to a mixture of a mercaptan (5–20 mole equivalents) and triethylamine (1.5–5 mole equivalents) at −20° (if methanethiol is employed) or at 0° (if ethanethiol or 1-butanethiol are used). The reaction mixture is allowed to warm to room temperature upon stirring. The precipitated triethylamine hydrochloride is filtered off and washed with ether or petroleum ether (b.p. 30–40°). The wash solvent, excess triethylamine, and the dialkyl disulfide formed are removed from the filtrate by distillation. If the reaction product is volatile, the residue is fractionated *in vacuo* to give the desired dichloromethyl substituted compound (II, IV, VI, VIII, or X) and a higher boiling, sulfur-containing material (XI and XIII were thus obtained in pure form and identified as mercaptals). If the reaction product is a solid, the residue is recrystallized from suitable solvents to isolate the dichloromethyl compound (II was isolated in one experiment by recrystallization of the residue from ligroin; compound IX was purified by dissolving the residue in ether and reprecipitation with ligroin, the mercaptal XII was contained in the triethylamine hydrochloride filter cake and was separated and purified by crystallization from water).

(b) Hydrogen sulfide was passed into a solution of 33 g. of 2,4,6-tris(trichloromethyl)-s-triazine (I) and 35.1 g. of triethylamine in 200 ml. of ether at 0° for 7 hr. The reaction mixture was allowed to stand for 12 hr. at room temperature. Then, 250 ml. of ether were added to the reaction mixture, the salts and sulfur formed were removed by filtration, and the ether distilled from the filtrate. The resulting dark residue was recrystallized from 25 ml. of ligroin. Upon cooling to −20°, crystals and an oily product separated from the ligroin. The crystals were collected and freed from adhering oil by pressing on a clay plate. Thus, 5.96 g. of 2,4,6-tris(dichloromethyl)-s-triazine (II) was isolated.

Compounds prepared according to these procedures are listed in Tables I and II. Dichloromethyl compounds for which an analysis is not recorded were identified either by a mixed melting point or by comparing the boiling point and refractive index with an authentic sample.

Acknowledgment. The author is indebted to the Olin Mathieson Chemical Corporation for its generous support of this work.

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(7) Ch. Grundmann, G. Weisse, and S. Seide, *Ann.*, **577**, 77 (1952).

(8) A. Pinner and F. Fuchs, *Ber.*, **10**, 1066 (1877).

(9) Ch. Grundmann and E. Kober, *J. Am. Chem. Soc.*, **79**, 944 (1957).

(10) J. W. Brühl, *Ann.*, **203**, 22 (1880).

[Contribution from the School of Pharmacy, Osaka University]

Reduction of Phthalimides with Sodium Borohydride

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Reduction of phthalimide derivatives with sodium borohydride in methanol results in the formation of 3-hydroxyphthalimidines (II), or a mixture of II and *o*-hydroxymethylbenzamides III depending on the amount of reducing agent present. The mechanism of this reduction is proposed.

Although it has been known that the imido group does not undergo reduction by sodium borohydride,[1] we have found that *N*-(6-oxo-5,6,7,8-tetrahydro-1-naphthyl)phthalimide is reduced by sodium borohydride in methanol to *o*-hydroxymethyl-*N*-(6-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)benzamide. It would be of interest to establish this novel reduction of the phthalimide since sodium borohydride has prominent selectivities toward various groups on reduction and, thus, this reduction may be expected to serve as a useful preparative method. The present paper describes the reduction of the phthalimide derivatives (Ia–i) shown in Fig. 1 with sodium borohydride.

