Reduction of Cyclic Imides. III.1) Reduction of 3- and 4-Substituted Phthalimides with Sodium Borohydride

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Reduction of 3-substituted phthalimides with sodium borohydride in 90% methanol was found to give one kind each of reduction product and solvolysis product. In the case of an electron-withdrawing nitro group, the carbonyl group in 2-position was selectively reduced to the hydroxyl group, whereas in the case of an electron-donating amino, acetamido, hydroxyl, or methoxyl group, the carbonyl group in 1-position was reduced to the methylene group, and the formation of a solvolysis product increased. In the case of 4-substituted compounds, two kinds each of reduction product and solvolysis product were obtained. When the substituent was a nitro group, ratio of the products from reduction of imidocarbonyl in 1- and 2-position was about 5:4, while this ratio became about 4:5 inversely in the case of electron-donating substituent groups. In the solvolysis products, the position attacked in the imidocarbonyl and the position reduced became the same, and their ratio was the same as in the reduction products.

Keywords—phthalimides; NaBH₄ reduction; phthalides; 3-hydroxyphthalides; solvolysis of phthalimides; LiBr-NaBH₄ reduction

We have previously reported the reduction of alicyclic imides with sodium borohydride.1,3) In the case of α-alkylsuccinimides, the carbonyl on the substituent side is more easily reduced. In the case of α-arylsuccinimides and α-alkylguanimides, the carbonyl on the side opposite to the substituent is more easily reduced, and an amide ester formed by alcoholysis is the main product in the case of glutarimides. Later examination of the reduction of 3-nitrophthalimide (1) with sodium borohydride showed a selective reduction of the carbonyl on the side of the nitro group, affording 3-hydroxy-4-nitro-phthalimidine (2) or -phthalide (3) in a good yield.4) Syntheses of 4-indolecarboxylic acid5) and 5-aminophthalazine derivatives6) by using 2 and 3 were also reported.

In the present series of work, electron-withdrawing nitro group and electron-donating hydroxyl, methoxyl, amino, or acetamido group were introduced into 3- and 4-positions of phthalimide, and the behavior of these substituted phthalimides to sodium borohydride reaction was comparatively examined.

Horii and others7) already made detailed studies on the sodium borohydride reduction of phthalimide, and obtained 3-hydroxyphthalimidine and o-hydroxymethylbenzamide as its reduction products. They reported that the formation ratio of these compounds varied with the amount of sodium borohydride used, reaction temperature, and reaction time. We made reference to these facts for determining the reaction conditions, obtained the following results.

1. Reduction of 3- and 4-Nitrophthalimides with Sodium Borohydride

a) Reduction of 3-Nitrophthalimide (1)—This reaction was re-examined. Reduction of 1 with 2 mol of sodium borohydride in 90% methanol gave 2, 4-nitrophthalalde2) (4), and

2) Location: 1432-1 Horinouchi, Hachioji, Tokyo, 192-03, Japan.
7-nitrophthalide$^8$ (5). Formation ratio of 2 and 4 + 5 with respect to reaction time is shown in Fig. 1. Use of dehydrated methanol shortens the reaction time, but methanolysis occurs to give methyl 6-nitrophthalamate (6) as a by-product.

The structure of 2 was identified by the agreement of its hydrolysis product with the known 3-hydroxy-4-nitrophthalide$^8$ (3). Structure of 6 was confirmed by its derivation to known 4 by reduction with lithium bromide-sodium borohydride and followed by hydrolysis$^9$ or by the Hofmann rearrangement followed by hydrolysis to 2-amino-6-nitrobenzoic acid.$^{10}$

As a similar reaction, 3-nitrophthalic anhydride was reduced with sodium borohydride in tetrahydrofuran at 0°, and 3, 4, and 5 were obtained but the yield of 3 was quite small. In this reaction, 3 was considered to be rapidly reduced to 4. We have already reported$^4$ the equilibrium relationship between 3 and 2-carboxy-6-nitrobenzaldehyde (3'), and the nuclear magnetic resonance (NMR) and infrared (IR) spectral data of 3-hydroxyphthalide and its derivatives are summarized in Table I. These data suggest that 3-hydroxy-4-nitrophthalide is largely in the form of 3 in solution, while both 3 and 3' are present in a crystalline state.

