Preparation of 3-Hydroxyisoindolin-1-ones and *o*-Acylbenzamides. A Study of Ring-Chain Tautomerism

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3-Hydroxyisoindolinones (ring form) as well as their chain tautomers, *o*-acylbenzamides, were prepared from the reactions of 3-benzalphthalide **1**, 3-halophthalides **3**, and *o*-acylbenzoic acids **6** or their esters **7** with amines **2**, and those of phthalimides **4** with Grignard reagents **5**. The characteristic spectroscopic properties of ring and chain forms are observed in the ir and ^{13}C-nmr spectra. The significance of the spectroscopic results is discussed, as is the relationship between the structure of the products and the position of the ring-chain equilibrium.

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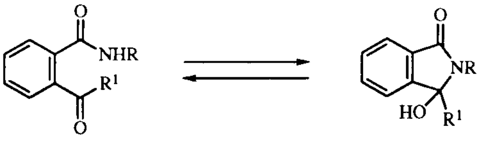
Ring-chain (or open) tautomerism is commonly encountered in diverse groups of compounds [1]. During an investigation of the reactivity of cyclic thioamide systems [2], we found that 3-hydroxyisoindolin-1-ones **R** reacted with 2,4-bis(*p*-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (**LR**), generally called Lawesson's reagent [3], give isoindoline-1-thiones in good yields by the direct thionation of the amide carbonyl and reductive elimination of the hydroxy group [4]. Various kinds of 3-hydroxyisoindolin-1-ones were prepared according to published procedures [5]. These substances are of a class which could show ring-chain tautomerism, *viz.* acyl-amide **C** and/or hydroxy-lactam **R**.

Scheme 1



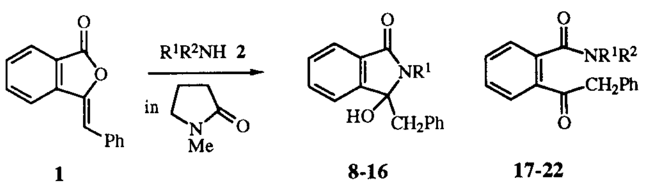
C (Chain) R (Ring)

The literature contains conflicting reports on the structure of 3-hydroxyisoindolin-1-ones and their tautomers, *o*-acylbenzamides. Flitsch concluded that 3-hydroxyisoindolin-1-ones exist in the ring-form **R** by nmr and ir spectroscopic investigation [5d]. Imai *et al.* reported that ir spectroscopy supported the chain structure for the compounds, which are prepared from 3-methylenephtalides and amines [5a]. We investigated the spectroscopic properties of 3-hydroxyisoindolin-1-ones and their chain form tautomers and here report that ^{13}C-nmr and ir spectra are effective for ring-chain structural determinations.

Reaction of 3-Benzalphthalide 1 with Amines 2.

The reaction of 3-benzalphthalide **1** with butylamine **2b** was claimed to yield *N*-butyl-*o*-phenylacetylbenzamide [5a], but we found that the product was not the open (chain) form, *N*-butyl-*o*-phenylacetylbenzamide but the ring form, 3-benzyl-3-hydroxy-2-butylisoindolin-1-one **9**. The ir spectrum showed absorptions at 3300 and 1680 cm^{-1} assignable to hydroxy and amide carbonyl, respectively. The ^{13}C-nmr spectrum showed two characteristic peaks at δ 91.2 (s) and 166.9 (s) due to C-3 quaternary and amide carbonyl carbons, respectively. Similarly, treatment of **1** with alkylamines **2a** and **2e-g** and aniline **2c** in *N*-methyl-2-pyrrolidone gave the corresponding 3-benzyl-3-hydroxyisoindolin-1-ones **8**, **12-14**, and **10** in good yields. 3-Benzyl-3-hydroxy-2-phenylisoindolin-1-one **10** thus obtained was treated with dilute hydrochloric acid to give 3-benzal-2-phenylisoindolin-1-one **50** as a mixture of *E* and *Z* isomers. Treatment of 3-hydroxyisoindolin-1-ones **8** and **10** with Lawesson's reagent (**LR**) yielded 3-benzalisoindolin-1-thiones **51** and **52** in good yields by the direct thionation of the amide carbonyl and dehydration of the hydroxy group. With 1-phenylethylamine **2d** and phenylglycine methyl ester **2h** two stereoisomeric isoindolinones, **11-1** and **11-2**, and **15-1** and **15-2**, respectively, were isolated. In the reaction of **1** with *tert*-butylamine **2i**, both ring and chain products, **16** and **17** were produced in 9 and 80% yields, respectively. In contrast, treatment of **1** with amines **2j-k** bearing a bulky substituent at the α-position, and secondary amines **2l-n** gave the chain tautomers, *o*-phenylacetylbenzamides **18-22** as the sole products. The structure of these products **8-22** was elucidated on the basis of spectroscopic properties and elemental analyses (see Experimental). Characteristically, in the ir spectra the ring form, isoindolinones **8-15**, showed absorptions at 3130-3510 (OH stretching band) and 1650-1680 cm^{-1} (CO stretching band) while the chain form, *o*-phenylacetylbenzamides **17-22**, showed two carbonyl stretching bands at 1675-1685 and 1620-1635 cm^{-1}. The ^{13}C-nmr spectra of isoindolinones **8-15** displayed two singlets at δ 90.5-92.9 and 166.2-167.9 assignable to C-3 quaternary and amide carbonyl carbons, respectively. On the other hand, the ^{13}C nmr spectra of *o*-acylbenzamides **17-22** showed amide carbonyl and carbonyl carbon peaks at δ 167.5-171.6 and 198.3-202.5,

Chart 1



	Amine 2		Reaction conditions		Yield (%) [a]	
	R^1	R^2	temp (°C)	time (h)		
a	*i*-Pr	H	90	0.25	**8** (85)	
b	Bu	H	rt [b]	2	**9** (61)	
c	Ph	H	90	20	**10** (100)	
d	PhCH(Me)	H	90	17	**11** [29 (41)] [c]	
e	Ph_2CH	H	90	18	**12** (96)	
f	*c*-C_6H_{11}	H	90	20	**13** (88)	
g	$PhCH(OH)CH_2$	H	rt	12	**14** (64)	
h	$PhCH(CO_2Me)$	H	90	23	**15** [41 (31)] [c]	
i	*t*-Bu	H	90	9	**16** (9) [d]	**17** (80) [d]
j	$PhCH_2CMe_2$	H	90	17		**18** (42)
k	Ad [e]	H	90	18		**19** (78)
l	Et	Et	90	14		**20** (85)
m	$PhCH_2$	$PhCH_2$	90	17		**21** (50)
n	$-(CH_2)_2-O-(CH_2)_2-$		90	12		**22** (71)

[a] Isolated yield. [b] Room temperature. [c] Another diastereomer. [d] yield was determined by nmr. [e] Admantyl.

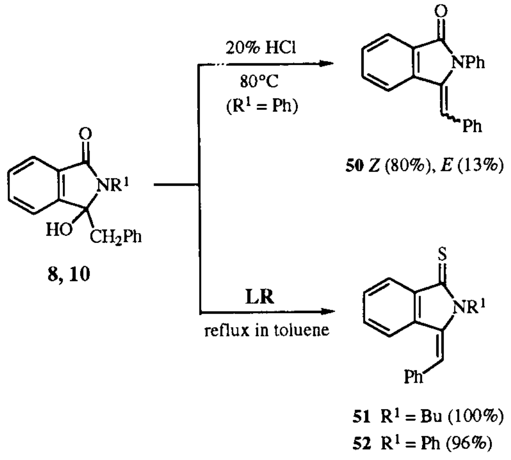


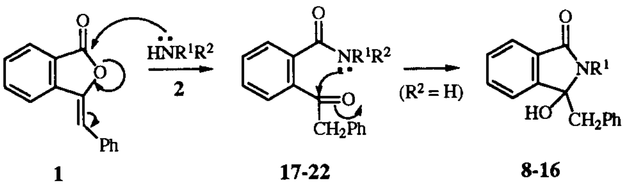
Figure 1.

respectively. The formation of *o*-acylbenzamides **17-22** can be understood in terms of nucleophilic attack of amines at the lactone carbonyl group of benzalphthalide **1** followed by ring-opening as shown in Scheme 2. Ring-closure of the corresponding *o*-acylbenzamides, although they could not be isolated, leads to isoindolinones **8-16**.

Reaction of 3-Halophthalides **3** with Amines **2**.

