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Studies on Aminobutenolide Compounds. I. The Reaction of *o*-Phthalaldehydic Acid with Amino Compounds

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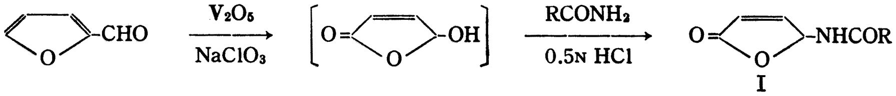
An investigation was made on the reaction between *o*-phthalaldehydic acid (II) and various primary amino compounds.

The reaction with aromatic amines afforded 3-arylaminophthalides (IIIa—j) in good yield. However, the reaction with aliphatic amines did not afford expected III type compounds, but 3,3′-(N-alkylimino)diphthalides (VIa—d). Similar type compounds (XIa—e) were prepared from ureas, acetamide, and ethyl carbamate.

3-Chlorophthalide (V) reacted with aniline to afford IIIa, but with aliphatic amines, 3-hydroxy-N-alkylphthalimidines (IXa—d).

Recently (±) 2-acetamide-2,5-dihydro-5-oxofuran (Ia) was isolated from *Fusarium nivale*[2] and *F. equiseti*.[3] We have been interested in the fact that Ia has a hemiacetal structure of active amide and furthermore it is one of the phytotoxic principles of these molds.[4,5]

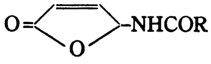
Some derivatives of butenolide were synthesized according to White's method[3] as shown in Chart 1, and examined for their herbicidal activities. The result showed that these compounds (Ib—d) had the herbicidal property in some degree.[6] Characteristics and spectral data of I are shown in Table I and II.



I

Chart 1

Table I. Characteristics of (±) 2-Acylamino-2, 5-dhydro-5-oxofuran (I)



I	R	mp (°C)	Appearance (solvent)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
b	CH_2CH_3	118—119	colorless needles (benzene)	40.2	$C_7H_9O_3N$	54.18	5.84	9.03	53.93	5.81	8.99
c	n-C_3H_7	100—101	colorless needles (benzene)	43.3	$C_8H_{11}O_3N$	56.71	6.55	8.28	56.33	6.76	8.22
d	OC_2H_5	94— 95	colorless needles (ether)	45.1	$C_7H_9O_4N$	49.12	5.30	8.18	49.28	5.22	8.31

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1) Location: *2-1, Hirosawa, Wako, Saitama.*

2) S.G. Yates, H.L. Tookey, and J.J. Ellis, *Tetrahedron Letters*, **1967**, 621.

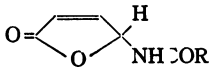
3) E.P. White, *J. Chem. Soc.* (*C*), **1967**, 346.

4) P.W. Brian, A.W. Dawkins, J.F. Grove, H.G. Hemming, D. Lowe, and G.L.F. Norris, *J. Exp. Bot.*, **12**, 1 (1961).

5) A.W. Dawkins, *J. Chem. Soc.* (*C*), **1966**, 116.

6) T. Tatsuno, K. Ishizuka, Y. Ueno, and I. Ueno, Abstracts of Papers, 89th Annual Meeting of Pharmaceutical Society of Japan, Nagoya, April, 1969, p. 565.

Table II. Spectral Data of Compounds I



Ia—d

I	IR (KBr, cm^{-1})		NMR (CDCl$_3$, TMS, ppm)		UV (λ_{max}^{EtOH}, mμ)
	ν_{NH}	$\nu_{C=O}$	methine proton	NH-proton	
a	3290	1785 1755	6.70	6.65	205
b	3290	1790 1760	6.70	6.35	205
c	3290	1800 1760	6.50	5.40	204
d	3400	1780 1745 1720	6.51	5.35	206

It is obvious that *o*-phthalaldehydic acid (II) adopts a stable lactol structure, that is, 3-hydroxyphthalide. Therefore, in this report, the reaction of II with various primary amino compounds was investigated in attempt to clarify the reactivity of lactol compounds and in order to synthesize aminobutenolide compounds.

