[Chem. Pharm. Bull. 26(10)3113—3116(1978)]

UDC 547.729.7.04 : 547.439.04

Cleavage of the Methylenedioxy Group with Sodium Methoxide in Dimethyl Sulfoxide

Shigeru Kobayashi, Masaru Kihara, and Yoshinobu Yamahara

Faculty of Pharmaceutical Sciences, Tokushima University[1]

(Received May 1, 1978)

The methylenedioxy ring in piperonal (**1**) and its 6-substituted derivatives (**5**, **6**, **9**, and **10**) was opened by heating with sodium methoxide in dimethyl sulfoxide to give the phenolic products, isovanillin (**4**) and its 6-substituted derivatives (**7**, **8**, **11**, and **12**), respectively. Similarly, the nitro compounds (**16** and **19**) gave phenolic products (**17** and **20**, respectively) by this method. However, the ring in the compounds having methyl (compound **21**), carboxyl (compound **22**), methoxycarbonyl (compound **23**), and amide (compound **24**) groups instead of the formyl group in **1** could not be opened by this method.

Keywords——cleavage of methylenedioxy groups; sodium methoxide; dimethyl sulfoxide; piperonal; 6-substituted piperonal; isovanillin; 6-substituted isovanillin; nucleophilic substitution; inductive effect; resonance effect

There are many reports of the cleavage of the methylenedioxy group with alkaline solutions, such as potassium hydroxide in methanol,[2] sodium methoxide in methanol,[3] or sodium ethoxide in ethanol.[3] Hodgeman and Prager[4] reported that only the methylenedioxy ring in acridone derivatives was opened with sodium methoxide in dimethyl sulfoxide (DMSO).

This paper reports selective cleavage of the methylenedioxy group in piperonal derivatives and nitro compounds with sodium methoxide in DMSO. Previously, Parijs[5] reported

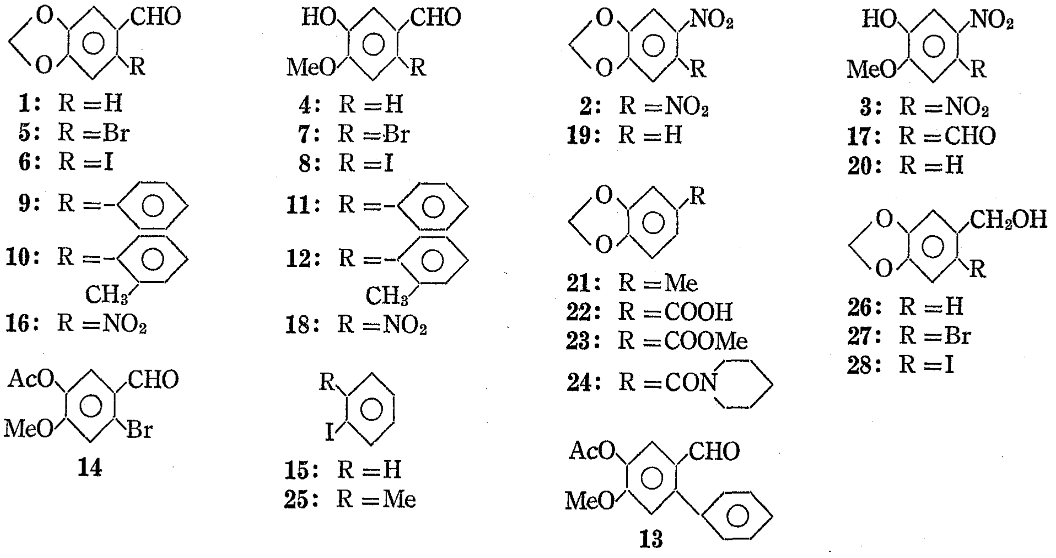

Chart 1

---

[1] Location: *1-78, Sho-machi, Tokushima, 770, Japan.*

[2] S. Hiraizumi, *Nippon Kagaku Zasshi*, **55**, 601 (1934); *idem.*, *Kogyo Kagaku Zasshi*, **34**, 584 (1931); S. Nagai, *ibid.*, **27**, 631 (1924); T. Kuwata, *ibid.*, **34**, 590 (1931).

