[Chem. Pharm. Bull. 24(9)2191—2198(1976)]

UDC 547.624.04 : 547.539.3.04

Syntheses of Methylenedioxydiphenides and Dimethoxydiphenides[1)]

SHIGERU KOBAYASHI, SATOSHI MINEO, MASARU KIHARA,
and SUSUMU TAGASHIRA

Faculty of Pharmaceutical Sciences, Tokushima University[2)]

(Received January 5, 1976)

Methylenedioxydiphenides (IIa and IIIa) and dimethoxydiphenides (IIb, c and IIIb, c) were prepared from unsymmetrical diphenaldehydes (IVa—c) by intramolecular Cannizzaro reactions and then lactonization of the resulting alcoholic acids (Va—c and VIa—c). The structures of IIa—c and IIIa—c were confirmed by comparison of physical and spectral data of these compounds with those of authentic samples prepared by unambiguous methods. The directions of the two kinds of intramolecular Cannizzaro reactions of IV to form V and VI are discussed.

In the previous paper in this series we reported[3)] that 6-(β-bromoethyl)-10,11-methylenedioxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (DA-VIII-MBr) has a more specific α-adrenergic blocking action than dibenamine or phenoxybenzamine. Diphenides are key intermediates in the syntheses of dibenz[*c*,*e*]azocines.

Recently we reported[4)] the preparations of diphenide (Ia) and its methoxyl derivatives (Ib—d) by two methods: (i) intramolecular Cannizzaro reactions of symmetrical diphenaldehydes, followed by lactonization of the resulting products, and (ii) partial reduction of monomethyl diphenates with sodium borohydride.

There are several reports on the intramolecular Cannizzaro reaction[5)] of symmetrical diphenaldehydes but none on the reaction of unsymmetrical ones.

This paper reports the preparation of diphenide (IIa) and new diphenides (IIb, c and IIIa—c) from unsymmetrical diphenaldehydes (IVa—c) by intramolecular Cannizzaro reactions and then lactonization of the resulting alcoholic acids (Va—c and VIa—c). The structures of IIa—c and IIIa—c were confirmed by comparison of physical and spectral data of these compounds with those of authentic samples prepared by unambiguous methods. Furthermore, the ratios of II to III in the reaction mixtures of the Cannizzaro reactions were estimated by nuclear magnetic resonance (NMR) and ultraviolet (UV) spectral analyses.

Syntheses of Diphenaldehydes (IVa—c)

4,5-Methylenedioxydiphenaldehyde (IVa), mp 94—95.5°, was prepared by Ullmann condensation of 6-bromopiperonal (VII) and 2-iodobenzaldehyde (VIII) in the presence of copper bronze in a sealed tube. The best yield (30.5% based on VII) of IVa was obtained when the VII/VIII molar ratio was 1/3 and dimethylformamide (DMF) was used as solvent, as shown in Table I. Condensation of VII and 2-bromobenzaldehyde (IX) (molar ratio, 1/3) gave IVa in 31.5% yield when carried out at 200° in the absence of the solvent (see Table II).

Using the same method as with IVa, 5,6-dimethoxydiphenaldehyde (IVb), mp 95—100°, was obtained from 2-bromoveratraldehyde (X) and VIII in 16.5% yield (based on X) and

---

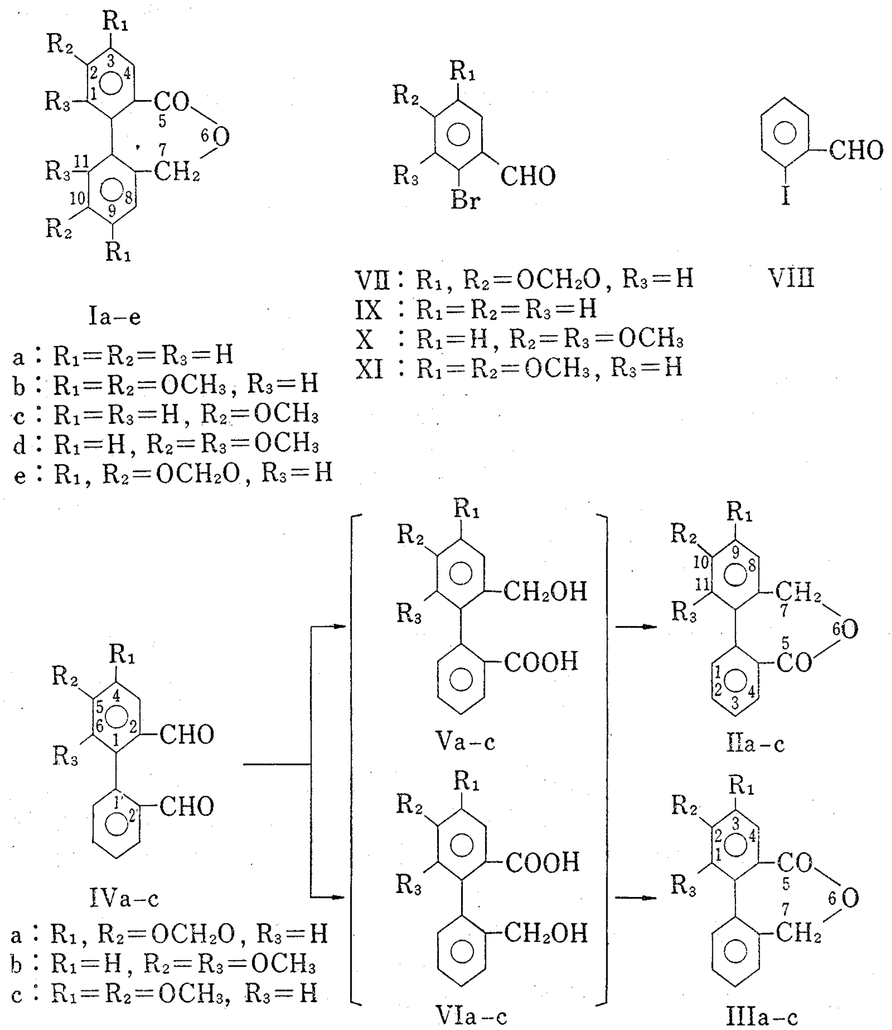
1) This forms Part XIII[3)] of "Studies on the Syntheses of Benzoheterocyclic Compounds" by S. Kobayashi.

