Notes

UDC 547.562.35

Shigeru Kobayashi, Sumiko Tagawa, and Shigeko Nakajima : The Reimer-Tiemann Reaction of *m*-Iodophenol.

(*Pharmaceutical Faculty, University of Nagasaki*[*1])

Hodgson and Jenkinson[1] originally reported on the preparation of 2-hydroxy-4-iodo- and 2-iodo-4-hydroxy-benzaldehydes in almost equal quantities by the Reimer-Tiemann reaction of *m*-iodophenol, but any conclusive evidences were not given for the assigned orientation of the introduced formyl group in these compounds.

For the purpose of providing 2-iodo-4-methoxybenzaldehyde (III) as a starting material for our synthetic approach to hydroxyapogalanthamine,[2] the procedure described by these authors was reexamined and several attempts to prepare 2-iodo-4-hydroxy-benzaldehyde (II) in a good yield were found to be unsuccessful. However, when the reaction was carried out by adding sodium hydroxide to the mixture, it proceeded readily to give three isomeric products of the molecular formula, $C_7H_5O_2I$, along with the starting material. Of these, non steam-volatile product, m.p. 157~160°, was obtained predominantly and characterized as 2-iodo-4-hydroxy-benzaldehyde (II), since the oxidation of its O-methylated product with potassium permanganate yielded 2-iodo-4-methoxybenzoic acid (V), identical with the compound obtained by diazotization of 2-amino-4-methoxy benzoic acid (VI), followed by treatment with potassium iodide. In agreement with this assignment, the acid IV obtained by silver oxide oxidation of the above aldehyde II had the same m.p. 215~216° as that reported for 2-iodo-4-hydroxybenzoic acid,[3] which gave, on methylation, 2-iodo-4-methoxybenzoic acid (V).

On the other hand, the semi-solid steam volatile fraction was not homogeneous and gave, on repeated crystallizations, an aldehyde, m.p. 60~62°, which was not described in the previous paper.[1] The aldehyde was characterized as its oxime, m.p. 168~169° and gave, on oxidation with silver oxide, an acid, m.p. 171~172°, which with dimethyl sulfate in an alkaline solution afforded an iodomethoxybenzoic acid, m.p. 130~132°. The same acid was also obtained by methylation of the aldehyde and subsequent oxidation. This acid was shown to be identical with an authentic 2-methoxy-6-iodo-benzoic acid (X) prepared by diazotization of 6-methoxyanthranilic acid (XI)[4] in 10% sulfuric acid and subsequent treatment with potassium iodide. Based on these findings, the hydroxyiodobenzaldehyde, m.p. 60~62°, might be 2-hydroxy-6-iodobenzaldehyde (VII).

A small amount of another aldehyde was isolated from the mother-liquors of the aldehyde VII. This aldehyde had m.p. 85~87° and its oxime, m.p. 130~133°. Silver oxide oxidation of the aldehyde gave an acid, m.p. 226~227.5°, identical in melting point with 2-hydroxy-4-iodobenzoic acid (XIII) reported in the literature.[1,5,6] Methylation of the hydroxyl group in this acid XIII with dimethyl sulfate afforded, as expected, 2-methoxy-4-iodo-benzoic acid (XIV), m.p. 146~148°, identical in all respects with a sample[7] of the same structure obtained by methylation of ethyl 2-hydroxy-4-iodobenzoate (XV)[5] followed

