SELECTIVE CLEAVAGE OF UNSYMMETRICAL 2,2-SPIRO-1,3-DIOXOLANES. II.[1] CLEAVAGE OF KETAL RING OF 5'-BROMO-6',7'-DIHYDRO-4-ISOPROPYL-AMINOMETHYL-1'-p-TOLUENESULFONYL-SPIRO[1,3-DIOXOLANE-2,4'-(5'H)-INDOLE] AND ITS ANALOGS

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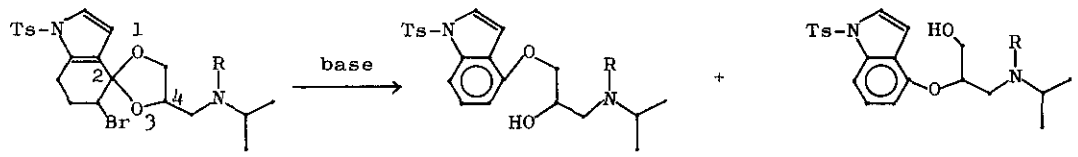
Abstract—The bromodioxolane and its analogs (1-5) were treated with organic base (DBU, DBN, or morpholine), acid (p-toluenesulfonic acid or Lewis acid), or Lewis acid/tertiary amine, and yielded 4-alkoxyindoles (6-17). Reaction of 1 with organic base gave two isomeric 4-alkoxyindoles, 6 (tosylpindolol, a secondary alcohol) and 11 (a primary alcohol), while tri-n-octylamine with stannic chloride afforded 6 (74 %) without producing 11.

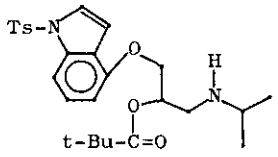
As reported in Part I of this series[1], bromodioxolane 1 was prepared from 5-bromo-1-p-toluenesulfonyl-4,5,6,7-tetrahydroindol-4-one 18 by ketalization with epibromohydrin or 3-bromo-1,2-propanediol and subsequent amination with isopropylamine. Dehydrobromination of the dioxolane 1 in toluene with 5 M equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 80°C for 21 h gave two 4-alkoxyindoles: a secondary alcohol 6 (35 % yield) formed by cleavage of the C(2)-O(3) bond and a primary alcohol 11 (39 %) by cleavage of the C(2)-O(1) bond (Scheme 1). These two compounds (6 and 11) were determined to be stereoisomers based on the position and nature of the alcoholic hydroxyl groups, from elemental analysis data and ir, nmr, and mass spectra[7]. No regioselective cleavage was observed in the reaction of the bromodioxolane or its amides 1-5 with morpholine or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), and the corresponding secondary and primary alcohols, 6-10 and 11-15, were obtained (Table 1).

Scheme 1



1	R = H	6	R = H	11	R = H
2	= Ac	7	= Ac	12	= Ac
3	= Bz	8	= Bz	13	= Bz
4	= COBu(t)	9	= COBu(t)	14	= COBu(t)
5	= COOMe	10	= COOMe	15	= COOMe

16 :



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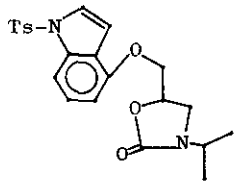


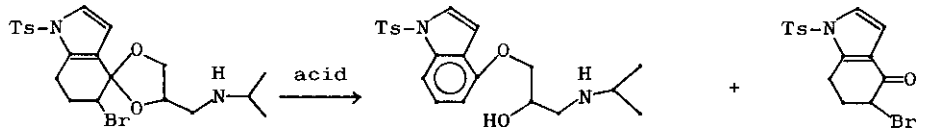
Table 1 Reaction of Dioxolanes 1-5 with Organic Base

Dioxolane	Base (M equiv.)	Solvent	Reaction		Yield (%)	
			Temp.(°C)	Time (h)	Sec. alc.	Prim. alc.
1[1]	DBU (5)	Toluene	80	21	6[7] (35)	11[7] (39)
"	Morpholine (55)	—	Reflux	27	" (36)	" (42)
2[6]	DBN (2)	$HCONMe_2$	60	72	7[7] (49)	12[7] (35)
3[6]	" "	"	80	21	8[7] (44)	13[7] (34)
4[6]	" "	"	60	85	9[7](9)+16[7](36)	14[7] (42)
5[6]	" "	"	"	72	10[7](16)+17[7](27)	15[7] (37)

In the cleavage of pivaloyl amide 4 or methoxycarbonyl amide 5, a by-product, the pivalate 16[7] (36 %) of the secondary alcohol 9 or the oxazolone 17[7] (27 %) cyclized from the corresponding secondary alcohol 10, was obtained together with the respective alcohols: 9 (9 %)/14 (42 %) and 10 (16 %)/15 (37 %). Neither dehydrobromination nor cleavage of the ketal ring was found under the action of triethylamine, N-methylmorpholine, or potassium t-butoxide, and the starting material 1 was recovered.