2) Location: *1-78, Sho-machi, Tokushima, 770, Japan.*

3) Part XII: S. Kobayashi, M. Kihara, K. Yamasaki, Y. Ishida, and K. Watanabe, *Chem. Pharm. Bull.* (Tokyo), **23**, 3036 (1975).

4) S. Kobayashi, F. Senoo, M. Kihara, and A. Miura, *Chem. Pharm. Bull.* (Tokyo), **19**, 1262 (1971).

5) J. Kenner and E.G. Turner, *J. Chem. Soc.*, **99**, 2101 (1911); M.G. Sturrock, E.L. Cline, and K.R. Robinson, *J. Org. Chem.*, **28**, 2340 (1963); E. Matarasso-Tchiroukhine, *Ann. Chim.* (Paris), **3**, 405 (1958).



Ia–e

a : $R_1=R_2=R_3=H$
b : $R_1=R_2=OCH_3$, $R_3=H$
c : $R_1=R_3=H$, $R_2=OCH_3$
d : $R_1=H$, $R_2=R_3=OCH_3$
e : R_1, $R_2=OCH_2O$, $R_3=H$

VII : R_1, $R_2=OCH_2O$, $R_3=H$
IX : $R_1=R_2=R_3=H$
X : $R_1=H$, $R_2=R_3=OCH_3$
XI : $R_1=R_2=OCH_3$, $R_3=H$

VIII

IVa–c

a : R_1, $R_2=OCH_2O$, $R_3=H$
b : $R_1=H$, $R_2=R_3=OCH_3$
c : $R_1=R_2=OCH_3$, $R_3=H$

Va–c

VIa–c

IIa–c

IIIa–c

Chart 1

Table I. Ullmann Condensation[a] of VII with VIII

Molar ratio VII	Molar ratio VIII	Solvent	Temp. (°C)	Reaction product (%) IVa[b]	XXI[c]	XXII[d]
1	1.5	—	200	5.2	19.1	8.6
1	3	—	220	16.3	23.7	—
1	3	$C_6H_5NO_2$	220	trace	28.4	—
1	3	DMF	170	30.5	34.0	10.1

a) The molar ratio of VII to Cu was 1/10. The reaction time was 2.5—3 hr.
b) The yield is based on VII.
c) This compound is diphenaldehyde and its yield is calculated based on VIII.
d) This compound is 4,5,4',5'-bis(methylenedioxy)diphenaldehyde and its yield is based on VII.

Table II. Ullmann Condensation[a] of VII with IX

Molar ratio VII	Molar ratio IX	Reaction product (%) IVa[b]	XXI[c]	XXII[d]
1	1.14	11.1	11.8	7.5
1	1.25	12.2	19.3	5.6
1	1.57	17.4	—	6.7
1	3.00	31.5	5.5	—

a) The reaction temperature was 200° and the reaction time was 4 hr.
b, *c*, and *d*) These yields are based on VII, IX, and VII, respectively.

4,5-dimethoxydiphenaldehyde (IVc), mp 107.5—108°, was prepared from 6-bromoveratraldehyde (XI) and VIII in 17.1% yield (from XI).

These diphenaldehydes (IVa—c) were identified by elemental analysis and by their infrared (IR) and NMR spectra, as shown in Table III.