We obtained new information that *o*-phthalaldehydic acid affords various products depending on the basicity of starting amino compounds.

(1) Reaction of *o*-Phthalaldehydic Acid (II) with Aromatic Amines

It was previously reported that the treatment of *o*-phthalaldehydic acid (II) with aniline gave a Shiff base (IV).⁷⁾ When this reaction was re-examined, the structure of the product was found to be not IV, but aminobutenolide compound, 3-anilinophthalide (IIIa), from its spectral data. That is to say, the infrared (IR) spectrum of IIIa exhibits characteristic peaks at 3320 (NH) and 1730 (C=O) cm^{-1}, and no absorption band due to COOH appearing in the region 3000—2500 cm^{-1}.

Compound IIIa was also obtained in lower yield by the reaction of 3-chlorophthalide (V)⁸⁾ with aniline.

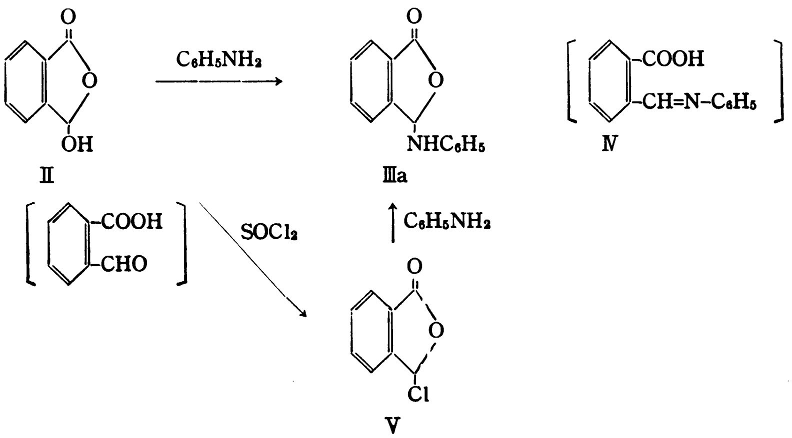


Chart 2

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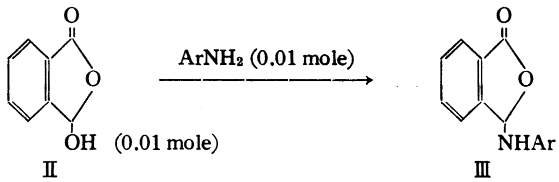
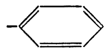
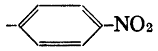
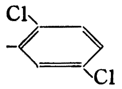
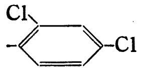
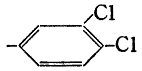
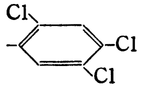
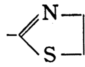
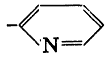
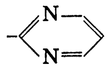
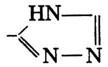
7) S. Racine, *Ann.*, **239**, 91 (1887).
8) S. Gabriel, *Ber.*, **49**, 1612 (1916).

Table III. Reaction of *o*-Phthalaldehydic Acid with Aromatic Amines



III	Ar	mp (°C)	Appearance (solvent)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a		179—180[a]	colorless needles (MeOH)	97.5	$C_{14}H_{11}O_2N$	74.65	4.92	6.22	74.26	4.90	6.22
b		251—253	pale yellow needles (MeOH)	88.0	$C_{14}H_{10}O_4N_2$	62.22	3.73	10.37	62.34	3.68	10.44
c		166—168	colorless needles (MeOH)	93.0	$C_{14}H_9O_2NCl_2$	57.14	3.06	4.76	57.11	3.10	4.66
d		148—151	colorless needles (MeOH)	86.8	$C_{14}H_9O_2NCl_2$	57.14	3.06	4.76	57.27	3.12	4.74
e		234—236	colorless needles (MeOH)	95.2	$C_{14}H_9O_2NCl_2$	57.14	3.06	4.76	57.01	3.07	4.83
f		209—212	colorless needles (MeOH)	96.0	$C_{14}H_8O_2NCl_3$	51.14	2.43	4.26	51.09	2.42	4.35
g		196—198	colorless columns (MeOH)	87.1	$C_{11}H_8O_2N_2S$	56.85	3.45	12.07	56.96	3.49	11.90
h		206—207	colorless prisms (MeOH)	93.0	$C_{13}H_{10}O_2N_2$	69.01	4.46	12.38	68.28	4.02	12.32
i		215—216	colorless prisms (MeOH)	85.9	$C_{12}H_9O_2N_3$	63.43	3.99	18.49	63.69	4.00	18.49
j		252—254	colorless needles (MeOH)	91.5	$C_{10}H_8O_2N_4$	55.55	3.73	25.92	55.73	3.46	26.20

