PREFERENTIAL CLEAVAGE OF THE METHOXYL GROUP ADJACENT TO A PHENOLIC FUNCTION IN POLYMETHOXYLATED ISOQUINOLINES†

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Boron trichloride selectively O-demethylated the methoxyl group adjacent to a phenolic function in various polymethoxylated isoquinolines to afford the corresponding catechol in excellent yield. While the carboxylic ester in (9) was unaffected by the reaction conditions, the methylenedioxy moiety in (11) was more labile than the methoxyl ortho to the phenol. The utility of the method was demonstrated by the facile synthesis of the alkaloid dicentrine (16).

Recently, we reported on the selective removal of a methylenedioxy group from a dimethoxymethylenedioxy-substituted isoquinoline *via* O-demethylenation with boron trichloride to the corresponding dimethoxy-catechol followed by hydrogenolysis of the bis-tetrazoyl ether.[1,2] As an extension of these studies, we now wish to describe a novel and facile alternate route to the intermediate dimethoxy-catechols based on preferential cleavage of the methoxyl group adjacent to a phenolic function in polymethoxylated isoquinolines with boron trichloride under controlled reaction conditions.

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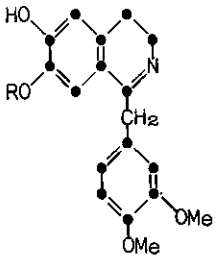
†Dedicated to Professor Emeritus Tetsuo Nozoe on the occasion of his seventy-seventh birthday.

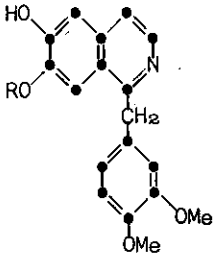
Treatment of the known[3] 6-hydroxy-trimethoxy-substituted 3,4-dihydroisoquinoline (1) with 2 equiv. of boron trichloride in methylene chloride at room temperature for 17 hours furnished the novel dimethoxy-catechol (2)[hydrochloride: 95% yield, mp 295-296°]. In a similar manner, selective O-demethylation of 6-desmethylpapaverine (3), obtained from (1) by dehydrogenation,[4] gave the corresponding catechol (4) [hydrochloride: 90% yield, mp 256-257°] and the 7-hydroxy-substituted tetrahydroisoquinoline[5] (5) afforded 90% of the known diphenol[6] (6). The latter was also obtained from 2 and 4 by catalytic hydrogenation.

In addition, the monohydroxy-carboxy-substituted protoberberine 7 [hydrochloride: 90% yield, mp 275° dec, obtained by Mannich reaction of 1-carboxy-1-(3,4-dimethoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline[7] with formaldehyde] and the corresponding ester (9) [hydrobromide: 70% yield, mp 192-194°, obtained by Pictet-Spengler condensation of 3-hydroxy-4-methoxyphenethylamine and ethyl 3,4-dimethoxyphenylpyruvate[8] followed by cyclization with formaldehyde], were reacted with 3 and 2 equiv. of boron trichloride, respectively, to afford the corresponding carboxy-catechol (8) [hydrochloride: 75% yield; mp 246-248°] and ester-catechol (10), also obtained by esterification of (8) [free base: 85% yield; mp 185-186°; λ_{max} (EtOH) 204 and 288 nm (log ε 4.84 and 3.92); λ_{max} (0.1NHCl) 204 and 285 nm (log ε 4.85 and 3.89); λ_{max} (0.1NKOH) 283 and 370 nm (log ε 3.79 and 3.72].

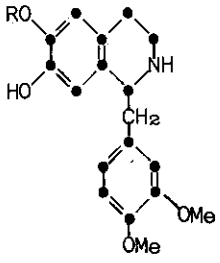
In contrast to the stability of the carboxylic ester function, the methylenedioxy moiety proved to be more labile than the methoxyl adjacent to a phenol since treatment of the known[9] hydroxymethoxymethylenedioxytetrahydroprotoberberine (11) at room temperature with 2 equiv. of boron trichloride furnished 75% of the monomethoxytriphenol (12) [free base: mp 235-237°; δ (DMSO-d6) 3.76 (3H,s,OCH3); m/e 313 (M^+)].



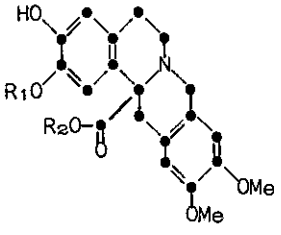
1, R = Me
2, R = H



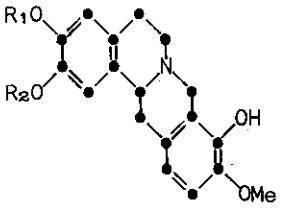
3, R = Me
4, R = H



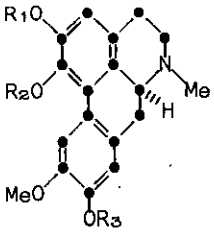
5, R = Me
6, R = H



7, R_1 = Me, R_2 = H
8, R_1 = R_2 = H
9, R_1 = Me, R_2 = Et
10, R_1 = H, R_2 = Et



11, $R_1 + R_2 = CH_2$
12, R_1 = R_2 = H



13, R_1 = R_3 = H, R_2 = Me
14, R_1 = H, R_2 = R_3 = Me
15, R_1 = R_2 = H, R_3 = Me
16, $R_1 + R_2 = CH_2$, R_3 = Me

Finally, to demonstrate the synthetic utility of the preferential cleavage of the methoxyl adjacent to a phenol, the aporphine alkaloid boldine (13) was readily transformed into the heretofore relatively inaccessible alkaloid dicentrine (16), previously prepared by a multistep synthesis and resolution.[10] O-Methylboldine (14), obtained by monomethylation of 13,[11] was treated with boron trichloride to yield 81% of the dimethoxy-catechol (15) [free base: mp 238-240°; $[\alpha]_D^{25}$ + 59.5° (c 0.5, MeOH)] followed by methylenation with methylene chloride (NaOH, DMSO) to afford the aporphine alkaloid dicentrine (16) [75% yield; mp 168-169°; $[\alpha]_D^{25}$ + 64° (c 1.4, $CHCl_3$), identical in mp, optical rotation, and nmr spectrum with natural dicentrine.[12]

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