TABLE III. Diphenaldehydes

Compd. No.	IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}		NMR (CDCl$_3$, τ)		Formula	Analysis (%)			
						Calcd.		Found	
	2-CHO	2′-CHO	2-CHO	2′-CHO		C	H	C	H
IVa	1670	1690	0.42	0.09	$C_{15}H_{10}O_4$	70.86	3.96	70.75	3.93
IVb	1680	1695	0.44	0.18	$C_{16}H_{14}O_4$	71.10	5.22	70.88	5.25
IVc	1675	1690	0.38	0.14	$C_{16}H_{14}O_4$	71.10	5.22	71.39	5.15

Alternative Syntheses of Diphenides (IIa—c and IIIa—c)

Very recently we reported[6] the preparation of 9,10-methylenedioxydiphenide (IIa) from methyl 2′-formyl-4′,5′-methylenedioxy-2-biphenylcarboxylate (XIIa).

10,11-Dimethoxydiphenide (IIb), mp 161.5—163°, was prepared by partial reduction of methyl 5′,6′-dimethoxy-2′-formyl-2-biphenylcarboxylate (XIIb)[7] with sodium borohydride in methanol in 76.5% yield. Similarly, 9,10-dimethoxydiphenide (IIc) (mp 158—160°), 2,3-methylenedioxydiphenide (IIIa) (mp 173—174°), and 2,3-dimethoxydiphenide (IIIc) (mp 197—198°), respectively were obtained from methyl 4′,5′-dimethoxy-2′-formyl-2-biphenylcarboxylate (XIIc)[7] in 84.9% yield, from methyl 2′-formyl-4,5-methylenedioxy-2-biphenylcarboxylate (XIIIa)[7] in 82.5% yield, and from methyl 4,5-dimethoxy-2′-formyl-2-biphenylcarboxylate (XIIIb)[7] in 90.4% yield.

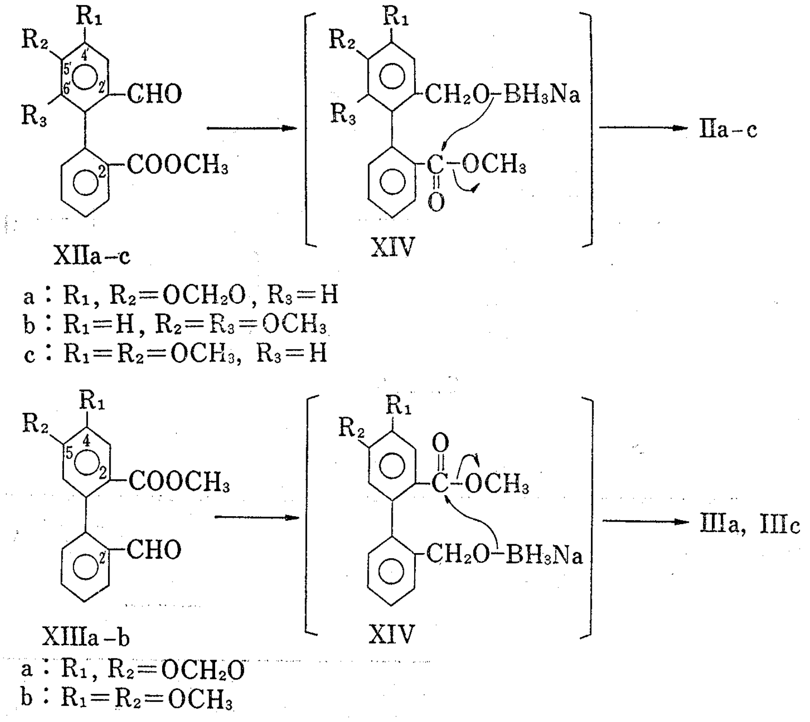


Chart 2

---

[6] S. Kobayashi, M. Kihara, T. Hashimoto, and T. Shingu, *Chem. Pharm. Bull.* (Tokyo), **24**, 716 (1976).

[7] The preparations of these new compounds will be reported elsewhere.

These diphenides (IIa—c, IIIa, and IIIc) were obtained directly from the respective reduction mixtures. These results indicate direct cyclization of the intermediates which are probably boron complexes (XIV) (see Chart 2) to the desired lactones.

On the other hand, IIIa was also prepared as follows: methyl 2'-methyl-4,5-methylenedioxy-2-biphenylcarboxylate (XV), mp 74—75°, was prepared by Ullmann condensation of methyl 6-bromopiperonylate (XVI) with 2-iodotoluene (XVII) in 58% yield based on XVI. The ester (XV) was brominated with N-bromosuccinimide (NBS) to give bromomethyl-ester (XVIII) as an oil in 64% yield. The ester (XVIII) was hydrolyzed with potassium hydroxide and cyclized to lactone (IIIa) in acidic medium in 50% yield (from XVIII). 1,2-Dimethoxydiphenide (IIIb), mp 141—142°, was prepared *via* 5,6-dimethoxy-2'-methyl-2-biphenylcarbaldehyde (XIX). The aldehyde (XIX) was obtained in good yield (53.1%) by Ullmann condensation of X with XVII. Bromination of XIX with NBS, accompanied by oxidation of the formyl group in XIX, gave bromomethyl-acid (XX), which was hydrolyzed with potas-

