[Chem. Pharm. Bull. 17(1) 89—93 (1969)]

UDC 547.563.3.04

The Reimer-Tiemann Reaction of *m*-Halophenols. II.[1] With *m*-Bromophenol[2]

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(Received April 30, 1968)

In contrast to results in the literature reported by Hodgson and Jenkinson the Reimer–Tiemann reaction of *m*-bromophenol yielded four products. Three of these were shown unambiguously to be 2-bromo-4-hydroxybenzaldehyde, 4-, and 6-bromosalicylaldehydes. The other product was assigned to be bromoformylhydroxybenzaldehyde.

In the previous paper,[1] we reported that three isomers of hydroxyiodobenzaldehyde were isolated in the Reimer–Tiemann reaction with *m*-iodophenol.

In the synthesis of dibenzoheterocyclic compounds, 2-bromo-4-hydroxybenzaldehyde (I) reported by Hodgson, *et al.*[4] was necessary as a starting material. These authors claimed that aldehyde (I), mp 159.5°, and 4-bromosalicylaldehyde (II), mp 52°, were obtained in almost equal quantities by the Reimer–Tiemann reaction with *m*-bromophenol, but no conclusive evidence was given for the assigned orientation of the formyl group introduced into these compounds.

To obtain aldehyde (I) and to determine the position of the formyl group introduced into these products, we reinvestigated the Reimer–Tiemann reaction with *m*-bromophenol under the conditions described by the above authors. On repetition of the reaction, a major product, I (mp 156.5—158°), and three minor ones, II (mp 50—51.5°), 6-bromosalicylaldehyde (III)[5] (mp 51—52°), and a new dialdehyde (IV) ($C_8H_5O_3Br$, mp 143—145°), were isolated, together with the starting material. Their structures were suggested by spectral examination and confirmed by chemical evidence.

In the NMR spectrum of III, as shown in Table I, the formyl proton peak was shifted downfield by the proximity effect[6] of the bromo substituent in the *ortho* position to the formyl group and the hydroxyl proton showed an intramolecular hydrogen bonding to the formyl group. These results are in agreement with the finding that the IR spectrum of 6-iodosalicylaldehyde[1] was very similar to that of III and quite unlike that of II. Furthermore, the result that the carbonyl absorption of III (1659 cm^{-1}) was lowered than that of II (1667 cm^{-1}) supports the fact that UV measurements of the methylation shift of III (19 mμ) show a stronger intramolecular hydrogen bond than that of II (4 mμ), as noted by Postmus, *et al.*[6]

The structure of III was confirmed by its conversion to the biphenyl derivative (VI); Methylation of III with dimethyl sulfate and sodium hydroxide gave the corresponding methyl ether (V), which underwent Ullmann condensation in the presence of copper bronze in a sealed tube. The product (VI) had an identical melting point and IR spectrum with those of authentic 3,3′-dimethoxy-2,2′-biphenyldicarboxaldehyde which has hitherto not been described

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[1] Part I: S. Kobayashi, S. Tagawa, and S. Nakajima, *Chem. Pharm. Bull.* (Tokyo), **11**, 123 (1963).

[2] This forms Part III of "Studies on the Syntheses of Benzoheterocyclic Compounds," by S. Kobayashi.

[3] Location: *No.* 78, *Sho-machi*-1-*chome*, *Tokushima*.

[4] H.H. Hodgson and T.A. Jenkinson, *J. Chem. Soc.*, **1927**, 3041.

[5] A nickel 6-bromosalicylaldehyde complex was reported by P. Manca [*Rend. Seminar. Fac. Sci. Univ. Cagliari*, **28**, 69 (1958); *C.A.*, **53**, 13706 (1959)]. But no report on the preparation and properties of III could be found in the literature.

[6] C. Postmus, Jr., I.A. Kaye, C.A. Craig, and R.S. Matthews, *J. Org. Chem.*, **29**, 2693 (1964).

and was prepared from 6-iodo-2-methoxybenzaldehyde (VII)[1] by Ullmann condensation. Oxidation of III by silver oxide gave 6-bromosalicylic acid (VIII).[7]

In the UV spectrum of II, the methylation shift is smaller than that of III, as mentioned above, and in the NMR spectrum the formyl and hydroxyl proton peaks were similar to those of 4-chlorosalicylaldehyde.[6] Therefore, the formyl group of II should be attached at the ortho position to the hydroxyl group and at the para position to the bromo substituent.

