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Cleavage of the Methylenedioxy Ring. III. Cleavage with Sodium Benzyloxide in Dimethyl Sulfoxide

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Cleavage of the methylenedioxy ring in aromatic formyl (**1**—**3**), nitro (**4** and **5**), and acetyl (**30**) compounds with *N*-sodium benzyloxide-benzyl alcohol in dimethyl sulfoxide gave 3-hydroxybenzene derivatives (**19**, **22**—**24**, **26**, **27**, and **33**). In the case of the acetyl compound **30**, the 4-hydroxybenzene derivative (**34**) was also obtained as a minor product. Regioselective cleavage of the ring in aromatic compounds having electron-withdrawing groups with nucleophilic oxide anions is discussed. Cleavage of the ring in **1**—**5** and **30** with 2 N sodium methoxide in dimethyl sulfoxide-dimethylformamide was found to be useful for the practical preparation of 3-hydroxybenzene derivatives (**6**—**10** and **31**).

Keywords——Cleavage of methylenedioxy ring; regioselectivity; piperonals; 3,4-methylenedioxy-nitrobenzene; 3,4-methylenedioxy-acetophenone; sodium methoxide; sodium phenoxide; sodium benzyloxide; dimethyl sulfoxide; dimethylformamide

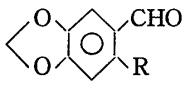
Recently we have reported[1] that regioselective cleavage of the methylenedioxy ring in aromatic formyl (**1**—**3**) and nitro compounds (**4**—**5**) with methoxide and phenoxide ions in dimethyl sulfoxide (DMSO) (under protic or aprotic conditions) give 3- and 4-hydroxybenzene derivatives (**6**—**10** and **11**—**14**, respectively). In the case of the cleavage of **1**—**3** with methoxide ion in DMSO (an aprotic medium), we also obtained the unexpected 3-hydroxybenzene derivatives (**15**—**17**), for the formation of which we have proposed the Type A mechanism[2]; the nucleophilic benzyloxide ion (**18**)[2] seems to be formed by the Cannizzaro-type reaction of **1**—**3** and then ipso-attack by the nucleophile (**18**)[2] at C-4 in **1**—**3** would give the 3-hydroxybenzene derivatives (**15**—**17**). In order to confirm this mechanism, we have investigated the cleavage of the methylenedioxy ring of **1**—**5** with benzyloxide anion in DMSO.

Cleavage of Aromatic Compounds (1—5) with 1 N Sodium Benzyloxide-Benzyl Alcohol in DMSO

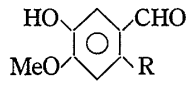
Treatment of 6-bromopiperonal (**1**) with 1 N sodium benzyloxide-benzyl alcohol in DMSO at 150°C for 9 min gave a new phenolic product (**19**), $C_{14}H_{11}BrO_3$, mp 128—129°C. The infrared (IR) spectrum of compound **19** showed absorptions due to a hydroxyl group at 3480 cm^{-1} and a formyl group at 1670 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum showed the presence of the formyl group at δ 10.04, a benzyloxy group [at δ 7.46 (5H, s, aromatic H) and at δ 5.13 (2H, s, methylene protons)], H-2 at δ 7.44 (1H, s), and H-5 at δ 7.09 (1H, s). Irradiation at δ 5.13 ($C_6H_5C\underline{H}_2O$) gave a 14% NOE (intramolecular nuclear Overhauser effect) increment in the signal (δ 7.09) of H-5. From these data the structure of the product was assigned as 4-benzyloxy-6-bromo-3-hydroxybenzaldehyde (**19**).

This assignment was confirmed by conversion of **19** into the methoxy derivative (**20**)[3] which was identical with an authentic sample prepared from **10**[4] as follows. Namely, treatment of **10** with benzyl chloride gave 4-benzyloxy-3-methoxy-6-nitrobenzaldehyde (**21**) ,mp 132—133°C, reduction of which with ferrous sulfate-ammonium hydroxide followed by the Sandmeyer reaction with cuprous bromide gave **20**.