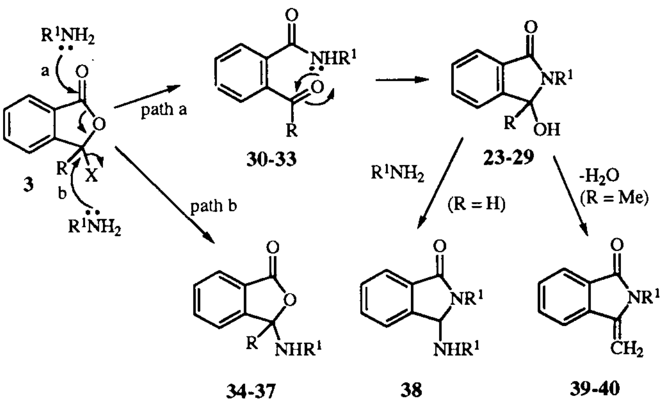
It is reported that 3-chlorophthalide reacted with aniline to give 3-anilino-3-phenylphthalide and *N*-phenyl-*o*-benzoylbenzamide [5b]. 3-Halophthalides are susceptible to

Scheme 2



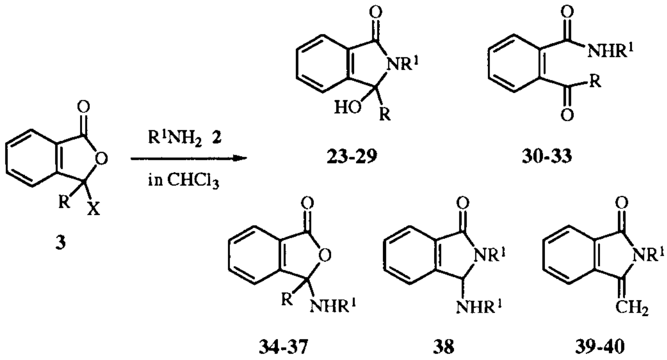
attack by nucleophiles at two centers. A sequence involving attack of amine at the lactone carbonyl group and elimination of hydrogen halide leads to a dicarbonyl compound, *o*-acylbenzamide or its tautomer, 3-hydroxyisoindolinone by cyclization (path a in Scheme 3) whereas displacement at the tetrahedral center (C-3) leads to a 3-aminophthalide (path b in Scheme 3).

Scheme 3



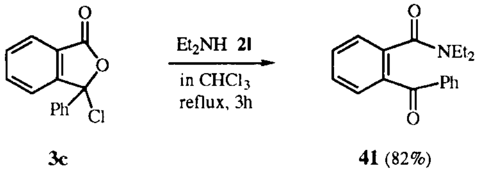
Next we carried out the reaction of 3-halophthalides **3** with various amines **2** to prepare 3-hydroxyisoindolinones or their tautomers, *o*-acylbenzamide derivatives and to get further information about their spectroscopic properties. Treatment of 3-bromophthalides **3a** with alkylamines **2i-k** and **m** gave 3-hydroxyisoindolin-1-ones **23-26** and 3-aminoisoindolin-1-one **38**, which was formed by displacement of the hydroxy group by amine at the tetrahedral center of **26**. However, treatment of **3a** with aniline **2c** gave the displacement product at C-3 of **3a**, 3-anilinophthalide **34**, in good yield. 3-Methyl-3-chlorophthalide **3b** was treated with *tert*-butylamine **2i** to yield both ring and chain products, **27** and **30**. The reaction of **3b** with amines **2j-k** which are substituted with a bulky group gave the chain products, *o*-acetylbenzamides **31-32**. Treatment of **3b** with benzylamine **2m** gave 3-methylideneisoindolinone **39**. With aniline **2c**, **3b** gave the displacement product **35** and 3-methylideneisoindolinone **40**. The formation of **39-40** is reasonably explained in terms of dehydration of 3-methyl-3-hydroxyisoindolin-1-ones. Treatment of 3-phenyl-3-chlorophthalide **3c** with *tert*-butyamine **2i** gave *o*-benzoylbenzamide **33** as the sole product, whereas treatment of **3c** with aromatic amines **2c** and **2o** gave 3-hydroxyisoindolinones **28-29** and displacement products **36-37**. 3-Phenyl-3-chlorophthalide **3c** reacted with the secondary amine, diethylamine **21**, to yield a single product, *N,N*-diethyl *o*-benzoylbenzamide **41** by the addition-elimination mechanism. The structure of 3-aminophthalides **34-37** was confirmed on the basis of spectral data and elemental analyses. The ir spectra of **34-37** showed two characteristic absorption bands at 3330-3350 (NH stretching) and 1725-1735 cm^{-1} (lactone carbonyl stretching). In the mass spectrum, two characteristic fragmentation peaks [(M$^+$-CO$_2$H) and (M$^+$-R^{1}NH$_2$)] were observed. Treatment of 3-aminophthalides **34-37** with **LR** gave isoindolin-1-thiones **46-49** in 34-100% yields, although the mechanism for the formation of **46-49** is not clear at present. The structure of **46-49** was confirmed by direct comparison of ir and nmr spectra with those of authentic samples [2d,4]. The products thus formed by the reaction of 3-halophthalides **3** with amines **2** seem to depend on both the substituents on the 3-position of phthalides **3** and those on the α-position of amines **2**, as shown in Chart 2.

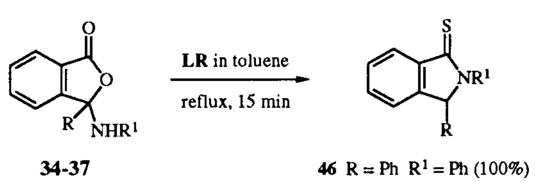
Chart 2



	3		Amine	Reaction conditions		Yield (%) [a]	
	R	X	R^1	temp (°C)	time (h)		
a	H	Br	*t*-Bu (**2i**)	rt [b]	3	**23** (51)	
			PhCH$_2$CMe$_2$ (**2j**)	Ref [c]	1	**24** (90)	
			Ad [d] (**2k**)	Ref	1	**25** (40)	
			PhCH$_2$ (**2m**)	rt	1	**26** (25)	**38** (71)
			Ph (**2c**)	rt	1	**34** (90)	
b	Me	Cl	*t*-Bu (**2i**)	rt	3	**27** (18)	**30** (32)
			PhCH$_2$CMe$_2$ (**2j**)	Ref	1	**31** (25)	
			Ad (**2k**)	Ref	3	**32** (43)	
			PhCH$_2$ (**2m**)	rt	3	**39** (76)	
			Ph (**2c**)	rt	3	**35** (8)	**40** (24)
c	Ph	Cl	*t*-Bu (**2i**)	rt	5	**33** (85)	
			Ph (**2c**)	rt	3	**28** (9)	**36** (63)
			p-Tol (**2o**)	rt	3	**29** (18)	**37** (29)

[a] Isolated yield. [b] Room temperature. [c] Reflux temperature. [d] Admantyl.





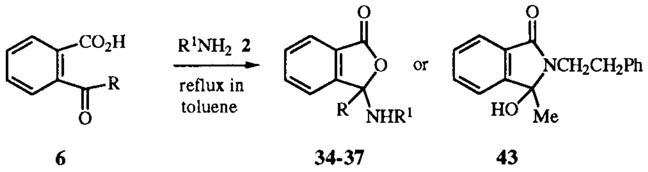
46 R = Ph R^1 = Ph (100%)
47 R = Ph R^1 = *p*-Tol (76%)
48 R = Me R^1 = Ph (90%)
49 R = H R^1 = Ph (34%)

Figure 2.

The Reaction of *o*-Acylbenzoic Acids **6** or Methyl *o*-Benzoylbenzoate **7** with Amines **2**.

Two groups have reported the synthesis of 3-hydroxyisoindolinones from *o*-acylbenzoic acids and amines [5c,d]. We carried out those modified procedures for the preparation of 3-hydroxyisoindolinones or their tautomers, *o*-acylbenzamides. Treatment of *o*-acylbenzoic acids **6** with aromatic amines **2c** and **o** in toluene at reflux yielded 3-aminophthalides **34-37** but not 3-hydroxyisoindolinones, while treatment of *o*-acetylbenzoic acid **6b** with the aliphatic amine, phenethylamine **2p**, gave 3-hydroxyisoindolin-1-one **43**. The formation of 3-aminophthalides **34-37** can be best explained in terms of substitution of the benzylic hydroxy group in the ring

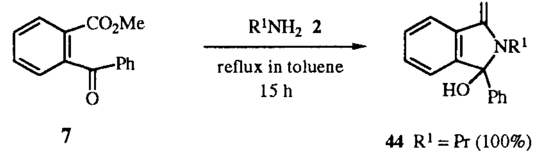
Chart 3



R	R^1	Reaction time [h]	Yield (%) [a]
H (**6a**)	Ph (**2c**)	3	**34** (90)
Me (**6b**)	Ph (**2c**)	15	**35** (46)
Ph (**6c**)	Ph (**2c**)	15	**36** (45)
Ph (**6c**)	*p*-Tol (**2o**)	15	**37** (57)
Me (**6b**)	PhCH$_2$CH$_2$ (**2p**)	15	**43** (75) [b]

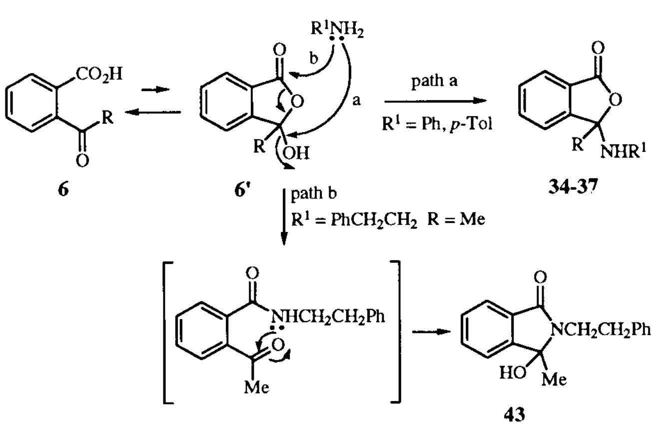
[a] Isolated yield. [b] 120° in a sealed tube.