The reduction was carried out by adding a methanolic solution of sodium borohydride to a suspension of the phthalimide in methanol at 25–30°, followed by stirring at this temperature for seven to ten hours. When two molecular equivalents of sodium borohydride was employed, the product was the 3-hydroxyphthalimidine (II) or a mixture of II and the *o*-hydroxymethylbenzamide (III). Thus, phthalimide (Ia) and *N*-methylphthalimide (Ib) were converted to 3-hydroxyphthalimidine (IIa) and 3-hydroxy-2-methylphthalimidine (IIb) in yields of 66% and 56%, respectively. Similarly, *N*-(*p*-nitrophenyl)phthalimide (Ii) was converted to 3-hydroxy-2-(*p*-nitrophenyl)phthalimidine (IIi) in 81% yield. Compounds IIa and IIb were prepared previously by reduction with zinc in sodium hydroxide solution[2] or with magnesium and ammonium chloride in methanol,[3]

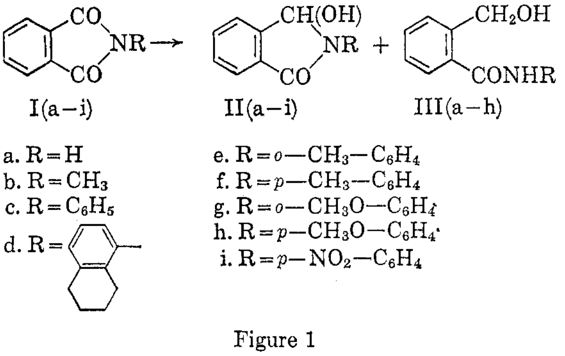

Figure 1

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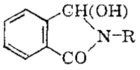
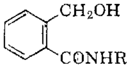
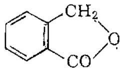
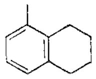
(1) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience, New York, 1956, p. 629.

(2) A. Reissert, *Ber.*, 46, 1484 (1913).

(3) A. Dunet and A. Willemart, *Bull. soc. chim. France*, 1081 (1948).

TABLE I

REDUCTION PRODUCTS OF THE PHTHALIMIDES WITH $NaBH_4$

R	Reaction Temp.	Reaction^{c} Time, Hr.	Yield, %			Method of Separation of Products
			 II	 III		
H^{a}	25–30°	7	66	—	3	^{d}
H^{b,f}	25–30°	14	—	45	30	^{d}
CH_3^{a}	25–30°	7	56.3	—	14.3	^{a}
C_6H_5^{a}	25–30°	7	23.5	50	—	^{e}
C_6H_5^{a}	50–53°	5	16	45	15	^{d,e}
C_6H_5^{a}	Reflux (CH_3OH)	5	—	40	33	^{d}
C_6H_5^{b}	25–30°	14	—	92	—	^{d}
	25–30°	7	37	55	—	^{d}
o-$CH_3C_6H_4$^{a}	25–30°	7	23	66	—	^{d,e}
p-$CH_3C_6H_4$^{a}	25–30°	10	40	37	—	^{e}
o-$CH_3OC_6H_4$^{a}	25–30°	8	27	40	—	^{d,e}
p-$CH_3OC_6H_4$^{a}	25–30°	8	18	47	—	^{e}
p-$NO_2C_6H_4$^{a}	25–30°	8	81	—	—	^{d}

[a] With two molecular equivalents of $NaBH_4$. [b] With four molecular equivalents of $NaBH_4$. [c] After completion of the addition of $NaBH_4$. [d] Products were separated by procedure (i) in the general method. [e] Products were separated by procedure (ii) in the general method. [f] The reduction was carried out using the same procedure as in the reduction of Ic by procedure c.

but this new reduction method with sodium borohydride offers a more convenient and reproducible method for these materials. However, the reductions of the other phthalimides investigated gave mixtures of the 3-hydroxyphthalimidine (II) and the *o*-hydroxymethylbenzamide (III), as indicated in Table I.

On the other hand, employment of four molecular equivalents of sodium borohydride in the reduction resulted in an increase in yield of III, accompanied with a simultaneous decrease in yield of II. Thus, the reduction of Ia with four moles of sodium borohydride gave *o*-hydroxymethylbenzamide (IIIa) in 45% yield, accompanied with the 30% yield of phthalide, instead of IIa. The formation of the phthalide, which was also observed to a lesser extent during the reduction of Ia and Ib using two moles of sodium borohydride, is ascribable to hydrolysis of IIIa. In the reduction of *N*-phenylphthalimide (Ic) with the four moles of sodium borohydride only *o*-hydroxymethyl-*N*-phenylbenzamide (IIIc) was obtained in 92% yield, although the reduction with two moles of sodium borohydride gave a mixture of 3-hydroxy-2-phenylphthalimidine (IIc) (24% yield) and *o*-hydroxymethyl-*N*-phenylbenzamide (IIIc) (50% yield).[4] This reduction provides a new preparative method for phthalide, since IIIc was hydrolyzed with ethanolic sodium hydroxide to yield phthalide in quantitative yield.

