[Chem. Pharm Bull. 26(2) 530—538 (1978)]

UDC 547.584.04 : 546.271.04

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

Tokuhiro Watanabe, Fumiko Hamaguchi, and Sadao Ohki

Tokyo College of Pharmacy[2]

(Received July 1, 1977)

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; $NaBH_4$ reduction; phthalides; 3-hydroxyphthalides; solvolysis of phthalimides; LiBr-$NaBH_4$ 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-alkylglutarimides, 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 acid[4] and 5-aminophthalazine derivatives[5] 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 others[6] 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[4] was re-examined. Reduction of **1** with 2 mol of sodium borohydride in 90% methanol gave **2**, 4-nitrophthalide[7] (**4**), and

1) Part II: T. Watanabe, F. Hamaguchi, and S. Ohki, *Yakugaku Zasshi*, 93, 845 (1973).
2) Locafion: *1432–1 Horinouchi, Hachioji, Tokyo, 192–03, Japan.*
3) S. Ohki, T. Watanabe, M. Uchiyama, E. Ozawa, and F. Hamaguchi, *Yakugaku Zasshi*, 93, 841 (1973).
4) T. Watanabe, F. Hamaguchi, and S. Ohki, *Chem. Pharm. Bull.* (Tokyo), **20**, 2123 (1972).
5) T. Watanabe, F. Hamaguchi, and S. Ohki, *Yakugaku Zasshi*, **96**, 721 (1976).
6) Z. Horii, C. Iwata, and Y. Tamura, *J. Org. Chem.*, **26**, 2273 (1961).
7) J. Tirouflet, *Bull. Soc. Sci. Bretargne Spec.*, 7 (1951) [*C.A.*, **47**, 8692*h* (1953)].

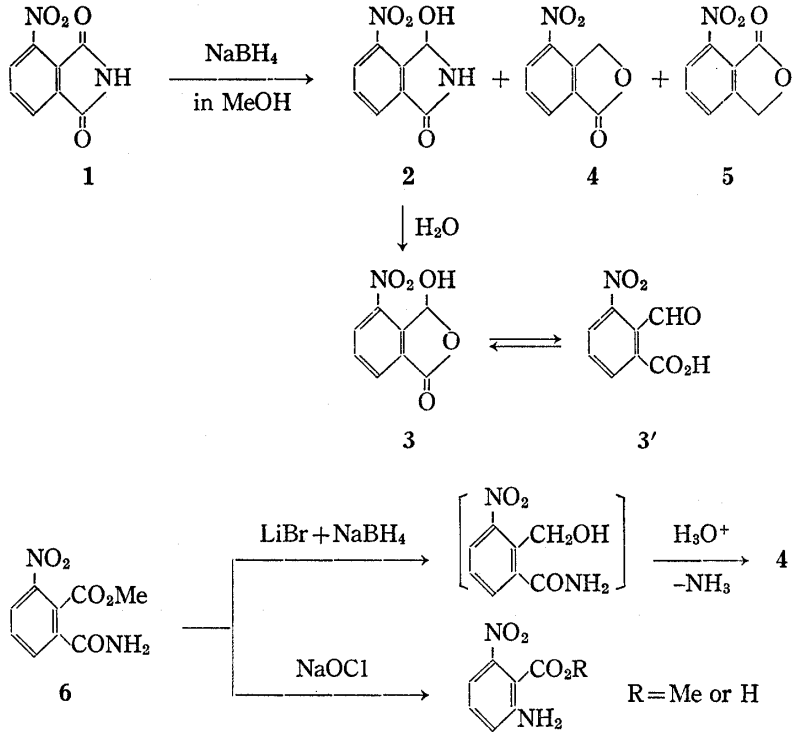


Chart 1

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[4] (**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]

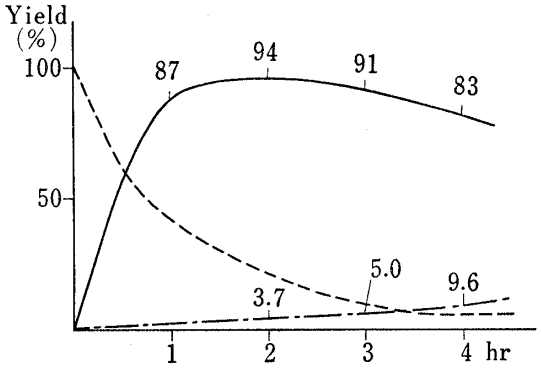


Fig. 1. Formation Ratio of **2** and **4**+**5** with respect to Reaction Time

——: **2**,
——: **4**+**5**,
----------: $NaBH_4$.

