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# Formic Acid Reduction. XIV.[1] Formation of 3-Arylphthalimidines from 3-Aryl-3-hydroxyphthalimidines

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It has now been found that reduction of 3-aryl-3-hydroxyphthalimidines to 3-arylphthalimidines are easily effected on heating with the formate reagent, TMAF, known as a constant boiling liquid composed of formic acid and trimethylamine. Fashon of the attack of formic acid in this reaction was clarified by means of using deuterated formate reagent.

In our investigation in development, as reducing agents,[3] of the salt-like materials of formic acid and trialkylamine, which are the polar liquids of constant boiling points, facile reduction of 3-aryl-3-hydroxyphthalimidines to 3-arylphthalimidines has now been found. Although a report[4] on the reduction of 3-hydroxy-3-phenylphthalimidine by the method of using zinc dust and acetic acid had been appeared, development of general method suitable for the reduction was an insoluble synthetic problem. On heating with the formate reagent, TMAF, given by $5HCO_2H \cdot 2N(CH_3)_3$ a variety of 3-aryl-3-hydroxyphthalimidines could be conveniently reduced to 3-arylphthalimidines in excelent yields. Eleven 3-aryl-3-hydroxyphthalimidines including seven new compounds, of which physical and analytical data are shown in Table II, were prepared by the reactions of potassium phthalimide[5] and of N-substituted phthalimide[6] with Grignard reagents. Normally, the reactions were carried out by heating the substrate with TMAF (as $HCO_2H$) in 1: 25 molar proportion, process of the reaction being checked by noting considerable emission of carbon dioxide. Our result and the reaction condition are summarized in Table I.

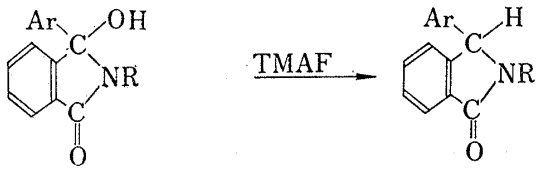
The products, 3-arylphthalimidines are listed in Table III with their infrared (IR) spectra and analytical data, which are consistent with their structures. Nuclear magnetic resonance (NMR) spectra of the seven representative products, of which solubilities permit the measurement, are shown in Table IV, where the presence of the methine proton signal as singlet at $\tau$ 4.67—3.97 and the other signals are clearly indicative of the assigned 3-arylphthalimidines.

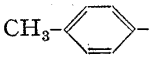
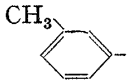
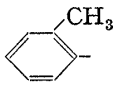
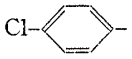
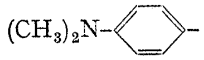
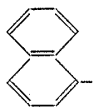
Then the method would be well suited for the reduction of 3-aryl-3-hydroxyphthalimidine derivatives with the advantages; high yield of the product and simplicity of the procedure. The method was not applicable for the reduction of 3-alkyl-3-hydroxyphthalimidines, since this system underwent dehydration on heating with TMAF to give 3-alkylidenephthalimidines.

Recently the reductive fission at the carbon-oxygen bond of the compound possessing the carbon bound to both ether oxygen and amine nitrogen has been realized in the TMAF reaction from this laboratory[1] with series of N,O-benzylidene and N,O-methylene compounds and oxazolidines. In relation to this fact, the reduction of 3-aryl-3-hydroxyphthalimidines to 3-arylphthalimidines appeared to imply the site of the reductive fission at the carbon-oxygen bond of such system possessing the carbon bound to amide nitrogen and hydroxy

1) Part XIII: K. Ito, H. Oba, and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **20**, 2112 (1972).
2) Location: *2-2-1, Oshika, Shizuoka.*
3) TMAF, bp 92° (18 mmHg): M. Sekiya and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **12**, 677 (1964); TEAF, bp 95° (15 mmHg): K. Ito, *Yakugaku Zasshi*, **86**, 1166 (1966).
4) H. Meyer, *Monatsch*, **28**, 1211 (1907).
5) M. Sekiya and T. Terao, *Yakugaku Zasshi*, **88**, 1085 (1968).
6) F. Sachs and F. Ludwig, *Ber.*, **37**, 385 (1904).

