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Cleavage of the Methylenedioxy Ring. II.[1] Cleavage with Sodium Phenoxide and Methoxide in Dimethyl Sulfoxide

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Regioselective cleavage of the methylenedioxy ring in piperonals (**1**, **6**, and **7**) and 3,4-methylenedioxynitrobenzenes (**8** and **9**) by oxide ions in dimethyl sulfoxide was achieved: the 4-hydroxybenzene derivatives (**2**, **10**—**13**, and **22**) were obtained with the phenoxide ion, while the 3-hydroxybenzene derivatives (**4**, **18**—**21**, **23**, **26**, and **29**) were obtained with the methoxide or benzyloxide ion.

Keywords——cleavage of methylenedioxy ring; regioselectivity; piperonals; 3,4-methylenedioxynitrobenzenes; sodium phenoxide; sodium methoxide; dimethyl sulfoxide; 3-hydroxybenzene derivatives; 4-hydroxybenzene derivatives; NMR spectra

Previously we reported[1] that the methylenedioxy ring[3] in piperonals and 3,4-methylenedioxynitrobenzenes could be easily opened with N-sodium methoxide-methanol in dimethyl sulfoxide (DMSO) (under protic conditions).

In the present paper, we describe a regioselective cleavage of the methylenedioxy ring in such compounds with sodium phenoxide (under protic and aprotic conditions) and with sodium methoxide (under aprotic conditions).

Table I. Cleavage of the Methylenedioxy Ring with Sodium Phenoxide

	Starting material			N–C_6H_5ONa–C_6H_5OH (ml)	C_6H_5ONa (mmol)	DMSO (ml)	Product[c]		
		mg	(mmol)					mg	Yield (%)
Protic medium[a]	**1**	500	(2.2)	3.0		2.4	**2**	393	55.7
	6	276	(1.0)	1.5		1.2	**10**	311	84.0
	7	333	(2.2)	2.0		1.6	**11**	90	16.6
	8	135	(0.8)	1.5		1.0	**12**	91	43.6
	9	244	(1.0)	1.5		1.0	**13**	68	20.2
							22	54	15.3
Aprotic medium[b]	**1**	250	(1.1)		1.5	1.2	**2**	85	24.1
	6	138	(0.5)		0.75	0.6	**10**	20	10.8
	7	1000	(6.7)		7.0	10.0	**11**	207	12.7
	8	135	(0.8)		1.5	1.0	**12**	149	71.4
	9	122	(0.5)		0.75	0.5	**13**	12	7.1
							22	7	4.0

a) Reactions at 170—190° for 4—20 min, except for the reaction of **7** at 110—120° for 1.5 hr.
b) Reactions at 170—190° for 2.5—11 min.
c) Isolation yield.

1) S. Kobayashi, M. Kihara, and Y. Yamahara, *Chem. Pharm. Bull.*, **26**, 3113 (1978).
2) Location: *1-78, Sho-machi Tokushima 770, Japan.*
3) In this paper, the term "a methylenedioxy ring" means a cyclic methylenedioxy group as in **1** and **6**—**9**, while the term "a methylenedioxy group" means a linear methylenedioxy group as in **2**, **10**—**13**, and **22**.