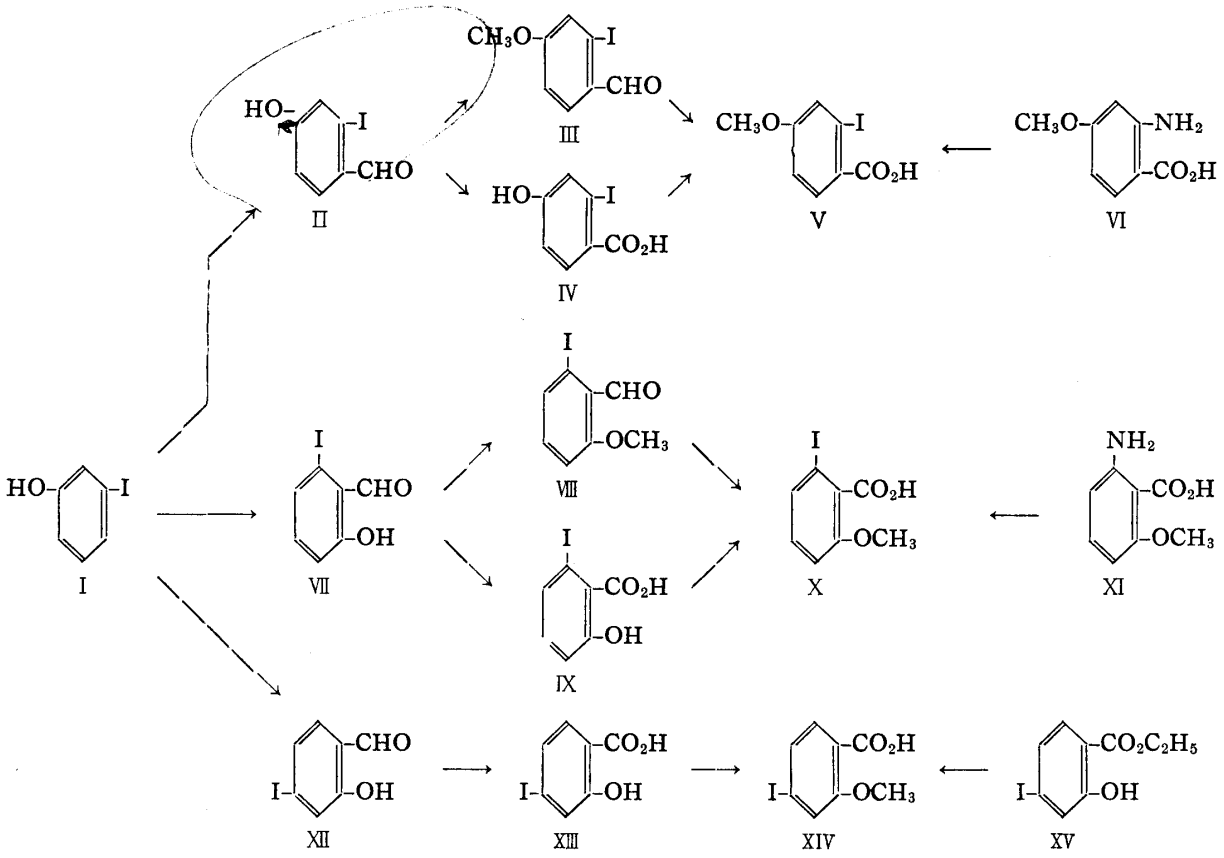
*1 Showa-machi, Nagasaki (小林 茂, 田川寿美子, 中島成子).

1) H. Hodgson, T. A. Jenkinson : J. Chem. Soc., **1927**, 3041.
2) S. Uyeo : Handbook XVIth IUPAC Congress, Paris, 1957, p.207.
3) P. Brenaus, C. Prost : Compt. rend., **178**, 1555 (1924); C. A., **19**, 646 (1925).
4) T. Takahashi, Y. Hamada : Yakugaku Zasshi, **75**, 755, 1435 (1955).
5) P. Brenaus, C. Prost : Compt. rend., **178**, 1010 (1924); C. A., **18**, 1657 (1924).
6) F. J. Sowa : U. S. Pat., 2.607.790 (1952); C. A., **47**, 6983 (1953).
7) S. Kobayashi, C. Kuraishi : This Bulletin, **10**, 1137(1962).

by hydrolysis. Thus the structure of the third aldehyde, m.p. 85~87°, was established as 2-hydroxy-4-iodobenzaldehyde (XII).