To confirm this, II was oxidized with silver oxide. The product (IX) was identical in all respects with authentic 4-bromosalicylic acid prepared by the Sandmeyer reaction of ethyl *p*-aminosalicylate, followed by hydrolysis.

Only one monoaldehyde (I) was isolated from the residue in the steam distillation flask. In its NMR spectrum the shift of the formyl proton peak was interpreted in the same way as for III and the hydroxyl proton peak showed nonintramolecular hydrogen bonding to the formyl group which is consistent with structure I.

The structure was established as I by Ullmann condensation of the methyl ether (XII) to 5,5′-dimethoxy-2,2′-biphenyldicarboxaldehyde (XIII),[8] which was identical with an authentic sample prepared previously from 2-iodo-4-methoxybenzaldehyde by the Ullmann method. Furthermore, an acid obtained by silver oxide oxidation of I had the same melting point, mp 206—207°, as that reported for 2-bromo-4-hydroxybenzoic acid (XIV) by Tomita, *et al.*[9] and Friedlich,[10] but its melting point was different from that (mp 151°) of a compound described as XIV by Hodgson, *et al.*[4] The compound with a lower melting point has been shown to be 2-bromo-4-hydroxybenznitrile by Tomita, *et al.*[9] Methylation of the acid (XIV) with diazomethane and hydrolysis of the resulting ester afforded, as expected, 2-bromo-4-methoxybenzoic acid (XV) with a melting point, mp 194—196°, identical to that reported in the literature.[4,9,10,11]

TABLE I. The NMR Spectra of Bromosalicylaldehydes and Related Compounds

Compound	Absorbance (δ, ppm)	
	CHO	OH
Benzaldehyde[a]	10.00	
o-Chlorobenzaldehyde[a]	10.55	
o-Bromobenzaldehyde[b]	10.40	
o-Iodobenzaldehyde[b]	10.07	
Salicylaldehyde[a]	10.00	11.12
6-Chlorosalicyladehyde[a]	10.53	12.02
6-Bromosalicylaldehyde	10.33	11.97
6-Iodosalicylaldehyde[c]	10.07	12.02
4-Chlorosalicylaldehyde[a]	9.88	11.25
4-Bromosalicylaldehyde	9.87	11.10
2-Bromo-4-hydroxybenzaldehyde	10.20	6.05
4-Hydroxy-2-iodobenzaldehyde[c]	9.95	6.00

a) The values for these compounds are from ref. 6.
b) The *o*-bromo and *o*-iodo-benzaldehydes were prepared by the procedures described by Brady, *et al.*,[13] and by Rapson, *et al.*,[14] respectively.
c) The compounds were reported in our paper previously.[1]

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7) The name of the acid (VIII) was reported by E.F. Grether and P.B. Dull in U.S. Patent 2234374 (1941) [*C.A.*, **35**, 3738 (1941)], but no report on its preparation and properties could be found in the literature.
8) J. Koizumi, S. Kobayashi, and S. Uyeo, *Chem. Pharm. Bull.* (Tokyo), **12**, 696 (1964).
9) M. Tomita and K. Fujitani, *Yakugaku Zasshi*, **76**, 1126 (1956).
10) K. Friedlich, *Chem. Ber.*, **94**, 834 (1961).
11) R.H. Griffith and E. Hope, *J. Chem. Soc.*, **1925**, 993.
12) J. Muller, *Chem. Ber.*, **42**, 3695 (1909).
13) O.L. Brady, A.N. Cosson, and A.J. Roper, *J. Chem. Soc.*, **1929**, 2427.
14) I.W.S. Rapson and R.G. Shuttleworth, *J. Chem. Soc.*, **1941**, 487.