In view of the results obtained in the reductions of Ic or Ia, it seems reasonable that the first reaction of sodium borohydride on the phthalimide (Ic) produces the phthalimidine (IIc), which is converted slowly to IIIc with an excess of sodium borohydride. This is also supported by the conversion of IIc into IIIc in 96% yield under exactly the same reduction conditions.[5] It has been observed that the reduction of some compounds containing the —N—C—O— grouping, with lithium aluminum hydride or sodium borohydride, resulted in cleavage of the carbon-nitrogen bond. The reduction of the *N*-acyl heterocyclic compounds,[6] the *N*-acyl-*N*-sulfonyl compounds,[7] the *N*-mono or dialkyl (or aryl) amides (including the lactam),[6,8] the *N*,*N*-diacyl amines,[6,9] etc., with lithium alumi-

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[4] On the reduction of Ic with two moles of sodium borohydride, raising a reaction temperature up to 50–67° did not improve the yields of IIc and IIIc, but prompted the formation of phthalide.

[5] The catalytic reduction of IIc over palladium-charcoal in dioxane or dioxane–glacial acetic acid at room temperature did not proceed.

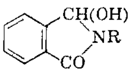
[6] N. G. Gaylord, *Reduction with Complex Metal Hydride*, Interscience, New York, 1956, pp. 575–590, 601, 619–622.

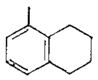
[7] A. Mustafa, *J. Chem. Soc.*, 2435 (1952); Z. Pravda and J. Rudinger, *Chem. listy.*, **48**, 1663 (1954).

[8] F. Galinovsky and R. Weiser, *Experientia*, **6**, 377 (1950); F. Galinovsky, A. Wagner, and R. Weiser, *Mh. Chem.*, **82**, 551 (1951); D. G. M. Diaper, *Can. J. Chem.*, **29**, 964 (1951); F. Weygand, G. Eberhardt, H. Linden, F. Schäfer, and I. Eigen, *Angew. Chem.*, **65**, 525 (1953); M. Davis, *J. Chem. Soc.*, 3981 (1956); H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, **81**, 502 (1959).

[9] E. Testa, L. Fontanella, G. F. Cristiani, and L. Mariani, *Helv. Chim. Acta*, **42**, 2370 (1959).

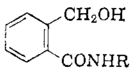
TABLE II

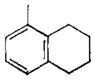
CHARACTERISTICS OF THE 3-HYDROXYPHTHALIMIDINES 

R	M.P.[a]	Recryst. from	Formula	Found, % C	Found, % H	Found, % N	Calcd., % C	Calcd., % H	Calcd., % N	Infrared Spectrum (in Nujol), —CO—N—R Cm.$^{-1}$, Amide I
H	179[b]	H_2O	$C_8H_7NO_2$	64.15	4.72	9.35	64.42	4.73	9.39	1698
CH_3	130[c]	$CH_3COOC_2H_5$	$C_9H_9NO_2$	66.21	5.49	8.66	66.24	5.56	8.58	1672
C_6H_5	171–172[d]	$CH_3COOC_2H_5$	$C_{14}H_{11}NO_2$	74.66	5.07	6.15	74.65	4.92	6.22	1689
	201	$C_2H_5OH—H_2O$	$C_{18}H_{17}NO_2$	77.54	6.09	5.01	77.39	6.13	5.01	1669 1692
o-$CH_3—C_6H_4$	192–193	$C_2H_5OH—H_2O$	$C_{15}H_{13}NO_2$	75.30	5.50	5.85	75.30	5.48	5.85	1672
p-$CH_3—C_6H_4$	167	$C_2H_5OH—H_2O$	$C_{15}H_{13}NO_2$	74.98	5.41	5.93	75.30	5.48	5.85	1664
o-$CH_3O—C_6H_4$	189–190	$CH_3COOC_2H_5$	$C_{15}H_{13}NO_3$	70.67	5.24	5.46	70.58	5.13	5.49	1669
p-$CH_3O—C_6H_4$	156	$CH_3COOC_2H_5$	$C_{15}H_{13}NO_3$	70.64	5.20	5.51	70.58	5.13	5.49	1661 1678
p-$NO_2—C_6H_4$	251–252	CH_3COOH	$C_{14}H_{10}N_2O_4$	62.33	3.89	10.24	62.22	3.73	10.37	1692