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10) R. Kahn, Ber., 35, 3863 (1902).
**Table I.** NMR and IR Spectra of 3-Hydroxyphthalide and Its Derivatives

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Chemical shifts of formyl or 3-methine proton (δ=ppm)</th>
<th>IR (cm⁻¹): νC=O</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Hydroxyphthalideᵃᵇ</td>
<td>6.75</td>
<td>KBr tablet</td>
</tr>
<tr>
<td>Sodium o-formylbenzoateᵃᵇ</td>
<td>10.15(CHO)</td>
<td>Solution in CHCl₂</td>
</tr>
<tr>
<td>3-Hydroxy-4-nitrophthalideᵇ (2)</td>
<td>7.06</td>
<td>1770, 1740</td>
</tr>
<tr>
<td>3-Methoxy-4-nitrophthalide</td>
<td>6.74</td>
<td>1790</td>
</tr>
<tr>
<td>3-Ethoxy-4-nitrophthalide</td>
<td>6.82</td>
<td>1784</td>
</tr>
<tr>
<td>Methyl 2-formyl-3-nitrobenzoate</td>
<td>10.65(CHO)</td>
<td>1770, 1740</td>
</tr>
</tbody>
</table>

b) Measured in d₆-dimethyl sulfoxide. Other compounds measured in CDCl₃.

**b) Reduction of 4-Nitrophthalimide**(11) (7) — Reduction of 7 under the same conditions as for 1 gave 5-nitro- (8) and 6-nitrophthalide (9), 4-nitro- (10) and 5-nitro-2-hydroxymethylbenzamide (11), and 5-nitro- (12) and 4-nitro-phthalimide (or phthalamic acid) (13). 10 and 11 were derived respectively to 8 and 9 by hydrolysis, and the carboxyl compounds of 12 and 13 were derived to methoxycarbonyl compounds with diazomethane, thereby collecting the products into four kinds of compound. Yield of the so treated products, 8, 9, and 12+13 was 21, 30, and 43.8%, respectively.

![Diagram](attachment:image.png)

**Chart 2**

12 and 13 were derived respectively to known 5-nitrophthalide(12) (8) and 6-nitrophthalide(13) (9) by reduction with lithium bromide-sodium borohydride. Structure of 12 and 13 was also determined by submitting each to the Hofmann rearrangement, conversion of the amino group into hydrogen through a diazonium salt, and deriving them respectively to methyl m- and p-nitrobenzoate, in the formation ratio of 2.6: 7.3, as indicated by gas chromatography.

From these results, it is found that reduction of the 3-nitro compound (1) results in selective reduction of the carbonyl group in 2-position, as is expected from the –I and –M

effect of the nitro group, while that of the 4-nitro compound (4) does not necessarily result in the selective reduction or solvolysis of the carbonyl group in 1-position, and there must be some factors other than the above effects in this case.

2. Sodium Borohydride Reduction of Phthalimides substituted in 3-, or 4-Position with Amino, Acetamido, Hydroxyl, or Methoxyl Group

In the reactions to be described below, phthalides and hydroxymethylbenzamides were obtained as the reduction product, and methoxycarbonyl- or carboxy-benzamides as the solvolysis product. The latter carboxyl compounds were converted to methoxycarbonyl compounds with diazomethane. The structure of these products was proved by their derivation to known phthalide derivatives by the same reactions as above, besides elemental and spectral analyses. Hydroxymethylbenzamides were hydrolyzed to phthalides, and methoxycarbonylbenzamide were reduced with lithium bromide-sodium borohydride followed by hydrolysis to phthalides.

a) Reduction of 3-Substituted Phthalimides (14) —— Results of the reaction are summarized in Table II.

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>NaBH₄ (mol)</th>
<th>Reaction temp.(°C)</th>
<th>Yield(%) of products</th>
</tr>
</thead>
<tbody>
<tr>
<td>14a(15)</td>
<td>NH₃</td>
<td>6</td>
<td>5—10</td>
<td>58</td>
</tr>
<tr>
<td>14b(16)</td>
<td>NHa</td>
<td>2</td>
<td>r.t.</td>
<td>Trace</td>
</tr>
<tr>
<td>14c(17)</td>
<td>OH</td>
<td>6</td>
<td>5—10</td>
<td>53</td>
</tr>
<tr>
<td>14d(18)</td>
<td>OMe</td>
<td>Excess</td>
<td>5—10</td>
<td>9</td>
</tr>
</tbody>
</table>

It was found that the presence of an electron-donating group in the 3-position resulted in selective reduction or solvolysis of the carbonyl group present in the position meta to such a substituent.

b) Reduction of 4-Substituted Phthalimide (18) —— Reduction was carried out under approximately the same conditions as in the case of 3-substituted compounds and its results are summarized in Table III.