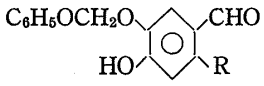
Similarly, the cleavage of **2**—**4** gave the corresponding 3-hydroxybenzene derivatives (**22**—**24**) as shown in Table I. The structures of these derivatives were supported by their physical and spectral data (Tables II—IV). The structure of **22** was further established by



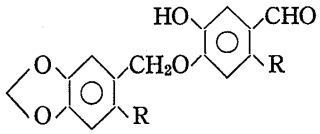
1: R=Br
2: R=I
3: R=H



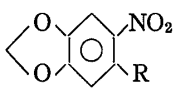
6: R=Br
7: R=I
8: R=H



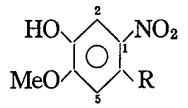
11: R=Br
12: R=I
13: R=H



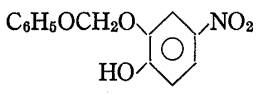
15: R=Br
16: R=I
17: R=H



4: R=H
5: R=CHO



9: R=H
10: R=CHO



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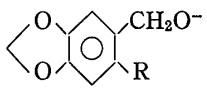

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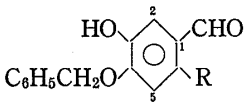
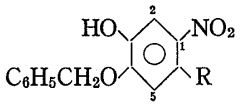
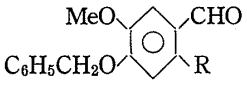


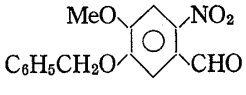
19: R=Br
22: R=I
23: R=H
27: R=NO_2



24: R=H
26: R=CHO



20: R=Br
21: R=NO_2
25: R=I



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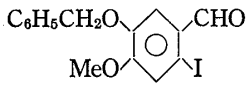

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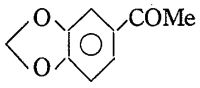

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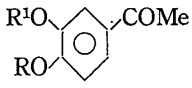


31: R=Me, R^1=H
32: R=H, R^1=$C_6H_5OCH_2$–
33: R=$C_6H_5CH_2$–, R^1=H
34: R=H, R^1=$C_6H_5CH_2OCH_2$–
35: R=$C_6H_5CH_2$–, R^1=Me
36: R=Me, R^1=$C_6H_5CH_2OCH_2$–
37: R=Me, R^1=Et

Chart 1

TABLE I. Cleavage of the Methylenedioxy Ring with Oxide Anions

Starting material No.	mg	(mmol)	1 N $C_6H_5CH_2ONa$ –$C_6H_5CH_2OH$ (ml)	0.8 N CH_3ONa –CH_3OH (ml)	1.5 N C_6H_5ONa –C_6H_5OH (ml)	DMSO (ml)	Reaction Time (min)	Reaction Temp. (°C)	Product[a] No.	mg	Yield (%)	Recovery of Starting material mg	(%)
1	229	(1.0)	1.0			1.2	9.0	150	**19**	77	(25)	131	(57)
2	138	(0.5)	0.7			2.0	1.5	180	**22**	24	(14)	43	(34)
3	147	(1.0)	1.0			2.0	1.4	150	**23**	52	(23)	10	(7)
4	167	(1.0)	1.0			2.0	1.4	155	24	132	(54)	50	(29)
5	196	(1.0)	1.0			2.0	1.3	150	**26**	114	(41)	76	(39)
									27	20	(7)		
30	110	(0.7)		0.6		0.7	10.0	190	**31**	25	(22)	55	(50)
30	100	(0.6)			0.5	2.0	15.0	190	**32**	32	(20)	64	(64)
30	150	(0.9)	1.0			1.8	1.5	190	**33**	17	(8)	9	(6)
									34	4	(2)		

a) Isolation yield.

conversion of **22** into the methoxy derivative (**25**), which was identical with an authentic sample of 4-benzyloxy-6-iodo-3-methoxybenzaldehyde, prepared by reduction of **21** followed by the Sandmeyer reaction with cuprous iodide.