Hodgson, *et al.* lost sight of the fact that the oxime of the product they considered to be II melted 17° higher than the oxime reported by Muller.[12] The melting point of the former oxime, mp 168°, agreed with that of the oxime of III and the melting point of the latter oxime was the same as that of II. The methyl ether of II melted at 67—69°, which was in agreement with the melting point of a compound reported as XI by Hodgson, *et al.*, but the melting point of the methyl ether of III (V) was 57—58°. These facts suggest that, although Hodgson, *et al.* prepared both bromosalicylaldehydes in addition to I, they erroneously regarded them as a single compound, designated as II, because of the similarity in their melting points.

The formula of dialdehyde (IV) could not be decided from elemental analysis alone, because the percentages of carbon and hydrogen in the mono-, di-, and tri-formyl derivatives of *m*-bromophenol are very similar. However, IV gave an IR spectrum with two aromatic carbonyl absorption at 1690 and 1655 cm^{-1}. In addition, in the NMR spectrum the formyl proton signals appeared at $\delta=10.40$ and 10.53 (ppm), and the ratio of the intergrated area of the proton signals to the hydroxyl proton signal at $\delta=12.70$ (ppm) was 2:1. These results indicate that IV is the diformyl derivative of *m*-bromophenol, $C_6H_2Br(OH)(CHO)_2$. We hope to report the structure of IV in a forthcoming paper.

