REGIOSELECTIVE O-DEMETHYLATION OF BISBENZYLISOQUINOLINE ALKALOIDS

Jun-ichi Kunitomo,*[a] Megumi Oshikata,[a] Michinori Akasu,[b] and Hisashi Ishii[c]

Faculty of Pharmaceutical Sciences, Mukogawa Women's University,[a] 11-68 *Koshien Kyuban-cho, Nishinomiya*, Hyogo, 663 Japan; Kaken Drug Co., Ltd.,[b] Shimorenjaku Mitaka, Tokyo, 181 Japan; and Faculty of Pharmaceutical Sciences, Chiba University,[c] 1-33, Yayoi-cho, Chiba, 260 Japan

Abstract ----- The cleavage of methyl ethers of several bisbenzylisoquinoline alkaloids was studied and regioselective O-demethylation was observed.

More than 300 kinds of bisbenzylisoquinoline alkaloids have been isolated from natural sources.[1] This report discusses the regioselective O-demethylation occurring among alkaloids of this type (excluding aporphine-benzylisoquinoline type alkaloids).

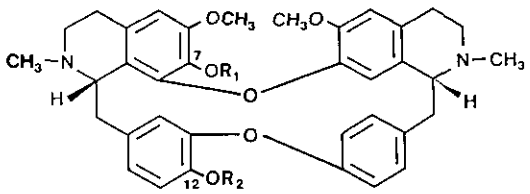
Reports on regioselective O-demethylation of bisbenzylisoquinoline alkaloids include those of tetrandrine (1)[2] and cycleanine (6) with hydrobromic acid[3] or pyridine hydrochloride[4] and the O-demethylation by pyrolysis of cycleanine (6) hydrochloride.[5] However, the reported O-demethylations have been done under drastic conditions such as heating with mineral acids, usually yielding mixtures of O-demethyl products that are difficult to separate. Also, the reaction of oxyacanthine (13) with hydrochloric acid causes inversion of the steric configuration.[6] Thus, mineral acid is not a recommendable reagent. From among many moderate O-demethylation agents,[7] this report discusses the use of dibenzyl diselenide,[8] iodotrimethylsilane[9] and methionine in methanesulfonic acid[10] for regioselective O-demethylation of bisbenzylisoquinoline alkaloids.

Table. Reagents for O-demethylation, O-demethylated products and their yields

Starting alkaloid	Reagent*	O-Demethylated product	Yield (%)
tetrandrine (1)	a	fangchinoline (7)	31.3
	b	atherospermoline (8)	6.7
	c	atherospermoline (8)	6.7
isotetrandrine (2)	a	thalrugosine (9)	20.6
	b	obamegine (10)	6.7
obaberine (3)	a	homoaromoline (11)	10.7
	b	homoaromoline (11)	14.9
		aromoline (12)	trace
cepharanthine (4)	b	cepharanoline (14)	13.5
isotrilobine (5)	a	cocsuline (15)	18.5
	b	cocsuline (15)	22.1
cycleanine (6)	a	norcycleanine (16)	15.5
	b	isochondodendrine (17)	20.1

* a, iodotrimethylsilane; b, methionine; c, dibenzyl diselenide

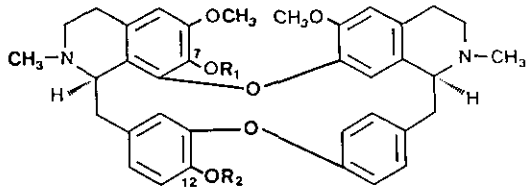
Tetrandrine (1), isotetrandrine (2), obaberine (3), cepharanthine (4), isotrilobine (5) and cycleanine (6) were subjected to O-demethylation by the reagents listed in the Table. In the O-demethylation of tetrandrine (1) with dibenzyl diselenide, the reaction did not proceed as smoothly as with the aporphine-benzylisoquinoline alkaloid (thalicarpine is readily converted into thalictropine[8]), and only atherospermoline (8), an O-demethyl derivative at C-7 position, was obtained in a low yield. The O-demethylation with this reagent for other bisbenzylisoquinoline alkaloids was found to be difficult, and only the starting material was recovered. On O-demethylation with iodotrimethylsilane or methionine, tetrandrine (1) gave fangchinoline (7) or atherospermoline (8), which were the products O-demethylated at C-7 or C-7 and C-12 position, respectively. These findings show that O-demethylation at C-7 position takes place most preferentially followed by that at C-12 as O-demethylation of tetrandrine (1) with hydrobromic acid.[2] O-Demethylation of isotetrandrine (2), a diastereoisomer of tetrandrine (1), with these reagents proceeded at C-7 in iodotrimetylsilane and at C-7 and C-12 positions in methionine in the presence of