Chart 4



44 R^1 = Pr (100%)
45 R^1 = PhCH$_2$CH$_2$ (79%)

Scheme 4



form of **6** [6] by amine **2** (Scheme 4). The reaction of methyl *o*-benzoylbenzoate **7** with aliphatic amine also gave 3-hydroxyisoindolin-1-ones **44-45**.

The Reaction of *N*-arylphthalimides **4** with Grignard Reagents **5**.

3-Hydroxyisoindolin-1-ones **28-29** and **42** were prepared by the reaction of *N*-arylphthalimides **4** with Grignard reagents **5** [5e]. The products **28-29** and **42** thus obtained were identified to be in the ring form, according to their spectroscopic properties (see Table l). Treatment of *N*-*tert*-butylphthalimide **4c**, which was prepared by oxidation of 3-hydroxy-2-*tert*-butylisoindolin-1-one **23** with chromium trioxide, with methyl magnesium iodide gave both ring and chain tautomers, **27** and **30** in 24 and 9% yield, respectively.

Spectroscopic Properties of 3-Hydroxyisoindolin-1-ones, *o*-Acylbenzamides and 3-Aminophthalides.

As mentioned above, either 3-hydroxyisoindolin-1-ones (ring form) or *o*-acylbenzamides (chain form) were exclusively formed by the reactions of 3-benzalphthalide **1**, 3-halophthalides **3**, *o*-acyl benzoic acids **6** and their esters **7** with amines **2**, and those of phthalimides **4** with Grignard reagent **5**. When 3-benzalphthalide **1** or 3-chloro-3-methylphthalide **3b** was treated with *tert*-butylamine **2i**, exceptionally both tautomers, 3-hydroxyisoindolinones **16** and **17** and *o*-acylbenzamides **27** and **30** were formed. Each tautomer (ring and chain form) showed characteristic spectroscopic properties, especially in the ir and ^{13}C-nmr spectra (see Table 1, 2, Chart 7 and Experimental). The ring form, 3-hydroxyisoindolinones showed two characteristic absorptions due to hydroxy (3130-3510 cm^{-1}) and amide carbonyl stretchings (1640-1680 cm^{-1}) in the ir spectrum while the chain form, *o*-acylbenzamides, showed two carbonyl stretching bands at 1660-1685 and 1615-1635 cm^{-1} due to acyl and amide carbonyls. In the ^{13}C-nmr spectrum, two characteristic peaks of 3-substituted 3-hydroxyisoindolinones appeared as two singlets at δ 88.6-93.1 and 166.2-167.9 assignable to C-3 quaternary and carbonyl carbons whereas those of *o*-acylbenzamides appeared at δ 167.5-170.6 and 196.6-202.5 due to amide carbonyl and carbonyl carbons, respectively. C-3 quaternary car-

Chart 5

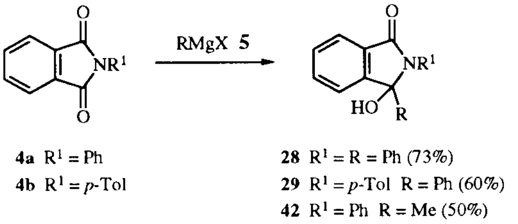


Chart 6

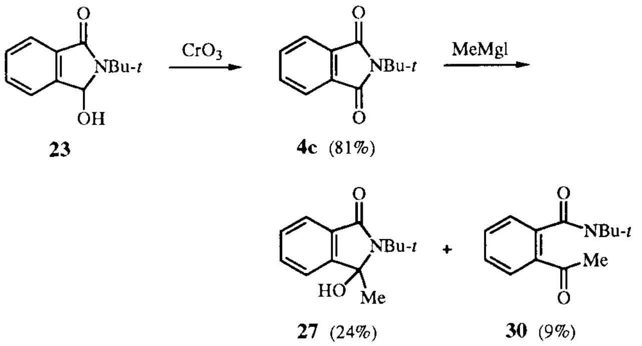


Table 1

IR and ^{13}C-NMR Data of 3-Hydroxyisoindolin-1-ones **8-15**, **23-29** and **42-45**

	IR (cm^{-1}/KBr)		^{13}C-NMR (δ in CDCl$_3$)	
	νOH	νCO-N	δC-3	δCO-N
8	3130	1665	91.2	166.6
9	3300	1680	91.2	166.9
10	3150	1660	92.9	166.7
11-1	3300	1660	91.8	166.7
11-2	3150	1650	91.5	167.1
12	3130	1665	91.4	166.3
13	3230	1665	91.4	166.6
14	3350	1660	90.5	166.2
15-1	3130	1665	91.1	167.9
15-2	3510	1665	92.0	167.5
23	3210	1650	82.3	168.0
24	3230	1640	82.3	168.5
25	3350	1675	81.7	167.9
26	3200	1640	81.0	167.5
27	3190	1660	91.4	167.6
28	3210	1665	93.1	167.1
29	3240	1670	92.6	167.5
42	3300	1665	90.5	167.1
43	3200	1670	88.6	167.1
44	3160	1665	91.3	167.9
45	3300	1660	91.2	167.9

Table 2

IR and ^{13}C-NMR Data of *o*-Acylbenzamides **17-22**, **30-33** and **41**

	IR (cm^{-1}/KBr)			^{13}C-NMR (δ in CDCl$_3$)	
	vNH	vCO	vCO-N	δCO-N	δCO
17	3360	1685	1625	167.7	202.4
18	3260	1680	1635	167.9	202.5
19	3300	1685	1625	167.5	202.4
20		1680	1620	170.6	198.6
21		1675	1620	171.6	198.5
22		1680	1620	170.3	198.3
30	3310	1685	1635	168.5	201.8
31	3350	1685	1625	168.6	202.0
32	3310	1680	1625	168.2	201.9
33	3270	1660	1625	167.0	197.8
41		1660	1615	169.9	196.6

Table 3

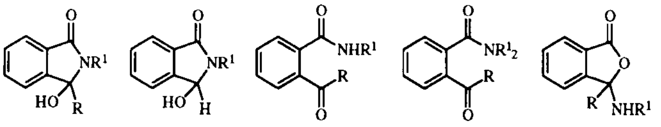
IR and ^{13}C-NMR Data of 3-Aminophthalides **34-37**

	IR (cm^{-1}/KBr)		^{13}C-NMR (δ in CDCl$_3$)	
	vNH	vCO-O	δC-3	δCO-O
34	3330	1735	87.6	169.3
35	3350	1725	97.3	168.5
36	3350	1730		
37	3350	1730	99.2	169.3

bon peaks (δ 81.0-82.3) of 3-monosubstituted isoindolinones **23-26** appeared as a doublet at lower field than those of 3,3-disubstituted isoindolinones. 3-Aminophthalides **34-37** also showed characteristic ir and ^{13}C-nmr spectra (see Table 3). Mass spectra are also helpful to determine these tautomers. Generally, a M$^+$-OH (or H$_2$O) peak was observed in the ring form, while both M$^+$ and M$^+$-R^{1}NH (or R$^1_2$N) peaks were observed in the chain form. The characteristic spectroscopic properties of 3-hydroxyisoindolin-1-ones, *o*-acylbenzamides, and 3-aminophthalides are summarized in Chart 7.

Chart 7

Characteristics of Spectroscopic Properties of 3-Hydroxyisoindolin-1-ones, *o*-Acylbenzamides and 3-Aminophthalides



vOH	3130-3510	3200-3350			
vCO	1650-1680	1640-1675	1660-1685	1660-1680	1725-1735
vCON		1625-1635	1615-1620		
vNH			3310-3360		3330-3350
δC-3	88.6-93.1	81.0-82.5			87.6-99.2
δCO			197.5-202.3	196.5-198.6	168.5-169.3
δCON	166.3-167.9	167.5-168.5	167.0-168.6	169.9-171.5	
MS	(M$^+$) M$^+$-OH or M$^+$-H$_2$O	M$^+$ M$^+$-OH or M$^+$-H$_2$O	M$^+$ M$^+$-R^{1}NH	M$^+$ M$^+$-R$^1_2$N	M$^+$ M$^+$-CO$_2$H M+-R^{1}NH

EXPERIMENTAL

Melting points were determined on Yanaco micro-melting point apparatus and are uncorrected. Compounds were recrystallized from chloroform-hexane. The ir spectra were recorded on a Hitach 260-30 photospectrometer (in potassium bromide and are in cm^{-1}). ^{1}H- and ^{13}C-nmr spectra were determined on Jeol FX-100 (100 MHz) and Jeol JNM-EX270 (270 MHz) spectrometers in deuteriochloroform using TMS as an internal standard (δ in ppm, J in Hz). Mass spectra were recorded on a Jeol-JMS-DX-300 spectrometer (direct insertion probe at 70 eV and 300 μA). Chromatographic purifications were carried out on a silica gel column (Kieselgel 60, Merck and Wakogel C-300).