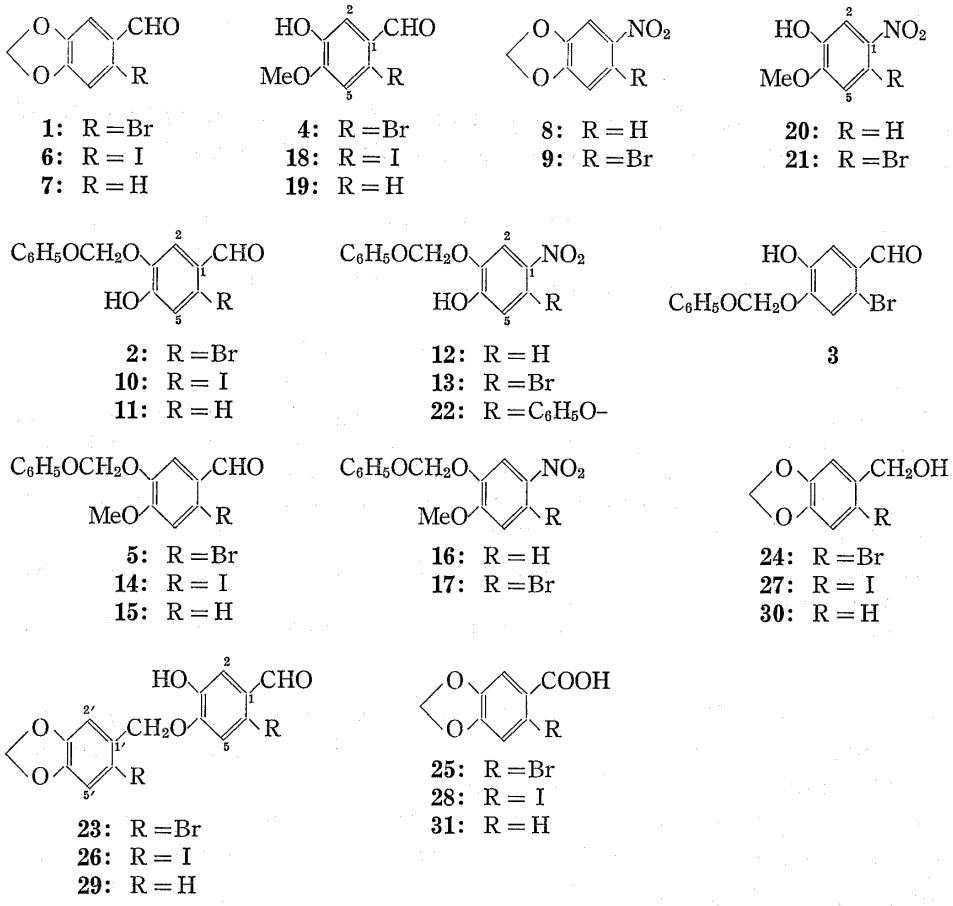


Chart 1

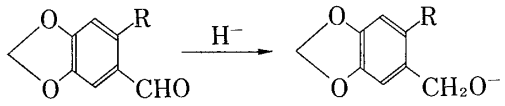
4-Hydroxybenzene Derivatives (2,10—13, and 22)

Treatment of 6-bromopiperonal (**1**) under protic conditions using N-sodium phenoxide–phenol in DMSO at 180° for 20 min gave a new phenolic product, $C_{14}H_{11}BrO_4$, mp 116—118°, which has a novel methylenedioxy group[3] (see Tables I-III). The infrared (IR) spectrum showed absorptions due to a hydroxy group at 3350 cm^{-1} and a formyl group at 1670 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum showed the presence of the formyl and novel methylenedioxy groups at δ 10.15 and 5.75, respectively. The protons of the methylenedioxy group[3] in this compound are shielded by 0.29 ppm compared with those of the methylenedioxy ring in **1**, because of the anisotropic effects of the two benzene rings (see Table IV). These effects were observed in the NMR spectra of other cleavage products, as shown in Table IV. From these data, the new product was assigned as 6-bromo-4-hydroxy-3-(phenoxymethoxy)-benzaldehyde (**2**) or its isomer (**3**); **2** seemed more likely on the basis of the Type B cleavage mechanism shown in Chart 2.

To comfirm this, compound (**2**) was converted to 6-bromoiso-vanillin (**4**): methylation of **2** with dimethyl sulfate and NaOH gave 6-bromo-4-methoxy-3-(phenoxymethoxy)benzaldehyde (**5**), which was identified by its NMR spectrum (see Table III): a nuclear magnetic double resonance (NMDR) experiment with irradiation at δ 5.75 ($-OCH_2O-$) gave a 19% NOE (intramolecular nuclear Overhauser effect) increment in the signal (δ 7.75) of C–2–H and irradiation at δ 3.89 ($-OCH_3$) gave a 14% NOE increment in the signal (δ 7.05) of C–5–H. This indicates that the cleavage product is **2**, not **3**.