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.

8) G. Wenner and R. Keller, Ger. 1126873 (Cl, 120), Apr. 5, 1962, Appl. Feb. 20, 1960 [*C.A.*, **57**, 7178*f* (1962)]; G. Wenner and R. Keller, Ger. 1154809 (Cl, CO7d), Sept. 26, 1963, Appl. Feb. 13, 1960 [*C.A.*, **60**, 5402*f* (1964)].
9) H.C. Brown, E.T. Mead, and B.C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).
10) R. Kahn, *Ber.*, **35**, 3863 (1902).

Table I. NMR and IR Spectra of 3-Hydroxyphthalide and Its Derivatives

Compounds	Chemical shifts of formyl or 3-methine proton (δ=ppm)	IR (cm^{-1}): $\nu_{C=O}$ KBr tablet	IR (cm^{-1}): $\nu_{C=O}$ Solution in $CHCl_3$
3-Hydroxyphthalide[a]	6.75		
Sodium *o*-formylbenzoate[a,b]	10.15(CHO)		
3-Hydroxy-4-nitrophthalide[b] (**2**)	7.08	1770, 1740	1780
3-Methoxy-4-nitrophthalide	6.74	1790	
3-Ethoxy-4-nitrophthalide	6.82	1784	
Methyl 2-formyl-3-nitrobenzoate	10.65(CHO)	1770, 1740	

a) J. Kagan, *J. Org. Chem.*, **32**, 4060 (1967).
b) Measured in d_6-dimethyl sulfoxide. Other compounds measured in $CDCl_3$.

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-phthalamate (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.

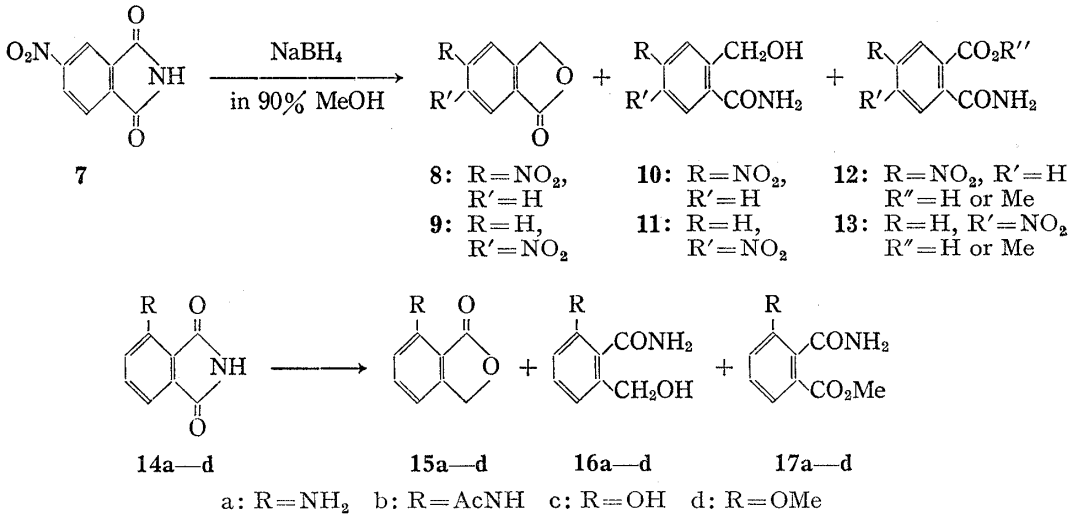


Chart 2

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

11) E.H. Hunterss and R.L. Shriner, "Organic Syntheses," Coll. Vol. II, ed. by A.H. Blatt, John Wiley & Sons, Inc., New York, 1950, p. 459.
12) A. Tasman, *Rec. Trav. Chim.*, **46**, 653 (1927) [*C.A.*, **22**, 240 (1928)].
13) S. Wanzonek, *J. Am. Chem. Soc.*, **68**, 1157 (1946).

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.