![Chart 3]

In the presence of an electron-donating group in the 4-position, the carbonyl group in its para or meta position is equally reduced or solvolysed. The formation ratio was about 4: 5 for 4-subst.- (21) and 5-subst. phthalamate (22), and for 5-subst.- (19) and 4-subst.-2-hydroxymethylbenzamide (20). In this case, solvolysis product tended to be the main product.
TABLE III. Reaction Conditions and Products of 4-Substituted Phthalimides (18) with NaBH₄ in 90% MeOH

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>NaBH₄ (mol)</th>
<th>Reaction temp.(°C)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt; of products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>19a—d</td>
<td>20a—d</td>
</tr>
<tr>
<td>18a&lt;sup&gt;19&lt;/sup&gt;</td>
<td>NH₂</td>
<td>6</td>
<td>5—10</td>
<td>8.6</td>
</tr>
<tr>
<td>18b&lt;sup&gt;19&lt;/sup&gt;</td>
<td>NHAc</td>
<td>2</td>
<td>r.t.</td>
<td>7.7</td>
</tr>
<tr>
<td>18c&lt;sup&gt;20&lt;/sup&gt;</td>
<td>OH</td>
<td>6</td>
<td>5—10</td>
<td>22.3</td>
</tr>
<tr>
<td>18d&lt;sup&gt;20&lt;/sup&gt;</td>
<td>OMe</td>
<td>Excess</td>
<td>5—10</td>
<td>8.4</td>
</tr>
</tbody>
</table>

<sup>a</sup> The values refer to yields of the hydrolysis, methylation, or reduction products of 19—22 (See Experimental section).

For the preparation of phthalides or hydroxymethylbenzamides substituted with an electron-donating group, such as 15, 16, 19, and 20, it was found to be better to reduce the methanolyis product with lithium bromide-sodium borohydride rather than a direct reduction of 14 or 18 with sodium borohydride.

**Discussion**

This reduction reaction is effected by the attack of a borohydride anion on the imidocarbonyl, and its side reaction of solvolysis is due to the nucleophilic attack of the alkoxide or hydroxide with the same group. The latter reaction is considered to be produced by solvation of the imidocarbonyl, followed by the attack of that solvent as an anion on the same position as shown in the following scheme (Chart 4). Such a nucleophilic reaction is thought to depend on the electron density of the carbonyl-carbon, steric hindrance, and the solvent effect.

![Chart 4](image)

The substituent in 3-position may have a steric hindrance on the carbonyl in the adjacent 2-position, and this can also be assumed from the presence of UV absorption of 3-substituted compounds in a shorter wavelength region than that of 4-substituted compounds (Table IV). The substituent in 3-position would be twisted due to steric hindrance, resulting in some hindrance of its conjugation with the phenyl group, and this shifts its absorption to a shorter wavelength region. When there is an electron-donating group (amino, acetamido, hydroxyl, 4-R-Phthalimides

<table>
<thead>
<tr>
<th>No.</th>
<th>R</th>
<th>λ&lt;sub&gt;max&lt;/sub&gt; nm (log ε)</th>
<th>4-R-Phthalimides</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NO₄</td>
<td>226 (4.06)</td>
<td></td>
</tr>
<tr>
<td>14a</td>
<td>NH₂</td>
<td>225, 237 (4.21, 4.19)</td>
<td>18a</td>
</tr>
<tr>
<td>14b</td>
<td>NHAc</td>
<td>226.5, 234 (4.28, 4.24)</td>
<td>18b</td>
</tr>
<tr>
<td>14c</td>
<td>OH</td>
<td>222 (4.19)</td>
<td>18c</td>
</tr>
<tr>
<td>14d</td>
<td>OMe</td>
<td>227.5 (4.21)</td>
<td>18d</td>
</tr>
</tbody>
</table>
and methoxyl) in the 3-position, electron density in the carbonyl at 2-position increases, accompanied by steric hindrance, and attack of the anion on the carbonyl in 2-position becomes difficult, resulting in the attack of the carbonyl in 1-position. However, since its activity is small, solvolysis that follows solvation tends to occur preferentially than the attack of borohydride anion ($\text{BH}_4^-$).