Reaction conditions were as follows; solvent: MeOH (20 ml); reaction time: 30 min; reaction temperature: reflux.
a) lit.[7] 178°

In a similar fashion, 3-arylaminophthalides (III) were prepared from the reaction of II with various aromatic amines. The result and the spectral data of the products (III) are shown in Table III and IV. In the nuclear magnetic resonance (NMR) spectra of these compounds, the coupling of the NH proton and the 3-proton appeared remarkably in dimethylsulfoxide.

(2) Reaction with Aliphatic Amines

In addition, a similar reaction was investigated with aliphatic amines. Concerning the reaction of *o*-phthalaldehydic acid (II) with aliphatic amines, it was previously reported that two equivalents of II reacted with one equivalent of aliphatic amines in benzene to afford 3,3'-(N-alkylimino) diphthalides (VI).[9] The reaction of II with equimolar ammonium chlo-

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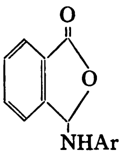
[9] D.D. Wheeler and D.C. Young, U.S. Patent 2912440 (1959).

Table IV. Spectral Data of Compounds III

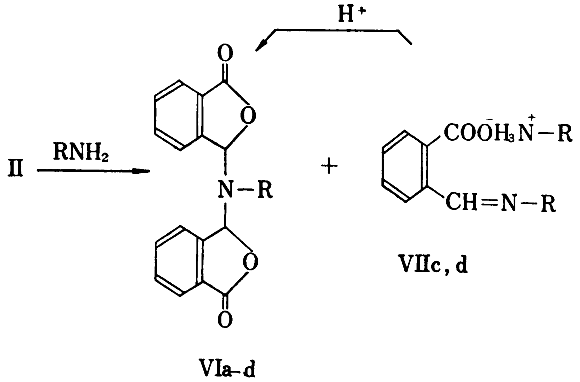


IIIa—j

III	IR (KBr, cm^{-1})		NMR (DMSO-d_6, TMS, ppm)		UV (λ_{max}^{EtOH}, mμ)
	ν_{NH}	$\nu_{C=O}$	3-proton	NH-proton	
a	3320	1730	*	*	273, 279
b	3300	1785	6.55 (d)	7.10 (d) J=9.0 cps	343
c	3375	1760	6.49 (d)	6.85 (d) J=9.0 cps	273, 281, 290
d	3325	1755 1735	6.65 (d)	7.02 (d) J=9.0 cps	273, 280, 296
e	3340	1740	6.68 (d)	7.05 (d) J=9.0 cps	279, 297
f	3370	1760	6.52 (d)	7.05 (d) J=10.0 cps	280, 303
g	3150	1760	7.15 (d)	8.87 (d) J=9.0 cps	330
h	3200	1760	6.70 (d)	7.48 (d) J=9.0 cps	287
i	3220	1755	6.86 (d)	7.42 (d) J=10.0 cps	275, 282
j	3280	1740	7.10 (d)	7.50 (d) J=11.0 cps	265, 272, 280

* not assigned

ride in the presence of sodium methoxide did not afford expected 3-aminophthalide, but 3,3'-iminodiphthalide (VIa).Furthermore, the reaction with propylamine or benzylamine produced not only 3,3'-(N-alkylimino)diphthalide (VI), but also VII.