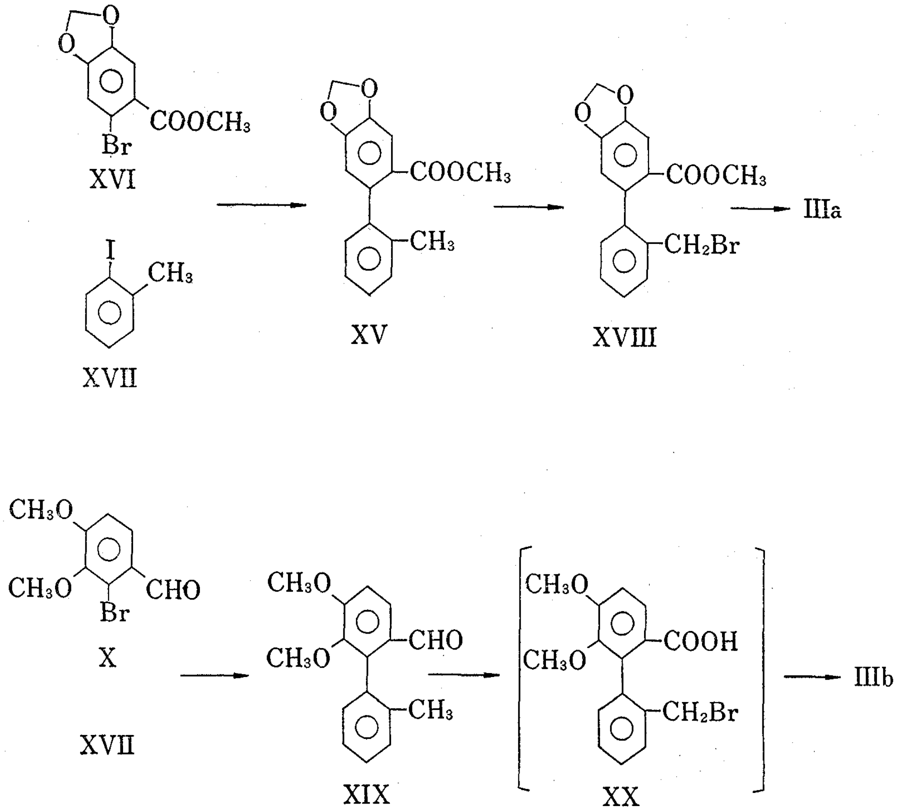


Chart 3

Table IV. Diphenides

Compd. No.	IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}		NMR ($CDCl_3$) C-7-CH_2 (τ)	Formula	Analysis (%)			
					Calcd.		Found	
	C=O	CH_2			C	H	C	H
IIa	1710	1375	5.16	$C_{15}H_{10}O_4$	70.86	3.96	70.70	3.92
IIb	1720	1375	5.12	$C_{16}H_{14}O_4$	71.10	5.22	71.04	5.28
IIc	1705	1375	5.06	$C_{16}H_{14}O_4$	71.10	5.22	71.20	5.30
IIIa	1690	1385	5.05	$C_{15}H_{10}O_4$	70.86	3.96	70.51	3.86
IIIb	1715	1370	5.06	$C_{16}H_{14}O_4$	71.10	5.22	71.11	5.25
IIIc	1690	1380	5.02	$C_{16}H_{14}O_4$	71.10	5.22	71.14	5.42

sium hydroxide and then cyclized to lactone (IIIb) with hydrochloric acid in 22.2% yield (from XIX). These diphenides (IIa—c and IIIa—c) were identified by elemental analyses, and IR and NMR spectral data (see Table IV). The IR spectra of these compounds showed strong bands at near 1380 cm^{-1}, which are characteristic of diphenides.[4]

Intramolecular Cannizzaro Reaction of Diphenaldehydes (IVa—c)

Diphenaldehyde (IVa) was refluxed with 10% aqueous potassium hydroxide in ethanol to give two alcoholic acids (Va and VIa), which were cyclized with hydrochloric acid to afford a mixture of IIa and IIIa in 72.8% yield (from IVa). Compounds, IIa and IIIa, were isolated from the reaction mixture by preparative thin-layer chromatography (TLC) and identified by direct comparison with authentic samples. The ratio of IIa to IIIa in the mixture was calculated as 52.3/47.7 by UV spectrometry following the method of Oota, *et al.*,[8] and as 56.3/43.7 from the integral values of C-7 methylene protons of IIa and IIIa in the NMR spectrum of the mixture. Similar results were obtained on the Cannizzaro reaction of IVb, c, as shown in Table V. If lactonization of the two alcoholic acids, Va—c and VIa—c, proceeded quantitatively, the ratios of II to III should show the directions of two Cannizzaro reactions in the formations of Va—c and VIa—c, respectively. The ratios in Table V, show that the 2′-formyl group in IVa—c was more reactive than the 2-formyl group with an electron donating group in the *para*-position, which may be reflecting the mechanism of Cannizzaro reaction that the rate determining step is hydride transfer.