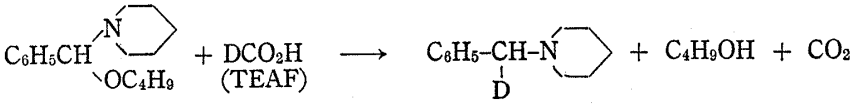
Table I. Reduction of 3-Aryl-3-hydroxyphthalimidines with TMAF[a)]




| Ar | R | React. Temp. (°C) | React. time (hr) | Product, yield[b)] (%) |
|---|---|---|---|---|
|  | H | 100—105 | 2 | 85 |
|  | H | 100—105 | 2 | 85 |
|  | H | 100—105 | 2 | 90 |
|  | H | 105—110 | 2 | 91 |
|  | H | 105—110 | 3 | 89 |
|  | H | 105—110 | 2 | 90 |
|  | H | 110—115 | 2.5 | 87 |
|  | $CH_3$ | 125—130 | 2 | 92 |
|  | $CH_3(CH_2)_2CH_2$ | 125—130 | 2.5 | 90 |
|  |  | 125—130 | 2.5 | 95 |
|  |  | 135—140 | 2.5 | 90 |

*a*) molar ratio; substrate: TMAF (as $HCO_2H$)=1:25
*b*) Yield is based on the product isolated.

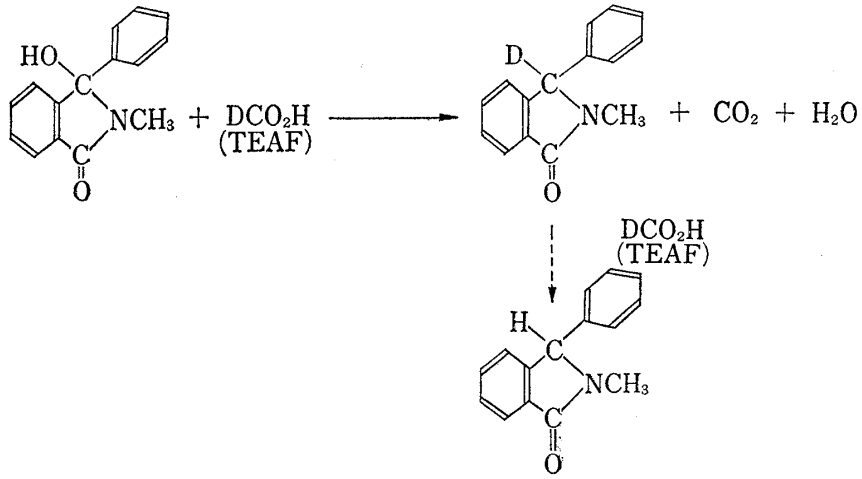
oxygen. Fashion of the TEAF reduction of 1-(α-butoxybenzyl)piperidine has been previously determined by the use of the deuterated TEAF, $5DCO_2H \cdot 2N(C_2H_5)_3$ and $5HCO_2D \cdot 2N(C_2H_5)_3$ as shown in the following.




If mechanistic path of the reduction of 3-aryl-3-hydroxyphthalimidines is similar to that of the above reduction, similar reduction mode may be expected.

An investigation was undertaken to see fashion of the reaction by carring out with deuterated TEAF,[1)] $5DCO_2H \cdot 2N(C_2H_5)_3$, using 3-hydroxy-2-methyl-3-phenylphthalimidine as a model substrate. It was needed beforehand to see whether the methine proton at 3-position of 2-methyl-3-phenylphthalimidine would be exchangeable in protic medium such as TEAF. In deuteronic medium decrease of content of the methine proton of 2-methyl-3-phenylphthalimidine caused by deuterium substitution could be measured by nuclear magnetic resonance (NMR) spectroscopic method, in which was compared the singlet peak of the methine proton at $\tau$ 4.67 with the singlet peak of the N-methyl proton at $\tau$ 7.04. On standing a solution of

nondeuterated 2-methyl-3-phenylphthalimidine in TEAF composed of formic acid-*d* for several days at room temperature deuterium substitution of the methine proton was not observed. However, at 130°, the same temperature as for the reduction of 3-hydroxy-2-methyl-3-phenylphthalimidine gradual deuterium substitution of the methine proton was observed; 48% for 30 min and 95% for 2 hr. We then carried out the reduction of 3-hydroxy-2-methyl-3-phenylphthalimidine by heating with TEAF composed of formic-*d* acid at 130° and checked deuterium substitution in the product. After 45 min, NMR spectrum of the partially formed product isolated showed 50% deuterium content at the methine position and, after completion of the reduction, 2 hr, that of the product showed 20% deuterium content at the same. These values of the deuterium substitution at the methine position after the selected periods can be well interpreted to be brought about by proton substitution, in the TEAF medium composed of formic-*d* acid, of 2-methyl-3-phenylphthalimidine deuterated at $C_3$, initially formed by the reduction of 3-hydroxy-2-methyl-3-phenylphthalimidine with the deuterated TEAF.