On the basis of the results obtained above, it is concluded that the Reimer-Tiemann reaction of *m*-iodophenol gives rise to three products, 2-iodo-4-hydroxy-, 2-hydroxy-6-iodo-, and 2-hydroxy-4-iodo-denzaldehydes, of which the 2-iodo-4-hydroxy derivative (II) constitutes the major product.

Although Hodgson and Jenkinson[1] have not reported an isolation of 2-hydroxy-6-iodobenzaldehyde (VII), the fact that the melting point given by them for the oxime of 2-hydroxy-4-iodobenzaldehyde was not in agreement with the correct one of this compound but with that of the oxime of 2-hydroxy-6-iodobenzaldehyde may suggest that some of the 6-iodo isomer should be contained in the steam-volatile fraction of the reaction mixture.



Experimental*2

Reimer-Tiemann reaction of *m*-Iodophenol (I)——To a mixture of $Ca(OH)_2$ (57 g.), Na_2CO_3 (48 g.), H_2O (892 ml.), and *m*-iodophenol (I) (50 g.) in 25% NaOH (228 g.), was added $CHCl_3$ (68 ml.) in six portions with stirring at 66~69° for 50 min. Stirring was continued for another 30 min. The mixture was made acidic with HCl and steam distilled until ca. 3 L. of the distillate was collected.

(A) The non-volatile fraction: The hot residue was filtered from some resinous substances and the filtrate gave after cooling, 4.75 g. of precipitates which were crystallized from EtOH to give 2-iodo-4-hydroxybenzaldehyde (II) as white cubes, m.p. 157~160°. (reported[1] m.p. 163°). *Anal.* Calcd. for $C_7H_5O_2I$: C, 33.90; H, 2.03. Found: C, 34.03; H, 2.11.

(B) The volatile fraction: A pale yellow semi-solid product which was separated from the aqueous layer by steam distillation was recrystallized from EtOH to give 2-hydroxy-6-iodobenzaldehyde (VII) (1.9 g.) as yellow plates, m.p. 60~62°. Found: C, 34.13; H, 1.85.

The aldehyde VII (0.2 g.), $NH_2OH \cdot HCl$ (0.2 g.), pyridine (1.3 ml.), and dry EtOH (1.3 ml.) were heated

*2 All melting points are uncorrected.

in a sealed tube for 2 hr. at 95°. The oxime thus formed was recrystallized from MeOH and then from benzene to the crystal of m.p. 168~169°. *Anal.* Calcd. for $C_7H_6O_2NI$: C, 31.96; H, 2.29; N, 5.32. Found: C, 32.59; H, 2.25; N, 5.35.

The above EtOH mother-liquors from VII was evaporated and triturated with EtOH to give 2-hydroxy-4-iodobenzaldehyde (XII) (100 mg.) as long prisms, m.p. 85~87°. (reported[1] m.p. 87°). Found: C, 34.08; H, 1.96. The oxime formed colorless prisms, m.p. 130~133° (from EtOH). (reported[1] m.p. 171°). Found: C, 32.49; H, 2.27; N, 5.29.

The aqueous layer separated from these aldehydes was extracted with Et_2O. Evaporation of the Et_2O, followed by the distillation of the residue gave unchanged *m*-iodophenol (35 g.), $b.p_{2.5}$ 106~108°.

2-Iodo-4-methoxybenzaldehyde (III)——To a solution of II (16.3 g.) in 5% NaOH (80 ml.), was added dropwise Me_2SO_4 (86 g.) at room temperature, maintaining the mixture to be alkaline by simultaneous addition of 10% NaOH (400 ml.). After working up in the usual way, the aldehyde III was crystallized from EtOH to give white needles (13.9 g.), m.p. 112~115°. (reported[1] m.p. 115°). *Anal.* Calcd. for $C_8H_7O_2I$: C, 36.63; H, 2.69. Found: C, 36.58; H, 2.98.

The oxime was obtained in the same manner as in the case of VII and had m.p. 97~99° (from EtOH). (recorded[1] m.p. 101°). *Anal.* Calcd. for $C_8H_8O_2NI$: C, 34.69; H, 2.91. Found: C, 35.07; H, 3.23.