Reaction of 3-Benzalphthalide **1** with Amines **2**: General Procedure.

A solution of **1** (0.005 mole) and an amine (0.01 mole) in *N*-methyl-2-pyrrolidone (10 ml) was stirred at room temperature or heated at 90° under argon. The reaction mixture was poured into water and extracted with dichloromethane. The extract was washed with water, then dried over anhydrous magnesium sulfate and the solvents were evaporated. The residue was chromatographed (benzene/ethyl acetate 4:1 to 9:1) to give the products **8-22**.

3-Benzyl-3-hydroxy-2-isopropylisoindolin-1-one (**8**).

This compound had mp 146-148°; ^{1}H-nmr: δ 1.51 (d, J = 6.6, 3H), 1.52 (d, J = 6.6, 3H), 2.88 (d, J = 13.5, 1H), 3.10 (d, J = 13.5, 1H), 3.97 (sep, J = 6.6, 1H), 6.73 (d, J = 7.3, 1H), 6.94-7.24 (m, 7H), 7.59-7.75 (m, 1H); ^{13}C-nmr: δ 20.5 (q), 21.2 (q), 43.6 (t), 44.2 (d), 91.2 (s), 122.8 (d), 123.1 (d), 127.0 (d), 127.9 (d), 129.5 (d), 130.7 (d), 131.1 (d), 132.3 (s), 135.1 (s), 145.6 (s), 166.6 (s); ms: 263 (M$^+$-H$_2$O, 100), 248 (25), 234 (24), 221 (50), 220 (55), 190 (M$^+$-PhCH$_2$, 12).

Anal. Calcd. for $C_{18}H_{19}NO_2$ (281.342): C, 76.84; H, 6.81; N, 4.98. Found: C, 76.79; H, 6.85; N, 5.01.

3-Benzyl-3-hydroxy-2-butylisoindolin-1-one (**9**).

This compound had mp 120-122°; ^{1}H-nmr: δ 0.94 (t, J = 7.3, 3H), 1.30-1.45 (m, 2H), 1.62-1.85 (m, 3H), 3.05 (d, J = 13.5, 1H), 3.18-3.34 (m, 1H), 3.52 (d, J = 13.5, 1H), 3.49-3.65 (m, 1H), 6.92-7.53 (m, 9H); ^{13}C-nmr: δ 13.8 (q), 20.6 (t), 31.4 (t), 39.3 (t), 43.2 (t), 91.2.(s), 122.8 (d), 122.9 (d), 129.6 (d), 127.9 (d), 129.3 (d), 130.2 (d), 131.3 (d), 134.7 (s), 146.1 (s), 166.9 (s); ms: 277 (M$^+$-H$_2$O, 100), 234 (75), 204 (M$^+$-PhCH$_2$, 85).

3-Benzyl-3-hydroxy-2-phenylisoindolin-1-one (**10**).

This compound had mp 170-171°; ^{1}H-nmr: δ 3.04 (d, J = 14.2, 1H), 3.40 (d, J = 14.2, 1H), 4.28 (br s, 1H), 6.74 (d, J = 6.9, 2H), 6.95-7.85 (m, 12H); ^{13}C-nmr: δ 42.8 (t), 92.9 (s), 122.9 (d), 123.4 (d), 125.9 (d), 126.4 (d), 126.8 (d), 127.6 (d), 128.6 (d), 129.6 (d), 130.4 (d), 130.5 (d), 132.2 (d), 134.3 (s), 135.8 (s), 145.9 (s), 166.7 (s); ms: 315 (M$^+$, 1.5), 297 (M$^+$-H$_2$O, 100), 224 (M$^+$-PhCH$_2$, 60), 220 (30).

3-Benzyl-3-hydroxy-2-(1'-phenylethyl)isoindolin-1-one (**11-1**).

This compound had mp 156-157°; ^{1}H-nmr: δ 1.58 (s, 1H), 1.92 (d, J = 7.3, 3H), 2.98 (d, J = 13.9, 1H), 3.65 (d, J = 13.9, 1H), 4.97 (q, J = 7.3, 1H), 6.79-6.83 (m, 1H), 7.05-7.42 (m, 10H), 7.60-7.64 (m, 3H); ^{13}C-nmr: δ 19.1 (q), 44.0 (t), 51.9 (d), 91.8 (s), 123.2 (d), 127.1 (d), 127.8 (d), 128.0 (d), 128.3 (d), 129.6 (d), 130.6 (d), 131.4 (d), 131.9 (s), 134.9 (s), 142.7 (s), 145.6 (s), 166.8 (s); ms: 325 (M$^+$-H$_2$O, 41), 221 (100), 105 (76).

Anal. Calcd. for $C_{23}H_{21}NO_2$ (343.408): C, 80.44; H, 6.16; N, 4.08. Found: C, 80.37; H, 6.15; N, 4.11.

3-Benzyl-3-hydroxy-2-(1'-phenylethyl)isoindolin-1-one (**11-2**).

This compound had mp 173-174°; ^{1}H-nmr: δ 1.90 (d, 3H), 2.64 (d, 1H), 3.30 (br s, 1H), 3.49 (d, 1H), 5.07 (q, J = 7.3, 1H), 6.61 (d, J = 7.6, 1H), 6.88-6.92 (m, 2H), 7.04-7.40 (m, 8H), 7.57-7.66 (m, 3H); ^{13}C-nmr: δ 21.3 (q), 44.3 (t), 52.3 (d), 91.5 (s), 123.1 (d), 123.4 (d), 126.8 (d), 127.0 (d), 127.2 (d), 127.5 (d), 128.5 (d), 129.5 (d), 130.8 (d), 131.2 (d), 135.0 (d), 143.3 (s), 145.4 (s), 167.1 (s); ms: 325 (M$^+$-H$_2$O, 39), 221 (100), 105 (66).

Anal. Calcd. for $C_{23}H_{21}NO_2$ (343.408): C, 80.44; H, 6.16; N, 4.08. Found: C, 80.57; H, 6.16; N, 4.14.

3-Benzyl-3-hydroxy-2-diphenylmethylisoindolin-1-one (**12**).

This compound had mp 207-209°; ^{1}H-nmr: δ 2.76 (dd, J = 1.3, 13.9, 1H), 3.02 (d, J = 1.3, 1H), 3.57 (d, J = 13.9, 1H), 6.15 (s, 1H), 6.65 (d, J = 7.3, 1H), 6.96-7.00 (m, 1H), 7.13-7.50 (m, 14H), 7.63-7.66 (m, 1H); ^{13}C-nmr: δ 44.8 (t), 59.6 (d), 91.4 (s), 123.5 (d), 127.0 (d), 127.2 (d), 128.0 (d), 128.4 (d), 128.8 (d), 129.2 (d), 129.7 (d), 131.0 (d), 131.4 (d), 131.7 (s), 134.9 (s), 140.1 (s), 140.5 (s), 145.4 (s), 166.3 (s); ms: 387 (M$^+$-H$_2$O, 16), 167 (100), 152 (10).

Anal. Calcd. for $C_{28}H_{23}NO_2$ (405.474): C, 82.93; H, 5.71; N, 3.45. Found: C, 82.60; H, 5.68; N, 3.45.

3-Benzyl-3-hydroxy-2-cyclohexylisoindolin-1-one (**13**).

This compound had mp 166-167°; ^{1}H-nmr: δ 1.20-1.45 (m, 3H), 1.60-1.95 (m, 6H), 2.25-2.50 (m, 1H), 2.84 (d, J = 13.9, 1H), 3.31-3.60 (m, 1H), 3.60 (d, J = 13.9, 1H), 6.68 (d, J = 7.6, 1H), 7.07-7.43 (m, 7H), 7.53 (d, J = 7.3, 1H); ^{13}C-nmr: δ 25.3 (t), 26.5 (t), 30.1 (t), 30.7 (t), 43.9 (t), 52.6 (d), 91.3 (s), 122.9 (d), 123.1 (d), 127.0 (d), 127.9 (d), 129.3 (d), 130.7 (d), 131.0 (d), 132.3 (d), 135.4 (s), 145.6 (s), 166.6 (s); ms: 303 (M$^+$-H$_2$O, 100), 222 (90), 132 (10).

Anal. Calcd. for $C_{21}H_{23}NO_2$ (321.404): C, 78.47; H, 7.21; N, 4.36. Found: C, 78.33; H, 7.20; N, 4.38.