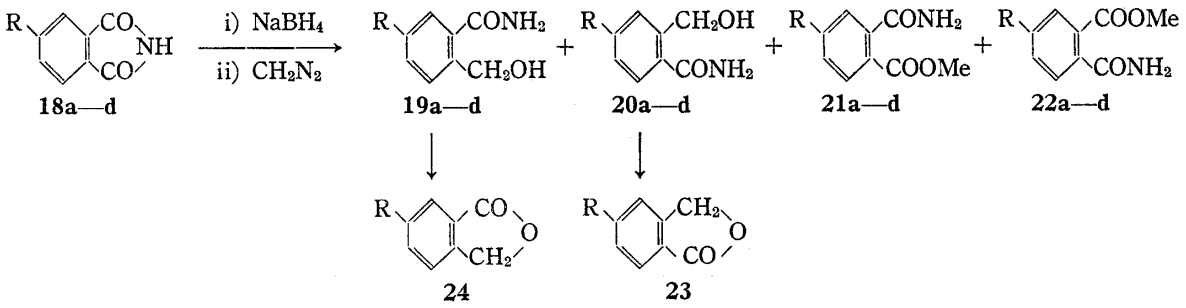
Table II. Reaction Conditions and Products of 3-Substituted Phthalimides (**14**) with $NaBH_4$ in 90% MeOH

Compd. No.	R	$NaBH_4$ (mol)	Reaction temp.(°C)	Yield(%) of products		
				15a—d	**16a—d**	**17a—d**
14a[15]	NH_2	6	5—10	58[a]		39
14b[16]	NHAc	2	r.t.	Trace	31	66
14c[17]	OH	6	5—10	53[b]		35
14d[18]	OMe	Excess	5—10	9	Trace	82

a) Added in **15a** derived from **16a**.
b) Indicated the yield of **15b** derived from **15c**.

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.



a: R=NH_2 b: R=NHAc c: R=OH d: R=OMe

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 $NaBH_4$ in 90% MeOH

Compd. No.	R	$NaBH_4$ (mol)	Reaction temp.(°C)	Yield (%)[a] of products			
				19a—d	**20a—d**	**21a—d**	**22a—d**
18a[19]	NH_2	6	5—10	8.6	10.4	26.4	35.5
18b[19]	NHAc	2	r.t.	7.7	9.6	27.9	35.0
18c[20]	OH	6	5—10	22.3	27.6	15.4	20.9
18d[20]	OMe	Excess	5—10	8.4	10.6	35.9	43.0

a) 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 methanolysis 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.

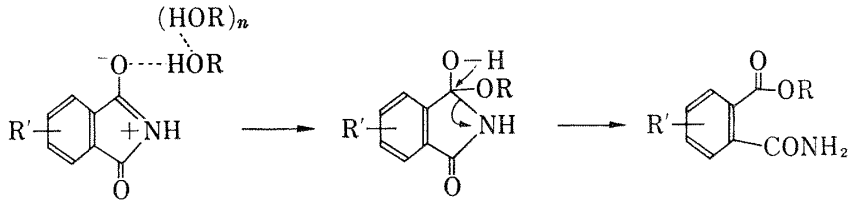


Chart 4

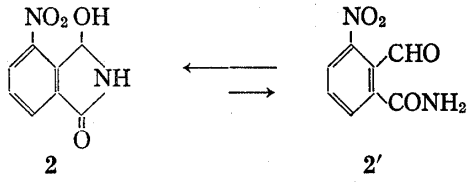
The substituent in 3-position may have a steric hindrance on the carbonyl in the adjacent 2-position, and this can also be assumed from the presence of UV absorption of 3-substituted compounds in a shorter wavelength region than that of 4-substituted compounds (Table IV). The substituent in 3-position 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,

Table IV. UV Spectra of 3- and 4-Substituted Phthalimides in EtOH

3-R-Phthalimides			4-R-Phthalimides		
No.	R	λ_{max}^{EtOH} nm (log ε)	No.	R	λ_{max}^{EtOH} nm (log ε)
1	NO_2	226 (4.06)	**7**	NO_2	233 (4.13)
14a	NH_2	225, 237 (4.21, 4.19)	**18a**	NH_2	245, 257 (4.36, 4.30)
14b	NHAc	226.5, 234 (4.28, 4.24)	**18b**	NHAc	249, 255 (4.34, 4.29)
14c	OH	222 (4.19)	**18c**	OH	225 (4.23)
14d	OMe	227.5 (4.21)	**18d**	OMe	234.5 (4.26)

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 (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.