Table V. II/III Ratio in the Reaction Mixture from the Cannizzaro Reaction of IVa—c

Starting material IV	Analytical method	Product distribution (%) II	III
a	UV	52.3	47.7
	NMR	56.3	43.7
b	UV	60.4	39.6
	NMR	53.7[a]	46.3[a]
c	UV	53.9	46.1
	NMR	52.9	47.1

a) This ratio was determined using integral values for the C-1-H protons of IIb and IIIb.

These findings are consistent with spectral data on IVa—c (see Table III). The reactivities of 2′-formyl groups in IVa—c for nucleophilic agents are greater than those of 2-formyl groups, because the carbonyl absorption bands of 2′-formyl groups in the IR spectra of IVa—c are at higher frequencies than those of 2-formyl groups and the signals of 2′-formyl protons in the NMR spectra of IVa—c are 0.24—0.33 ppm downfield from those of 2-formyl protons.

The Chemical Shifts of Aromatic Protons in Diphenides

From studies on nuclear magnetic double resonance (NMDR), the signals of aromatic protons in 2,3,9,10-bis(methylenedioxy)diphenide (Ie),[7] 1,2,10,11-tetramethoxydiphenide (Id),[4] and 2,3,9,10-tetramethoxydiphenide (Ib)[4] were assigned as shown in Table VI. The chemical shifts of C-1-H, C-4-H, C-8-H, and C-11-H in Ie were found to be identical with those of C-1-H and C-4-H in IIIa, and of C-8-H and C-11-H in IIa, respectively. These results show that the methylenedioxy group on one benzene ring in Ie does not affect the chemical

---

[8] E. Oota, S. Nakajima, and S. Nakagami, *Yakugaku Kenkyu*, **28**, 819 (1956).

TABLE VI. NMR Spectra of Diphenides

Compd.	Aromatic proton ($CDCl_3$, τ)					
	C-1-H	C-3-H	C-4-H	C-8-H	C-9-H	C-11-H
IIa				3.11		2.97
IIIa	3.03		2.63			
Ie	3.07		2.62	3.11		3.00
IIb				2.85[a]	3.08[a]	
IIIb		2.95[a]	2.30[a]			
Id		2.96[a]	2.39[a,b]	2.86[a]	3.08[a]	
IIc				3.06		2.89
IIIc	3.00		2.54			
Ib	3.02		2.55	3.06		2.93

a) These signals are doublets ($J=9$ Hz) and other signals are singlets.
b) This value differs from that of the corresponding signal in IIIb.

shift of the protons of the other benzene ring. The same phenomena were also observed when substituents were mono-methoxy and two methoxy groups.

Antimicrobial Activities of Diphenides

The antimicrobial activities of diphenides, Ia—e, IIa—c, and IIIa—c were measured by the agar dilution method using nutrient agar for bacteria. Compound Ia inhibited the growth of *Staphylococcus aureus* 209P and *Escherichia coli* NIHJ at a concentration of 100 μg/ml. Compound IIb exhibited weak antibacterial activity against gram-positive bacteria at a concentration of 100 μg/ml.

Experimental[9]

4,5-Methylenedioxydiphenaldehyde (IVa)——(i) A mixture of VII (10.59 g), VIII (32.05 g), Cu bronze (35.84 g), and DMF (37.78 g) was heated in a sealed tube at 170° for 3 hr. The reaction mixture was taken up in $CHCl_3$ and the solvent was evaporated off under N_2 *in vacuo*. The residue (21.82 g) was extracted with ether. Concentration of the extract gave crude 4,5,4′,5′-bis(methylenedioxy)diphenaldehyde (XXII). The mother liquor of XXII were evaporated and fractionally distilled under vacuum. Five fractions were collected: (a) bp 43—90° (0.01 mmHg) (1.868 g): (b) 78—120° (0.01 mmHg) (7.381 g): (c) 96—113° (0.02 mmHg) (244 mg): (d) 115—145° (0.02 mmHg) (7.286 g): and (e) a residue. Fraction (a) gave piperonal and VII by crystallization. On trituration with ether fraction (b) gave diphenaldehyde (XXI) (4.942 g, 34.0% based on VIII) as white plates, mp 63.5—64° (lit. mp 62°,[10] mp 63°[11]). Mass Spectrum *m/e*: 210 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). NMR ($CDCl_3$) τ: 2.71—2.62 (2H, m, C-6-H and C-6′-H), 2.50—2.27 (4H, m, aromatic H), 1.90—1.89 (2H, m, C-3-H and C-3′-H), 0.15 (2H, s, CHO × 2). *Anal.* Calcd. for $C_{14}H_{10}O_2$: C, 79.98; H, 4.78. Found: C, 80.11; H, 4.64. Fraction (c) was found to be a mixture of XXI and IVa by TLC and was not investigated further. On triturated with ether fraction (d) gave white plates of IVa (3.581 g, 30.5% from VII), mp 94—94.5° (from ether). Mass Spectrum *m/e*: 254 (M^+). IR ν_{max}^{KBr} cm^{-1}: 918 (OCH_2O). NMR ($CDCl_3$) τ: 3.25 (1H, s, C-6-H), 2.71—2.61 (1H, m, C-6′-H), 2.51 (1H, s, C-3-H), 2.44—2.34 (2H, m, C-4′-H and C-5′-H), 2.00—1.89 (1H, m, C-3′-H). Fraction (e) gave XXII. The crude XXII fractions were combined and XXII (732 mg, 10.1% from VII) was obtained by recrystallization from ethyl acetate as white plates, mp 237—238° (lit.[12] mp 238—240°). Mass Spectrum *m/e*: 298 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1675 (C=O), 925 (OCH_2-O). NMR ($CDCl_3$) τ: 3.90 (4H, s, $OCH_2 \times 2$), 3.26 (2H, s, C-6-H and C-6′-H), 2.54 (2H, s, C-3-H and C-3′-H), 0.36 (2H, s, CHO × 2). *Anal.* Calcd. for $C_{16}H_{10}O_6$: C, 64.43; H, 3.38. Found: C, 64.50; H, 3.32.