[a] Uncorrected. [b] Reported m.p. 178°, A. Dunet and A. Willemart, *Compt. rend.*, **226**, 821 (1948). [c] Reported m.p. 129°, A. Dunet and A. Willemart, *Bull. soc. chim. France,* 1081 (1948). [d] Reported m.p. 170°, *Bull. soc. chim. France,* 1081 (1948).

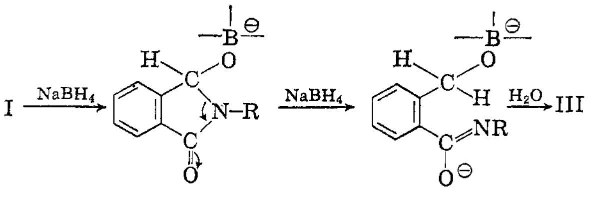
TABLE III

CHARACTERISTICS OF THE o-HYDROXYMETHYLBENZAMIDES, 

R	M.P.[a]	Recryst. from	Formula	Found, % C	Found, % H	Found, % N	Calcd., % C	Calcd., % H	Calcd., % N	Infrared Spectrum (in Nujol), Cm.$^{-1}$, —CONHR Amide I	Amide II
H	150–151[b]	$CH_3COOC_2H_5$	$C_8H_9NO_2$	63.55	5.95	9.13	63.56	6.00	9.27	1653	1618
C_6H_5	144	C_2H_5OH	$C_{14}H_{13}NO_2$	74.00	5.50	6.19	73.99	5.77	6.16	1639	1531
	193	C_2H_5OH	$C_{18}H_{19}NO_2$	76.90	6.75	5.06	76.84	6.81	4.98	1637	1527
o-$CH_3C_6H_4$	179	C_2H_5OH	$C_{15}H_{15}NO_2$	74.91	6.45	5.53	74.66	6.27	5.81	1637	1527
p-$CH_3C_6H_4$	173	C_2H_5OH	$C_{15}H_{15}NO_2$	74.82	6.23	5.85	74.66	6.27	5.81	1647	1536
o-$CH_3O—C_6H_4$	133	C_2H_5OH	$C_{15}H_{15}NO_3$	70.24	5.76	5.48	70.02	5.88	5.44	1639	1541
p-$CH_3O—C_6H_4$	161–162	C_2H_5OH	$C_{15}H_{15}NO_3$	69.99	5.91	5.51	70.02	5.88	5.55	1631	1527

[a] Uncorrected. [b] Reported m.p. 149–150°, J. J. Brown, J. Blair, and G. T. Newbold, *J. Chem. Soc.*, 708 (1955).

num hydride, lithium diethoxyaluminohydride, or lithium borohydride would be included in this type of reaction. Gaylord[10] recently reported that the reduction of the benztriazol derivatives with lithium aluminum hydride or sodium borohydride resulted in cleavage of the carbon-nitrogen bond. The transformation of IIc to IIIc would seem to proceed in a similar fashion and, thus the following representation for the reduction is proposed;



The procedure was found to be suitable for the reduction of aliphatic imides, and thus the reduction of N-phenylsuccinimide using four molecular equivalents of sodium borohydride yielded γ-butyrolactone in 40% yield, together with a small amount of γ-hydroxy-N-phenylbutyramide.