Similar cleavage of **5**, having two electron-withdrawing groups (a formyl group and a nitro group), gave two types[5] of 3-hydroxybenzene derivatives, **26** and **27**, respectively.

These structures were established by their physical and spectral data (Tables II—IV) and also in the following way. Treatment of **27** with dimethyl sulfate gave **21**. The other product, **26**, was methylated with dimethyl sulfate to give the methylated product (**28**).[6] Reduction of **28** with ferrous sulfate-ammonium hydroxide followed by the Sandmeyer reaction with cuprous iodide gave an iodo compound (**29**), mp 139—140°C, which was identical with an authentic sample of 3-benzyloxy-6-iodo-4-methoxybenzaldehyde prepared by treatment of **7**[4] with benzyl chloride. These results confirm that a nucleophilic benzyloxide anion, such as **18**, could cleave the methylenedioxy ring in **1**—**3** to give 3-hydroxybenzene derivatives[1] (**15**—**17**).

Cleavage of 3,4-Methylenedioxyacetophenone (30) with Sodium Methoxide, Phenoxide, and Benzyloxide in DMSO

Treatment of **30** with sodium methoxide-methanol in DMSO at 190°C for 10 min gave the 3-hydroxybenzene derivative (**31**).[7] Similar treatment of **30** with sodium phenoxide–phenol in DMSO gave a new 4-hydroxybenzene derivative (**32**), mp 75—77°C. Treatment of **30** with 1 N sodium benzyloxide–benzyl alcohol in DMSO gave 3-hydroxybenzene derivative (**33**)[8] and 4-hydroxybenzene derivative (**34**), mp 106—110°C. The structures of **31**—**34** were supported by their physical and spectral data as shown in Tables II—IV. Furthermore, the structures of **33**, **34**, and **31** were confirmed by conversion of these products into methylated compounds (**35**[9] and **36**) and an ethylated compound (**37**),[10] respectively.

Cleavage of 1—5 and 30 with 2 N Sodium Methoxide-Methanol in DMSO–Dimethylformamide (DMF)

In order to improve the yield of the cleavage products, we tried to cleave the methylenedioxy ring in **1**—**5** and **30** with sodium methoxide in toluene, DMF, or DMSO–DMF as a solvent, since our previous results[4] using only DMSO were not very good. The best results were obtained by treatment with 2 N sodium methoxide–methanol in DMSO–DMF (2.5 : 1) at 150°C as shown in Table V. This procedure is useful for practical preparation

Table II. Phenolic Compounds (**19**, **22**—**24**, **26**, **27**, and **31**—**34**)

Compd.	mp (°C) (from)	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{KBr} (cm^{-1}) OH	CHO	NO_2
19	128—129 ($CHCl_3$–CCl_4)	$C_{14}H_{11}BrO_3$	54.75 (54.49	3.61 3.41)		3480	1670	
22	121—125 (hexane–$CHCl_3$)	$C_{14}H_{11}IO_3$	47.48 (47.39	3.13) 2.99)		3500	1680	
23	113—117 (benzene)	$C_{14}H_{12}O_3$	73.67 (73.70	5.30 5.25)		3200	1670	
24	80—81 (hexane–$CHCl_3$)	$C_{13}H_{11}NO_4$	63.67 (64.08	4.52 4.44	5.71 5.49)	3400		1510, 1350
26	148—149 ($CHCl_3$)	$C_{14}H_{11}NO_5$[a]	273.0637 (273.0652)			3150	1670	1510, 1330
27	123—126 ($CHCl_3$)	$C_{14}H_{11}NO_5$	61.54 (61.39	4.06 3.94	5.13 4.88)	3400	1680	1510, 1330
31	91—93 ($CHCl_3$)	$C_8H_9O_3$	65.05 (65.21	6.07 6.09)		3300	1660	
32	83—86 ($CHCl_3$)	$C_{15}H_{14}O_4$	69.75 (69.45	5.46 5.61)		3200	1660	
33	120—122 (hexane–$CHCl_3$)	$C_{15}H_{14}O_3$	74.36 (74.56	5.83 5.86)		3200	1650	
34	106—110 (hexane–$CHCl_3$)	$C_{16}H_{16}O_6$[a]	272.1048 (272.1053)			3400	1660	

a) Determined by high resolution mass spectrometry.

of these 3-hydroxybenzene derivatives (**6**—**10** and **31**).