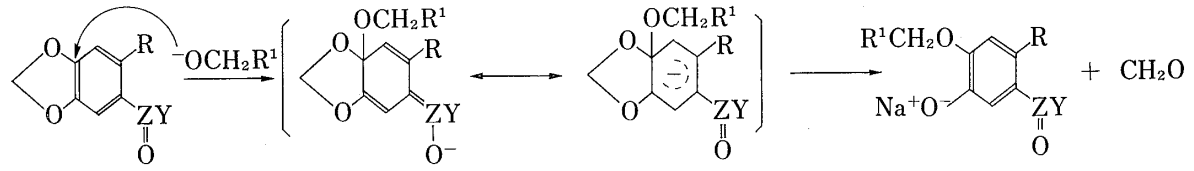
Hydrolysis of **5** with conc. HCl in EtOH gave a phenolic product (**4**). This compound was identical with an authentic sample of **4**, which was obtained by the cleavage of **1** under protic conditions.[1]

Similarly, the cleavage of piperonals (**6** and **7**) and 3,4-methylenedioxynitrobenzenes (**8** and **9**) gave the corresponding 4-hydroxybenzene derivatives (**10**—**13**, respectively) (see Tables I—III). The structures of these compounds (**10**—**13**) were established by NMDR studies (see "Experimental") of the methylated derivatives (**14**—**17**) and by conversion of the

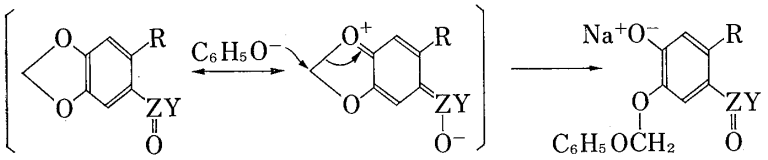


32

Type A



Type B



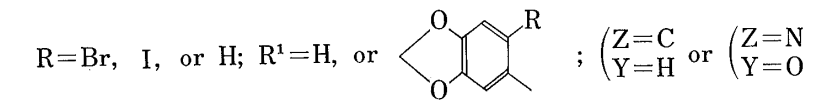


Chart 2

Table II. Phenolic Compounds (**2**, **10**—**13**, **22**, **23**, **26** and **29**)

Compd.	mp (°C) (from)	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{KBr} (cm^{-1}) OH	CHO	NO_2
2	116—118 (petr. ether)	$C_{14}H_{11}BrO_4$	52.04 (51.94)	3.43 (3.38)		3350	1670	
10	115—116 (CCl_4)	$C_{14}H_{11}IO_4$	45.43 (45.34)	2.99 (2.94)		3300	1670	
11	94—95 (acetone)	$C_{14}H_{12}O_4$	68.84 (68.83)	4.95 (4.66)		3300	1670	
12	117—118 (EtOH)	$C_{13}H_{11}NO_5$	59.77 (59.87)	4.24 (4.17)	5.36 (5.34)	3400		1510 1340
13	201—202 (acetone–$CHCl_3$)	$C_{13}H_{10}BrNO_5$[a]	338.9741 (338.9726) 340.9723 (340.9723)			3400		1510 1330
22	Oil	$C_{19}H_{15}NO_6$[a]	353.0900 (353.0937)			3450		1530 1330
23	207—209 (acetone)	$C_{15}H_{10}Br_2O_5$	41.89 (41.47)	2.34 (2.43)		3530	1680	
26	192—196 (acetone)	$C_{15}H_{10}I_2O_5$	34.36 (34.49)	1.92 (2.03)		3400	1670	
29	amorphous	$C_{15}H_{12}O_5$[a]	272.0683 (272.0630)			3280	1660	

a) Determined by high resolution mass spectrometry.

derivatives (**14**—**17**) to phenolic compounds (**18**—**21**) in the same manner as for **2**. In the case of the cleavage of **9**, an unexpected new product (**22**) was obtained as well as **13**. The spectral data in Tables II and III were consistent with the 6-phenoxyl structure (**22**). Compound (**22**) seems to be formed by the Ullmann-type condensation of **13** with sodium phenoxide, since the bromo substituent in **13** may be activated by the nitro group *ortho* to it.