3-Benzyl-3-hydroxy-(β-hydroxyphenethyl)isoindolin-1-one (**14**).

This compound had mp 151-152°; ^{1}H-nmr: δ 3.15 (d, J = 13.9, 1H), 3.43 (d, J = 13.9, 1H), 3.42-3.49 (m, 1H), 3.96 (dd, J = 2.3, 14.5, 1H), 4.48 (br s, 1H), 5.03-5.08 (m, 1H), 5.20 (br s, 1H), 6.75-6.87 (m, 2H), 6.99-7.11 (m, 2H), 7.23-7.48 (m, 10H); ^{13}C-nmr: δ 43.6 (t), 48.0 (t), 71.8 (d), 90.5 (s), 122.5 (d), 123.0 (d), 125.9 (d), 126.9 (d), 127.9 (d), 128.6 (d), 129.3 (d), 130.0 (d), 130.4 (s), 132.0 (d), 134.6 (s), 141.4 (s), 146.8 (s), 166.2 (s); ms: 341 (M$^+$-H$_2$O, 32), 250 (46), 233 (80), 234 (100).

Anal. Calcd. for $C_{23}H_{21}NO_3$ (359.408): C, 76.89; H, 5.89; N, 3.90. Found: C, 76.76; H, 5.86; N, 3.89.

3-Benzyl-3-hydroxy-2-(α-carbomethoxybenzyl)isoindolin-1-one (**15-1**).

This compound had mp 170-171°; ir: ν 3130, 1740, 1665; ^{1}H-nmr: δ 2.85 (d, J = 14.2, 1H), 3.38 (d, J = 14.2, 1H), 3.73 (s, 3H), 5.38 (s, 1H), 6.76 (d, J = 7.3, 2H), 6.93-7.14 (m, 3H), 7.25-7.48 (m, 6H), 7.54-7.60 (m, 2H), 7.71-7.76 (m, 1H); ^{13}C-nmr: δ 46.9 (t), 53.3 (q), 58.0 (d), 91.1 (s), 123.5 (d), 123.7 (d), 126.9 (d), 128.2 (d), 128.4 (d), 129.6 (d), 129.8 (d), 130.5 (s), 130.7 (d), 132.1 (d), 134.2 (s), 136.3 (s), 146.4 (s), 167.9 (s), 170.9 (s); ms: 369 (M$^+$-H$_2$O, 56), 310 (39), 232 (100).

Anal. Calcd. for $C_{24}H_{21}NO_4$ (387.418): C, 74.40; H, 5.46; N, 3.61. Found: C, 74.28; H, 5.45; N, 3.58.

3-Benzyl-3-hydroxy-2-(α-carbomethoxybenzyl)isoindolin-1-one (**15-2**).

This compound had mp 166-167°; ir: ν 3510, 1735, 1665. ^{1}H-nmr: δ 2.64 (d, J = 13.9, 1H), 3.13 (d, J = 13.9, 1H), 3.78 (s, 3H), 5.95 (s, 1H), 6.79-6.94 (m, 3H), 7.09-7.43 (m, 8H), 7.58-7.70 (m, 3H); ^{13}C-nmr: δ 44.0 (t), 53.1 (q), 58.8 (d), 92.0 (s), 123.2 (d), 123.5 (d), 126.8 (d), 127.4 (d), 128.6 (d), 128.8 (d), 129.5 (d), 130.1 (s), 130.6 (d), 131.9 (d), 134.5 (s), 135.1 (s), 147.2 (s), 167.4 (s), 172.3 (s); ms: 369 (M$^+$-H$_2$O, 68), 310 (44), 232 (100).

Anal. Calcd. for $C_{24}H_{21}NO_4$ (387.418): C, 74.40; H, 5.46; N, 3.61. Found: C, 74.54; H, 5.50; N, 3.59.

3-Benzyl-3-hydroxy-2-*t*-butylisoindolin-1-one (**16**) and *N*-*t*-Butyl-*o*-phenylacetylbenzamide (**17**).

These two compounds could not be separated completely, mp [a mixture of **16** and **17** (*ca* 1:9)] 107-109°; ^{1}H-nmr: (for **16**) δ 1.70 (s, 9H), 3.22 (d, J = 14.2, 1H), 3.88 (d, J = 14.2, 1H), 6.88-6.97 (m, 3H), 7.11-7.65 (m, 6H); (for **17**) δ 1.45 (s, 9H), 4.15 (s, 2H), 5.78 (br s, 1H), 7.20-7.50 (m, 9H); ^{13}C-nmr: (for **17**) δ 28.6 (q), 49.1 (t), 52.0 (s), 126.9 (d), 127.1 (d), 127.7 (d), 128.6 (d), 129.7 (d), 129.9 (d), 130.4 (d), 134.1 (s), 136.4 (s), 139.8 (s), 167.7 (s), 202.4 (s); ms: (for **17**) 277 (M$^+$-H$_2$O, 0.3), 223 (M$^+$-BuNH, 6), 204 (M$^+$-PhCH$_2$, 31), 148 (100).

Anal. Calcd. for $C_{19}H_{21}NO_2$ (295.368) (a mixture of **16** and **17**): C, 77.26; H, 7.17; N, 4.74. Found: C, 77.25; H, 7.23; N, 4.74.

N-(β,β-Dimethylphenethyl)-*o*-phenylacetylbenzamide (**18**).

This compound had mp 114-115°; ^{1}H-nmr: δ 1.43 (s, 6H), 3.15 (s, 2H), 4.17 (s, 2H), 5.61 (br s, 1H), 7.19-7.49 (m, 14H); ^{13}C-nmr: δ 27.2 (q), 45.9 (t), 49.2 (t), 54.9 (s), 126.5 (d), 126.9 (d), 127.7 (d), 128.0 (d), 128.3 (d), 128.6 (d), 129.7 (d), 130.1 (d), 130.3 (d), 130.6 (d), 134.2 (s), 136.1 (s), 140.3 (s), 137.8 (s), 167.9 (s), 202.5 (s).

Anal. Calcd. for $C_{25}H_{25}NO_2$ (371.46): C, 80.83; H, 6.78; N, 3.77. Found: C, 81.11; H, 6.82; N, 3.81.

N-Admantyl-*o*-phenylacetylbenzamide (**19**).

This compound had mp 185-187°; ^{1}H-nmr: δ 1.71 (br s, 5H), 2.11 (br s, 10H), 4.16 (s, 2H), 5.65 (br s, 1H), 7.19-7.62 (m, 9H); ^{13}C-nmr: δ 29.4 (d), 36.3 (t), 41.4 (t), 49.1 (t), 52.8 (s), 126.9 (d), 127.1 (d), 127.8 (d), 128.5 (d), 129.7 (d), 129.9 (d), 130.3 (d), 134.2 (s), 136.5 (s), 139.7 (s), 167.5 (s), 202.4 (s); ms: 355 (M$^+$-H$_2$O, 5), 282 (M$^+$-PhCH$_2$, 22), 222 (M$^+$-AdNH$_2$, 7), 135 (100).

Anal. Calcd. for $C_{25}H_{27}NO_2$ (373.476): C, 80.40; H, 7.29; N, 3.75. Found: C, 80.10; H, 7.28; N, 3.74.

N,N-Diethyl-*o*-phenylacetylbenzamide (**20**).

This compound had mp 84-85°; ^{1}H-nmr: δ 1.01 (t, J = 7.3, 3H), 1.28 (t, J = 7.3, 3H), 3.07 (q, J = 7.3, 2H), 3.56 (q, J = 7.3, 2H), 4.23 (s, 2H), 7.20-7.55 (m, 8H), 7.83 (d, J = 7.6, 1H); ^{13}C-nmr: δ 11.3 (q), 13.5 (q), 38.8 (t), 42.8 (t), 46.8 (t), 126.9 (d), 127.2 (d), 128.4 (d), 128.6 (d), 129.1 (d), 129.5 (d), 130.2 (d), 134.2 (s), 135.2 (s), 138.3 (s), 170.6 (s), 198.6 (s); ms: 295 (M^+, 0.2), 222 (M^+-Et_2NH, 18), 204 (M^+-$PhCH_2$, 100).

Anal. Calcd. for $C_{19}H_{21}NO_2$ (295.368): C, 77.26; H, 7.15; N, 4.74. Found: C, 77.50; H, 7.15; N, 4.63.

N,N-Dibenzyl-*o*-phenylacetylbenzamide (**21**).

This compound had mp 142-144°; ^{1}H-nmr: δ 4.08 (s, 2H), 4.25 (s, 2H), 4.71 (s, 2H), 7.07-7.11 (m, 2H), 7.20-7.51 (m, 16H), 7.83 (d, J = 7.6, 1H); ^{13}C-nmr: δ 46.5 (t), 46.8 (t), 51.2 (t), 126.9 (d), 127.3 (d), 127.6 (d), 128.4 (d), 128.6 (d), 128.7 (d), 129.0 (d), 129.6 (d), 132.1 (d), 134.1 (s), 135.5 (s), 136.0 (s), 136.6 (s), 137.4 (s), 171.6 (s), 198.5 (s); ms: 419 (M^+, 3), 328 (M^+-$PhCH_2$, 15), 222 (M^+-$(PhCH_2)_2NH$, 5), 196 (44), 91 (100).