[3] *a*) K. Ono and M. Imoto, *Nippon Kagaku Zasshi*, **59**, 359 (1938); *b*) G.M. and R. Robinson, *J. Chem. Soc.*, **1917**, 109, 929.

[4] D.K.C. Hodgeman and R.H. Prager, *Aust. J. Chem.*, **25**, 1751, 1761 (1972).

[5] A.H. Parijs, *Rec. Trav. Chim.*, 49, 33 (1930) [*C.A.*, **24**, 2445 (1930)]. In this paper he only stated that opening the methylenedioxy ring with sodium alkoxide occurred with 4,5-methylenedioxy-2-nitrochlorobenzene and 6-bromopiperonal (**5**), but gave no further details.

that the methylenedioxy ring in piperonal (**1**) could not be opened with sodium methoxide in methanol, although 1,2-dinitro-4,5-methylenedioxybenzene (**2**) gave 4,5-dinitro-2-methoxyphenol (**3**) with this reagent. However, on heating **1** (4.1 mmol) in DMSO (3 ml) with N-sodium methoxide (4.1 mmol) at 150° for 140 sec unitil the reaction mixture became brown we obtained a phenolic product, isovanillin (**4**) (13.7% yield) and unchanged **1** (60.0%). Similarly, the 6-substituted derivatives, 6-bromopiperonal (**5**)[5] and 6-iodopiperonal (**6**) gave 6-bromoisovanillin (**7**) and 6-iodoisovanillin (**8**), respectively, as shown in Table I. The latter product (**8**) is a new compound, which was identified by its elementary analysis and spectral data (see Tables II and III): on study of nuclear magnetic double resonance (NMDR), monitoring the line (δ 7.29) of C-5-H gave an NOE (intramolecular nuclear Overhauser effect) peak at δ 3.97, since irradiation at δ 3.97 (C-4-OCH_3) gave a 10% NOE increment in the signal of C-5-H.

6-Phenylpiperonal (**9**) and 6-(2-tolyl)piperonal (**10**) were similarly treated to give the new isovanillin derivatives, **11** and **12**, respectively (see Table I). The former compound

TABLE I. Cleavage of the Methylenedioxy Ring[a]

Starting material	(mg)	N-MeONa (ml)	DMSO (ml)	Reaction time (sec)	Product	(mg)	Yield (%)	By-prodyct	(mg)	Yield (%)	Recovery of starting material	(mg)	Yield (%)
1	(612)	4.1	3	140	**4**	(85)	13.7	**26**	(52)	8.4	**1**	(367)	60.0
5	(598)	2.7	3	70	**7**	(404)	67.0	**27**	(41)	6.8	**5**	(108)	18.1
6	(246)	0.9	1	80	**8**	(110)	44.4	**28**	(20)	8.1	**6**	(53)	21.5
9	(216)	1.0	1	210	**11**	(155)	71.1				**9**	(12)	5.6
10	(255)	1.1	1	210	**12**	(177)	68.8				**10**	(32)	12.5
16	(236)	1.2	1	20	**17**	(121)	50.8				**16**	(29)	12.3
19	(230)	1.4	1	35	**20**	(172)	73.9				**19**	(15)	6.5

a) Reaction temperature, 150°.