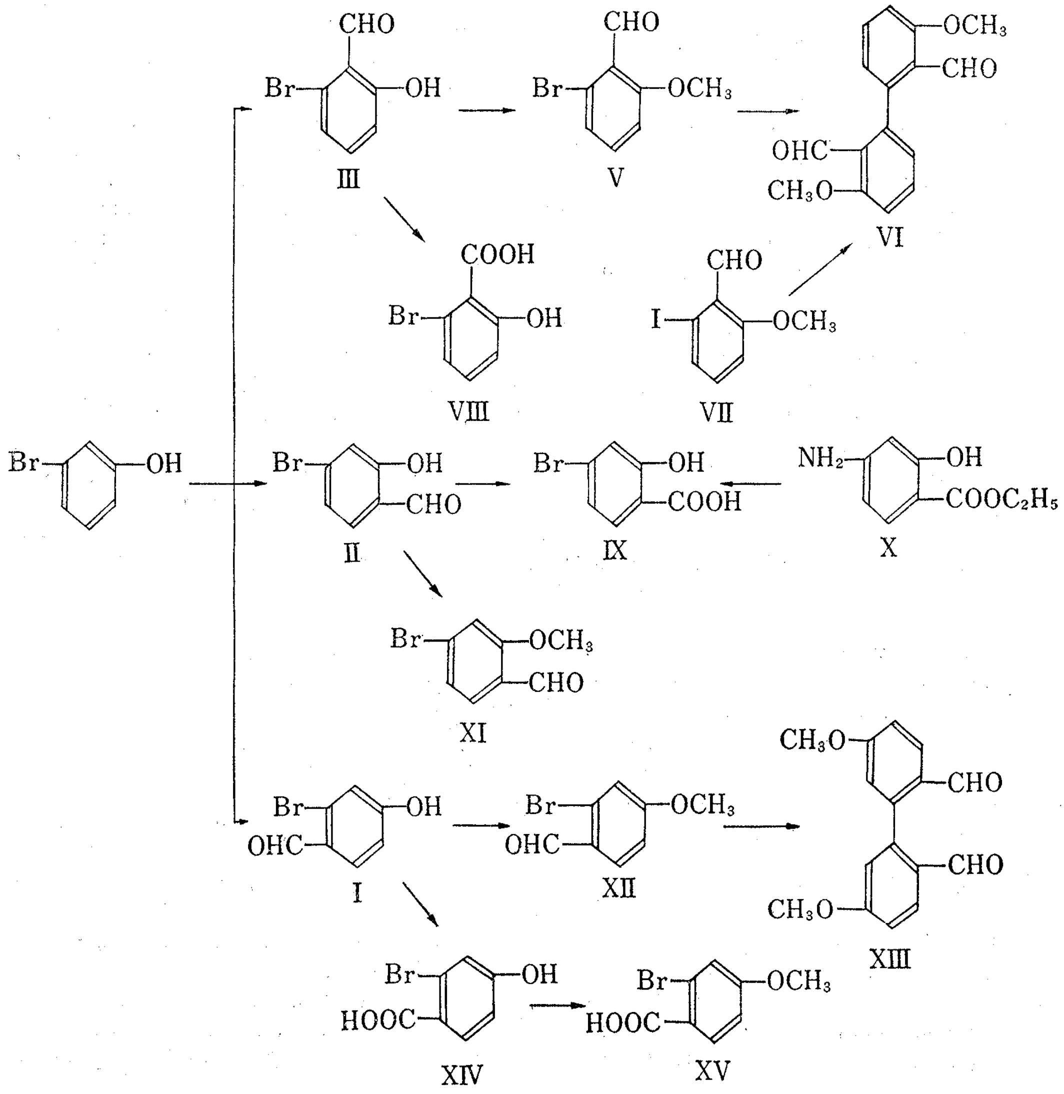

Chart 1

Experimental[15]

Reimer-Tiemann Reaction of *m*-Bromophenol——To a mixture of *m*-bromophenol (25 g), $Ca(OH)_2$ (45 g), Na_2CO_3 (51.9 g), and H_2O (320 ml) was added $CHCl_3$ (36.7 g) under nitrogen with stirring at 70—76° for 2 hr. Stirring was continued for 20 min without heating and then for 100 min with heating. The reaction mixture was acidified with 36% HCl (120 ml) and steam distilled until *ca.* 4.3 liters of distillate had been collected.

2-Bromo-4-hydroxybenzaldehyde (I)——The hot residue in the steam distillation flask was treated with charcoal and filtered. On chilling, the crude product precipitated from the filtrate. This was recrystallized from ether to give I as white cubes (3.04 g, yield 16.8%), mp 156.5—158° (reported[16] mp 159.5°). *Anal.* Calcd. for $C_7H_5O_2Br$: C, 41.81; H, 2.51. Found: C, 41.98; H, 2.31. IR cm^{-1} (KBr): $\nu_{C=O}$ 1650; ν_{OH} 3100. UV λ_{max}^{EtOH} mμ (log ε): 238 (4.09); 284 (4.12).

The aldehyde (I) (80 mg), dry EtOH (1 ml), $NH_2OH \cdot HCl$ (100 mg), and pyridine (1 ml) were heated in a sealed tube for 2.5 hr at 95°. The oxime thus obtained melted at 179—181° (reported mp 185°,[4] mp 128.5°[16]). *Anal.* Calcd. for $C_7H_6O_2BrN$: C, 38.92; H, 2.80. Found: C, 39.42; H, 3.21.

4-Bromosalicylaldehyde (II) and 6-Bromosalicylaldehyde (III)——After removal of dialdehyde (IV) by filtration the steam distillate was extracted with ether. The ether extracts were evaporated to give a red oil. This was converted to the sodium bisulfite adduct as a solid and purified by washing with dry EtOH, followed by ether. The adduct was decomposed by heating with saturated aqueous Na_2CO_3 at 60° to give crude free aldehydes as an oil. On chilling, there were isolated white needles of III (251 mg), mp 51—52°, after recrystallization from petr. ethr. *Anal.* Calcd. for $C_7H_5O_2Br$: C, 41.81; H, 2.51. Found: C, 42.09; H, 2.56. IR cm^{-1} (CCl_4): $\nu_{C=O}$1659. UV λ_{max}^{EtOH} mμ (log ε): 270 (3.90); 344 (3.50).

The oxime was obtained in the same way as I and had mp 165—167° (from petr. ether). *Anal.* Calcd. for $C_7H_6O_2BrN$: C, 38.92; H, 2.80; N, 6.48. Found: C, 39.26; H, 3.07; N, 6.08.

The oil which was separated from the needles of III was chromatographed in petr. ether on silica gel. The first petr. ether eluate gave an additional 222 mg of III, mp 51—52°, (total yield 2.6%). The second petr. ether eluate afforded a crystalline mass which was recrystallized from petr. ether to give 4-bromosalicylaldehyde (II), 136 mg (yield 0.8%), as needles, mp 50—51.5°. *Anal.* Calcd. for $C_7H_5O_2Br$: C, 41.81; H, 2.51. Found: C, 41.84; H, 2.57. IR cm^{-1} (CCl_4): $\nu_{C=O}$1667. UV λ_{max}^{EtOH} mμ (log ε): 266 (4.15); 325 (3.65).