Regioselective Cleavage of the Methylenedioxy Ring

Cleavage of the methylenedioxy ring in aromatic compounds having electron-withdrawing

Table III. Chemical Shifts[a] of Compounds **19**, **22**—**24**, **26**, **27**, and **31**—**34** ($CDCl_3$, δ)

Compd.	Aromatic H			CHO	OCH_2O	OCH_3	$ArCH_2O$	$COCH_3$
	C-2	C-5	C-6					
19	7.44	7.09		10.04			5.13	
22	7.46	7.24		9.80			5.14	
22[b]	c)	7.57		9.77			5.28	
23	7.39	7.00 (d, 8)	7.39	9.76			5.16	
24	7.78 (d, 2)	6.95 (d, 9)	7.78 (dd, 9, 2)	9.79			5.18	
26[b]	7.48	7.53		10.17			5.33	
27[b]	7.29	7.79		10.23			5.34	
31	7.50 (d, 2)	6.84 (d, 8)	7.50 (dd, 8, 2)			3.91		2.53
32	7.81 (d, 2)	6.94 (d, 8)	7.59 (dd, 8, 2)		5.72			2.50
33	7.52 (d, 2)	6.92 (d, 8)	7.49 (dd, 8, 2)				5.15	2.52
34	7.75 (d, 2)	6.96 (d, 8)	7.60 (dd, 8, 2)		4.75		5.36	2.53

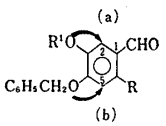
a) Signals are singlets except where otherwise indicated in parentheses. The numerical values in parentheses are coupling constants in Hz.
b) In acetone-d_6.
c) Obscured signal.

Table IV. NOE Increments in the H-2 and H-5 Signals of Compounds **19**—**28** and **31**—**36**[a]

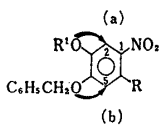
NOE increment (%) of	Compd.							
	19	**20**[c]	**21**[b]	**22**[b]	**23**	**24**	**25**[c]	**26**[b]
H-2(a)		23 (3.88)	19 (4.00)				19 (4.00)	
H-5(b)	14 (5.13)	34 (5.23)	20 (5.23)	26 (5.28)	15 (5.16)	15 (5.18)	20 (5.23)	19 (5.23)

NOE increment (%) of	Compd.							
	27[b]	**28**	**31**	**32**	**33**	**34**	**35**	**36**
H-2(a)		16 (3.98)		13 (5.72)		14 (5.36)		10 (5.37)
H-5(b)	15 (5.34)	11 (5.21)	12 (5.21)		22 (5.15)		17 (5.19)	17 (3.91)

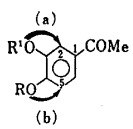
a) Irradiation position (δ) in parenthesis. In $CDCl_3$ except where otherwise indicated.
b) In acetone-d_6.
c) In acetone-d_6–$CDCl_3$ (1:1).



19—**23**, **25**, and **27**



24, **26**, and **28**



31—**36**

Table V. Cleavage of the Methylenedioxy Ring with 2 N Sodium Methoxide–Methanol in DMSO–DMF[a)]

	Starting material mg (mmol)	2 N MeONa–MeOH (ml)	DMSO (ml)	DMF (ml)	Reaction time (h)		Product[b)] mg	Yield (%)
1	458(2.0)	2.4	1.5	0.6	3	**6**	376	82
2	145(0.5)	0.6	1.0	0.4	1.5	**7**	99	68
3	75(0.5)	0.6	1.0	0.4	5	**8**	35	47
4	83(0.5)	0.6	1.0	0.4	1.5	**9**	69	82
5	938(5.0)	4.0	5.0	2.0	2	**10**	714	72
30	30(0.2)	0.9	1.0	0.4	6	**31**	13	43

a) Reactions at 150°C.
b) Isolation yield.
c) See ref. 3.