Therefore, it can be said that in the formic acid reduction of 3-aryl-3-hydroxyphthalimidines the formyl hydrogen of formic acid is transferred to the $C_3$-carbon of the formed 3-arylphthalimidines. Thus the mode of the reduction was recognized to be similar to that of the reduction reported[1] reduction of the compound which possesses amine nitrogen and ether oxygen bound to the same carbon.

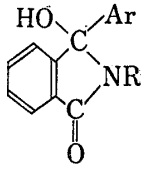
## Experimental[7]

**TMAF Reduction of 3-Aryl-3-hydroxyphthalimidines**——General Procedure: The substrates, 3-aryl-3-hydroxyphthalimidines including seven new compounds, used for the TMAF reduction, are listed in Table II with their IR spectra and analytical data. Among these, the N-unsubstituted compounds were prepared according to the method previously reported by M. Sekiya, *et al.*[5] The N-substituted compounds were prepared from the corresponding N-substituted phthalimides by the reaction[6] with phenylmagnesium bromide.

The following is general procedure for the TMAF reduction. A mixture of 0.02 mole of 3-aryl-3-hydroxyphthalimidine and 34.8 g of TMAF (0.5 mole as $HCO_2H$) was heated with constant stirring. Dry air free from $CO_2$ was occasionally passed through the reaction vessel in order to check transfer of emission of $CO_2$ by $Ba(OH)_2$ solution. At about 60° the mixture turned to a homogeneous liquid, and the temperature was maintained (100—140°) at which considerable emission of $CO_2$ was observed. In runs with 2-unsubstituted-3-aryl-3-hydroxyphthalimidines and 2,3-diphenyl-3-hydroxyphthalimidine, after subsidence of the emission of $CO_2$, most of the products were deposited on cooling and collected by filtration. In the other runs concentration of the reaction mixture gave the products as crystalline residue. Conditions and yields of the products are listed in Table I. Their physical, spectral and analytical data are recorded in Table

7) NMR spectra were measured on a JEOL JNM-C-60H spectrometer.

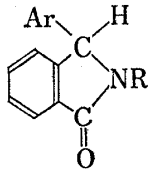
TABLE II. Physical and Analytical Date of 3-Aryl-3-hydroxyphthalimidines



| Compound Ar | R | Appearance (Recryst. solvent) | mp (°C) | IR $\nu_{max}^{KBr}$ (cm$^{-1}$) | Formula | Analysis (%) Calcd. | Found | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| $C_6H_5$ | H | needles (AcOEt) | 164—165 (164—165)[a] | 3280 (OH, NH) 1710 (C=O) | | | | |
| $p$-$CH_3C_6H_4$ | H | needles (AcOEt) | 168—169 | 3215 (OH, NH) 1689 (C=O) | $C_{15}H_{13}O_2N$ | 75.30 | 5.48 | 5.85 |
| | | | | | | 75.34 | 5.65 | 5.62 |
| $m$-$CH_3C_6H_4$ | H | plates (AcOEt) | 163—164 | 3170 (OH, NH) 1676 (C=O) | $C_{15}H_{13}O_2N$ | 75.30 | 5.48 | 5.85 |
| | | | | | | 75.24 | 5.43 | 5.92 |
| $o$-$CH_3C_6H_4$ | H | needles (EtOH) | 165—166 | 3220 (OH, NH) 1690 (C=O) | $C_{15}H_{13}O_2N$ | 75.30 | 5.48 | 5.85 |
| | | | | | | 75.24 | 5.46 | 5.81 |
| $p$-$ClC_6H_4$ | H | granules (AcOEt) | 205—206 (214—216)[b] | 3260 (OH, NH) 1703 (C=O) | $C_{14}H_{10}O_2NCl$ | 64.76 | 3.88 | 5.39 |
| | | | | | | 64.73 | 3.94 | 5.43 |
| $p$-$(CH_3)_2NC_6H_4$ | H | needles (EtOH) | 180—181 | 3150 (OH, NH) 1677 (C=O) | $C_{16}H_{16}O_2N_2$ | 71.62 | 6.01 | 10.44 |
| | | | | | | 71.52 | 6.18 | 9.98 |
| $\alpha$-$C_{10}H_7$ | H | granules (AcOEt) | 161—162 (161—162)[a] | 3280 (OH, NH) 1700 (C=O) | | | | |
| $C_6H_5$ | $CH_3$ | prisms (EtOH) | 181—182 (182—182.5)[c] | 3254 (OH) 1675 (C=O) | $C_{15}H_{13}O_2N$ | 75.30 | 5.48 | 5.85 |
| | | | | | | 75.25 | 5.44 | 5.89 |
| $C_6H_5$ | $CH_3(CH_2)_2CH_2$ | prisms (EtOH) | 158—159 | 3170 (OH) 1674 (C=O) | $C_{18}H_{19}O_2N$ | 76.84 | 6.81 | 4.98 |
| | | | | | | 76.77 | 6.82 | 5.01 |
| $C_6H_5$ |  | prisms (EtOH) | 204—205 | 3245 (OH) 1672 (C=O) | $C_{22}H_{21}O_2N$ | 77.94 | 6.77 | 4.45 |
| | | | | | | 78.14 | 6.89 | 4.56 |
| $C_6H_5$ | $C_6H_5$ | prisms (EtOH) | 192—193 | 3165 (OH) 1668 (C=O) | $C_{20}H_{15}O_2N$ | 79.71 | 5.02 | 4.65 |
| | | | | | | 79.66 | 5.06 | 4.57 |