The oxime formed colorless needles, mp 152—154° (from benzene) (reported[12] mp 151°). *Anal.* Calcd. for $C_7H_6O_2BrN$: N, 6.48. Found: N, 6.22.

The precipitates (89 mg) of IV which were separated from the steam distillate were crystallized from MeOH to give white prisms, mp 143—145°. *Anal.* Calcd. for $C_8H_5O_3Br$ (bromoformylhydroxybenzaldehyde): C, 41.95; H, 2.20. Found: C, 41.90; H, 2.10. IR cm^{-1} (CCl_4): $\nu_{C=O}$ 1690, 1655.

Unchanged *m*-bromophenol (9.6 g), bp 91.5° (3 mmHg), was recovered from an oil which was separated from the solid sodium bisulfite adduct.

6-Bromo-2-methoxybenzaldehyde (V)——To a solution of III (139 mg) in 2% NaOH (11 ml) were added Me_2SO_4 (3.52 g) and 4% NaOH (18.7 ml) with stirring at 78°. The resulting product was crystallized from EtOH to give needles (38 mg), mp 57.5—58°. *Anal.* Calcd. for $C_8H_7O_2Br$: C, 44.63; H, 3.28. Found: C, 44.63; H, 3.22. UV λ_{max}^{EtOH} mμ (log ε): 265 (3.74); 325 (3.52).

3,3′-Dimethoxy-2,2′-biphenyldicarboxaldehyde (VI)——i) From V: The aldehyde (V) (65 mg) and copper bronze (600 mg) were heated in a sealed tube at 175—190° for 3.5 hr. The reaction mixture was taken up in $CHCl_3$. The solvent was evaporated off and the residue was extracted with ether. The extracts were evaporated to dryness and crystallized from ether to afford white prisms (14 mg), mp 134—137°. *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.37; H, 5.47. IR cm^{-1} (KBr): $\nu_{C=O}$ 1690.

ii) From 6-Iodo-2-methoxybenzaldehyde (VII)[1]: The same aldehyde (39 mg) was synthesized by Ullmann condensation of VII (292 mg) at 180—185° for 3.5 hr and after recrystallization from benzene–petr. ether had mp 134—137°. Found: C, 70.92; H, 5.25.

The aldehyde (VI) obtained by method i) was identical with the sample prepared from VII by method ii).

6-Bromosalicylic Acid (VIII)——A mixture of III (60 mg), Ag_2O (from 150 mg of $AgNO_3$ and excess 10% NaOH), and 10% NaOH (1 ml) was heated with stirring at 67—80° for 40 min. The mixture was filtered, the filtrate was acidified with 10% HCl, and the acid solution was extracted with ether. The extracts were evaporated to give a solid, which was recrystallized from petr. ether–ether as white prisms (41 mg), mp 159.5—161°. *Anal.* Calcd. for $C_7H_5O_3Br$: C, 38.74; H, 2.32. Found: C, 39.20; H, 2.56.

4-Bromosalicylic Acid (IX)——i) From II: The aldehyde (II) (47 mg), Ag_2O (from 120 mg of $AgNO_3$ and excess 10% NaOH) and 10% NaOH (1.5 ml) were heated with stirring at 57—76° for 30 min. After

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15) All melting points are uncorrected. UV spectra were measured with Hitachi Recording Spectrophotometer, EPS-2. IR spectra were taken on Hitachi EPI-G2 in KBr pellets and on Hitachi EPI-2 in CCl_4 solution, and NMR spectra on Varian A-60 using TMS as an internal standard.