TABLE III. Chemical Shifts[a] of Compounds **2**, **5**, **10**—**17**, **22**, **23**, **26**, and **29** ($CDCl_3$, δ)

Compd.	Aromatic H					CHO	OCH_2O	OCH_3	$ArCH_2O$
	C-2	C-5	C-6	C-2′	C-5′				
2	7.75	7.16				10.15	5.75		
5	7.75	7.05				10.13	5.75	3.89	
10	7.75	7.49				9.84	5.78		
11	7.75 (d, 2)	[d]	7.51 (dd, 8, 2)			9.79	5.79		
12[b]	8.06 (d, 2)	6.85 (d, 8)	7.84 (dd, 8, 2)				5.77		
13	7.97	[d]					5.80		
14	7.76	[d]				9.84	5.76	3.90	
15	7.73 (d, 2)	6.97 (d, 8)	7.55 (dd, 8, 2)			9.81	5.77	3.89	
16	8.11 (d, 2)	6.86 (d, 8)	7.98 (dd, 8, 2)				5.78	3.93	
17	8.01	[d]					5.84	3.94	
22		8.00	6.53				5.76		
23[c]	7.49	7.05		6.87	6.91	10.14	5.88		5.07
26[c]	7.55	7.37		6.91	7.13	9.86	5.85		4.99
29	7.43 (d, 2)	6.99 (d, 8)	7.38 (dd, 8, 2)			9.80	5.96		5.06

a) Signals are singlets except where otherwise indicated in parentheses. The numerical values in parentheses are coupling constants in Hz.
b) In $CDCl_3$–CD_3OD (1:2).
c) In $CDCl_3$–pyridine-d_5 (3:1).
d) Obscured signal.

TABLE IV. Chemical Shifts of the Methylenedioxy Ring Protons in Compounds **1** and **6**—**9**, and of the Methylenedioxy Group Protons in Compounds **2**, **5**, and **10**—**17**, and the Differences between the corresponding Chemical Shifts ($CDCl_3$, δ)

Compd.	**1**	**2**	**5**	**6**	**10**	**14**	**7**	**11**	**15**	**8**	**12**	**16**	**9**	**13**	**17**
OCH_2O	6.04	5.75	5.75	6.03	5.78	5.76	6.01	5.79	5.77	6.12	5.77	5.78	6.11	5.80	5.84
Diff.[a]		0.29	0.29		0.25	0.27		0.22	0.24		0.35	0.34		0.31	0.27

a) ppm.

TABLE V. Cleavage of the Methylenedioxy Ring with Sodium Methoxide (An Aprotic Medium)[a]

	Starting material mg	MeONa mg (mmol)	DMSO (ml)	Product[b] mg (Yield, %)							
1	100 (0.44)	25 (0.46)	0.5	**4**	8 (7.9)	**23**	29 (30.9)	**24**	30 (29.7)	**25**	6 (5.6)
6	100 (0.36)	20 (0.37)	0.4	**18**	18 (17.4)	**26**	16 (16.9)	**27**	19 (18.9)	**28**	8 (7.6)
7	100 (0.67)	36 (0.67)	0.5	**19**	19 (18.8)	**29**	16 (17.6)	**30**	18 (18.0)	**31**	16 (14.5)
8	135 (0.78)	54 (1.00)	0.6	**20**	98 (71.8)						
9	66 (0.27)	25 (0.46)	1.0	**21**	18 (27.1)						

a) Reactions at 150° for 35—120 sec.
b) Isolation yield.

Under aprotic conditions using sodium phenoxide in DMSO, the same products (**2** and **10**—**13**) were obtained from **1** and **6**—**9** respectively, but except for the nitro compound (**12**) the yields were lower than those obtained under the protic conditions described above, as shown in Table I.

3-Hydroxybenzene Derivatives (4, 18—21, 23, 26, and 29)

Under aprotic conditions using sodium methoxide in DMSO, the cleavage of **1** gave a new 3-hydroxybenzene derivative (**23**), $C_{15}H_{14}Br_2O_5$, mp 207—209°, 6-bromopiperonyl alcohol (**24**), and 6-bromopiperonylic acid (**25**) in addition to the 3-hydroxybenzene derivative (**4**)[1] (see Table V). The IR, NMR, and mass spectral data, listed in Tables II, III, and VI, respectively showed the new product to be 6-bromo-3-hydroxy-4-(6′-bromo-3′,4′-methylenedioxybenzyloxy)benzaldehyde (**23**): in the NMDR study, irradiation at δ 5.07 ($ArCH_2O$–) gave a 13% NOE increment in the signal (δ 7.05) of C–5–H.