2-Methoxy-6-iodo-benzaldehyde (VIII)——The crude compound III, obtained by usual treatment of VII (2 g.) with 8% NaOH and Me_2SO_4, was crystallized from EtOH as needles (0.53 g.), m.p. 55.5~56.2°. Found: C, 36.78; H, 2.72.

The oxime gave needles, m.p. 178~179° (from EtOH). Found: C, 35.09; H, 3.01.

2-Iodo-4-benzoic Acid (IV)——A mixture of the aldehyde II (0.8 g.), Ag_2O (from 1.6 g. of $AgNO_3$ and an excess of NaOH) and 10% NaOH (6 ml.) was heating with stirring at 80° for 20 min. The mixture was filtered and SO_2 was then passed through the filtrate to form precipitates which were collected, dried, and crystallized from EtOH-benzene to give IV (0.57 g.) as needles, m.p. 215~216° (decomp.). [reported m.p. 179°(decomp.)[1] and 215°(decomp.)[3]]. *Anal.* Calcd. for $C_7H_5O_3I$: C, 31.84; H, 1.91. Found: C, 31.97; H, 1.78.

2-Hydroxy-4-iodobenzoic Acid (XIII)——A mixture of the aldehyde XII (86 mg.), Ag_2O (from 0.15 g. of $AgNO_3$ and excess NaOH), and 10% NaOH (0.5 ml.) was treated as described above to give XIII as white prisms, m.p. 226~227°(decomp.) (from benzene). [reported m.p. 228°(decomp.)[5] and 230° (decomp.)[1,6]]. Found: C, 32.52; H, 1.96.

2-Hydroxy-6-iodobenzoic Acid (IX)——This compound IX was prepared from 0.3 g. of VII, Ag_2O (from 0.45 g. of $AgNO_3$ and an excess of NaOH), and 10% NaOH (2.7 ml.) in the same manner as for IV. The crude acid IX (195 mg.) was recrystallized from benzene to give needles, m.p. 171~172°. Found: C, 32.22; H, 1.98.

2-Iodo-4-methoxbyenzoic Acid (V)——(i) From IV: To a solution of IV (0.59 g.) in 6% NaOH (5 ml.), were added 10% NaOH (80 ml.) and Me_2SO_4 (13 g.) with stirring at room temperature. The resulting product was crystallized from EtOH-benzene to give V as white prisms (0.14 g.), m.p. 181~183°. (reported[1] m.p. 184°). *Anal.* Calcd. for $C_8H_7O_3I$: C, 34.55; H, 2.54. Found: C, 34.50; H, 2.46.

(ii) From III: The same acid was also obtained by oxidation of III (0.1 g.) in Me_2CO (100 ml.) with powdered $KMnO_4$ (0.3 g.) at 55~60°.

The samples of the acid thus obtained by two methods, (i) and (ii), were identical with an authentic sample[2] prepared from 4-methoxyanthranilic acid (VI).

2-Methoxy-4-iodobenzoic Acid (XIV)——This compound XIV was synthesized from XIII (35 mg.), 10% NaOH (33 ml.), and Me_2SO_4 (4 ml.) by the same procedure as for V (i) and formed after recrystallization from Et_2O-petr. ether white plates, m.p. 146~148°. (reported[1] m.p. 150°). Found: C, 35.08; H, 2.78.

The acid thus obtained was identical with an authentic sample of 2-methoxy-4-iodobenzoic acid (XIV)[7] prepared from ethyl 2-hydroxy-4-iodobenzoate (XV).[5]

2-Methoxy-6-iodobenzoic Acid (X)——(i) From IX: The foregoing IX (0.11 g.) was treated with 10% NaOH (33 ml.), and Me_2SO_4 (4 ml.) in the same manner as for V (i). Crystallization from EtOH and then from benzene gave X as white prisms (80 mg.), m.p. 130~132°. Found: C, 35.09; H, 2.62.

(ii) From VIII: The same acid was obtained by oxidation of VIII in the same manner as for V (ii). Found: C, 35.03; H, 2.53.