*a*) see lit.5)
*b*) J.R. Gergy, Swit. patent 374068 [*C.A.*, **62**, 10416 (1965)]
*c*) G. Wittig, G. Closs, and F. Mindermann, *Ann.*, **594**, 89 (1955)

TABLE III. Physical and Analytical Data of 3-Arylphthalimidines

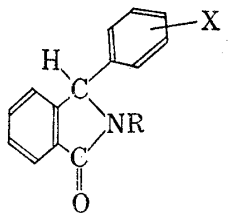


| Compound Ar | R | Appearance (Recryst. solvent) | mp (°C) | IR $\nu_{max}^{KBr}$ (cm$^{-1}$) C=O | NH | Formula | Analysis (%) Calcd. | Found | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | C | H | N |
| $C_6H_5$ | H | plates (EtOH) | 215—216 (218—220)[a] | 1681 | 3162 3045 | $C_{14}H_{11}ON$ | 80.36 | 5.30 | 6.69 |
| | | | | | | | 80.10 | 5.39 | 6.66 |
| $p$-$CH_3C_6H_4$ | H | needles (EtOH) | 206—208 | 1677 | 3145 3038 | $C_{15}H_{13}ON$ | 80.69 | 5.87 | 6.27 |
| | | | | | | | 80.55 | 5.86 | 6.29 |
| $m$-$CH_3C_6H_4$ | H | prisms (AcOEt) | 243—245 | 1668 | 3208 3052 | $C_{15}H_{13}ON$ | 80.69 | 5.87 | 6.27 |
| | | | | | | | 80.52 | 5.45 | 6.38 |
| $o$-$CH_3C_6H_4$ | H | prisms (EtOH) | 195—197 | 1686 | 3143 3060 | $C_{15}H_{13}ON$ | 80.69 | 5.87 | 6.27 |
| | | | | | | | 80.62 | 5.85 | 6.32 |
| $p$-$ClC_6H_4$ | H | granules | 236—237 (decomp.) | 1678 | 3174 3058 | $C_{14}H_{10}ONCl$ | 69.00 | 4.14 | 5.75 |
| | | | | | | | 68.79 | 3.96 | 5.72 |
| $p$-$(CH_3)_2NC_6H_4$ | H | needles (EtOH) | 235—236 | 1676 | 3174 3058 | $C_{16}H_{16}ON$ | 76.16 | 6.39 | 11.10 |
| | | | | | | | 76.18 | 6.60 | 11.05 |

| Compound Ar | Compound R | Appearance (Recryst. solvent) | mp (°C) | IR $\nu_{max}^{KBr}$ ($cm^{-1}$) C=O | IR NH | Formula | Analysis (%) Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| α-$C_{10}H_7$ | H | needles (EtOH) | 235—238 | 1708 | 3174 3058 | $C_{18}H_{13}ON$ | 83.37 | 5.05 | 5.40 | 83.27 | 5.13 | 5.42 |
| $C_6H_5$ | $CH_3$ | prisms (EtOH) | 103—104 (72—75)[b] | 1673 | | $C_{15}H_{13}ON$ | 80.69 | 5.87 | 6.27 | 80.95 | 5.83 | 6.37 |
| $C_6H_5$ | $CH_3(CH_2)_2CH_2$ | needles (EtOH) | 90—91 | 1674 | | $C_{18}H_{19}ON$ | 81.47 | 7.22 | 5.28 | 81.18 | 7.10 | 5.18 |
| $C_6H_5$ |  | needles (EtOH) | 140—141 | 1682 | | $C_{20}H_{21}ON$ | 82.44 | 7.26 | 4.18 | 82.42 | 7.18 | 4.72 |
| $C_6H_5$ | $C_6H_5$ | leaflets (EtOH) | 192—193 (192—194)[c] | 1677 | | $C_{20}H_{15}ON$ | 84.18 | 5.30 | 4.91 | 83.80 | 5.17 | 4.90 |