When there is an electron-withdrawing group (nitro) in the 3-position, electron density of the carbonyl group in 2-position decreases and the carbonyl group in 1-position is in a blocked state due to solvation, resulting in a facile attack of the borohydride anion on the carbonyl in 2-position. In this case, steric hindrance is considered to be relatively small because the nitro group is greatly deviated from the phenyl plane by the electronic repulsion between two oxygen atoms of 3-nitro and 2-imidocarbonyl groups. Equilibrium between the hydroxylated compound (2) of the reduction product and 2' is thought to incline towards 2 greatly in a solution, similar to the relationship between 3 and 3'. Consequently, formation of 4-nitrophthalide (4) or 2-hydroxymethyl-3-nitrobenzamide derived from 2' is very small.

![Chart 5](image)

When there is an electron-withdrawing or electron-donating group in 4-position, attack on the anion on imidocarbonyl in 1- and 2-position is in the ratio of about 5:4 or 4:5, and this suggests that the electronic effect of such a substituent has some influence on these positions. As shown in Table III, however, there is little difference in spite of a good conjugation between the substituent in 4-position and the phenyl group. It is possible that the selectivity of the two imidocarbonyl to nucleophilic reagents is decreased by solvation and this interferes with the attack of a borohydride anion, making solvolysis preferential as illustrated below for phthalimid ehaving an electron-donating group in 4-position (Chart 6).

![Chart 6](image)

**Experimental**

Reduction of 3-Nitrophthalimide (1) with NaBH$_4$—The reduction of 1 (4.3 g) in 90% MeOH was carried out by the method described in ref. 4. The crude product was separated into two substances by the solubility in acetone. The substance, relatively insoluble in acetone, was recrystallized from acetone to give 3.9 g (89%) of 2, mp 214—215°C. The substance, easily soluble in acetone, was dissolved in saturated NaHCO$_3$ solution.

(1) All melting points were determined on a Yanagimoto micro melting apparatus and uncorrected. Boiling points were also uncorrected. IR spectra were determined on a Hitachi EPI-G3 spectrophotometer. UV spectra were measured in EtOH solutions with a Hitachi EPS-II spectrophotometer. NMR spectra were recorded at 100 MHz with JEOL Model JNM-MH-100 using tetramethylsilane (TMS) as the internal standard.
aq, and additional 160 mg of 2 was obtained by filtration. The filtrate was neutralized with conc. HCl and the precipitate was extracted with CHCl₃. The solvent was evaporated from its extract, the residue was purified by column chromatography over 2 g of Wakogel C-200 and elution of the column with benzene gave 135 mg of 4 and 81 mg of 5.

When this reduction was carried out in anhyd. MeOH, methyl 3-nitrophthalamide (6) was obtained as a by-product. 6 was derived to 4 by the same way as in the reduction of 12 (or 13) and to 2-amino-6-nitrobенzoic acid by the Hofmann rearrangement.

Reduction of 4-Nitrophthalimide (7) with NaBH₄——A solution of 1.0 g (5.2 mmol) of 7 in 10 ml of 90% MeOH was stirred at room temperature, 300 mg of NaBH₄ was added in small portions during 30 min, and the mixture was stirred for 2 hr. The solution was neutralized with 10% HCl and evaporated to dryness. The residue was extracted with (CH₃)₂CO. The solvent was evaporated from this extract, ether solution of CH₂N₂ was added to its residue, and ether was evaporated after generation of N₂ had ceased. The reaction mixture so obtained was chromatographed over 3 g of Wakogel C-200 and the column was eluted with CHCl₃. From its effluent, 3 mg of 7, 480 mg (51.5%) of a mixture of 5-nitro- (8) and 6-nitrophthalide (9), and 510 mg (48.8%) of a mixture of 5-nitro- (12) and 4-nitrophthalimide (13) were obtained. The mixture of 8 and 9 was again chromatographed over a column of Wakogel C-200 and the column was eluted with benzene–CHCl₃, affording 195.5 mg (21%) of 8, mp 150—151°, and 379 mg (80%) of 9, mp 141—142°. 8 and 9 were identified with the authentic samples.