(1) $R_1 = R_2 = CH_3$

(7) $R_1 = H$, $R_2 = CH_3$

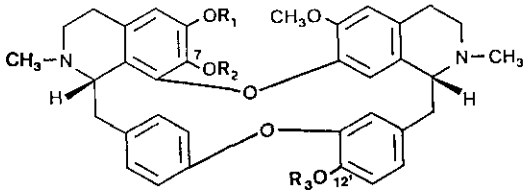
(8) $R_1 = R_2 = H$



(2) $R_1 = R_2 = CH_3$

(9) $R_1 = H$, $R_2 = CH_3$

(10) $R_1 = R_2 = H$



(3) $R_1 = R_2 = R_3 = CH_3$

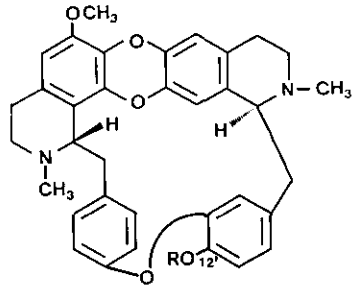
(11) $R_1 = R_3 = CH_3$, $R_2 = H$

(12) $R_1 = CH_3$, $R_2 = R_3 = H$

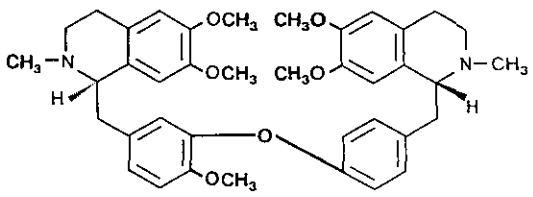
(13) $R_1 = R_2 = CH_3$, $R_3 = H$

(4) $R_1 + R_2 = CH_2$, $R_3 = CH_3$

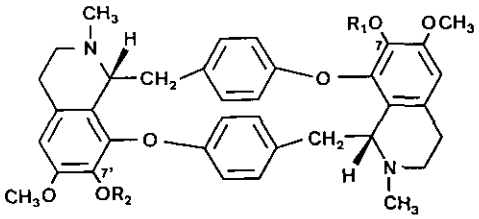
(14) $R_1 + R_2 = CH_2$, $R_3 = H$



(5) R= CH_3 (15) R= H

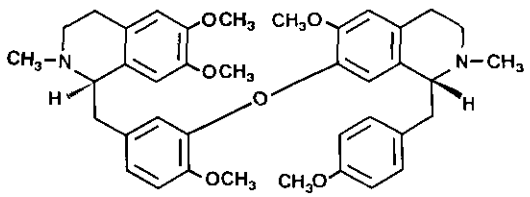


(18)



(6) $R_1 = R_2 = CH_3$ (16) $R_1 = CH_3$, $R_2 = H$

(17) $R_1 = R_2 = H$



(19)

methanesulfonic acid, as that of tetrandrine (1), giving rise to thalrugosine (9) or obamegine (10), respectively. This shows that there is no relationship between O-demethylation by these reagents and the absolute configuration of bisbenzylisoquinoline alkaloids.

For obaberine (3), O-demethylation at C-7 position occurs smoothly, producing homoaromoline (11), but O-demethylation at C-12' position scarcely proceeds. Aromoline (12) was produced only trace amount by reaction with methionine.

For cepharanthine (4), which has a methylenedioxy group at C-6 and C-7 positions instead of methoxy groups, O-demethylation at the C-12' position occurred by reaction with methionine in methanesulfonic acid, to give cepharanoline (14).

For isotrilobine (5), which has a dibenzo-p-dioxin skeleton, O-demethylation occurred at C-12' position and cocsuline (15) was obtained, by either of the above two reagents.

With cycleanine (6), in which methoxy groups are present at C-7 and C-7' but absent at C-12 and C-12' positions, we can obtain norcycleanine (16) or isochondodendrine (17) via O-demethylation which progresses at C-7 with iodotrimethylsilane or at the two methoxy groups at C-7 and C-7' positions with methionine, respectively.