---

9) All melting points are given as uncorrected values. The spectrophotometers used were a Hitachi, EPI-G2 model for IR spectra, a Hitachi, 124 model for UV spectra, and a JEOL, JNM-PS-100 or a Hitachi, R-22 model for NMR spectra using TMS as an internal standard. Chemical shifts are reported as τ values. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.
10) R.G.R. Bacon and W.S. Lindsay, *J. Chem. Soc.*, **1958**, 1375.
11) W.S. Rapson and R.G. Shuttleworth, *J. Chem. Soc.*, **1941**, 487.
12) T. Ikeda, W.I. Taylor, Y. Tsuda, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, **1956**, 4749.

(ii) A mixture of VII (1.002 g), IX (2.443 g), and Cu bronze (3.331 g) was heated in a sealed tube at 200° for 4 hr. The reaction mixture was treated by the same procedure as for IVa (i) and gave piperonal (235 mg), XXI (146 mg, 5.5% from IX), and IVa (510 mg, 31.5% from VII), mp 89—90°

5,6-Dimethoxydiphenaldehyde (IVb)——A mixture of X (600 mg), VIII (1.7 g), and Cu bronze (1.9 g) in DMF (2.5 ml) was heated in a sealed tube at 170° for 3 hr. The reaction mixture was treated by the same procedure as for IVa (i). A fraction, bp 90—100° (0.5 mmHg) (109 mg, 16.5% from X) gave IVb as white prisms, mp 95—100° (from ether). NMR ($CDCl_3$) τ: 6.53 (3H, s, C-6-OCH_3), 6.04 (3H, s, C-5-OCH_3), 2.89 (1H, d, $J=9$ Hz, C-4-H), 2.70 (1H, m, C-6'-H), 2.38 (2H, m, C-4'-H and C-5'-H), 2.15 (1H, d, $J=9$ Hz, C-3-H), 1.93 (1H, m, C-3'-H).

4,5-Dimethoxydiphenaldehyde (IVc)——Crude IVc (391 mg), prepared by Ullmann condensation of XI (600 mg) and VIII (1.7 g) in DMF (2.5 ml) in the presence of Cu bronze (1.9 g) by a similar method to that for preparation of IVa (i), was recrystallized from ether to give IVc (227 mg, 17.1% from XI) as white prisms, mp 106—107°. NMR ($CDCl_3$) τ: 6.11 (3H, s, C-4-OCH_3), 6.05 (3H, s, C-5-OCH_3), 3.27 (1H, s, C-6-H), 2.56—2.24 (3H, m, aromatic H), 2.47 (1H, s, C-3-H), 1.96 (1H, m, C-3'-H).

9,10-Methylenedioxydiphenide (IIa)⁶⁾——NMR ($CDCl_3$) τ: 4.01 (2H, s, OCH_2O), 2.68—2.30 (3H, m, C-1-H—C-3-H), 2.10 (1H, m, C-4-H). UV λ_{max}^{EtOH} nm (log ε): 270 (3.76), 305 (3.84).

10,11-Dimethoxydiphenide (IIb)——A mixture of XIIb⁷⁾ (305 mg), $NaBH_4$ (300 mg), and MeOH (15.3 ml) was stood overnight at room temperature. After removal of the solvent and addition of H_2O, the mixture was extracted with benzene. The extract was washed with H_2O, dried, and evaporated to give IIb (210 mg, 76.5%) as white prisms, mp 161.5—163° (from benzene). Mass Spectrum *m/e*: 270 (M^+). NMR ($CDCl_3$) τ: 6.52 (3H, s, C-11-OCH_3), 6.12 (3H, s, C-10-OCH_3), 2.64—2.30 (3H, m, C-1-H—C-3-H), 2.08 (1H, m, C-4-H). UV λ_{max}^{EtOH} nm (log ε): 220 (4.57), 287 (3.67).