2 **2′**

Chart 5

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 phthalimide having an electrondonating group in 4-position (Chart 6).

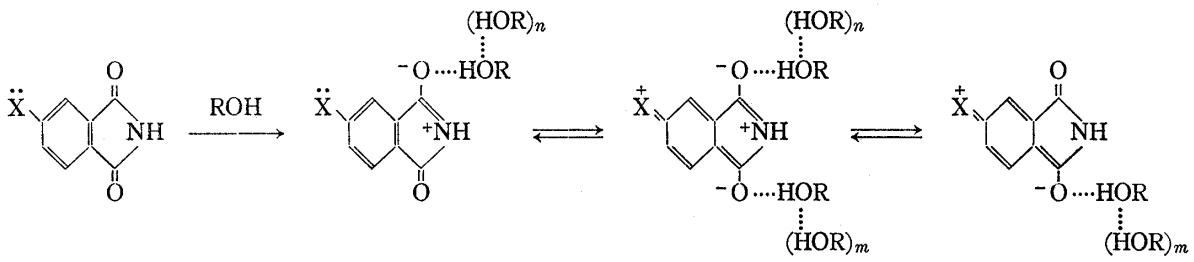


Chart 6

Experimental[14]

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°. The substance, easily soluble in acetone, was dissolved in saturated $NaHCO_3$

14) 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 $CHCl_3$. 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-nitrophthalamate (**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-nitrobenzoic acid[10] by the Hofmann rearrangement.

Reduction of 4-Nitrophthalimide (7) with $NaBH_4$——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 $NaBH_4$ 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 $(CH_3)_2CO$. The solvent was evaporated from this extract, efher solution of CH_2N_2 was added to its residue, and ether was evaporated after generation of N_2 had ceased. The reaction mixture so obtained was chromatographed over 3 g of Wakogel C-200 and the column was eluted with $CHCl_3$. 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 (43.8%) of a mixture of 5-nitro- (**12**) and 4-nitrophthalamate (**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–$CHCl_3$, affording 195.5 mg (21%) of **8**, mp 150—151°, and 279 mg (30%) of **9**, mp 141—142°. **8** and **9** were identified with the authentic samples.[12,13]

Reduction of Methyl 4- and 5-Nitrophthalamates (12+13) with LiBr-$NaBH_4$——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 N_2 gas, a solution of 76 mg (2 mmol) of $NaBH_4$ 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 Na_2SO_4, 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-Nitrophthalamate——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 Br_2, made homogeneous by suitable addition of KI and MeOH, was stirred at room temperature for 6 hr, Br_2 was decomposed by the addition of $Na_2S_2O_4$, 10 ml of H_2O was added, and the solution was extracted with ether. The reaction product extracted with ether, without purification of anthranilic acid derivatives, was dissolved in 50 ml of 20% HCl, chilled to 5° in an ice bath, and 105 mg (1.5 mmol) of $NaNO_2$ 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 H_2O was added to its residue, and the solution was extracted with ether. This extract was dried over Na_2SO_4, ether was evaporated, and ether solution of CH_2N_2 was added to the residue. ether was evaporated after generation of N_2 had ceased 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[15] (14a) with $NaBH_4$——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 $NaBH_4$ 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 CH_2N_2 was added to its residue, and ether was evaporated when evolution of N_2 ceased. To this residue, 5 ml of MeOH and 10 ml of 20% HCl were added, the miature was stirred at room tempereture for 30 min, and the mixture was adjusted to pH 6—7 with Na_2CO_3. After evaporation of MeOH, the residue was extracted with $CHCl_3$, the extract was dried over $CaCl_2$, and $CHCl_3$ was evaporated to leave 808 mg of a mixture of **15a** and **17a**. This mixture was separated by column chromatography over wakogel 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-aminophthalamate (**17a**). Reduction of 194 mg (1 mmol) of **17a** with LiBr–$NaBH_4$ as above gave 113 mg of **15a**. **15a** was identified with the authentic sample.[7]

Reduction of 3-Acetamidophthalimide[16] (14b) with $NaBH_4$——A solution of 1.0 g of **14b** dissolved in 10 ml of 90% MeOH was stirred af room temperature and 380 mg of $NaBH_4$ 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 $(CH_3)_2CO$ 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 (31%) of 2-acetamido-6-hydroxymethylbenzamide (**16b**) and 780 mg (66%) of methyl 3-acefaminophthalamafe (**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** wifh LiBr-$NaBH_4$ and hydrolysis of its product gave 256 mg (52% from **17b**) of **15a**.