groups with nucleophilic oxide anions in DMSO can be classified into two types, ipso–attack (type A) and attack at the carbon atom of the methylenedioxy ring (Type B).[2)] The order of basicity of the nucleophiles is $MeO^- > C_6H_5CH_2O^- > C_6H_5O^-$ and the order of electron–withdrawing effects is nitro group>formyl group>acetyl group. On cleavage of the aromatic compounds (**1**—**5** and **30**) in DMSO, methoxide ion gave 3-hydroxybenzene derivatives (**6**—**10** and **31**, respectively) (Type A) and phenoxide ion gave 4-hydroxybenzene derivatives (**11**—**14** and **32**, respectively) (Type B). On cleavage of **1**—**5**, benzyloxide ion gave 3-hydroxybenzene derivatives (**19**, **22**—**24**, **26** and **27** respectively) (Type A), but in the case of **30**, it gave 3- and 4-hydroxybenzene derivatives (**33** and **34**, respectively) (Types A and B). Consequently, the regioselectivity seems to depend on both the basicity of the nucleophile and the electron–withdrawing effect of the functional groups in the aromatic compounds.

Experimental[11)]

Cleavage of 6-Bromopiperonal (1) with 1 N Sodium Benzyloxide-Benzyl Alcohol in DMSO——A mixture of **1** (229 mg, 1 mmol) and 1 N sodium benzyloxide–benzyl alcohol (1 ml) in DMSO (2 ml) was stirred at 150°C for 9 min. The reaction mixture was diluted with H_2O (25 ml) and 10% NaOH (5 ml), and washed with ether. From the ethereal solution the starting material (**1**) (131 mg) was recovered. The aqueous layer was acidified (pH 5) with conc. HCl and extracted with ether. The extract was washed with H_2O, dried, and concentrated under reduced presure. The residue was subjected to PLC using SiO_2–$CHCl_3$. Elution of the material of *Rf* 0.54 with acetone gave **19** (77 mg, 25%), mp 128—129°C (from CCl_4–$CHCl_3$).

The cleavage of **2**—**5** was carried out similarly, (Table I), and gave products **22**—**24**, and **26** plus **27**, respectively.

4-Benzyloxy-3-methoxy-6-nitrobenzaldehyde (21)——(i) From **10**:[4)] A mixture of **10** (141 mg), DMF (0.8 ml), benzyl chloride (109 mg), and K_2CO_3 (60 mg) was stirred at 100°C for 2 h. Work-up in the usual way gave **21** (186 mg, 90%), mp 132—133°C (from hexane–$CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 1670 (CHO), 1510 and 1330 (NO_2). NMR (acetone-d_6) δ: 10.40 (1H, s, CHO), 7.63 (1H, s, H-5), 7.42 (1H, s, H-2), 5.23 (2H, s, C_6H_5-CH_2O–), 4.00 (3H, s, OCH_3). High–resolution MS: Calcd for $C_{15}H_{13}NO_5$: 287.0792. Found: 287.0756.

(ii) From **27**: Compound **27** (10 mg) was dissolved in 2% NaOH (2 ml), and dimethyl sulfate (1.5 ml) and 2% NaOH (25 ml) were added at 85°C. The mixture was kept at this temperature for 1 h to give **21** (12 mg), mp 130—132°C. This compound was identical with an authentic sample prepared by procedure (i) as judged by direct comparison of their IR and NMR spectra and by the mixed melting point determination.