NH_3 (a), CH_3NH_2 (b), $CH_3CH_2CH_2NH_2$ (c), $C_6H_5CH_2NH_2$ (d)

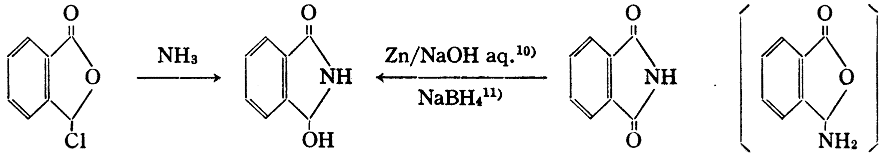
Chart 3

The structure of VII was obvious from the spectral data and elemental analysis, that is, the IR spectrum of VII showed no carbonyl absorption band, but the broad ammonium band in the region 3000—2500 cm^{-1}.

Compound VII was converted into VI by neutralization with acid. Therefore attempts to obtain aminophthalides from the reaction with aliphatic amines were unsuccessful.

In 1887, Racine7) reported that the reaction of 3-bromophthalide with dry ammonia gave 3-aminophthalide (VIII). Upon reexamining this reaction using 3-chlorophthalide (V) as a starting material, we obtained a product of the same properties. However, the structure of the product was not 3-aminophthalide (VIII), but 3-hydroxyphthalimidine (IXa). Compound IXa was proved to be identical with the authentic sample of 3-hydroxyphthalimidine reported by Reissert[10] or Horii, *et al.*[11]

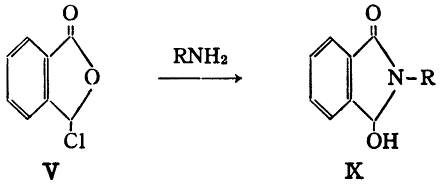
The reaction of V with other aliphatic amines was investigated, and the characteristics of the product and the spectral data are shown in Table V and VI.



V IXa VIII

Chart 4

TABLE V. Reaction of 3-Chlorophthalide with Aliphatic Amines

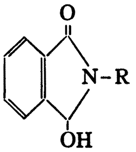


V IX

IX	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	H	169—171[a)]	58.4	$C_8H_7O_2N$	64.42	4.73	9.39	64.55	4.82	9.34
b	CH_3	129—130[b)]	65.6	$C_9H_9O_2N$	66.24	5.56	8.58	66.63	5.70	8.30
c	n-C_3H_7	92— 93	61.8	$C_{11}H_{13}O_2N$	69.09	6.85	7.33	68.83	6.67	7.21
d	$CH_2C_6H_5$	133—134	59.4	$C_{15}H_{13}O_2N$	75.30	5.48	5.85	75.45	5.51	5.99

a) lit.[10] 178°
b) lit.[11] 130°

TABLE VI. Spectral Data of Compounds IX



IXa—d

IX	IR (KBr, cm^{-1}) ν_{OH}	$\nu_{C=O}$	NMR ($CDCl_3$, TMS, ppm) 3-proton	OH-proton	UV (λ_{max}^{EtOH}, mμ)
a	3320	1690	5.94 (d)[a)]	6.39 (d) J=8.5 cps	272, 281
b	3280	1675	5.52 (d)	4.96 (d) J=11.0 cps	281
c	3250	1655	5.68 (d)	4.83 (d) J=10.2 cps	282
d	3200	1657	5.55 (d)	4.35 (d) J=9.0 cps	283

a) in DMSO-d_6

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10) A. Reissert, *Ber.*, **46**, 1484 (1913).
11) Z. Horii, C. Iwata, and Y. Tamura, *J. Org. Chem.*, **26**, 2273 (1961).

In the NMR spectra of these compounds, the hydroxyl proton was coupled with the 3-methine proton distinctly.