Cleavage of the bromodioxolane 1 with acid (p-toluenesulfonic acid or Lewis acid such as boron trichloride, titanium tetrachloride, and stannic chloride) gave the secondary alcohol 6 and/or the deketalized product 18 (Scheme 2). Treatment of the bromodioxolane 1 with p-toluenesulfonic acid (1.0 M equiv.) in

Scheme 2



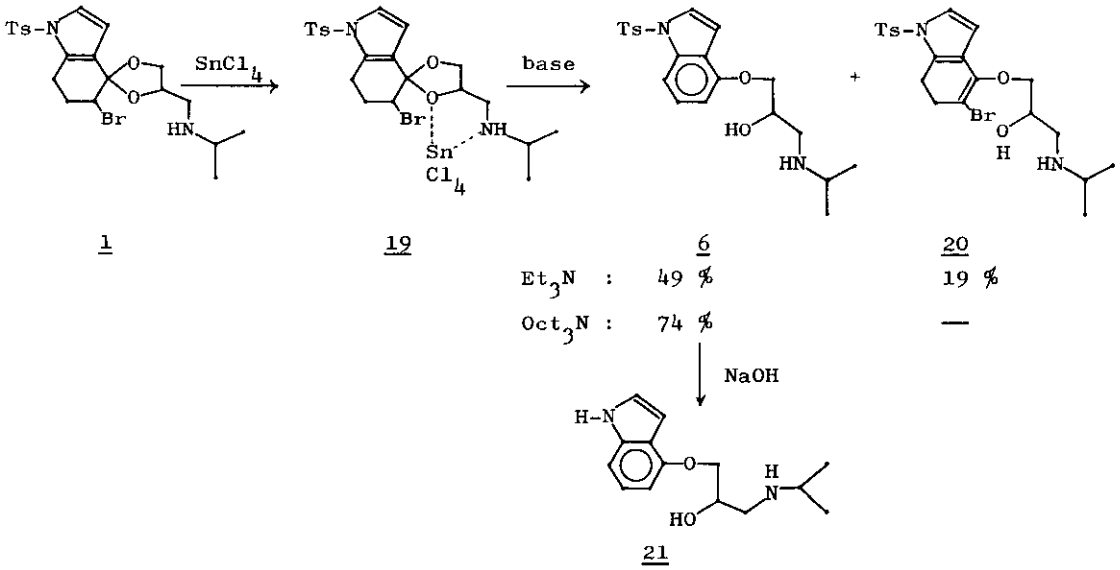
1 6 18

xylene (reflux 6 h) gave the secondary alcohol 6 and the bromoindolone 18 in 23 and 17 % yields, respectively, without the primary alcohol 11. This result can be reasonably interpreted by considering that the p-toluenesulfonic acid salt of 1 would lead to easier cleavage of the C(2)-O(3) bond than the C(2)-O(1) bond by an interaction of the ammonium ion (Table 2).

Table 2 Selective Cleavage of Bromodioxolane 1 with Acid

Acid (M equiv.)	Solvent	Reaction		Yield (%)		Recovery (%)
		Temp.(°C)	Time (h)	6	18	of 1
TsOH (1.0)	Xylene	Reflux	6	23	17	7
BCl_3 (1.0)	$MeNO_2$	-17～20	48	65	19	—
$TiCl_4$ (1.0)	"	-18～20	24	—	75	12
$SnCl_4$ (1.0)	"	"	"	—	4	88

Scheme 3



1 19 6 20

Et_3N : 49 % 19 %

Oct_3N : 74 % —

21

Selective cleavage of bromodioxolane 1 with Lewis acid (beryllium dichloride, titanium tetrachloride, or stannic chloride) in the presence of tertiary

amine (triethylamine, tri-n-butylamine, tri-n-octylamine, or tri-n-dodecylamine) gave only the secondary alcohol 6 (Table 3). It seems rational that stannic chloride, for example, could form a five-membered complex 19 with the dioxolane 1 in favor of the selective cleavage of the C(2)-O(3) bond (Scheme 3). In fact, higher yield (74 %) of the secondary alcohol 6 was obtained from the bromodioxolane 1 by reaction with tri-n-octylamine in the presence of stannic chloride. When triethylamine was used instead of tri-n-octylamine, 6 and bromo-enol ether 20 were obtained in 49 and 19 % yields, respectively. The tosyl group of the secondary alcohol 6 was removed by hydrolysis with sodium hydroxide in ethanol (reflux 14 h), giving pindolol 21 (92 %) which was identical with the authentic sample of pindolol, one of the β-adrenergic blocking agents on the market[5].