TABLE II. Phenolic Compounds

Compd.	mp (C°) (recrystn. solvent)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1} OH	CHO	NO_2
4[a]	111—112 (Benzene)	$C_8H_8O_3$	63.15	5.30		62.88	5.26		3230	1670	
7[b]	104—108 (Benzene)	$C_8H_7BrO_3$	41.59	3.05		41.80	3.06		3450	1670	
8	141—143 (Chloroform)	$C_8H_7IO_3$	34.56	2.54		34.78	2.88		3450	1680	
11	104—106 (Ether)	$C_{14}H_{12}O_3$	73.67	5.30		73.50	5.22		3430	1680	
12	98—100 (Benzene-Pentane)	$C_{15}H_{14}O_3$	74.36	5.82		74.23	5.91		3500	1670	
17[c]	207—209 (Acetic acid)	$C_8H_7NO_5$	48.74	3.58	7.10	48.43	3.59	7.05	3180	1670	1520, 1310
20[d]	103—104 (Benzene)	$C_7H_7NO_4$	49.71	4.17	8.28	49.61	4.21	8.14	3400		1510, 1350

a) R. Wegscheider, *Monatsh.*, **3**, 793 (1882).
b) H. Pauly, *Chem. Ber.*, **48**, 2010 (1915).
c) L.C. Raiforo and W.C. Stoesser, *J. Am. Chem. Soc.*, **50**, 2559 (1928).
d) L. Pauly, *Chem. Ber.*, **39**, 2779 (1906).

Table III. Chemical Shifts[a] of the Phenolic Compounds ($CDCl_3$, δ)

Compd.	Aromatic H					OCH_3	OH	CHO
	C–2	C–3	C–4	C–5	C–6			
4	7.42 (d, 2)[b]			6.95 (d, 9)	7.38 (q, 9, 2)	3.94	7.90 (bs)	9.83
7	7.43			7.00		3.92	8.31 (bs)	10.16
8	7.49			7.33		3.98	5.72	9.91
11	7.58			6.82		3.94	5.81	9.84
12	7.55			6.68		3.89	5.98 (bs)	9.56
17	7.35			7.50		3.95	10.60 (bs)	10.21
20		6.87 (d, 9)	7.83 (q, 9, 2)		7.78 (d, 2)	3.97	5.92 (bs)	

a) Signals are for singlets except for those combined with parentheses.
b) The numerical values in parentheses are coupling constants as Hz values.

(**11**) was identical with an authentic sample prepared by hydrolysis of O-acetyl-6-phenylisovanillin (**13**), which was obtained by Ullmann condensation of O-acetyl-6-bromoisovanillin (**14**) with iodobenzene (**15**). The latter compound (**12**) was identified by its elementary analysis and spectral data: on study of NMDR, monitoring the line (δ 6.69) of C-5-H gave an NOE peak at δ 3.90, since irradiation at δ 3.90 (C-4-OCH_3) gave a 15% NOE increment in the signal of C-5-H.

In the case of 6-nitropiperonal (**16**), the phenolic product was found to be 6-nitrovanillin (**17**), not 6-nitroisovanillin (**18**). Similarly, 3,4-methylenedioxynitrobenzene (**19**) gave 2-methoxy-5-nitrophenol (**20**), as reported by Robinson.[3b]

The methylenedioxy ring in the compounds having methyl (compound **21**), carboxyl (compound **22**), methoxycarbonyl (compound **23**), and amide (compound **24**) groups instead of the formyl group in **1** could not be opened by this method. In the case of **23**, an acid (**22**) was obatined in good yield.

Nucleophilic substitution with methoxide ion gave an intermediate which carries a negative charge (see Chart 2). From these findings, we concluded that a group with strong —I (inductive) and —R (resonance) effects (such as a nitro or formyl group), if located *para* to the site of attack, will stabilize the intermediate, and that the effects of a nitro group are stronger than those of a formyl group, as shown in the case of **16**. Such a group will accelerate the cleavage reaction of the methylenedioxy group.

