arrangement of the OH functions on the aromatic ring as well as molecular rigidity influence the biological effect, the isomeric tetrahydropseudoberberine (7a) was also prepared. Finally, it was of interest to evaluate the optical antipodes of the above compounds for possible differences in pharmacological spectra.

Resolution of the known[3] racemic 1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline, while at best only partially successful with a variety of the common resolving agents,[4] was readily accomplished with R-(-)-2,2'-(1,1'-binaphthyl)phosphoric acid[5] in ethanol followed by neutralization and conversion to the hydrobromide to afford in 92% yield the dextrorotatory isomer (2a) [mp 230-231°; $[\alpha]_D^{25}$ + 16° (c 1, MeOH); CD $_{max}$ (c 0.005 M, MeOH) $[\theta]_{275}$ -1940, $[\theta]_{266}$ -1480, $[\theta]_{247}$ -2220]. Since the negative Cotton effect at 275 nm is consistent with the behavior of model 1-α-alkyl-substituted tetrahydroisoquinolines,[6] (2a) possesses the R-configuration. O-Demethylation of (2a) with BBr_3 in CH_2Cl_2 yielded the related catechol (3a) [mp 120-121°; $[\alpha]_D^{25}$ + 18.9° (c 1, MeOH)].

Neutralization of the mother liquors obtained from the above resolution followed by acidification of the resulting free base with ethanolic HBr furnished in 84% yield the enantiomeric tetrahydroisoquinoline (2b) [mp 230-231°; $[\alpha]_D^{25}$ -16° (c 1, MeOH); ORD and CD mirror images of (2a)]. De-etherification of (2b) with

BBr_3 gave the corresponding diphenol (3b) [mp 120-121°; $[\alpha]_D^{25}$ -18.2° (c 1, MeOH)].

Reductive condensation of the free base of (2a) with formaldehyde and $NaBH_4$ followed by acidification with ethanolic HBr provided the tertiary amine (4a) [mp 140-142°; $(\alpha)_D^{25}$ -70.1° (c 1, MeOH); nmr[7] δ 2.84 (s,3H, NCH_3)] which was O-demethylated with BBr_3 to afford the "open-apomorphine" (5a) [mp 75-77°[8]; $[\alpha]_D^{25}$ -78.7° (c 1, MeOH)]. Similarly, (2b) was converted via its N-methyl derivative (4b) into the dextrorotatory diphenolic tetrahydroisoquinoline (5b) [mp 75-77°[8]; $[\alpha]_D^{25}$ + 78.8° (c 1, MeOH); ORD and CD mirror images of (5a)].

Mannich condensation of (2a) with 37% formaldehyde in aqueous solution (pH 3) at 95° for 15 min yielded exclusively the dextrorotatory tetrahydropseudoberberine hydrobromide (6a) [mp 252-254°; $[\alpha]_D^{25}$ + 218° (c 0.5, MeOH)]. The 10, 11 substitution pattern was indicated by its nmr at δ 6.82, 6.85 (each s, 2H, 9-H, 12-H) and the R-configuration could be assigned in accord with Kametani and Ihara's[9] demonstration that Mannich cyclization does not induce racemization about the C-1 position of tetrahydroisoquinolines. O-Demethylation of (6a) with BBr_3 gave the corresponding dihydroxytetrahydropseudoberberine (7a) [mp 320° (decomp.), $[\alpha]_D^{25}$ + 236.6° (c 0.5, MeOH); δ 6.58, 6.65 (each s, 2H, 9-H, 12-H), 8.0 (br, 2H, 2 X OH)]. In a similar manner, (2b) was cyclized to (6b) which was transformed into (7b). The ORD and CD spectra of (6b) and (7b)

were mirror images of (6a) and (7a), respectively.

Alternatively, Mannich reaction of the dextrorotatory diphenolic tetrahydroisoquinoline hydrobromide (3a) with 37% formaldehyde gave, as expected,[10] a mixture which was neutralized and separated by silica gel chromatography to afford (7a) and the 9,10-dihydroxy-substituted isomer (8a) [mp 305-306° (decomp.), $[\alpha]_D^{25}$ + 238° (c 0.5, MeOH); δ 6.58, 6.79 (each d, 2H, J=8.5 Hz, 11-H, 12-H), 9.31, 8.86, (each s, 2H, 2 X OH)]. In a similar manner, cyclization of the enantiomer (3b) provided the diphenolic tetrahydroprotoberberine (8b) [ORD and CD mirror images of (8a)].

In a preliminary evaluation[11] of the novel optically-active catechols (5a,b), (7a,b), and (8a,b) as potential anti-Parkinson agents, all were devoid of the agonist activity exhibited by apomorphine (1) against dopamine-sensitive adenylate cyclase from the rat caudate nucleus. Instead, the enantiomeric tetrahydroprotoberberines (8a,b) behaved as weak antagonists with the S-isomers being more inhibitory than their antipodes.

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