Table 3 Selective Cleavage of Bromodioxolane 1 with Lewis Acid/Tertiary Amine in Dichloromethane

Lewis Acid (M equiv.)	Tert. Amine (M equiv.)	Reaction Temp.(°C)	Reaction Time (h)	Yield (%) Sec. alc. 6	Yield (%) By-product	Recovery of 1 (%)
$BeCl_2$ (4)	Et_3N (4)	12	19	32	56 (18)	—
BCl_3 (1)	" (1)	-17～25	48	32	10 (11)	—
$ZrCl_4$ (4)	" (4)	-17～12	19	33	21 (18)	—
$SnCl_4$ (2.5)	" (5)	-75～28	24	49	19 (20[7])	9
" (3.5)	Bu_3N (5)	-15～29	3	70	17 (20[7])	—
$TiCl_4$ (3.5)	Oct_3N (5)	-17～30	3	51	trace (20[7])	—
$SnCl_4$ (3.5)	" (5)	-20～25	3	74	" "	4
" (3.5)	Dod_3N (5)	2～29	3	63	10 (20[7])	—

The influence of the functional group at position 4 or 5' on the selective cleavage of the 2,2-spiro-1,3-dioxolane ring was examined by using analogous dioxolanes 22-25 with the same reagent system consisting of stannic chloride and tri-n-octylamine (Table 4). It seems necessary for the selective cleavage to have an aminomethyl group at position 4 on the 1,3-dioxolane ring.

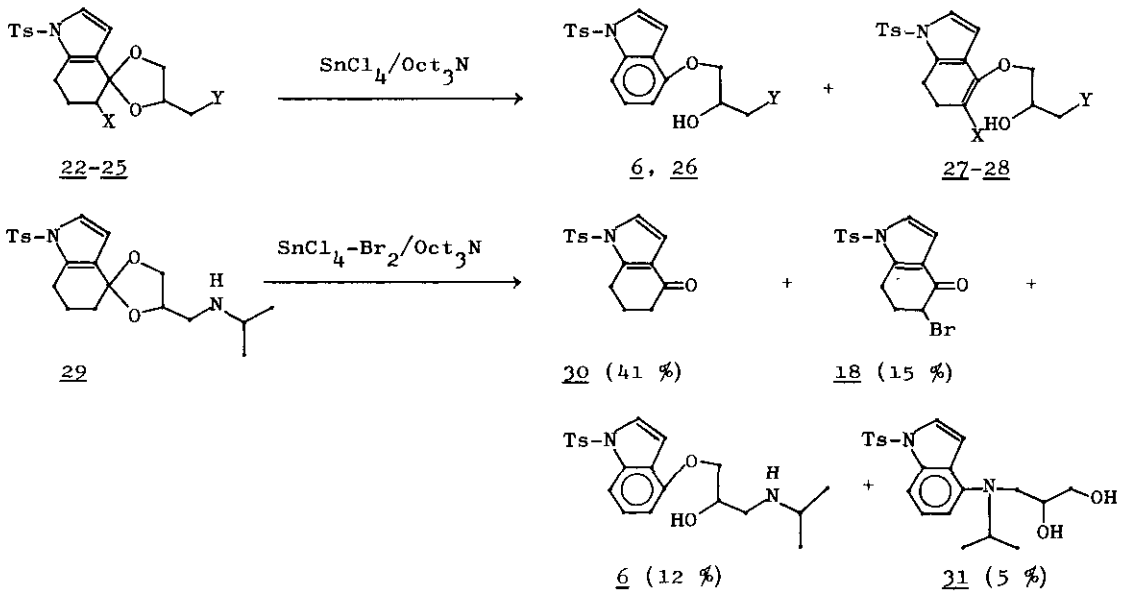
It is interesting to note that when a solution of stannic chloride (3.5 M equiv.) and bromine (1.3 M equiv.) in 1,2-dichloroethane was added dropwise to a cooled solution of the tetrahydroindole-dioxolane 29[4] and tri-n-octylamine (5 M equiv.) with stirring at -17°C for 15 min and the mixture was allowed to stand for 3 h up to 25°C and treated with 5N sulfuric acid, four products were

obtained by column chromatography: deketalized ketone 30 (41 %), bromoketone 18 (15 %), tosylpindolol 6 (12 %), and an aromatized tertiary amine 31[7] (5 %) (Scheme 4).