Anal. Calcd. for $C_{29}H_{25}NO_2$ (419.5): C, 83.03; H, 6.00; N, 3.34. Found: C, 82.75; H, 5.90; N, 3.22.

N-Morphorino-*o*-phenylacetylbenzamide (**22**).

This compound had mp 100-101°; ^{1}H-nmr: δ 3.12 (t, J = 4.6, 2H), 3.56 (t, J = 4.6, 2H), 3.79 (s, 4H), 4.25 (s, 2H), 7.21-7.36 (m, 6H), 7.41-7.61 (m, 2H), 7.88 (dd, J = 1.0, 6.9, 1H); ^{13}C-nmr: δ 42.0 (t), 46.5 (t), 47.2 (t), 66.2 (t), 66.5 (t), 127.0 (d), 127.4 (d), 128.7 (d), 128.9 (d), 129.3 (d), 129.5 (d), 132.5 (d), 133.9 (s), 135.2 (s), 137.2 (s), 170.3 (s), 198.3 (s); ms: 222 (M^+-C_4H_9ON, 66), 218 (M^+-$PhCH_2$, 100).

Anal. Calcd. for $C_{19}H_{19}NO_3$ (293.352): C, 73.76; H, 6.19; N, 4.53. Found: C, 73.61; H, 6.14; N, 4.52.

Reaction of 3-Halophthalides **3** with Amines **2**: General Procedure.

A solution of 3-halophthalide **3** (0.005 mole) and amine (0.01 mole) in chloroform (20 ml) was stirred at room temperature or refluxed under argon. The reaction mixture was poured into water and extracted with dichloromethane. The extract was dried over anhydrous magnesium sulfate and the solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography (benzene/ethyl acetate 9:1 to 4:1) as eluant to give products **23-41**. Products **28** [5d], **36** [5c] and **40** [5e] were confirmed by direct comparison of their ir and nmr spectra with those of authentic materials independently prepared.

3-Hydroxy-2-*t*-butylisoindolin-1-one (**23**).

This compound had mp 139-140°; ^{1}H-nmr: δ 1.57 (s, 9H), 3.18 (d, J = 11.2, 1H), 5.96 (d, J = 11.2, 1H), 7.38-7.60 (m, 4H); ^{13}C-nmr: δ 28.3 (q), 54.7 (s), 82.3 (d), 122.7 (d), 122.9 (d), 129.6 (d), 131.9 (d), 132.6 (s), 143.6 (s), 168.0 (s); ms: 205 (M^+, 7), 190 (56), 188 (M^+-OH, 3), 133 (100).

Anal. Calcd. for $C_{12}H_{15}NO_2$ (205.25): C, 70.22; H, 7.37; N, 6.82. Found: C, 70.22; H, 7.43; N, 6.82.

3-Hydroxy-2-(α,α-dimethylbenzyl)isoindolin-1-one (**24**).

This compound had mp 147-148°; ^{1}H-nmr: δ 1.63 (s, 3H), 1.65 (s, 3H), 1.73 (br s, 1H), 3.22-3.37 (dd, J = 13.2, 21.4, 2H), 5.51 (d, J = 11.6, 1H), 7.07-7.19 (m, 5H), 7.36-7.54 (m, 3H), 7.73-7.77 (m, 1H); ^{13}C-nmr: δ 26.7 (q), 26.8 (q), 44.6 (t), 58.1 (s), 82.3 (d), 122.8 (d), 123.0 (d), 126.4 (d), 128.0 (d), 129.7 (d), 130.4 (d), 132.1 (d), 138.5 (s), 143.7 (s), 168.5 (s); ms: 263 (M^+-H_2O, 5), 248 (15), 190 (100), 133 (94).

Anal. Calcd. for $C_{18}H_{19}NO_2$ (281.342): C, 76.84; H, 6.81; N, 4.98. Found: C, 76.68; H, 6.75; N, 4.90.

3-Hydroxy-2-admantylisoindolin-1-one (**25**).

This compound had mp 200-201°; ^{1}H-nmr: δ 1.67-1.89 (m, 6H), 2.13 (br s, 3H), 2.29-2.42 (m, 6H), 2.92 (br s, 1H), 6.02 (d, J = 11.2, 1H), 7.35-7.60 (m, 4H); ^{13}C-nmr: δ 29.8 (d), 36.4 (t), 40.3 (t), 56.3 (s), 81.7 (d), 122.7 (d), 123.0 (d), 129.7 (d), 131.9 (d), 132.8 (s), 143.6 (s), 167.9 (s); ms: 283 (M^+, 75), 267 (11), 266 (M^+-OH, 10), 226 (75), 133 (100).

Anal. Calcd. for $C_{18}H_{21}NO_2$ (283.358): C, 76.30; H, 7.47; N, 4.94. Found: C, 76.17; H, 7.70; N, 4.63.

3-Hydroxy-2-benzylisoindolin-1-one (**26**).

This compound had mp 141-142°; ^{1}H-nmr: δ 4.18 (dd, J = 1.3, 14.8, 1H), 4.14-4.25 (m, 1H), 4.75 (dd, J = 2.0, 14.8, 1H), 5.56 (d, J = 11.5, 1H), 7.22-7.28 (m, 6H), 7.35-7.46 (m, 1H), 7.50-7.61 (m, 2H); ^{13}C-nmr: δ 42.5 (t), 81.0 (d), 123.3 (d), 123.5 (d), 127.6 (d), 128.4 (d), 128.7 (d), 129.7 (d), 131.1 (d), 132.4 (d), 136.7 (s), 133.0 (s), 167.5 (s); ms: 239 (M^+, 1.5), 222 (89), 221 (M^+-H_2O, 100), 77 (15).

Anal. Calcd. for $C_{15}H_{13}NO_2$ (239.264): C, 75.30; H, 5.48; N, 5.85. Found: C, 75.33; H, 5.40; N, 5.81.

3-Hydroxy-3-methyl-2-*t*-butylisoindolin-1-one (**27**).

This compound had mp 132-133°; ^{1}H-nmr: δ 1.64 (s, 9H), 1.89 (s, 3H), 3.18 (s, 1H), 7.39-7.62 (m, 4H); ^{13}C-nmr: δ 27.7 (q), 29.1 (q), 56.3 (s), 91.4 (s), 120.6 (d), 122.7 (d), 129.2 (d), 130.8 (s), 132.0 (d), 149.2 (s), 167.6 (s); ms: 219 (M^+, 10), 204 (23), 201 (M^+-H_2O, 12), 176 (7), 147 (100).

Anal. Calcd. for $C_{13}H_{17}NO_2$ (219.276): C, 71.21; H, 7.81; N, 6.39. Found: C, 70.90; H, 7.82; N, 6.30.

3-Hydroxy-3-phenyl-2-*p*-tolylisoindolin-1-one (**29**).

This compound had mp 191-193°; ^{1}H-nmr: δ 2.23 (s, 3H), 4.57 (s, 1H), 6.92 (d, J = 8.2, 2H), 7.17-7.36 (m, 10H), 7.43-7.53 (m, 2H); ^{13}C-nmr: δ 21.0 (q), 92.6 (s), 122.6 (d), 123.6 (d), 125.4 (d), 126.1 (d), 128.1 (d), 128.3 (d), 129.1 (d), 129.4 (d), 129.8 (d), 133.0 (d), 135.7 (s), 138.7 (s), 148.7 (s), 167.5 (s); ms: 315 (M^+, 13), 298 (M^+-OH, 0.7), 209 (100), 152 (12).

Anal. Calcd. for $C_{21}H_{17}NO_2$ (315.356): C, 79.98; H, 5.43; N, 4.45. Found: C, 79.82; H, 5.42; N, 4.59.

N-*t*-Butyl-*o*-acetylbenzamide (**30**).

This compound had mp 115-116°; ^{1}H-nmr: δ 1.47 (s, 9H), 2.56 (s, 3H), 5.78 (br s, 1H), 7.43-7.58 (m, 4H); ^{13}C-nmr: δ 28.6 (q), 29.3 (q), 52.0 (s), 127.3 (d), 127.9 (d), 129.7 (d), 130.9 (d), 137.1 (s), 139.1 (s), 168.5 (s), 201.8 (s); ms: 219 (M^+, 7), 147 (M^+-BuNH, 100), 204 (19), 201 (9).

Anal. Calcd. for $C_{13}H_{17}NO_2$ (219.276): C, 71.21; H, 7.81; N, 6.39. Found: C, 71.17; H, 7.94; N, 6.33.

N-(α,α-Dimethylphenethyl)-*o*-acetylbenzamide (**31**).