4-Benzyloxy-6-bromo-3-methoxybenzaldehyde (20)——(i) From **21**: To a mixture of **21** (190 mg), $FeSO_4 \cdot 7H_2O$ (2 g), and H_2O (10 ml), 25% NH_4OH (1.2 ml) was added dropwise during 5 min at 100°C. The mixture was stirred at 100°C for 5 min and filtered hot. The precipitate was extracted with acetone to give a crude amino compound. NMR ($CDCl_3$) δ: 9.56 (1H, s, CHO), 7.70 (aromatic H), 6.87 (1H, s, H-2), 6.10 (1H, s, H-5), 5.07 (2H, s, $C_6H_5CH_2O$–), 3.80 (3H, s, OCH_3). Since this product is very unstable, it was not further purified. Treatment of the crude amino compound with 20% HBr (1.5 ml) and $NaNO_2$ (69 mg) in H_2O (1 ml) followed by treatment with 47% HBr (2 ml) in the presence of CuBr [prepared from $CuSO_4 \cdot 5H_2O$ (823 mg), NaBr (680 mg), Na_2SO_3 (176 mg), and H_2O (6 ml)] gave **20** (8 mg, 4% from **21**), mp 97—99°C (from hexane–$CHCl_3$) (lit.[3)] mp 96—97°C) IR ν_{max}^{KBr} cm^{-1}: 1670 (CHO). NMR (acetone-d_6) δ: 10.15 (1H, s, CHO), 7.43 (1H, s, H-2), 7.26 (1H, s, H-5), 7.23 (2H, s, $C_6H_5CH_2O$–), 3.88 (3H, s, OCH_3). *Anal.* Calcd for $C_{15}H_{13}$-

BrO_3: C, 56.10; H, 4.08. Found: C, 56.03; H, 4.13.

(ii) From **19**: By the same procedure as for **27**, **19** (50 mg) was methylated with dimethyl sulfate (1.5 ml). The resulting product (40 mg, 77%), mp 97—99°C, was identical with an authentic sample of **20** prepared by procedure (i), as judged by the mixed melting point determination and comparison of their IR and NMR spectra.

4-Benzyloxy-6-iodo-3-methoxybenzaldehyde (**25**)——(i) From **22**: Compound **22** (20 mg) was methylated with dimethyl sulfate (1 ml) by the same procedure as for **27**. The product (**25**) (20 mg, 94%) melted at 114—115°C. IR ν_{max}^{KBr} 1670 cm^{-1}. NMR [$CDCl_3$–acetone-d_6 (1:1)] δ: 9.80 (1H, s, CHO), 7.51 (1H, s, H-5), 7.38 (1H, s, H-2), 5.23 (2H, s, $C_6H_5C\underline{H}_2O$–), 3.87 (3H, s, OCH_3). *Anal.* Calcd for $C_{15}H_{13}IO_3$: C, 48.94; H, 3.56. Found: C, 48.99; H, 3.45.

(ii) From **21**: Compound **21** (200 mg) was reduced with $FeSO_4 \cdot 7H_2O$ (3 g), H_2O (15 ml) and 25% NH_4OH (5 ml) as described above to give the crude amine (76 mg). Treatment of the amine (20 mg) in AcOH (2 ml)–H_2O (1 ml)–10% H_2SO_4 (0.7 ml) with $NaNO_2$ (7 mg) in H_2O (0.2 ml) followed by decomposition of the resulting diazonium salt with KI (128 mg) in the presence of CuI [prepared from Cu (50 mg), H_2O (0.5 ml), and I_2 (79 mg)] gave **25** (4 mg, 5% yield based on **21**), mp 113—114°C (from EtOH–acetone). The samples of **25** prepared by procedures (i) and (ii) were identical as judged by mixed melting point determination and by comparison of IR spectra.

3-Benzyloxy-6-iodo-4-methoxybenzaldehyde (**29**)——(i) From **7**: A mixture of compound **7** (60 mg) in DMF (0.5 ml), benzyl chloride (53 mg), and K_2CO_3 (35 mg) was stirred at 100°C for 2 h. Work-up in the usual way gave **29** (66 mg, 81%), mp 140—141°C (from acetone). IR ν_{max}^{KBr} 1670 cm^{-1} (CHO). NMR (acetone-d_6) δ: 9.92 (1H, s, CHO), 7.45 (1H, s, H-2), 7.40 (1H, s, H-5), 5.10 (2H, s, $C_6H_5C\underline{H}_2O$–), 3.92 (3H, s, OCH_3). *Anal.* Calcd for $C_{15}H_{13}IO_3$: C, 48.94; H, 3.56. Found: C, 48.64; H, 3.36.