15) H. Kauffmann and A. Beisswengen, *Ber.*, **36**, 2496 (1903).
16) M.T. Bogert and F.L. Jouard, *J. Am. Chem. Soc.*, **31**, 488 (1909).

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° 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°. The reaction mixture was neutralized with 10% HCl, evaporated to dryness under reduced pressure, and ether solution of CH_2N_2 was added to the residue. This mixture was kept at 5° for 12 hr, filtered, and the filtrate was dried over Na_2SO_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-methoxyphthalide (**15d**) and 729 mg (35% from **14c**) of methyl 3-methoxyphthalamate (**17d**). Reduction of **17d** with LiBr–$NaBH_4$ gave 485 mg (29.6%) of **15d**. **15d**: colorless crystals, mp 90° (from *n*-hexane). M^+ 164.044 (164.047 calcd. for $C_9H_8O_3$). IR ν_{max}^{Nujol} cm^{-1}: 1769, 1739 (CO). NMR ($CDCl_3$) δ: 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_2N_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° by stirring in an 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_2N_2 was added to the MeOH extract and the solvent was evaporated after evolution 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-amino- (**21a**) and 5-aminophthalamafe (**22a**), and then 157.7 mg (19%) of a mixture of 5-amino- (**19a**) and 4-amino-2-hydroxymethylbenzamide (**20a**). The mixture of **19a** and **20a** was refluxed in 50 ml of 20% HCl for 1 hr and the hydrolysis product was extracfed 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-aminophthalide[7] (**23a**), mp 194—196° and 63 mg (8.6%) of 6-aminophthalide[7] (**24a**), mp 179—181°. **23a** and **24a** were identified with the authentic samples.[7]

The mixture of **21a** and **22a** was reduced with LiBr–$NaBH_4$, its product of hydrolyzed, and purificafton 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[20] (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 $(CH_3)_2CO$. After evaporation of $(CH_3)_2CO$ from the extract, ether solution of CH_2N_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-acetamidophthalamate (**22b**), and 172 mg (17%) of a mixture of 5-acetamido- (**19b**) and 4-acetamido-2-hydroxymethylbenzamide (**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_2SO_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 (9.6%) of **23a** and 56.6 mg (7.7%) of **24a**.

Reduction of the mixture of **21b** and **22b** with LiBr–$NaBH_4$ and hydrolysis of its product gave 254.8 mg (35.0%) of **23a** and 204 mg (27.9%) of **24a**.

Reduction of 4-Hydroxyphthalimide[20] (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° by stirring in an ice bath, 2.0 g of $NaBH_4$ was added in small portions, and the mixture was stirred at below 10° for 2 hr. This reaction mixture was neutralized with 10% HCl, the solvent was evaporated under reduced pressure, and the residue was extracted with $(CH_3)_2CO$. The solvent was evaporated from this extract, was added to the residue, and ether was evaporated when evolution of N_2 ceased. The residue was purified by column chromatography over 16 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-hydroxymethylbenzamide (**20d**), and a mixture of 4-hydroxy- (**21d**) and 5-hydroxyphthalamate (**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-methoxyphthalide (**23d**), mp 118—119° and 363 mg (22.3%) of 6-methoxyphthalide (**24d**), mp 119—120°. **23d** and **24d** were identified with the authentic samples.[7]

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).
18) W.H. Bentley, R. Robinson, and C. Weizmann, *J. Chem. Soc.*, **1907**, 104.
19) M.T. Bogert and L.R. Renshaw, *J. Am. Chem. Soc.*, **30**, 1141 (1908).

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 $(CH_3)_2CO$. 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[7] (**23d**) and 69 mg (8.4%) of 6-methoxyphthalide[7] (**24d**). Another product of solvolysis, 815 mg (78%) of a mixture of 4-methoxy- (**21d**) and 5-methoxyphthalamate (**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 362 mg (43.0%) of **23d** and 294 mg (35.9%) of **24d**.

20) W.H. Bentley and C. Weizmann, *J. Chem. Soc.*, **1907**, 100.