This compound had mp 103-105°; ^{1}H-nmr: δ 1.44 (s, 6H), 2.56 (s, 3H), 3.15 (s, 2H), 5.60 (br s, 1H), 7.21-7.79 (m, 9H); ^{13}C-nmr: δ 27.1 (q), 29.5 (q), 45.1 (t), 54.9 (s), 126.4 (d), 127.2 (d), 127.8 (d), 128.0 (d), 129.9 (d), 130.7 (d), 130.8 (d), 136.8 (s), 137.8 (s), 139.6 (s), 168.6 (s), 202.0 (s); ms: 295 (M^+, 0.1); 204 (M^+-$PhCH_2$, 12), 147 (M^+-$PhCH_2C(NH)Me_2$, 83), 91 (100).

Anal. Calcd. for $C_{19}H_{21}NO_2$ (295.368): C, 77.26; H, 7.17; N, 4.74. Found: C, 77.05; H, 6.95; N, 4.60.

N-Admantyl-*o*-acetylbenzamide (**32**).

This compound had mp 156-157°; ^{1}H-nmr: δ 1.67-1.77 (m, 6H), 2.33 (br s, 9H), 2.57 (s, 3H), 5.60 (br s, 1H), 7.40-7.58 (m, 4H); ^{13}C-nmr: δ 29.5 (d), 36.4 (t), 41.5 (t), 52.8 (s), 127.3 (d), 127.9 (d), 129.8 (d), 130.9 (d), 137.2 (s), 139.2 (s), 168.2 (s), 201.9 (s); ms: 297 (M$^+$, 36), 282 (48), 279 (40), 147 (M$^+$-AdNH, 100).

Anal. Calcd. for $C_{19}H_{23}NO_2$ (297.384): C, 76.76; H, 7.79; N, 4.71. Found: C, 76.66; H, 7.78; N, 4.66.

N-t-Butyl-*o*-benzoylbenzamide (**33**).

This compound had mp 114-115°; ^{1}H-nmr: δ 1.16 (s, 9H), 5.75 (br s, 1H), 7.26-7.68 (m, 7H), 7.79 (d, J = 8.6, 2H); ^{13}C-nmr: δ 28.2 (q), 51.8 (s), 127.4 (d), 128.4 (d), 128.5 (d), 129.8 (d), 130.2 (d), 133.3 (d), 137.0 (s), 137.1 (s), 138.7 (s), 167.0 (s), 197.8 (s); ms: 281 (M$^+$, 20), 209 (M$^+$-BuNH, 100).

Anal. Calcd. for $C_{18}H_{19}NO_2$ (281.342): C, 76.84; H, 6.81; N, 4.98. Found: C, 76.68; H, 6.86; N, 4.92.

3-Phenylaminophthalide (**34**).

This compound had mp 172-173°; ^{1}H-nmr: δ 1.73 (br s, 1H), 4.77 (br s, 1H), 6.83-6.98 (m, 3H), 7.24-7.33 (m, 2H), 7.59-7.79 (m, 3H), 7.88-7.93 (m, 1H); ^{13}C-nmr: δ 87.6 (d), 115.2 (d), 121.1 (d), 123.4 (d), 125.6 (d), 128.0 (s), 129.5 (d), 130.8 (d), 134.4 (d), 143.7 (s), 145.3 (s), 169.3 (s); ms: 225 (M$^+$, 48), 197 (13), 181 (19), 180 (M$^+$-CO$_2$H, 22), 133 (M$^+$-PhNH, 100).

Anal. Calcd. for $C_{14}H_{11}NO_2$ (225.238): C, 74.65; H, 4.92; N, 6.21. Found: C, 74.39; H, 4.81; N, 6.13.

3-Methyl-3-phenylaminophthalide (**35**).

This compound had mp 117-118°; ^{1}H-nmr: δ 1.96 (s, 3H), 4.74 (br s, 1H), 6.52-6.56 (m, 2H), 6.81-6.87 (m, 1H), 7.01-7.08 (m, 2H), 7.53-7.72 (m, 3H), 7.87-7.91 (m, 1H); ^{13}C-nmr: δ 28.6 (q), 97.3 (s), 119.5 (d), 121.9 (d), 122.2 (d), 125.7 (d), 127.6 (s), 128.9 (d), 130.1 (d), 134.4 (d), 141.9 (s), 150.1 (s), 168.9 (s); ms: 239 (M$^+$, 18), 194 (M$^+$-CO$_2$H, 19), 147 (M$^+$-PhNH, 100).

Anal. Calcd. for $C_{15}H_{13}NO_2$ (239.264): C, 75.30; H, 5.48; N. 5.85. Found: C, 75.00; H, 5.49; N, 5.83.

3-Phenyl-3-*p*-tolylaminophthalide (**37**).

This compound had mp 209-211°; ^{1}H-nmr: δ 2.19 (s, 3H), 6.63 (d, J = 8.6, 2H), 6.87 (d, J = 8.6, 2H), 7.25-7.40 (m, 3H), 7.48-7.71 (m, 5H), 7.88 (d, J = 7.3, 1H); ^{13}C-nmr: δ 20.5 (q), 99.2 (s), 119.5 (d), 123.1 (d), 125.9 (d), 128.9 (d), 129.1 (d), 129.4 (d), 130.2 (d), 131.0 (s), 134.6 (d), 139.3 (s), 139.5 (s), 150.7 (s), 169.3 (s); ms: 315 (M$^+$, 16), 270 (M$^+$-CO$_2$H, 6), 209 (M-PhNH, 100).

Anal. Calcd. for $C_{21}H_{17}NO_2$ (315.356): C, 79.98; H, 5.43; N, 4.44. Found: C, 79.80; H, 5.41; N, 4.46.

3-Benzylamino-2-benzylisoindolin-1-one (**38**).

This compound had mp 222-224°; ir: ν 3330, 1665; ^{1}H-nmr: δ 2.04 (br s, 1H), 3.31 (dd, J = 12.9, 21.3, 2H), 4.33 (d, J = 14.9, 1H), 5.18 (d, J = 14.9, 1H), 5.31 (s, 1H), 7.14-7.36 (m, 11H), 7.49-7.56 (m, 2H), 7.88 (d, J = 1.0, 1H); ^{13}C-nmr: δ 43.3 (t), 45.6 (t), 72.3 (d), 123.2 (d), 123.6 (d), 127.2 (d), 127.6 (d), 128.1 (d), 128.3 (d), 128.4 (d), 128.8 (d), 129.2 (d), 131.9 (d), 132.8 (s), 137.4 (s), 139.6 (s), 143.3 (s), 167.7 (s).

Anal. Calcd. for $C_{22}H_{20}N_2O$ (328.4): C, 80.46; H, 6.14; N, 8.53. Found: C, 80.54; H, 6.23; N, 8.41.

3-Methylene-2-benzylisoindolin-1-one (**39**).

This compound had mp 112-113°; ir: ν 1700, 1635; ^{1}H-nmr: δ 4.78 (d, J = 2.0, 1H), 5.00 (s, 2H), 5.14 (d, J = 2.0, 1H), 7.20-7.35 (m, 6H), 7.47-7.68 (m, 2H), 7.88 (d, J = 7.3, 1H); ^{13}C-nmr: δ 43.1 (t), 90.0 (t), 119.9 (d), 123.3 (d), 127.1 (d), 127.4 (d), 128.6 (d), 129.0 (s), 129.2 (d), 129.5 (d), 136.4 (s), 136.8 (s), 141.5 (s), 167.2 (s); ms: 235 (M$^+$, 50), 220 (6), 206 (18), 91 (100).

Anal. Calcd. for $C_{16}H_{13}NO$ (235.274): C, 81.68; H, 5.57; N, 5.95. Found: C, 81.71; H, 5.67; N, 5.89.

N,N-Diethyl-*o*-benzoylbenzamide (**41**).

This compound had mp 53-54°; ^{1}H-nmr: δ 1.07 (t, J = 7.0, 3H), 1.11 (t, J = 7.0, 3H), 3.26 (q, J = 7.0, 2H), 3.43 (q, J = 7.0, 2H), 7.26-7.60 (m, 7H), 7.78-7.82 (m, 2H); ^{13}C-nmr: δ 12.1 (q), 13.7 (q), 38.8 (t), 43.2 (t), 126.7 (d), 128.1 (d), 128.2 (d), 129.8 (d), 130.2 (d), 130.8 (d), 133.0 (d), 136.9 (s), 137.2 (s), 138.3 (s), 159.9 (s), 196.6 (s); ms: 281 (M$^+$, 1.6), 209 (M$^+$-Et$_2$N, 82), 181 (6), 152 (21), 72 (100).

Anal. Calcd. for $C_{18}H_{19}NO_2$ (281.342): C, 76.84; H, 6.81; N, 4.98. Found: C, 76.98; H, 6.86; N, 4.97.

Reaction of *N*-Arylphthalimide **4** with Grignard Reagent **5**.