16) L. Gattermann, *Ann.*, 357, 334 (1907).

filtration of the mixture, the filtrate was made acidic with 10% HCl to give needles (43 mg), mp 210—212° (from ether–petr. ether) (reported mp 214°,[4] mp 212°[17]). *Anal.* Calcd. for $C_7H_5O_3Br$: C, 38.74; H, 2.32. Found: C, 39.19; H, 2.56.

ii) From Ethyl *p*-Aminosalicylate (X): The ester (X) (2 g) was treated with 47% HBr (10 ml) and $NaNO_2$ (0.8 g) at 0° and the resulting diazonium salt was added to a mixture of CuBr (from 8.6 g of $CuSO_4 \cdot 5H_2O$, 5 g of NaBr, and 1.3 g of Na_2SO_3) and 47% HBr (10 ml) at 95—98°. After working up in the usual way, the crude product (818 mg) was chromatographed on Al_2O_3 with petr. ether–benzene to give ethyl 4-bromosalicylate (291 mg) as an oil. This was hydrolyzed by refluxing in 1% EtOH–KOH (20 ml) for 1 hr. After standard procedures, the crude product was crystallized from ether–petr. ether as white needles (190 mg), mp 208—211°. Found: C, 39.19; H, 2.56. The acid (IX) obtained by method i) was identical with the sample prepared from X by method ii).

4-Bromo-2-methoxybenzaldehyde (XI)——The crude product (XI), prepared by usual treatment of II (75 mg) with Me_2SO_4 (5 g) and 4% NaOH (7.5 mg), was recrystallized from ether as white needles, mp 67—69° (reported[4] mp 71°). UV λ_{max}^{EtOH} mμ (log ε): 265 (4.20); 320 (3.84).

2-Bromo-4-methoxybenzaldehyde (XII)——To a solution of I (2 g) in 4% NaOH (30 ml) were added Me_2SO_4 (14.1 g) and 4% NaOH (80 ml) with stirring at 60—70°. The resulting product was crystallized from MeOH to afford white needles (1.21 g), mp 76—76.5° (reported[4] mp 77°). *Anal.* Calcd. for $C_8H_7O_2Br$: C, 44.63; H, 3.28. Found: C, 44.83; H, 3.23.

5,5′-Dimethoxy-2,2′-biphenyldicarboxaldehyde (XIII)——2-Bromo-4-methoxybenzaldehyde (400 mg) and copper bronze (1 g) were heated in a sealed tube at 170—180° for 3.5 hr. The reaction mixture was treated in the same way as VI to give white needles (84 mg), mp 98—100° (from ether). *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.08; H, 5.36. IR ν cm^{-1} (KBr): $\nu_{C=O}$1670. The sample thus obtained was identical with an authentic sample of 5,5′-dimethoxy-2,2′-biphenyldicarboxaldehyde[8] judged by the mixed melting point and IR spectrum.

2-Bromo-4-hydroxybenzoic Acid (XIV)——A mixture of I (500 mg), Ag_2O (from 1.25 g of $AgNO_3$ and excess NaOH), and 10% NaOH (7.5 ml) was treated by the same procedure as for VIII. The crude acid (480 mg) was crystallized from MeOH to afford white needles, mp 206—207° (reported[9,10] mp 206—208°). *Anal.* Calcd. for $C_7H_5O_3Br$: C, 38.74; H, 2.32. Found: C, 38.94; H, 2.59.

2-Bromo-4-methoxybenzoic Acid (XV)——A mixture of diazomethane (from 5 g of nitrosomethylurea and 15 ml of 50% KOH) in dry ether and XIV (500 mg) was allowed to stand overnight at room temperature. Evaporation of ether and distillation of the residue under vacuum gave methyl 2-bromo-4-methoxybenzoate (487 mg), bp 123—127° (2 mmHg). The ester (170 mg) thus obtained was hydrolyzed by refluxing in 2.5% EtOH–KOH (30 ml) for 1 hr. After working up in the usual way, the crude product was recrystallized from MeOH as white needles (80 mg), mp 194—196° (reported mp 196—197°,[10] mp 197—198°,[9] mp 199°[4,11]). *Anal.* Calcd. for $C_8H_7O_3Br$: C, 41.58; H, 3.06. Found: C, 41.90; H, 3.26.

Acknowledgement The authors wish to thank Dr. T. Shingu, Kyoto University, for NMR spectral measurements. Thanks are also expressed to Mrs. F. Shimizu of this Faculty for elemental analysis and Miss S. Shirakami for IR spectral measurements.

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[17] H. Ohta, *Nippon Kagaku Zasshi*, **78**, 1608 (1957).