(3) Reaction with Ureas and Acid Amides

It has been reported that the reaction of II with urea gave a Shiff base type compound (X).[12] When this reaction was re-examined, the structure of the product was N-(3-phthalidyl)-urea (XIa). The treatment of II with urea in water or methanol gave the product (XIa),

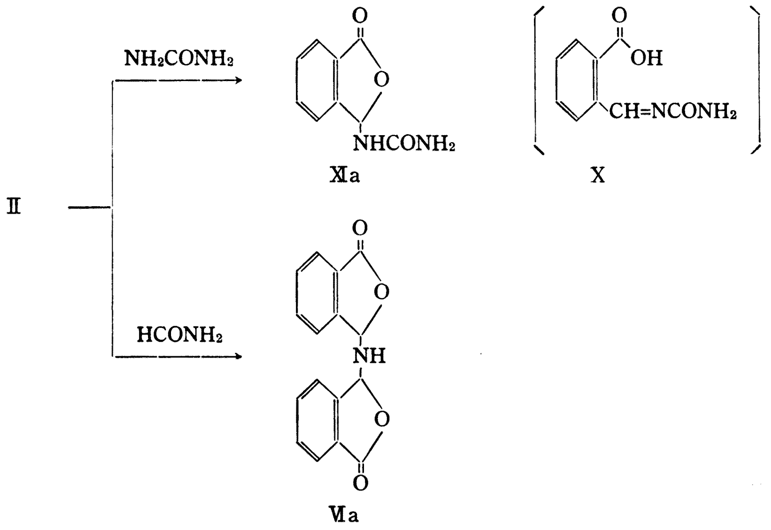
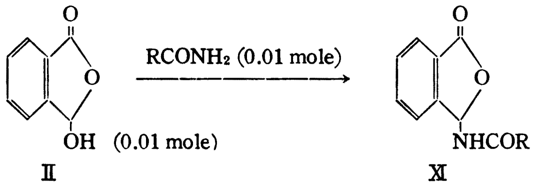


Chart 5

Table VII. Reaction of *o*-Phthalaldehydic Acid with Ureas, Ethyl Carbamate and Acid Amides



XI	R	mp (°C)	Appearance (solvent)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	NH_2	238—240[a)] (decomp.)	colorless needles (MeOH)	93.7	$C_9H_8O_3N_2$	56.25	4.20	14.58	56.12	4.22	14.74
b	$NHCH_3$	215—216 (decomp.)	colorless needles (MeOH)	89.9	$C_{10}H_{10}O_3N_2$	58.25	4.89	13.58	58.57	4.91	13.79
c	$N(CH_3)_2$	181—183	colorless needles (benzene–MeOH)	85.4	$C_{11}H_{12}O_3N_2$	59.99	5.49	12.72	60.02	5.55	12.98
d	OC_2H_5	162—163	colorless needles (benzene–MeOH)	73.4	$C_{11}H_{11}O_4N$	59.72	5.01	6.33	60.01	5.11	6.37
e	CH_3	211—213	colorless needles (AcOEt–MeOH)	56.4	$C_{10}H_9O_3N$	62.82	4.75	7.33	63.06	4.74	7.28

Reaction conditions were as follows; solvent: MeOH (20 ml); reaction time: 30 min; reaction temperature: reflux.
a) lit.[12] 240° (decomp.)

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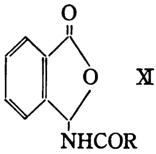
12) S. Racine, *Compt. Rend.*, **106**, 948 (1888).

Table VIII. Spectral Data of Compounds XI



XIa—b

XI	R	IR (KBr, cm^{-1})		NMR (DMSO-d_6, TMS, ppm)		UV (λ_{max}^{EtOH}, mμ)
		ν_{HN}	$\nu_{C=O}$	3-proton	NH-proton	
a	NH_2	3430 3300 3260	1755 1670	6.95	7.48 $J=10.2$ cps	273 281
b	$NHCH_3$	3350 3290	1760 1640	6.95	7.48 $J=10.6$ cps	273 281
c	$N(CH_3)_2$	3260	1760 1650	7.14[a]	5.70 $J=10.5$ cps	273 281
d	OC_2H_5	3260	1710 1700	6.92[a]	5.72 $J=10.5$ cps	273 281
e	CH_3	3260	1770 1665	7.00	9.12 $J=9.1$ cps	273 289