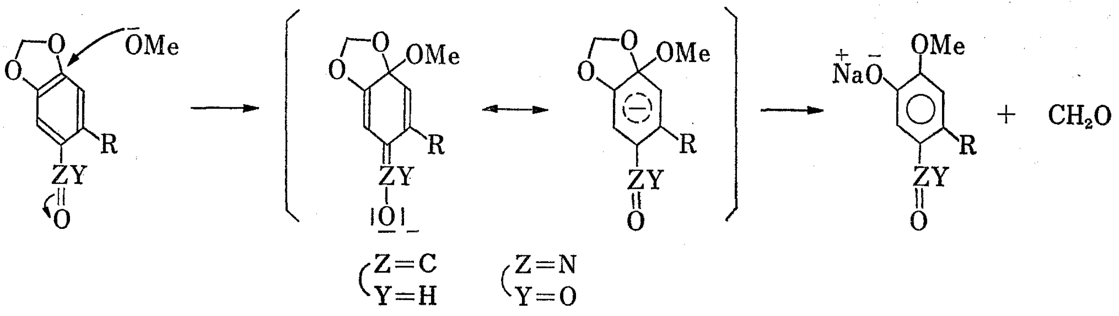

Chart 2

Experimental

All melting points are given as uncorrected values. The spectrophotometers used were a Hitachi EPI-G2 model for infrared (IR) spectra, and a JEOL JNM-PS-100 or a Hitachi R-22 model for nuclear magnetic resonance (NMR) spectra with TMS as an internal standard. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet.

Reaction of Piperonal (1) with Sodium Methoxide in DMSO——A mixture of **1** (612 mg, 4.1 mmol) in DMSO (3 ml) and N-MeONa (4.1 ml, 4.1 mmol) was stirred at 150° for 140 sec until the reaction mixture became brown. The solvent was evaporated off and the residue was diluted with H_2O (8 ml) and washed with ether. The aqueous layer was acidified with conc. HCl, extracted with ether, washed with H_2O, dried, and evaporated to give a yellow solid (281 mg). The solid was submitted to preparative thin-layer chromatography (TLC) using SiO_2-[benzene–acetone (4:1)]. Elution of the material of *Rf* 0.37—0.49 with $CHCl_3$–MeOH gave **4** as white needles (from benzene) (see Tables II and III).

The washed ethereal solution (449 mg) separated from the aqueous layer was submitted to preparative TLC using SiO_2-[benzene–acetone (4:1)]. Elution of the material of *Rf* 0.71—0.78 with $CHCl_3$ gave **1** (367 mg, 60.0%), mp 35—36°. Elution of the material of *Rf* 0.47—0.49 with $CHCl_3$–MeOH afforded piperonyl alcohol (**26**) as white needles (52 mg, 8.4%), mp 50—51° (from benzene) [lit.6) mp 51°]. *Anal.* Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.00; H, 5.09. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3450 (OH). NMR ($CDCl_3$) δ: 1.70 (1H, s, OH), 4.56 (2H, s, $C\underline{H}_2OH$), 5.92 (2H, s, OCH_2O), 6.80 (1H, d, $J=2$ Hz, C-2-H), 6.82 (1H, q, $J=2$ and 9 Hz, C-6-H), 6.83 (1H, d, $J=9$ Hz, C-5-H).

Cleavage of the methylenedioxy ring in **5**, **6**, **9**, **10**, **16**, and **19** was carried out similarly, as shown in Table I. Physical and spectral data on the products (**7**, **8**, **11**, **12**, **18**, and **20**) are summarized in Tables II and III.

In the cases of **5** and **6**, the corresponding alcohols (**27** and **28**, respectively) were obtained as by-products. The by-product (**27**) melted at 86—87° (from $CHCl_3$) [lit.7) mp 90°]. *Anal.* Calcd. for $C_8H_7BrO_3$: C, 41.59; H, 3.05. Found: C, 41.46; H, 3.04. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3200 (OH). NMR ($CDCl_3$) δ: 2.06 (1H, bs, OH), 4.62 (2H, s, $C\underline{H}_2OH$), 5.95 (2H, s, OCH_2O), 6.94 (1H, s, C-2-H), 6.96 (1H, s, C-5-H). The by-product (**28**) (mp 106—107°, from benzene) was a new compound. *Anal.* Calcd. for $C_8H_7IO_3$: C, 34.56; H, 2.54. Found: C, 34.94; H, 2.51. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3260 (OH). NMR ($CDCl_3$) δ: 2.04 (1H, bs, OH), 4.56 (2H, s, $C\underline{H}_2OH$), 5.96 (2H, s, OCH_2O), 6.98 (1H, s, C-2-H), 7.23 (1H, s, C-5-H).