EXPERIMENTAL

Starting materials. The various phthalimide derivatives were prepared by refluxing a mixture of appropriate amines and phthalic anhydride in glacial acetic acid for 7–15 hr., while N-methylphthalimide was obtained by reaction of potassium phthalimide with methyl p-toluenesulfonate.[11]

General method of the reduction. A solution of 2 moles of sodium borohydride in methanol (20–25 ml. per 1 g.) was added to a suspension of 1 mole of the phthalamide in 90% methanol (6–8 ml. per 1 g.) at 25–30° dropwise while stirring (20–40 min.). The reaction mixture was stirred for an addi-

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(10) N. G. Gaylord and D. J. Kay, *J. Org. Chem.*, **23**, 1574 (1958).

(11) E. J. Sakellarious, *Helv. Chim. Acta*, **29**, 1675 (1946).

tional 7–10 hr. at 25–30° then allowed to stand overnight at room temperature. Excess hydride was decomposed with glacial acetic acid. The reaction mixture was concentrated *in vacuo,* then water was added to the residual solid, and filtered. The filter cake was purified by the following two methods. i) In the case of Ia, b, d, e, g, or i, the products IIa, b, d, e, g, or i were separated and purified by recrystallization of the filter cake from an appropriate solvent. ii) In the case of Ic, f, or h,[12] a part of the filter cake was recrystallized once from ethanol to give IIIc, f, or h. The rest of the filter cake was hydrolyzed by boiling with sodium hydroxide-ethanol, yielding IIc, f or h and the phthalide, which were separated by recrystallization.

Reduction of N-phenylphthalimide (Ic). a) A solution of 1.2 g. (0.03 mole) of sodium borohydride in 25 ml. of methanol was added to a suspension of 3.4 g. (0.015 mole) of (Ic) in 25 ml. of 90% methanol at 25–30° dropwise over a period of 25 min. The reaction mixture was stirred for 7 hr. at 25–30°, then allowed to stand overnight at room temperature. Excess hydride was decomposed with glacial acetic acid. The mixture was concentrated *in vacuo,* water was added to the residue and filtered. The filter cake was washed with five 30-ml. portions of ether and the white solid obtained was recrystallized from ethanol to give 1 g. (29%) of IIIc, m.p. 144°. The ether washings were combined and concentrated and the residue was hydrolyzed by refluxing with a solution of 1 g. of sodium hydroxide in 30 ml. of ethanol for 7 hr. After removal of ethanol on a steam bath, 30 ml. of water was added to the cooled residue and the mixture was extracted with ethyl acetate.

The water layer was acidified with concd. hydrochloric acid under ice cooling. The precipitate was collected and recrystallized from water to yield 0.45 g. (21%) of phthalide, m.p. 73–74°, which was identified by comparison with the authentic sample. The ethyl acetate extract was concentrated *in vacuo* to give a semisolid, which was washed with a small amount of ether and recrystallized from ethyl acetate to 0.8 g. (23.5%) of IIc m.p. 171–172°. Concentration of this ether washing yielded aniline, which was proved to be acetanilide.

This experiment would indicate that the crude reduction product before hydrolysis consisted of IIc (23.5% yield) and IIIc (50% yield), because phthalide would be formed by hydrolysis of IIIc.[12]

b) A solution of 0.8 g. (0.022 mole) of sodium borohydride in 20 ml. of methanol was added to a suspension of 2.5 g. (0.011 mole) of Ic in 25 ml. of 90% methanol in the same manner as in the general method. The reaction mixture was kept at room temperature for 30 min. and, then at 50–53° for 5 hr. with stirring. Excess hydride was decomposed with glacial acetic acid. The reaction mixture was concentrated *in vacuo,* water was added to the residue, and the mixture filtered. The filter cake was washed with a small amount of ethyl acetate (*ca.* 5 ml.) and hydrolyzed as described in procedure a), giving 0.6 g. (45%) of phthalide, m.p. 73–74° and 0.4 g. (16%) of IIc m.p. 171–172°. The ethyl acetate wash was concentrated and the residue was recrystallized from water to yield 0.2 g. (15%) of phthalide, m.p. 73–74°.