Table 4 Reaction Product from Analogous Dioxolanes 22-25 with Stannic Chloride and Tri-n-Octylamine

Dioxolane	Substituent -X	Substituent -Y	Yield (%) of ether: Sec. alc.	Yield (%) of ether: Halo-enol	Recovery (%) of Dioxolane
22[2]	-Br	-N⟨⟩	65 (26[7])	7 (27[7])	—
23[1]	"	-Br	—	—	93
24[1]	"	-OTs	—	—	99
25[3]	-Cl	-NH-Pr(i)	62 (6[7])	13 (28[7])	—

Scheme 4



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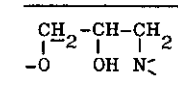
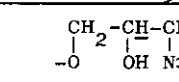
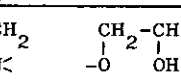
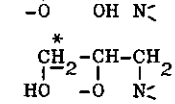
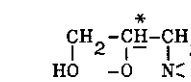
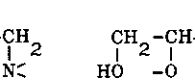
REFERENCES AND NOTES

1. Part I: M. Sakai, this journal, in press.
2. The piperidino-dioxolane 22 was prepared from the corresponding 4-(bromomethyl)dioxolane 23[1] with piperidine. Yield: 72 %.
3. The chlorodioxolane 25 was prepared from 1-p-toluenesulfonyl-4,5,6,7-tetrahydroindol-4-one 30[1] in the following sequence: by chlorination with $CuCl_2/HC(OMe)_3$ in methanol [the chloroindolone, mp 155-156°C, 83 % yield, ms m/z (M^+) = 325, 323], ketalization with epibromohydrin/$SnCl_4$[1] [the chlorodioxolane, 88 % yield, ms m/z (M^+) = 463, 461, 459], then aminolysis with isopropylamine (83 %).
4. The tetrahydroindole-dioxolane 29 was prepared by ketalization of the ketone 30[1] with epibromohydrin/$SnCl_4$ (91 %) and followed by amination with isopropylamine (85 %).
5. Sandoz Ltd., Swiss Patents 469,002 and 472,404 (1969).

6.

Cpd	ir $\nu_{max}^{CHCl_3}$ cm^{-1}	^{1}H-nmr ($CDCl_3$) δ (Hz)	ms m/z (M^+)
2	1630	2.13 (s, -COMe), 2.41 (s, p-Me)	526, 524
3	1624	2.40 (s, p-Me)	
4	1611	1.26 (s, $-COCMe_3$), 2.39 (s, p-Me)	568, 566
5	1693	2.40 (s, p-Me), 3.68 (s, -COOMe)	542, 540

7.

Cpd	mp (°C)	ir $\nu_{max}^{CHCl_3}$ (cm^{-1})	^{1}H-nmr ($CDCl_3$) δ (Hz)			ms m/z (M^+)
						
						
6	225-6 (HCl salt)	3370 (br)	3.84-4.25 (m)	3.84-4.25 (m)	2.6-3.1	402
7	—	3350 (br) 1615	3.9-4.3	3.9-4.3	3.28-3.85 (m)	444
8	—	3350 (br) 1600	3.4-4.5	3.4-4.5	3.4-4.5	506
9	—	3340 (br) 1592	3.86-4.22 (m)	3.86-4.22 (m)	3.25-3.73 (m)	
10	—	3400 (br) 1666	3.9-4.4	3.9-4.4	3.42 (d, J=4)	460
11	169-9.5 (HCl salt)	3340 (br)	3.46 (d, J=4.5)*	4.57 (tt, J=4.5, 4.5)*	3.08 (d, J=4.5)*	402
12	—	3400 (br) 1620	3.6-4.2*	4.48-4.78(m)*	3.49 (1H, dd, J=5, 20)*	444
13	—	3405 (br) 1613	3.4-4.2*	4.77-5.08(m)*	3.4-4.2*	506
14	154-5	3400 (br) 1600	3.5-3.8*	4.60-4.80(m)*	3.19 (1H, dd, J=6, 14)*	486
15	—	3440 (br) 1680	3.5-4.2*	4.48-4.77(m)*	3.5-4.2*	460
16	—	1724	4.20 (d, J=6)	5.25 (tt, J=6, 6)	2.92 (d, J=6)	
17	144.5-5	1748	3.9-4.3	4.31-4.96 (m)	3.44 (dd,J=8.5, 6) 3.63 (dd,J=8.5, 8.5)	428
20	140.5-1	3330 (br) 1635	3.97-4.10 (m)	3.97-4.10 (m)	2.5-3.1	
26	204-6 (HCl salt)	3375 (br)	3.93-4.27 (m)	3.93-4.27 (m)	2.2-2.8	428
27	—	3330 (br) 1637	3.76-4.26 (m)	3.76-4.26 (m)	2.2-2.6	(510 508
28	125.5-7	3340 (br) 1644	3.74-4.04 (m)	3.74-4.04 (m)	2.6-3.2	(440 438
31	—	3370 (br)	3.3-3.8 (m)	3.3-3.8 (m)	2.9-3.3 (m)	402

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