Similarly, the cleavage of compounds **6** and **7** gave four products in each case (**26**—**28**, **18**, and **29**—**31**, **19**, respectively), while compounds **8** and **9** gave only the 3-hydroxybenzene derivatives (**20** and **21**, respectively). The structures of the new products (**26** and **29**) were confirmed in the same way as for **23** (see Tables II, III, IV, and "Experimental"). The formation of **23**, **26**, or **29** can be explained in terms of the Type A mechanism in Chart 2: (i) the nucleophilic benzyloxide anion (**32**) seems to be formed by the Cannizzaro-type reaction of **1**, **6**, or **7** with methoxide ion, since the corresponding benzyl alcohol and benzoic acid were isolated from the reaction mixture. (ii) Ipso-attack by the nucleophile (**32**) at C-4 in **1**, **6**, or **7** gave the 3-hydroxybenzene derivative (**23**, **26**, or **29**).

Regioselective Cleavage of the Methylenedioxy Ring

On the basis of these results, the cleavage of the methylenedioxy ring in aromatic formyl compounds (**1**, **6**, and **7**) and nitro compounds (**8** and **9**) with a nucleophilic oxide anion in DMSO can be regioselectively classified into two types, ipso-attack (Type A) and attack at the carbon atom of the methylenedioxy ring (Type B) by the nucleophile. A 3-hydroxybenzene derivative (**4**, **18**—**21**, **23**, **26**, or **29**) is an important cleavage product of the corresponding methylenedioxy compound (**1** or **6**—**9**), resulting from ipso-attack by a nucleophile, such as a methoxide ion (in a protic[1] or an aprotic medium) or a benzyloxide ion (**32**) at C-4, followed by opening of the ring and loss of formaldehyde. On the other hand, a 4-hydroxybenzene derivative (**2**, **11**—**13**, or **22**) is also an important product of the cleavage of the same starting material, resulting from attack by a phenoxide ion (in a protic or an aprotic medium) at the ring carbon atom, followed by opening of the ring. The regioselectivity seems to depend on the basicity of the nucleophile, since a methoxide or benzyloxide ion is a stronger base than a phenoxide ion.

Experimental

All melting points are given as uncorrected values. The spectrophotometers used were a Hitachi model 215 for IR spectra, a JEOL model JMS-D 300 for mass spectra, and a JEOL model JNM-PS-100 for NMR spectra with TMS as an internal standard. The plates used for preparative thin-layer chromatography (PLC) were coated with silica gel (Kieselgel, PF_{254} Merck).

Cleavage of 6-Bromopiperonal (1) with N-Sodium Phenoxide-Phenol in DMSO (A Protic Medium)——A mixture of **1** (500 mg, 2.2 mmol) in DMSO (2.4 ml) and N-sodium phenoxide (348 mg, 3.0 mmol)–phenol (3 ml) was stirred at 170—180° for 20 min until the reaction mixture became brown. The reaction mixture was then diluted with H_2O (15 ml), acidified (pH 5) with conc. HCl and extracted with ether. The extract was washed with H_2O, dried, and concentrated under reduced pressure. The residue was subjected to PLC using SiO_2-[benzene–acetone (8: 1)]. Elution of the material of *Rf* 0.5 with acetone gave **2** (393 mg, 55.7%) as colorless needles. Elution of the material of *Rf* 0.7 with acetone gave **1** (146 mg, 29.2%).

The cleavage of **6**—**9** under protic conditions was carried out similarly, as shown in Table I. In the case of **9**, the resulting crude materials were subjected to PLC using SiO_2-[$CHCl_3$–acetone (100: 1)]. The products **13** (68 mg, 20.2%) and **22** (54 mg, 15.3%) were obtained from the materials of *Rf* 0.6 and 0.7, respectively, after double development.