6-Phenylpiperonal (9)——This compound [mp 88—90° (lit.8) mp 87°] was obtained from **5** (3 g), **15** (8 g), and copper powder (15 g) by the method reported by Spath and Kahovec.8) *Anal.* Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.24; H, 4.46. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1670 (C=O). NMR ($CDCl_3$) δ: 6.05 (2H, s, OCH_2O), 6.80 (1H, s, C-6-H), 9.75 (1H, s, CHO).

6-(2-Tolyl)piperonal (10)——A mixture of **5** (3 g), 2-iodotoluene (**25**) (8.6 g), and copper powder (7.6 g) was heated in a sealed tube at 205° for 4 hr. The reaction mixture was extracted with $CHCl_3$. The solvent was evaporated off and the residue was extracted with ether. The extract was evaporated to give a brown oil (5.62 g), which on distillation *in vacuo* afforded a yellow solid (1.624 g, 51.1% form **5**). The solid (172 mg) was submitted to preparative TLC using SiO_2-[benzene–petr. ether (3:1)]. Elution of the material of *Rf* 0.34—0.45 gave **10** as white prisms, mp 71—72° (from ether–cyclohexane). *Anal.* Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.16; H, 5.17. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1670 (C=O). NMR ($CDCl_3$) δ: 2.12 (3H, s, CH_3), 6.17 (2H, s, OCH_2O), 6.69 (1H, s, C-5-H), 7.45 (1H, s, C-2-H), 9.51 (1H, s, CHO).

3-Acetyl-6-phenylisovanillin (13)——A mixture of 3-acetyl-6-bromoisovanillin (**14**)9) (208 mg), **15** (465 mg), and copper powder (1.2 g) was heated in a sealed tube at 200° for 4 hr. The reaction mixture was extracted first with $CHCl_3$ and then ether as described for **10**. Then the residue (218 mg) was submitted to preparative TLC using SiO_2-[benzene–acetone (15:1)]. Elution of the material of *Rf* 0.41—0.55 with $CHCl_3$–MeOH gave **13** (77 mg, 37.7% based on **15**), mp 147—148° (from MeOH). *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.79; H, 5.22. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1780 and 1670 (C=O). NMR ($CDCl_3$) δ: 2.32 (3H, s, O=C–CH_3), 3.87 (3H, s, OCH_3), 6.90 (1H, s, C-5-H), 7.72 (1H, s, C-2-H), 9.83 (1H, s, CHO).

6-Phenylisovanillin (11)——A mixture of **13** (36 mg), 6% Ba(OH_2) (2.5 ml), and EtOH (2.5 ml) was refluxed for 2 hr. Working up in the usual way gave 26 mg of **11** as white cubes, mp 103—105° (from ether). This was identical with the sample obtained by treatment of **9** with MeONa in DMSO.

Acknowledgement The authors wish to express their thanks to Professor T. Shingu, Kobe Gakuin University, for NMDR spectral measurements. They also thank Miss K. Tokunaga and Miss Y. Yamaoka for technical assistance.

---

6) R. Fittig and I. Remsen, *Ann.*, **159**, 130, 138 (1971).

7) R.G. Naik and T.S. Wheeler, *J. Chem. Soc.*, **1938**, 1780.

8) E. Spath and L. Kahovec, *Chem. Ber.*, **67B**, 1501 (1934).

9) L.C. Raiford and M.F. Ravely, *J. Org. Chem.*, **5**, 204, 210, (1940).