These results can be summarized as follows.

i) The methoxy groups at C-7 or C-7' positions are O-demethylated most preferentially, followed by methoxy groups at C-12 or C-12' positions. The methoxy groups must be adjacent to diphenyl ether bonding in bisbenzylisoquinoline alkaloids.

ii) Iodotrimethylsilane is effective for O-demethylation only at C-7 and methionine for O-demethylation of both methoxy groups at C-7 and C-7'or C-7 and C-12'.

The O-demethylation of bisbenzylisoquinoline alkaloid having only one diphenyl ether bonding such as O-methyldauricine (18), O,O-dimethylliensinine (19) and phenolic alkaloid such as oxyacanthine (13) hardly proceeds at all.

These experimental results suggest that, if O-demethylating agents are appropriately selected, the non-phenolic bisbenzylisoquinoline alkaloids can be regioselectively O-demethylated to the expected phenolic alkaloids.

EXPERIMENTAL

All melting points were measured on a Yanagimoto micro-melting point apparatus and are uncorrected. Ir spectra and uv spectra were recorded on a Hitachi EPI-G3 spectrophotometer and on a Hitachi 340 spectrophotometer, respectively. ^{1}H-Nmr spectra were recorded on a JNM-FX 200 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were measured using a Hitachi RMU-6E spectrometer with a direct inlet system. CD and ORD spectra were measured on a JASCO J-500A spectropolarimeter and a JASCO J-20 spectropolarimeter, respectively. $[\alpha]_D$ was measured on a JASCO DIP-140 digital polarimeter. Column chromatography and thin layer chromatography were carried out using Merck Silica gel 60 (70~230 mesh) and Kiesel gel 60F-254 (Merck) with appropriate solvents.

Identification of the product was done by direct comparison [uv(EtOH), ir($CHCl_3$), ^{1}H-nmr($CDCl_3$), *ms, CD, ORD and mixed melting point*] with the natural products, the phenolic bisbenzylisoquinoline alkaloids.[11]

General methods. O-Demethylation with iodotrimethylsilane

Iodotrimethylsilane (1.5 ml, 0.01 mmol) was added dropwise to a solution of the alkaloid (0.2 mmol) in anhyd. chloroform (1.5 ml) with ice-cooling and stirring under an argon atmosphere. After stirring had continued for 4 h under the same conditions, the excess reagent was decomposed by addition of MeOH and the solvent was evaporated off in vacuo. The residue was made alkaline with aqueous 10% NH_4OH and extracted several times with CH_2Cl_2. The organic layer was extracted with aqueous 10% NaOH solution and separated into non-phenolic and phenolic base fractions. Enough solid NH_4Cl was added to the aqueous solution and extraction with CH_2Cl_2 was done several times. The CH_2Cl_2 solution was washed with water, dried over anhyd. $MgSO_4$, and evaporated. The residue was subjected to silica gel column chromatography monitored by tlc. The eluate showing a single spot on tlc was evaporated and residue was recrystallized from the solvent as described previously.[11]

O-Demethylation with methionine in methanesulfonic acid

The alkaloid (0.25 mmol), methionine (0.4 g, 0.27 mmol) and methanesulfonic acid (1.0 ml) were stirred at room temperature for 24 h. The reaction mixture was poured into icewater (10 ml). After the non-alkaloid fraction had been removed

with benzene, the aqueous layer was made basic with aqueous 10% NaOH solution, then the non-phenolic bases were extracted with CH_2Cl_2. The aqueous 10% NaOH layer was worked up as above to afford pure phenolic alkaloid.

O-Demethylation with dibenzyl diselenide

Sodium borohydride (100 mg) was added to a solution of dibenzyl diselenide (0.22 g, 0.65 mmol) in DMF (10 ml) at room temperature under nitrogen atmosphere. The mixture was stirred for 15 min. The solution of alkaloid (0.5 mmol) in anhyd. DMF (20 ml) was gradually added dropwise to the above mixture with stirring. The reaction mixture was refluxed with stirring for an additional 10 h and the solvent was evaporated off in vacuo. The residue was extracted several times with aqueous 10% H_2SO_4 solution, and the acidic aqueous solution was washed with benzene. The acidic solution was made alkaline with aqueous 10% NaOH solution, then extracted with CH_2Cl_2. The alkaline layer was worked up as above to give pure phenolic alkaloids.

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