9,10-Dimethoxydiphenide (IIc)——A mixture of XIIc⁷⁾ (140 mg), $NaBH_4$ (140 mg), and MeOH (4 ml) was stood overnight at room temperature. The resulting precipitate was recrystallized from benzene–petr. ether to afford IIc (107 mg, 84.9%) as white needles, mp 158—160°. NMR ($CDCl_3$) τ: 6.07 (6H, s, $OCH_3 \times 2$), 2.64—2.32 (3H, m, C-1-H—C-3-H), 2.04 (1H, m, C-4-H). UV λ_{max}^{EtOH} nm (log ε): 268 (3.95), 301 (3.83).

2,3-Dimethoxydiphenide (IIIc)——In a similar manner, a mixture of XIIIb⁷⁾ (150 mg), $NaBH_4$ (150 mg), and MeOH (6 ml) gave IIIc (122 mg, 90.4%) as white needles, mp 197—198° (from MeOH). NMR ($CDCl_3$) τ: 6.10 (6H, s, OCH_3), 2.62—2.34 (4H, m, C-8-H, C-11-H). UV λ_{max}^{EtOH} nm (log ε): 246 (4.41), 282 (4.02).

2,3-Methylenedioxydiphenide (IIIa)——(i) Similarly, white prisms of IIIa (mp 173—174°) (from ether) were obtained in 82.5% yield (33 mg) from a mixture of XIIIa⁷⁾ (45 mg), $NaBH_4$ (50 mg), and MeOH (4 ml). NMR ($CDCl_3$) τ: 3.96 (2H, s, OCH_2O), 2.70—2.40 (4H, aromatic H). UV λ_{max}^{EtOH} nm (log ε): 243 (4.37), 285 (3.90).

(ii) A mixture of XV (100 mg), NBS (65.9 mg), CCl_4 (2 ml), and benzoyl peroxide (2 mg) was refluxed for 2 hr. NBS (33 mg) and benzoyl peroxide (2 mg) were added to the reaction mixture twice more at 2 hr intervals. After removal of succinimide and addition of H_2O, the mixture was extracted with ether, and the extract was washed with H_2O, dried, and evaporated. The residue was purified by preparative TLC using SiO_2–benzene to obtain methyl 2'-bromomethyl-4,5-methylenedioxy-2-biphenylcarboxylate (XVIII) (83 mg, 64%) as an oil. IR ν_{max}^{KBr} cm^{-1}: 1725 (C=O). NMR ($CDCl_3$) τ: 6.49 (3H, s, $COOCH_3$), 5.84 and 5.68 (each 1H, d, $J=10$ Hz, CH_2Br), 3.96 (2H, s, OCH_2O), 3.25 (1H, s, C-6-H), 3.10—2.50 (4H, m, aromatic H), 2.53 (1H, s, C-3-H).

The bromide XVIII (74 mg) was refluxed with 15% EtOH–KOH (30 ml) for 2 hr. The EtOH was evaporated off and the aqueous mixture was washed with ether and acidified with conc. HCl. The acidic solution was heated at 95° for 20 min, and then extracted with ether. The extract was washed with 2% Na_2CO_3, dried, and evaporated. The residue gave IIIa (28 mg, 50% from XV) as white cubes, mp 173—174° (from ether). The diphenide (IIIa) obtained by method (i) was identical with the sample prepared from XV by method (ii).

Methyl 2'-methyl-4,5-Methylenedioxy-2-biphenylcarboxylate (XV)——A mixture of XVI (3 g), XVII (5.7 g), and Cu bronze (4.8 g) was heated in a sealed tube at 205° for 4 hr. The reaction mixture was taken up in $CHCl_3$ and the solution was evaporated. The residue was mixed with ether giving a white precipitate which was recrystallized from MeOH to afford dimethyl 4,5,4',5'-bis(methylenedioxy)diphenate (34 mg), as white needles, mp 158—159° (lit.¹²⁾ 155—157°). NMR ($CDCl_3$) τ: 6.34 (6H, s, $OCH_3 \times 2$), 3.90 (4H, s, $OCH_2O \times 2$), 3.34 (2H, s, C-6-H and C-6'-H), 2.47 (2H, s, C-3-H and C-3'-H). *Anal.* Calcd. for $C_{18}H_{14}O_8$: C, 60.34; H, 3.94. Found: C, 60.51; H, 4.02. The ethereal solution separated from the white precipitate was evaporated and fractionally distilled under vacuum to give a fraction, bp 80—100° (0.07 mmHg). This was crystallized from ether to give XV (2.067 g, 57.9% from XVI) as colorless prisms, mp 74—75°. IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O). NMR ($CDCl_3$) τ: 7.96 (3H, s, C-2'-CH_3), 6.48 (3H, s, $COOCH_3$), 3.98 (2H, s, OCH_2O), 3.38 (1H, s, C-6-H), 3.08—2.72 (4H, m, aromatic H), 2.56 (1H, s, C-3-H). *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.17; H, 5.07.