Reduction of Methyl 4- and 5-Nitrophthalamates (12+13) with LiBr-NaBH₄——A solution of 224 mg (1 mmol) of a mixture of 12 and 13 in 1 ml of diglyme and 261 mg (3 mmol) of LiBr in diglyme was stirred at room temperature while bubbling N₂ gas, a solution of 76 mg (2 mmol) of NaBH₄ in 2 ml of dehyd. diglyme was added dropwise during 30 min, and the mixture was stirred for 3—4 hr, diglyme was distilled off as completely as possible under reduced pressure, 1 ml of 2%, HCl was added to its residue, and this was extracted with ether. The extract was dried over Na₂SO₄, ether was evaporated, and 152 mg (79%) of a mixture of 8 and 9 was obtained. Separation of 8 and 9 was made by column chromatography as above and 59 mg (33.0%) of 8 and 82 mg (45.8%) of 9 were obtained.

Preparation of Methyl p- and m-Nitrobenzoate from Methyl 4- and 5-Nitrophthalaldehyde——A mixture of 112 mg (0.5 mmol) of a mixture of 12 and 13, 5 ml of 10% NaOH, and 336 mg (2.1 mmol) of Br₂ made homogeneous by suitable addition of KI and MeOH, was stirred at room temperature for 6 hr, Br₂ was decomposed by the addition of Na₂S₂O₃, 10 ml of H₂O was added, and the solution was extracted with ether. The reaction product extracted with ether, without purification of antranilic acid derivatives, was dissolved in 50 ml of 20% HCl, chilled to 5° in an ice bath, and 165 mg (1.5 mmol) of NaNO₂ was added slowly. The mixture was stirred at below 5° for 1 hr, lyophilized, and refluxed for 4 hr in 20 ml of anhyd. EtOH. EtOH was then evaporated, a small amount of H₂O was added to its residue, and the solution was extracted with ether. This extract was dried over Na₂SO₄, ether was evaporated, and ether solution of CH₂N₂ was added to its residue. Ether was evaporated after generation of N₂ and 37 mg (40.8%) of a mixture of methyl p- and m-nitrobenzoate was obtained. Gas chromatographic comparison of this mixture with authentic samples showed the ratio of p-nitrobenzoate to m-nitrobenzoate was 7:3:2.6.

Reduction of 3-Aminophthalimide (14a) with NaBH₄——A solution of 810 mg (5 mmol) of 14a in 10 ml of 90% MeOH was cooled to below 10° in an ice bath and 1.0 g of NaBH₄ was added slowly over ca. 2 hr. The solution was adjusted to pH 6—7 with 10% HCl, MeOH was evaporated, and residue was extracted with AcOEt. The solvent was evaporated from this extract, ether solution of CH₂N₂ was added to its residue, and ether was evaporated when evolution of N₂ ceased. To this residue, 5 ml of MeOH and 10 ml of 20% HCl were added, the mixture was stirred at room temperature for 30 min, and the mixture was adjusted to pH 6—7 with Na₂CO₃. After evaporation of MeOH, the residue was extracted with CHCl₃, the extract was dried over CaCl₂, and CHCl₃ was evaporated to leave 808 mg of a mixture of 15a and 17a. This mixture was separated by column chromatography over Wako gel C-200 and elution of the column with benzene and MeOH afforded 422 mg (58%) of 7-aminophthalide (15a), mp 193—195°, and 379 mg (39%) of methyl 3-aminophthalaldehyde (17a). Reduction of 194 mg (1 mmol) of 17a with LiBr-NaBH₄ as above gave 113 mg of 15a. 15a was identified with the authentic sample.

Reduction of 3-Acetamidophthalimide (14b) with NaBH₄——A solution of 1.0 g of 14b dissolved in 10 ml of 90% MeOH was stirred at room temperature and 380 mg of NaBH₄ was added slowly during 2 hr. This mixture was neutralized with 10% AcOH and the solution was evaporated to dryness under reduced pressure. The completely dried residue was extracted with (CH₃)₂CO and the extracted residue was purified by column chromatography over 10 g of Wakogel C-200. Elution of the column with benzene and MeOH gave 322 mg (91%) of 3-acetamide-6-hydroxybenzamidine (16b) and 780 mg (60%) of methyl 3-acetaminophthalaldehyde (17b), with recovery of 13 mg (1.3%) of 14b. A solution of 16b in 5 ml of 20% HCl was stirred at room temperature for 4 hr and extraction of its residue gave 233 mg (91% from 16b) of 15a. Reduction of 17b with LiBr-NaBH₄ and hydrolysis of its product gave 256 mg (52% from 17b) of 15a.