Physical and spectral data for the produtcs (**2**, **10**—**13**, and **22**) are summarized in Tables II and III.

Cleavage of 6-Bromopiperonal (1) with Sodium Phenoxide in DMSO (An Aprotic Medium)——Sodium phenoxide (174 mg, 1.5 mmol) was added to a solution of **1** (250 mg, 1.1 mmol) in DMSO (1.2 ml) and the mixture was stirred at 170—180° for 11 min. Water (15 ml) and NaOH (30 mg) were then added to the mixture. After work-up as described above, the mixture gave **2** (85 mg, 24.1%).

Cleavage of the methylenedioxy ring in **6**—**9** under aprotic conditions was carried out similarly, as shown in Table I.

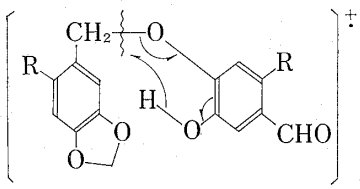
Conversion of the 4-Hydroxybenzene Derivative (2) to the 3-Hydroxybenzene Derivative (4)——A solution of **2** (60 mg) in 2% NaOH (6 ml) was treated with dimethyl sulfate (1 ml) and 2% NaOH (10 ml) at 90° for 50 min. Work-up in the usual way gave **5** (25 mg, 40.0%). Hydrolysis of **5** (5 mg) with conc. HCl (0.5 ml) and EtOH (1.5 ml) in the usual way gave **4** (2.2 mg), mp 105—107° (lit.[1] mp 104—108°). This compound (**4**) was identical with a sample obtained by the cleavage of **1** under protic conditions.[1]

The methylated products (**14**—**17**) were similarly obtained from the 4-hydroxybenzene derivatives (**10**—**13**, respectively) and identified by NMR spectroscopy (see Table III): irradiation of the methylenedioxy proton signal (δ 5.76, 5.77, 5.78 or 5.84) in **14**, **15**, **16** or **17** gave an NOE increment (14%, 16%, 16% or 18% respectively) in the signal (δ 7.76, 7.73, 8.11 or 8.01, respectively) of C-2-H. Irradiation at δ 7.76 or 7.73 (C-2-H) of **14** or **15**, respectively, gave an 8% or 12% NOE increment of the signal of the formyl group.

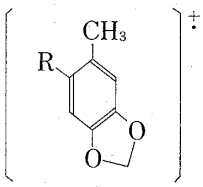
The 3-hydroxybenzene derivatives (**18**—**21**) were obtained from **14**—**16**, respectively, by the same method as for **4**, and appeared to be identical with authentic samples of **18**,[1] **19**,[1] **20**,[1] and **21** (see below), mp 114—116° (lit.[4] mp 118—119°), respectively by direct comparison.

Cleavage of 6-Bromopiperonal (1) with Sodium Methoxide in DMSO (An Aprotic Medium)——A mixture of sodium methoxide (25 mg, 0.44 mmol), **1** (100 mg, 0.46 mmol), and DMSO (0.5 ml) was stirred at 150° for 70 sec, cooled, diluted with H_2O, and extracted with ether. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated to give a residue, which was subjected to PLC using SiO_2-[benzene–acetone (10: 1)]. Elution of the materials of *Rf* 0.4 with acetone gave **24** (30 mg, 29.7%), mp 87—89° (lit.[1] mp 86—87°). Elution of the materials of *Rf* 0.5 with acetone gave **23** (12 mg), mp 207—209°. Elution of the materials of *Rf* 0.7 with acetone gave **1** (8 mg, 8.0%). The aqueous solution separated from the ethereal extract was acidified (pH 5) with conc. HCl and extracted with ether. After removal of the solvent, the residue was subjected to PLC using SiO_2-[benzene–acetone (10: 4)]. Elution of the materials of *Rf* 0.1