a) A. Rosenthal, R.F. Astbury, and A. Hubscher, *J. Org. Chem.*, **23**, 1037 (1958)
b) M.H. Sherlock, U.S. Patent 3296276 (1964) [*C.A.*, **67**, 73519 (1967)]
c) E.F. Ullman and J.E. Mieks, *J. Am. Chem. Soc.*, **86**, 3814 (1964)

TABLE IV. NMR Spectral Data[a] of 3-Arylphthalimidines ($\tau$)




| Compound X | Compound R | Solvent | -CH | Other signals |
|---|---|---|---|---|
| H | H | $CF_3CO_2H$ | 4.03 (s) | 1.8—2.8 (9H, m, $C_6H_4$, $C_6H_5$), 0.4—0.9 (1H, br, NH) |
| *p*-$CH_3$ | H | $CF_3CO_2H$ | 4.04 (s) | 7.65 (3H, s, $CH_3$), 1.7—3.0 (9H, m, $C_6H_4$, $C_6H_4$), 0.3—0.9 (1H, br, NH) |
| *o*-$CH_3$ | H | $(CD_3)_2SO$ | 4.04 (s) | 7.59 (3H, s, $CH_3$), 2.1—3.2 (8H, m, $C_6H_4$, $C_6H_4$), 0.4—0.6 (1H, br, NH) |
| H | $CH_3$ | $CDCl_3$ | 4.67 (s) | 7.02 (3H, s, $NCH_3$), 2.0—3.0 (9H, m, $C_6H_4$, $C_6H_5$) |
| H | $CH_3(CH_2)_2CH_2$ | $CDCl_3$ | 4.54 (s) | 5.9—6.3, 6.9—7.4, 8.2—9.3 (9H, m, $C_4H_9$), 2.0—3.0 (9H, m, $C_6H_4$, $C_6H_5$) |
| H |  | $CDCl_3$ | 4.52 (s) | 5.8—6.3, 7.1—9.2 (11H, m, $C_6H_{11}$), 2.0—3.0 (9H, m, $C_6H_4$, $C_6H_5$) |
| H | $C_6H_5$ | $CDCl_3$ | 3.93 (s) | 2.0—3.0 (9H, m, $C_6H_4$, $C_6H_5$), 2.73 (5H, s, $NC_6H_5$) |

a) Following abbreviations were used; s=singlet, m=multiplet, br=broad

III and IV. In Table IV NMR spectra of the seven representative products which permit the measurement are shown. These spectral data shown in Table III and IV are well indicative of their structures.

**Deuterium Substitution of the Methine Proton of 2-Methyl-3-phenylphthalimidine in TEAF Composed of Formic Acid-*d*——**A solution of 1.1 g (0.005 mole) of 2-methyl-3-phenylphthalimidine in 4.4 g (0.05 mole as $HCO_2D$) of deuterated TEAF [$5HCO_2D \cdot 2N(C_2H_5)_3$], which was prepared according to previously reported method,[1] was heated at 130° with stirring. After periods of 0.5 hr and 2 hr parts of the reaction solution were pipeted. From these fraction 2-methyl-3-phenylphthalimidine was recovered and subjected to measurement of their NMR spectra. In their NMR spectra decrease of the methine proton peak appearing as the singlet at $\tau$ 4.67, owing to deuterium substitution, was calculated in comparison with the peak area of the N-methyl proton at $\tau$ 7.02 to give the following deuterium content; 48% for 0.5 hr and 95% for 2 hr.

**Reduction of 3-Hydroxy-2-methyl-3-phenylphthalimidine with TEAF Composed of Formic-*d* Acid**—A mixture of 2.4 g (0.01 mole) of 3-hydroxy-2-methyl-3-phenylphthalimidine and 8.8 g (0.1 mole as $DCO_2H$) of TEAF [$5DCO_2H \cdot 2N(C_2H_5)_3$][1] was heated at 130° with stirring. After 45 min a part of the reaction solution was pipeted and from this 2-methyl-3-phenylphthalimidine formed was isolated after removal of the unreacted starting material. Deuterium content at 3-position was measured by the same manner as described in the above experiment and was shown to be 50%. After 2 hr, when emission of carbon dioxide was ceased, the product obtained from the reaction solution showed deuterium content at 3-position 20% by the same treatment.

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