

PREFERENTIAL REMOVAL OF A METHYLENEDIOXY GROUP
FROM OPTICALLY ACTIVE ISOQUINOLINES[†]

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The optically active dimethoxymethylenedioxy-substituted benzyl-isoquinoline (2a) and tetrahydroprotoberberine (3a) were O-demethylenated with boron trichloride followed by hydrogenolysis of the bistetrazoyl ether intermediate over Pd-C to afford, with retention of absolute configuration, (2d) and (3d), respectively. In contrast, hydrogenolysis of the dextrorotatory bistetrazoyl aporphine (4c) -a substrate that can readily dehydrogenate-gave the racemate of (4d).

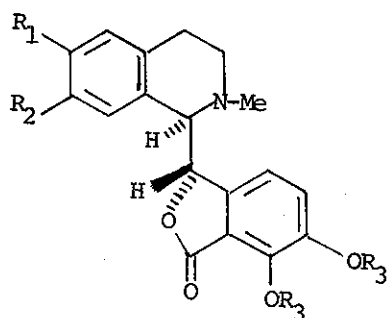
In our initial communication on the selective removal of a methylenedioxy group from a dimethoxymethylenedioxy-substituted isoquinoline, the alkaloid (-)- β -hydrastine (1a) was O-demethylenated with boron trichloride to the catechol (1b), converted to the bistetrazoyl ether (1c), and hydrogenolyzed over Pd-C to afford the optically active phthalide (1d)¹. As a consequence of our

[†] Dedicated to Dr. Ken'ichi Takeda on the occasion of his seventieth birthday.

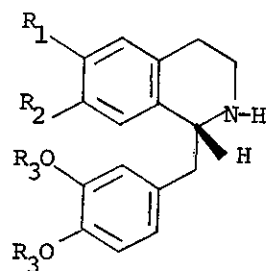
interest in the synthetic potential of this procedure, other optically active isoquinolines have been subjected to demethylenedioxylation and we now wish to report the results obtained with a benzylisoquinoline, a tetrahydroprotoberberine, and an aporphine.

Resolution of racemic 1-(3,4-dimethoxybenzyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline² with R-(-)-2,2'-(1,1'-binaphthyl)-phosphoric acid³ in methanol followed by neutralization afforded the dextrorotatory isomer (2a) [hydrochloride: 67% yield, mp 242-243°, $[\alpha]_D^{25} +25^\circ$ (c 1, MeOH)] whose absolute configuration was established by its de-etherification with boron tribromide to the known⁴ R-(+)-tetrahydropapaveroline hydrochloride. Preferential O-demethylenation of (2a) with boron trichloride provided the dimethoxy-catechol (2b) [75% yield, mp 264-265°, $[\alpha]_D^{25} +52^\circ$ (c 0.5, DMF)] which was then reacted with 2 equivalents of 5-chloro-1-phenyl-1H-tetrazole in refluxing acetone containing anhydrous potassium carbonate to furnish the bistetrazoyl ether (2c) [hydrochloride: 85% yield, mp 146-147°, $[\alpha]_D^{25} +36.4^\circ$ (c 0.5, DMF)]. Hydrogenation of (2c) in acetic acid at 3 atmospheres and 40° in the presence of 10% Pd-C for 17 hr gave 63% of the known⁵ R-isomer (2d).

In a similar manner, S-(-)-canadine (3a)⁶ was O-demethylenated with boron trichloride to the dimethoxy-catechol (3b) [hydrochloride: 80% yield, mp 260-262°, $[\alpha]_D^{25} -174^\circ$ (c 0.5, MeOH)], transformed into the bistetrazoyl

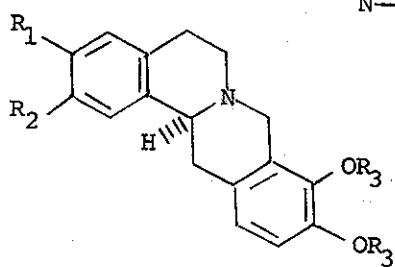
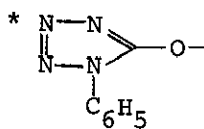


(1a-d)

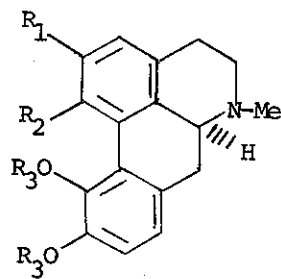


(2a-d)

	R ₁	R ₂	R ₃
a	-OCH ₂ O-		Me
b	OH	OH	Me
c	*	*	Me
d	H	H	Me
e	H	H	H



(3a-e)



(4a-d)

ether (3c) [hydrobromide: 87% yield, mp 219-220°, $[\alpha]_D^{25} -116^\circ$ (c 0.5, DMF)] and hydrogenolyzed over Pd-C in acetic acid to provide the desired dimethoxyberberine (3d) [hydrochloride: 72% yield, mp 220-222°, $[\alpha]_D^{25} -195^\circ$ (c 1, MeOH)]. O-Demethylation of (3d) with boron tribromide then afforded the known hydrobromide⁵ of the S-isomer (3e).

In contrast, demethylenedioxylation of an optically active aporphine gave a racemic product. Selective cleavage of the methylenedioxy group in O-methyl bulbocapnine (4a) with boron trichloride provided the known⁷ S-dihydroxy-dimethoxyaporphine (4b) which was converted with 5-chloro-1-phenyl-1H-tetrazole into the dextrorotatory bis-ether (4c) [70% yield, mp 110°, $[\alpha]_D^{25} +209^\circ$ (c 0.35, CHCl₃)]. However, hydrogenolysis of (4c) in acetic acid in the presence of 10% Pd-C at 40° and 3 atmospheres for 17 hr furnished the racemate of (4d) [75% yield, zero rotation, identical in tlc and nmr with the antipode of (4d), 6a R-10,11-dimethoxyaporphine⁸].

As a possible explanation of the above results, it would appear that hydrogenolysis is accompanied by racemization when the substrate is susceptible to catalytic dehydrogenation. Thus, the retention of configuration in the benzylisoquinoline (2d) and the tetrahydroprotoberberine (3d) is consistent with the observations by Kametani and co-workers that benzylisoquinolines⁹ and tetrahydroprotoberberine¹⁰ were not racemized by hydrogenation over

palladium catalyst. While a similar study with aporphines has not been reported¹¹, it was recently demonstrated by Cava and collaborators¹² that aporphines, unlike benzylisoquinolines, dehydrogenate readily when refluxed in acetonitrile in the presence of Pd-C. It therefore follows that since hydrogenolysis over Pd did not racemize the phthalide (1c), the benzylisoquinoline (2c), and the tetrahydroprotoberberine (3c), these substrates are much less susceptible to catalytic dehydrogenation than the aporphine (4c).

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