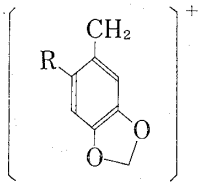
Table VI. Mass Spectral Data



$C_{15}H_{10}O_5R_2$



$C_8H_7O_2R$



$C_8H_6O_2R$

23[a]: R=Br *m/e* 429 (M+1, 9.8%) *m/e* 431 (M+1, 15.7%) *m/e* 433 (M+1, 7.8%)	R=Br *m/e* 214 (19.6%) Found: 213.9607 Calcd: 213.9628 *m/e* 216 (17.6%) Found: 215.9564 Calcd: 215.9609	R=Br *m/e* 213 (100%) Found: 212.9572 Calcd: 212.9552 *m/e* 215 (98%) Found: 214.9522 Calcd: 214.9530
26: R=I *m/e* 524 (<1%)	R=I *m/e* 261 (10.5%) Found: 261.9472 Calcd: 261.9487	R=I *m/e* 261 (100%) Found: 260.9429 Calcd: 260.9411
$C_{15}H_{12}OR_2$		
29: R=H *m/e* 272 (1.5%) Found: 272.0630 Calcd: 272.0683	R=H *m/e* 136 (17.5%) Found: 136.0571 Calcd: 136.0525	R=H *m/e* 135 (100%) Found: 135.0436 Calcd: 135.0445

a) Observed by CI mass spectrometry.

4) L.C. Raiford and R.E. Silker, *J. Org. Chem.*, **2**, 346 (1937).

with acetone gave **25** (6 mg, 5.6%) mp 197—199° (lit.[5] mp 203.8°), while elution of the materials of *Rf* 0.3 with acetone gave **4**[1] (8 mg, 7.9%). Elution of the materials of *Rf* 0.4 with acetone gave an additional 17 mg of **23** (total 29 mg, 30.8%).

Similar cleavages of **6**—**9** with sodium methoxide under aprotic conditions were carried out, as shown in Table V. The physical and spectral data for the new compounds (**23** and **26**) thus obtained are summarized in Tables II, III, and VI: in the NMDR studies, irradiation of the benzyl proton signal (δ 4.99 or 5.06) in **23** or **26** gave an NOE increment (26% or 10%, respectively) in the signal (δ 7.37 or 6.99, respectivly) of C-5-H.

Other products [**27**, mp 103—105° (lit.[1] mp 106—107°), **28**, mp 206—210° (lit.[6] mp 218.5—221°), **30**, mp 50—51° (lit.[1] mp 50—51°), **31**, mp 222—225°] were identical with authentic samples of **27**, **28**, **30**, and **31**, respectively, by direct comparison.

Cleavage of 6-Bromo-3,4-methylenedioxynitrobenzene (9) with N-Sodium Methoxide-Methanol in DMSO (A Protic Medium)——Amixture of **9** (246 mg, 1.0 mmol), DMSO (1.2 ml), sodium methoxide (76 mg, 1.4 mmol), and MeOH (1.4 ml) was stirred at 150° for 2 min. Work-up in the usual way gave **9** (40 mg, 16.3%) and **21**[4] (196 mg, 79.0%), mp 115—117° (from CCl_4–$CHCl_3$). *Anal.* Calcd for $C_7H_6BrNO_4$: C, 33.90; H, 2.44; N, 5.65. Found: C, 33.49; H, 2.53; N, 5.58. IR ν_{max}^{KBr} cm^{-1}: 3470 (OH), 1520, 1330 (NO_2). NMR ($CDCl_3$, δ) 3.98 (3H, s, OCH_3), 5.87 (1H, br s, OH), 7.11 (1H, s, C-5-H), 7.60 (1H, s, C-2-H).

Cleavage of 6-Bromo-3,4-methylenedioxynitrobenzene (9) with Sodium Methoxide in DMSO (An Aprotic Medium)——Treatment of **9** (66 mg, 0.27 mmol), DMSO (1 ml), and sodium methoxide (25 mg, 0.46 mmol) at 150° for 1 min gave **21**[4] (18 mg, 27.1%) and **9** (36 mg, 54.5%).

Acknowledgement The authors wish to thank Assistant Professor M. Kihara, Tokushima University, for valuable advice, and Mr. K. Kida for NMDR spectral measurements.

5) F. Dallacker, *Ann.*, **633**, 14 (1960).
6) S. Kobayashi, M. Kihara, T. Hashimoto, and T. Shingu, *Chem. Pharm. Bull.*, **24**, 716 (1976).