15) H. Kauffmann and A. Beisswenger, Bcr., 36, 2496 (1903).
Reduction of 3-Hydroxyphthalimide\(^{17}\) (14c) with NaBH\(_4\) — A solution of 1.63 g (0.01 mol) of 14c in 20 ml of 90% MeOH was cooled to below 10\(^\circ\) in an ice bath, 2.0 g of NaBH\(_4\) was added slowly during 1 hr while stirring, and the mixture was stirred for 2 hr at below 10\(^\circ\). The reaction mixture was neutralized with 10% HCl, evaporated to dryness under reduced pressure, and ether solution of CH\(_2\)N\(_2\) was added to the residue. This mixture was kept at 5\(^\circ\) for 12 hr, filtered, and the filtrate was dried over Na\(_2\)SO\(_4\). Ether was evaporated from the dried filtrate and the residue was purified by column chromatography over 15 g of Wakogel C-200. Elution of the column with benzene and MeOH gave 870 mg (53% from 14c) of 7-methoxyphthalimide (15d) and 729 mg (35% from 14c) of methyl 3-methoxyphthalalamide (17d). Reduction of 17d with LiBr–NaBH\(_4\) gave 485 mg (29.6%) of 15d. 15d: colorless crystals, mp 90\(^\circ\) (from n-hexane). M\(^+\) 164.044 (164.047 calcd. for C\(_8\)H\(_7\)O\(_2\)). IR \(\nu_{\text{max}}\) cm\(^{-1}\): 1769, 1739 (CO). NMR (CDCl\(_3\)): \(\delta\) 4.07 (3H, s, OCH\(_3\)), 5.32 (2H, s, CH\(_2\)), 6.9–7.7 (3H, m, aromatic protons).

Reduction of 3-Methoxyphthalimide\(^{18}\) (14d) with NaBH\(_4\) — Reduction of 885 mg (5 mmol) of 14d in 10 ml of 90% MeOH with 1.0 g of NaBH\(_4\) as in the case of 14c, without treatment with CH\(_2\)N\(_2\), gave 74 mg (9%) of 15d and 808 mg (82%) of 17d.

Reduction of 4-Aminophthalimide\(^{19}\) (18a) with NaBH\(_4\) — A solution of 810 mg (5 mmol) of 18a in 10 ml of 90% MeOH was cooled to below 10\(^\circ\) by stirring in ice bath, 1.0 g of NaBH\(_4\) was added slowly, and the mixture was stirred at the temperature for 2 hr. This was neutralized with 10% AcOH, evaporated to dryness under reduced pressure, and the residue was extracted with MeOH. Ether solution of CH\(_2\)N\(_2\) was added to the MeOH extract and the solvent was evaporated after evaporation of N\(_2\) ceased. The residue was purified by column chromatography over 10 g of Wakogel C-200 and elution of the column with benzene and then with MeOH gave 756.6 mg (78%) of a mixture of 4-aminophthalimide (21a) and 5-aminophthalalamide (22a), and then 137.7 mg (19%) of a mixture of 5-aminophthalalamide (19a), and 4-aminophthalalamide (20a). The mixture of 19a and 20a was refluxed in 50 ml of 20% HCl for 1 hr and the hydrolysis product was extracted with CHCl\(_3\). The residue obtained after evaporation of CHCl\(_3\) was purified by column chromatography over 5 g of Wakogel C-200 and elution of the column with benzene gave 76 mg (10.4%) of 5-aminophthalalamide\(^{7}\) (23a), mp 194–196\(^\circ\) and 63 mg (8.6%) of 6-aminophthalimide\(^{9}\) (24a), mp 179–181\(^\circ\). 23a and 24a were identified with the authentic samples.

The mixture of 21a and 22a was reduced with LiBr–NaBH\(_4\), its product of hydrolyzed, and purification of its product gave 265 mg (35.5% from 18a) of 23a and 197 mg (26.4% from 18a) of 24a.