a) in $CDCl_3$

colorless needles, mp 238—240° (decomp.) (lit.[12] mp 240° (decomp.)), in good yield. The IR spectrum of the product exhibited a carbonyl absorption band (1755, 1670 cm^{-1}). Furthermore, in the NMR spectrum, the doublet (6.95 ppm, 1H) could be assigned to the 3-methine proton. Therefore the structure of the product should not be X but XIa. Similar products were also prepared from N-methylurea, N,N-dimethylurea, acetamide, and ethyl carbamate. Benzamide did not react, and formamide gave N-iminodiphthalide (VIa). The results are shown in Table VII and VIII.

Although the reaction of *o*-phthalaldehydic acid with various amino compounds was investigated for the purpose of obtaining biological active aminobutenolide compounds, we thus obtained interesting information that the products are different depending on the basicity of the starting material, and that the oxygen of the hydroxyl group or that of the ring in lactol compounds can be successfully replaced by nitrogen.

Experimental[13]

Synthesis of 2-Acylamino-2,5-dihydro-5-oxofuran (I) (General Procedure)——This reaction was based upon White's method.[3] To a solution of $NaClO_3$ (23.4 g, 0.22 mole) in H_2O (50 ml) was added V_2O_5 (0.2 g) and heated with stirring. To the mixture was added furfural (10.57 g, 0.11 mole) at 98—100°, and the mixture was allowed to react vigorously with stirring. After cooling immediately, the mixture was extracted with AcOEt. After drying over anhydrous Na_2SO_4, the solvent was evaporated off under reduced pressure. The residue was dissolved in 0.5 N HCl aq. (120 ml), and to this solution was added acid amide (0.09 mole), then the mixture was refluxed for 1 min. After cooling, the solvent was evaporated off under reduced pressure at 32—35°. The residual oil was recrystallized from benzene.

Reaction of *o*-Phthalaldehydic Acid (II) with Aromatic Amines (General Procedure)——To a solution of II (1.5 g, 0.01 mole) in MeOH (20 ml) was added aromatic amine (0.01 mole). The mixture was refluxed for 30 min. After cooling, the separated crystals were collected. Recrystallization from MeOH gave 3-arylaminophthalides (IIIa—j).

Reaction of 3-Chlorophthalide (V)[8] with Aniline——To a solution of V (1.68 g, 0.01 mole) in abs. ether (50 ml) was added a solution of aniline (0.93 g, 0.01 mole) in abs. ether (10 ml) with ice-cooling and stirring. The mixture was stirred for 1 hr at room temperature. The reaction mixture was diluted with H_2O and

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[13] All melting points were not corrected.

the ethereal layer was dried over anhydrous Na_2SO_4. After removal of the ether, the residue was recrystallized from AcOEt–MeOH. 3-Anilinophthalide (IIIa) was obtained as colorless prisms, mp 175—176° (lit.[7] 178°); 0.75 g (33%).

Reaction of *o*-Phthalaldehydic Acid (II) with Aliphatic Amines——i) To a solution of II (1.5 g, 0.01 mole) and NH_4Cl (0.535 g, 0.01 mole) in MeOH (10 ml) was added a solution of Na (0.23 g, 0.01 mole) in MeOH (10 ml). The mixture was refluxed for 30 min. NaCl was filtered off. After cooling, the separated crystals were collected. Recrystallization from MeOH gave 3,3′-iminodiphthalide (VIa), colorless needles, mp 195—196° (lit.[9] 209—210°), 0.9 g. IR ν_{max}^{KBr} cm^{-1}: 3350 (NH), 1780, 1743 (C=O), 1600 (C=C).

ii) In the same fashion, from II (1.5 g, 0.01 mole), $CH_3NH_2 \cdot HCl$ (0.675 g, 0.01 mole), Na (0.23 g, 0.01 mole) and MeOH (20 ml), there was obtained 0.9 g, of 3,3′-(N-methylimino)diphthalide (VIb), colorless prisms, mp 228—230° (lit.[9] mp 231—233°). IR ν_{max}^{KBr} cm^{-1}: 1755 (C=O), 1602 (C=C).