2'-Methyl-5,6-dimethoxy-2-biphenylcarbaldehyde (XIX)——A mixture of X (1 g), XVII (1.8 g), and Cu bronze (1.6 g) was heated in a sealed tube at 205° for 4 hr. The reaction mixture was treated by the same procedure as for XV to afford a fraction, bp 60—120° (0.5 mmHg), from which XIX (552 mg, 53.1% from X) was obtained as white prisms, mp 107—109° (from ether). IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O). NMR ($CDCl_3$) τ: 7.94 (3H, s, C-2'-CH_3), 6.52 (3H, s, C-6-OCH_3), 6.07 (3H, s, C-5-OCH_3), 2.96 (1H, d, $J=8$ Hz, C-4-H), 2.92—

2.64 (4H, m, aromatic H), 2.18 (1H, d, $J=8$ Hz, C-3-H). *Anal.* Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.00; H, 6.27.

1,2-Dimethoxydiphenide (IIIb)——White needles of IIIb (mp 141—142°) (from ether) were obtained in 22.2% yield (24 mg) from a mixture of XIX (100 mg), NBS (139 mg), benzoyl peroxide (5 mg), and CCl_4 (2 ml) by a similar method to that for preparation of IIIa (ii). NMR ($CDCl_3$) τ: 6.49 (3H, C-1-OCH_3), 6.07 (3H, s, C-2-OCH_3) 2.57 (4H, m, C-8-H, C-11-H). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (log ε): 242 (4.52), 295 (3.47).

Intramolecular Cannizzaro Reaction of IVa——A mixture of IVa (50 mg), 10% KOH (5 ml), and EtOH (5 ml) was refluxed for 1 hr. The EtOH was evaporated off. The residue was diluted with H_2O, washed with ether, and acidified with conc. HCl. The mixture was heated at 95° for 30 min. The reaction mixture was extracted with ether and the extract was evaporated to give white crystals (36.4 mg, 72.8%). The crystals (32.3 mg) was submitted to preparative TLC using SiO_2–benzene. Elution of material with an *Rf* of 0.35—0.4 with $CHCl_3$–benzene gave IIa (20 mg), mp 149—151° (from ether). Material with an *Rf* of 0.45—0.5 was eluted with $CHCl_3$–benzene. The eluate afforded IIIa (9 mg, mp 173—174°) (from ether).

The ratio of IIa to IIIa in the crude crystals (the reaction mixture) was determined by UV spectral analysis as described by Oota, *et al.*[8]: the concentrations (C) of IIa and IIIa in the reaction mixture (the ratio of IIa to IIIa) were calculated using equation (1) from the absorbance (E) at each wave-length of the reaction mixture and the absorptivity (K) at each wave-length of standard samples of IIa and IIIa (these values are summarized in Table VII).

$$E_{(\mathrm{mixture})} = K_{\mathrm{IIa}}C_{\mathrm{IIa}} + K_{\mathrm{IIIa}}C_{\mathrm{IIIa}} \quad \text{-------------} \quad (1)$$

TABLE VII. UV Spectra of Diphenides

Type	Wave-length (nm)	Absorptivity ($k\times10^{-5}$)		Absorbance (E) of the reaction mixture
		II	III	
a	245	29.61	90.80	0.334
	280	20.60	30.20	0.143
b	220	138.67	55.07	0.707
	245	41.33	118.22	0.480
c	250	32.40	88.25	0.520
	285	22.67	38.50	0.268

Intramolecular Cannizzaro Reaction of IVb——Compound IVb (132 mg) was treated by a similar procedure to that described for the Cannizzaro reaction of IVa to give a reaction mixture (112 mg, 84.9% from IVb). IIb (12 mg) and IIIb (7 mg) were obtained from the reaction mixture (46 mg) by preparative TLC. The ratio of IIb to IIIb in the mixture was calculated in the same method as that in the mixture from IVa from the results of UV spectral analysis.

Intramolecular Cannizzaro Reaction of IVc——In a similar manner, IVc (50 mg) was converted to a mixture (40 mg, 80.2% from IVc) of IIc and IIIc, from 18 mg of which IIc (6 mg) and IIIc (4 mg) were obtained. The ratio of IIc to IIIc was calculated like that of IIa to IIIa from UV spectral analysis.

Acknowledgement The authors wish to express their thanks to Mr. M. Ozaki, Research Laboratories, Nippon Shinyaku Co. Ltd. for carrying out the antibacterial tests and to Professor T. Shingu, Kobe Gakuin University, for NMDR spectral measurements. They also thank Mrs. F. Senoo, Mr. S. Miki, and Mr. H. Yamamoto for technical assistance.