When this reduction was carried out by stirring at room temperature for 30 min. and at reflux temperature for an additional 5 hr., the following result was obtained. After excess of hydride was decomposed with glacial acetic acid, the reaction mixture was concentrated *in vacuo.* Water was added to the residue and the insoluble material was recrystallized from ethanol to yield 1 g. (40%) of IIIc, m.p. 144°. The mother liquor was concentrated on a steam bath and the residual solid was recrystallized from water to yield 0.5 g. (33%) of phthalide, m.p. 73–74°.

c) A solution of 0.8 g. (0.022 mole) of sodium borohydride in 20 ml. of methanol was added to a suspension of 2.5 g. (0.011 mole) of Ic in 15 ml. of 90% methanol in the same manner as in procedure a). After standing overnight, an additional 0.8 g. (0.22 mole) of sodium borohydride in 20 ml. of methanol was added to the reaction mixture as outlined above. Excess hydride was decomposed with glacial acetic acid and the reaction mixture was concentrated *in vacuo.* Water was added to the residue, filtered, and the filter cake was recrystallized from ethanol to yield 2.3 g. (92%) of IIIc, m.p. 144°.

A mixture of 0.7 g. of IIIc and 0.2 g. of sodium hydroxide in ethanol was refluxed for 5 hr. The reaction mixture was concentrated on a steam bath and water was added to the residue. Extraction with ethyl acetate yielded aniline. The aqueous layer was acidified with concd. hydrochloric acid and the precipitate was recrystallized from water to yield 0.35 g. (98%) of phthalide, m.p. 73–74°.

Reduction of 3-hydroxy-2-phenylphthalimidine (IIC). A solution of 0.8 g. (0.022 mole) of sodium borohydride in 20 ml. of methanol was added to a suspension of 2.5 g. (0.011 mole) of IIc in 15 ml. of 90% methanol and worked up as usual. The product was recrystallized from ethanol to yield 2.4 g. (96%) of IIIc, m.p. 144°.

Reduction of N-phenylsuccinimide. A solution of 2.3 g. (0.06 mole) of sodium borohydride in 45 ml. of methanol was added to a suspension of 5 g. (0.03 mole) of *N*-phenylsuccinimide in 45 ml. of methanol dropwise with stirring. The reaction mixture was kept at 10–15° during the addition (*ca.* 40 min.) and stirred for an additional 7 hr. at 10–15°, then allowed to stand overnight at room temperature. An additional 2.3 g. (0.06 mole) of sodium borohydride in 45 ml. of methanol was added dropwise to the above reaction mixture with stirring at 10–15° (*ca.* 40 min.). After being stirred for 10 hr. at 10–15°, the reaction mixture was allowed to stand overnight at room temperature. Excess hydride was decomposed by addition of 10% hydrochloric acid. The mixture was concentrated on a steam bath and the residual semisolid was extracted with ether. The dried ether extract was distilled to yield 1.1 g. (44%) of γ-butyrolactone b.p.$_{108}$ 134°, which was identified by comparison with the infrared spectrum of the authentic sample. The distillation residue was recrystallized from ether to yield 0.2 g. (4%) of γ-hydroxy-*N*-phenylbutyramide, m.p. 83–84°.

Anal. Calcd. for $C_{10}H_{13}O_2N$; C, 67.02; H, 7.31; N, 7.82. Found: C, 67.12; H, 7.29; N, 7.82. The infrared spectra in chloroform indicated maxima at 3401, 3322, 1669, 1603, 1538 (shoulder), 1524, and 1502 cm.$^{-1}$

When acetic acid was used instead of 10% hydrochloric acid to decompose excess hydride in this reduction, the main product was γ-hydroxy-*N*-phenylbutyramide (34% yield), accompanied with a small amount of γ-butyrolactone.

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(12) In this case, complete separation into III and II by recrystallization was difficult to be attained and, further, it was found that III was easily hydrolyzed with sodium hydroxide–ethanol to give phthalide, while II did not undergo hydrolysis.