From **26**: Methylation of **26** (73 mg) with dimethyl sulfate (1 ml) by the same procedure as for **27** gave **28** (32 mg, 42%), mp 128—130°C (from EtOH–acetone). IR ν_{max}^{KBr} cm^{-1}: 1680 (CHO), 1520 and 1340 (NO_2). NMR (acetone-d_6) δ: 10.32 (1H, s, CHO), 7.55 (1H, s, H-5), 7.42 (1H, s, H-2), 5.21 (2H, s, $C_6H_5C\underline{H}_2O$), 3.98 (3H, s, OCH_3). High-resolution MS: Calcd for $C_{15}H_{13}NO_5$: 287.0794. Found: 287.0788. Reduction of **28** (40 mg) with $FeSO_4 \cdot 7H_2O$ (88 mg) and 25% NH_4OH (1.5 ml) by the same procedure as for **21** gave a crude amine, which was treated with 10% H_2SO_4 (0.7 ml) and $NaNO_2$ (6.5 mg) and then with KI (128 mg) in the presence of CuI. The resulting iodo compound (**29**, 5 mg, 8% based on **28**), mp 139—141°C, was identical with a sample prepared from **7** as judged by mixed melting point determination and IR comparison.

Cleavage of 3,4-Methylenedioxyacetophenone (**30**)——(i) With Sodium Methoxide–Methanol in DMSO (A Protic Medium): A mixture of **30** (110 mg), MeONa–MeOH (0.6 ml) and DMSO (0.7 ml) was heated in a sealed tube at 190°C for 10 min. The reaction mixture was diluted with H_2O (40 ml) and 10% NaOH (10 ml), and washed with ether. From the ethereal solution, **30** (55 mg, 50%) was recovered. The aqueous solution was acidified (pH 5) with conc. HCl and extracted with ether. The extract was purified by PLC using SiO_2-[$CHCl_3$–MeOH (15:1)] to give **31** (25 mg, 22%), mp 91—93°C (from $CHCl_3$) (lit.[7] mp 67—68°C).

(ii) With Sodium Methoxide in DMSO (An Aprotic Medium): A mixture of **30** (300 mg), MeONa (180 mg), and DMSO (3 ml) was stirred at room temperature for 3 h. Work-up in the usual way gave **31** (71 mg, 24%), mp 91—93°C, and **30** (46 mg, 15%). The samples of **31** prepared by procedures (i) and (ii) were identical as judged by mixed melting point determination and by comparison of IR and NMR spectral data.

(iii) With 1.5 N Sodium Phenoxide–Phenol in DMSO (A Protic Medium): A mixture of 1 N sodium phenoxide–phenol (0.5 ml) and **30** (100 mg) in DMSO (2 ml) was heated in a sealed tube at 190—200°C for 15 min. Work-up in the usual way gave **32** (32 mg, 20%), mp 83—86°C, and **30** (64 mg, 64%).

(iv) With Sodium Phenoxide in DMSO (An Aprotic Medium): A mixture of **30** (100 mg), sodium phenoxide (85 mg), and DMSO (2 ml) was stirred at 190—200°C for 15 min. Work-up in the usual way gave **32** (48 mg, 31%) and **30** (43 mg, 43%). The samples of **32** prepared by procedure (iii) and (iv) were identical as judged by mixed melting point determination and by comparison of IR and NMR spectral data.

(v) With 1 N Sodium Benzyloxide–Benzyl Alcohol in DMSO (A Protic Medium): Compound **30** (150 mg), sodium benzyloxide (121 mg), benzyl alcohol (0.9 ml), and DMSO (1.8 ml) were stirred at 190°C for 1.5 min. Work-up in the usual way and purification by PLC using SiO_2–Al_2O_3 (1:1)-[$CHCl_3$–ethyl acetate (1:1)] gave **33** (*Rf* 0.42, 16 mg, 7%), **34** (*Rf* 0.38, 4 mg, 2%), and **30** (*Rf* 0.69, 9 mg, 6%).