Reduction of 4-Acetamidophthalimide\(^{10}\) (18b) with NaBH\(_4\) — To a solution of 1.0 g of 18b dissolved in 10 ml of 90% MeOH, 200 mg of NaBH\(_4\) was added in small portions and the mixture was stirred for 2 hr. The reaction mixture was neutralized with 10% HCl, evaporated to dryness, and the residue was extracted with (CH\(_3\)\(_2\))CO. After evaporation of (CH\(_3\)\(_2\))CO from the extract, ether solution of CH\(_2\)N\(_2\) was added to its residue and ether was evaporated under reduced pressure when evolution of N\(_2\) ceased. The residue so obtained was purified by column chromatography over 5 g of Wakogel C-200 and elution of the column with benzene and MeOH gave 931 mg (79%) of a mixture of 4-acetamino- (21b) and 5-acetamidophthalalamide (22b), and 172 mg (17%) of a mixture of 5-acetamido- (19b) and 4-acetamido-2-hydroxyphenylbenzamide (20b). The mixture of 19b and 20b was refluxed with 10 ml of 20% HCl for 2 hr, the product was extracted with CHCl\(_3\), and the solvent was evaporated after drying the extract over Na\(_2\)SO\(_4\). This residue was purified by column chromatography over 1.5 g of Wakogel C-200 and elution of the column with benzene gave 70 mg (8.6%) of 23a and 56.6 mg (7.7%) of 24a.

Reduction of 4-Hydroxyphthalimide\(^{10}\) (18c) with NaBH\(_4\) — A solution of 1.60 g (10 mmol) of 18c in 20 ml of 90% MeOH was cooled to below 10\(^\circ\) by stirring in ice bath, 2.0 g of NaBH\(_4\) was added in small portions, and the mixture was stirred at below 10\(^\circ\) for 2 hr. This reaction mixture was neutralized with 10% HCl, the solvent was evaporated under reduced pressure, and the residue was extracted with (CH\(_3\)\(_2\))CO. The solvent was evaporated from this extract, added to the residue, and ether was evaporated when evolution of N\(_2\) ceased. The residue was purified by column chromatography over 18 g of Wakogel C-200 and elution of the column with benzene-MeOH (50:1) gave a mixture of 5-hydroxy- (19d) and 4-hydroxy-2-hydroxyphenylbenzamide (20d), and a mixture of 4-hydroxy- (21d) and 5-hydroxyphthalalamide (22d). The mixture of 19d and 20d was refluxed with 20 ml of 10% HCl for 1 hr, HCl was distilled off, and its residue was purified by column chromatography over 10 g of Wakogel C-200. Elution of the column with benzene gave 455 mg (27.6%) of 5-methoxyphthalalamide (23d), mp 118–119\(^\circ\) and 363 mg (22.3%) of 6-methoxyphthalalamide (24d), mp 119–120\(^\circ\). 23d and 24d were identified with the authentic samples.

Reduction of 739 mg of a mixture of 21d and 22d with LiBr–NaBH\(_4\), hydrolysis of its product, and purification of the hydrolysis product by column chromatography gave 340.5 mg (20.9%) of 23d and 250.5 mg (15.4%) of 24d.

17) J.V. Braun, Ber., 56, 2342 (1923).
Reduction of 4-Methoxyphthalimide$^{20}$ (18d) with NaBH$_4$—A solution of 885 mg (5 mmol) of 18d in 10 ml of 90\% MeOH was cooled to below 10° by stirring in an ice bath, 1.0 g of NaBH$_4$ was added, and the mixture was stirred for 2 hr. This reaction mixture was neutralized with 10\% HCl, evaporated to dryness under reduced pressure, and the residue was extracted with (CH$_3$)$_2$CO. The solvent was evaporated from this extract and the residue was purified by column chromatography to give 172 mg (19\%) of a mixture of 5-methoxy- (19d) and 4-methoxy-2-hydroxymethylbenzamide (20d) as the reduction products. Hydrolysis of this mixture gave 87 mg (10.6\%) of 5-methoxyphthalide$^{22}$ (23d) and 69 mg (8.4\%) of 6-methoxyphthalide$^{25}$ (24d). Another product of solvolysis, 815 mg (78\%) of a mixture of 4-methoxy- (21d) and 5-methoxyphthalalamate (22d), was also obtained and this mixture was reduced with LiBr-NaBH$_4$ followed by hydrolysis to give the mixture of phthalides which was separated into 302 mg (43.0\%) of 23d and 294 mg (35.9\%) of 24d.