(iii) From 6-methoxyanthranilic acid (XI): To a solution of XI (146 mg.), prepared according to the method of Takahashi, *et al.*,[4] in 10% H_2SO_4 (2 ml.) was added 2% $NaNO_2$ (6 ml.) in portions at −3°. Being continued of stirring for 1 hr., 12% KI (7.5 ml.) was added over a period of 10 min. The mixture was allowed to stand overnight at room temperature, and then heated to 40°. The product was taken up in Et_2O, which was extracted with 2% Na_2CO_3 (20 ml.). The alkaline extracts were made acidic with 9% HCl and again extracted with Et_2O, and it was washed with $Na_2S_2O_3$, then with H_2O and evaporated to give a red oil (162 mg.) which was chromatographed in benzene on acid-washed alumina. Elution with benzene gave X as prisms, m.p. 131.5~132°, after recrystallization from EtOH-benzene. Found: C, 34.87; H, 2.47.

The products obtained by the methods (i) and (ii) were identical with the sample prepared by the procedure (iii).

The authors are grateful to prof. S. Uyeo of Kyoto University for his kind guidance and to Prof. M. Yanai for his encouragement. Their thanks are also given to Mrs. H. Mazume for the micro-analyses and Mr. M. Honda for the infrared spectra measurements.

Summary

The Reimer-Tiemann reaction of *m*-iodophenol yielded three products in contrast with literature reported by Hodgson and Jenkinson and the products were confirmed unambiguously to be 2-iodo-4-hydroxy-, 2-hydroxy-6-iodo-, and 2-hydroxy-4-iodo-benzaldehydes, respectively.

(Received November 27, 1961)

UDC 547.514.72

Shingo Matsumura and Shuichi Seto : Studies on the Cyclopentadienide Anion.

(*The Chemical Research Institute of Non-Aqueous Solutions, Tohoku University*[*1])

Hafner and Vöpel[1] have already found that the condenstions of one molar equivalent of 6-dimethylamino-3,4-fulvenedicarboxaldehyde (I) with two molar equivalents of various active methylene compounds formed 6-dimethylamino-3,4-divinylfulvene derivatives represented as the formula II. In analogy with the reaction mechanism of azulene synthetic process elaborated by Nozoe and the present authors,[2] there is also a possibility of the formation of 6-aminoazulene derivatives by the reacion of I with malononitrile or cyanoacetic ester. This paper describes some results obtained on examination of this point.

The reaction of one molar equivalent of I with three molar equivalents of malononitrile, in the presence of one drop of diethylamine, afforded red crystals III in a good yield. The condensation of one molar equivalent of 6-hydroxy-3,4-fulvenedicarboxaldehyde[1] (IV) with three molar equivalents of malononitrile, in the presence of over one molar equivalent of diethylamine, produced red crystals V in a fairly good yield. The analytical values of III and V respectively correspond to molecular formulae of $C_{19}H_{13}N_7$ and $C_{21}H_{17}N_7$.

The reaction of one molar equivalent of I or IV with three molar equivalents of malononitrile, by the use of over one molar equivalent of potassium hydroxide in place of diethylamine, formed red crystals VI, whose analytical values correspond to the molecular formula of $C_{17}H_5N_6K \cdot \frac{1}{2}H_2O$.

The ultraviolet absorption spectra (Table I) of these condensation products are very similar to each other and these compounds are assumed to have a common skeletal

---

*1 Katahira-cho, Sendai (松村進午, 瀬戸秀一).

1) K. Hafner, K. H. Vöpel : Angew. Chem., **71**, 672 (1959); K. Hafner : *Ibid.*, **72**, 574 (1960).
2) *a*) T. Nozoe, S. Matsumura, Y. Murase, S. Seto : Chem. & Ind. (London), **1955**, 1257; *b*) T. Nozoe, S. Seto, S. Matsumura, T. Asano : Proc. Japan Acad., **32**, 339 (1956); *c*) S. Matsumura : This Bulletin, in press.