4-Benzyloxy-3-methoxyacetophenone (**35**)——Compound **33** (8 mg) in MeOH (1 ml) was treated with ethereal diazomethane [prepared from *p*-toluenesulfonylmethylnitrosoamide (1.6 g)] at room temperature for 1 h. Work-up in the usual way gave **35** (6 mg, 70%), mp 85—86°C (from $CHCl_3$) (lit.[9] mp 85—87°C). IR ν_{max}^{KBr} 1680 cm^{-1}. NMR ($CDCl_3$) δ: 7.52—7.26 (7H, m, aromatic H), 6.86 (1H, d, J=8 Hz, H-5), 5.19 (2H, s, $C_6H_5C\underline{H}_2O$–), 3.89 (3H, s, OCH_3), 2.52 (3H, s, $COCH_3$). *Anal.* Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.72; H, 6.28.

3-Benzyloxymethoxy-4-methoxyacetophenone (**36**)——Treatment of **34** (2 mg) with ethereal diazomethane [prepared from *p*-toluenesulfonylmethylnitrosoamide (1.6 g)] gave **36** (1 mg, 45%), mp 79—82°C (from hexane–$CHCl_3$). IR ν_{max}^{KBr} 1960 cm^{-1} (CO). NMR ($CDCl_3$) δ: 7.30 (5H, s, aromatic H), 7.80 (1H, d, J=2 Hz, H-2), 7.64 (1H, dd, J=8, 2 Hz, H-6), 6.91 (1H, d, J=8 Hz, H-5), 5.37 (2H, s, $C_6H_5C\underline{H}_2O$–), 4.76 (2H, s, OCH_2O), 3.91 (3H, s, OCH_3), 2.52 (3H, s, $COCH_3$). *Anal.* Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34.

Found: C, 71.53; H, 6.38.

3-Ethoxy-4-methoxyacetophenone (**37**)——Treatment of **31** (30 mg) with ethereal diazoethane [prepared from *p*-toluenesulfonylethylnitrosoamide (4.5 g)] gave **37** (19 mg, 54%), mp 70—71°C (from hexane) (lit.[10] mp 70—71°C). IR ν_{max}^{KBr} 1670 cm^{-1} (CO). NMR ($CDCl_3$) δ: 7.47 (1H, dd, $J=9$, 2 Hz, H-6), 7.44 (1H, d, $J=2$ Hz, H-2), 6.79 (1H, d, $J=9$ Hz, H-5), 4.05 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 3.82 (3H, s, OCH_3), 2.46 (3H, s, CH_3CO), 1.21 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$). High-resolution MS: Calcd for $C_{11}H_{14}O_3$: 194.0942. Found: 194.0952.

Cleavage of 6-Bromopiperonal (1) with 2 N Sodium Methoxide-Methanol in DMSO-DMF——A mixture of **1** (458 mg), 2 N MeONa–MeOH (2.4 ml), DMSO (1.5 ml), and DMF (0.6 ml) was stirred at 150°C for 3 h. Work-up in the usual way gave **6** (376 mg, 82%) and unreacted **1** (60 mg, 13%). The cleavage of **2**—**5** and **30** was carried out similarly, as shown in Table V.

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References and Notes

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5) In compound **26** or **27**, a hydroxyl group is regarded as being at the 3-position, since ipso–attack by the nucleophilic benzyloxide anion at the *p*-position to the nitro group or to the formyl group gave **26** or **27**.
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11) All melting points are given as uncorrected values. The spectrophotometers used were a JEOL model JNM-PS-100 for NMR spectra (with TMS as an internal standard), a JEOL model JMS-D-300 for mass spectra, and a Hitachi model 215 for IR spectra. The plates used for preparative thin-layer chromatography (PLC) were coated with silica gel (Kieselgel, PF_{254} Merck).