iii) To a solution of II (1.5 g, 0.01 mole) in MeOH (20 ml) was added propylamine (0.59 g, 0.01 mole). The mixture was refluxed for 30 min. After the mixture was left overnight at 5—6°, the separated crystals were collected. Recrystallization from AcOEt gave 3,3′-(N-propylimino)diphthalide (VIc), colorless needles, mp 175—176°, 0.78 g. IR ν_{max}^{KBr} cm^{-1}: 1745 (C=O), 1600 (C=C). *Anal.* Calcd. for $C_{19}H_{17}O_4N$ (VIc): C, 70.57; H, 5.30; N, 4.33. Found: C, 70.41; H, 5.25; N, 4.17. From the mother liquor, 0.52 g of the crystals with mp 104—106° was obtained. Recrystallization from benzene gave VIIc, colorless prisms, mp 106—107°. IR ν_{max}^{KBr} cm^{-1}: 3000—2500 (NH_3^+), 1630 (C=N), 1600—1550, 1390 (COO^-). *Anal.* Calcd. for $C_{14}H_{22}O_2N_2$ (VIIc): C, 67.18; H, 8.86; N, 11.19. Found: C, 67.52; H, 8.90; N, 11.23.

iv) 1.5 g (0.01 mole) of II and 1.07 g (0.01 mole) of benzylamine were refluxed in MeOH (20 ml) for 30 min. Working up in a similar manner as above, there was obtained 1.2 g of 3,3′-(N-benzylimino)diphthalide (VId), colorless needles, mp 143—145° (lit.[9] 126—128°). IR ν_{max}^{KBr} cm^{-1}: 1760 (C=O), 1600 (C=C). From the mother liquor, 0.92 g of VIId was obtained as colorless prisms (benzene) with mp 120—122°. IR ν_{max}^{KBr} cm^{-1}: 3000—2600 (NH_3^+), 1630 (C=N), 1600—1560, 1390 (COO^-). *Anal.* Calcd. for $C_{22}H_{22}O_2N_2$ (VIId): C, 76.27; H, 6.35; N, 8.09. Found: C, 76.15; H, 5.83; N, 8.05.

Reaction of 3-Chlorophthalide (V) with Aliphatic Amines——i) To a solution of V (1.68 g, 0.01 mole) in abs. ether (50 ml) in the presence of anhydrous K_2CO_3 (1.38 g, 0.01 mole) was added 28% NH_4OH aq. (10 ml) with cooling and stirring. After addition, the mixture was stirred at room temperature for 30 min. 20 ml of H_2O was added to the reaction mixture, then the ethereal layer was separated and dried over anhydrous Na_2SO_4. The aqueous layer was extracted with AcOEt. From the organic layer, 0.87 g of 3-hydroxyphthalimidine (IXa) was obtained.

ii) 1.68 g (0.01 mole) of V and 10 ml of 30% NH_2CH_3 aq. were reacted in abs. ether (50 ml) in a similar manner. 1.07 g of 3-hydroxy-N-methylphthalimidine (IXb) was obtained.

iii) From 1.68 g (0.01 mole) of V, 0.59 g (0.01 mole) of propylamine and abs. ether (50 ml), there was obtained 1.12 g of 3-hydroxy-N-propylphthalimidine (IXc).

iv) From 1.68 g (0.01 mole) of V, 1.07 g (0.01 mole) of benzylamine and abs. ether (50 ml), there was obtained 1.42 g of 3-hydroxy-N-benzylphthalimidine (IXd).

Reaction of *o*-Phthalaldehydic Acid (II) with Urea, Acid Amides, Ethyl Carbamate (General Procedure)—— From II (1.5 g, 0.01 mole), the corresponding starting amino compounds (0.01 mole) and MeOH (20 ml), compounds (XIa—e) were obtained in the same fashion.

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