To a stirred solution of **4** (0.005 mole) in dry THF-ether (1:1, 30 ml) under argon was added dropwise a solution of the corresponding Grignard reagent **5** (0.01 mole) in ether at room temperature. After stirring for 3 hours, the usual work-up gave 3-hydroxyisoindolin-1-ones **28** [5d], **29** [5d] and **42** [5d].

Reaction of *o*-Acylbenzoylbenzoic Acid **6** with Amines **2**.

A solution of **6** (0.01 mole) and **2** (0.02 mole) in toluene (50 ml) was refluxed under argon for 15 hours. Work-up gave products **34-37** and **43**.

3-Hydroxy-3-methyl-2-phenethylisoindolin-1-one (**43**).

This compound had mp 110-111°; ^{1}H-nmr: δ 1.57 (s, 3H), 2.81-2.91 (m, 1H), 2.96-3.08 (m, 1H), 3.23-3.35 (m, 1H), 3.51-3.63 (m, 1H), 3.71 (br s, 1H), 7.16-7.38 (m, 6H); 7.45-7.53 (m, 3H); ^{13}C-nmr: δ 24.1 (q), 34.9 (t), 40.4 (t), 88.6 (s), 121.5 (d), 123.0 (d), 126.3 (d), 128.4 (d), 128.8 (d), 129.3 (d), 130.2 (s), 132.2 (d), 139.2 (s), 148.2 (s), 167.1 (s); ms: 267 (M$^+$, 3), 249 (M$^+$-H$_2$O, 47), 158 (100).

Anal. Calcd. for $C_{17}H_{17}NO_2$ (267.316): C, 76.38; H, 6.41; N, 5.24. Found: C, 76.35; H, 6.36; N, 5.21.

Reaction of Methyl *o*-Benzoylbenzoate **7** with Amines **2**.

A solution of **7** (0.01 mole) and **2** (0.02 mole) in toluene (50 ml) was heated to reflux under argon for 15 hours. Usual work-up gave **44-45**.

3-Hydroxy-3-phenyl-2-propylisoindolin-1-one (**44**).

This compound had mp 160-162°; ^{1}H-nmr: δ 0.73 (t, J = 7.3, 3H), 1.20-1.55 (m, 2H), 2.79-2.89 (m, 1H), 3.24-3.36 (m, 1H), 4.23 (s, 1H), 7.24-7.48 (m, 8H), 7.58 (d, J = 6.8, 1H); ^{13}C-nmr: δ 11.6 (q), 21.9 (t), 41.2 (t), 91.3 (s), 122.6 (d), 123.1 (d), 126.2 (d), 128.4 (d), 129.3 (d), 130.5 (s), 132.5 (d), 138.8 (s), 149.1 (s), 167.9 (s); ms: 267 (M$^+$, 25), 250 (M$^+$-OH, 10), 272 (7), 209 (100).

Anal. Calcd. for $C_{17}H_{17}NO_2$ (267.316): C, 76.36; H, 6.41; N, 5.24. Found: C, 76.01; H, 6.40; N, 5.27.

3-Hydroxy-3-phenyl-2-phenethylisoindolin-1-one (**45**).

This compound had mp 191-192°; ^{1}H-nmr: δ 2.44-2.55 (m, 1H), 2.86-2.98 (m, 1H), 3.06-3.18 (m, 1H), 3.53-3.65 (m, 1H), 7.02-7.47 (m, 13H), 7.66 (d, J = 7.3, 1H); ^{13}C-nmr: δ 34.6 (t), 41.4 (t), 91.2 (s), 122.7 (d), 123.2 (d), 126.2 (d), 128.4 (d), 128.5 (d), 128.8 (d), 129.5 (d), 130.4 (s), 132.6 (d), 138.6 (s), 139.3 (s), 149.0 (s), 167.9 (s); ms: 329 (M$^+$, 14), 312 (M$^+$-OH, 0.3), 238 (10), 209 (100).

Anal. Calcd. for $C_{22}H_{19}NO_2$ (329.382): C, 80.22; H, 5.81; N, 4.25. Found: C, 80.28; H, 5.72; N, 4.18.

Reaction of 3-Aminophthalides **34-37** with **LR**.

A solution of aminophthalide (0.001 mole) and **LR** (0.001 mole) in toluene (50 ml) was heated to reflux under argon for 15 minutes. After removal of the solvent, the residue was chromatographed (benzene/ethyl acetate 9:1) to give isoindoline-1-thiones **46-49**. Thiones **46**, **48** and **49** were confirmed by direct comparison of their ir and nmr spectra with those of authentic samples [2c].

3-Phenyl-2-*p*-tolylisoindoline-1-thione **47**.

This compound had mp 140-141°; ir: ν 1605, 1585, 1505, 1315, 1305, 1260, 820, 770, 720, 700; ^{1}H-nmr: δ 2.26 (s, 3H), 6.05 (s, 1H), 6.95-7.23 (m, 8H), 7.73 (s, 2H), 7.47-7.54 (m, 2H), 8.15-8.22 (m, 1H); ^{13}C-nmr: δ 21.1 (q), 74.9 (d), 122.4 (d), 125.9 (d), 126.8 (d), 127.9 (d), 128.2 (d), 128.7 (d), 128.8 (d), 129.6 (d), 132.0 (d), 135.7 (s), 135.9 (s), 137.7 (s), 138.8 (s), 144.2 (s), 194.3 (s).

Anal. Calcd. for $C_{21}H_{17}NS$ (315.426): C, 79.96; H, 5.43; N, 4.44. Found: C, 79.70; H, 5.40; N, 4.41.

Oxidation of 3-Hydroxy-2-*t*-butylisoindolin-1-one (**23**).

To a solution of **23** (1.5 g) in acetone (30 ml) was added dropwise a solution of chromium trioxide (750 mg) in sulfuric acid-water (5:2, 7 ml) at 0° (ice-bath). After stirring for 1 hour at rt, the usual work-up gave **4c** in 81% yield.

t-Butylphthalimide (**4c**).

This compound had mp 230° (sublimination); ir: ν 1765, 1700; ^{1}H-nmr: δ 1.70 (s, 9H), 7.65-7.81 (m, 4H); ^{13}C-nmr: δ 29.1 (q), 57.8 (s), 122.6 (d), 132.2 (s), 133.7 (d), 169.7 (s).

Reaction of **4c** with Methylmagnesium Iodide **5b**.

To a solution of methylmagnesium iodide [from magnesium (0.005 mole) and methyl iodide (0.005 mole) in ether (10 ml) was added a solution of **4c** (0.004 mole) in ether-THF (1:1 30 ml) in a similar manner as described above. Usual work-up gave **26** (24%) and **29** (9%).

Reaction of 3-Hydroxyisoindolin-1-one **10** with Hydrogen Chloride.

A solution of **10** (0.002 mole) in 6*N* hydrochloric acid solution (10 ml) and methanol (30 ml) was heated at 80° for 3 hours. The usual work-up gave *E* and *Z*-**50**.

3-*E*-Benzylidene-2-phenylisoindolin-1-one (**50-E**).

This compound had mp 194-196°; ir: ν 1700, 1640; ^{1}H-nmr: δ 6.82-7.20 (m, 10H), 7.24-7.26 (m, 1H), 7.51-7.70 (m, 2H), 7.84-7.94 (m, 2H); ^{13}C-nmr: δ 107.6 (d), 119.4 (d), 123.8 (d), 126.5 (d), 126.7 (d), 127.2 (d), 127.8 (s), 128.1 (d), 129.1 (d), 129.4 (d), 132.4 (d), 133.5 (d), 134.3 (d), 135.8 (s), 138.6 (s), 167.9 (s).

Anal. Calcd. for $C_{21}H_{15}NO$ (297.34): C, 84.82; H, 5.08; N, 4.71. Found: C, 84.84; H, 5.02; N, 4.70.

3-*Z*-Benzylidene-2-phenylisoindolin-1-one (**50-Z**).

This compound had mp 108-109°; ir: ν 1700, 1635; ^{1}H-nmr: δ 6.63 (s, 1H), 7.24-7.63 (m, 13H), 7.92-7.96 (m, 1H); ^{13}C-nmr: δ 112.3 (d), 123.1 (d), 123.6 (d), 127.8 (d), 128.4 (d), 128.6 (d), 128.9 (d), 129.4 (d), 129.5 (d), 129.6 (d), 130.0 (s), 132.4 (d), 134.9 (s), 135.1 (s), 138.1 (s), 166.3 (s).

Anal. Calcd. for $C_{21}H_{15}NO$ (297.34): C, 84.82; H, 5.08; N, 4.71. Found: C, 84.91; H, 5.15; N, 4.88.

Reaction of 3-Hydroxyisoindolin-1-one **8** and **10** with **LR**.

A solution of 3-hydroxyisoindolin-1-one (0.002 mole) and **LR** (0.0021 mole) in toluene (50 ml) was refluxed for 15 minutes. The usual work-up gave 3-benzylideneisoindolin-1-ones **51** and **52**.

3-Benzylidene-2-butylisoindoline-1-thione (**51**).

This compound had mp 96-97°; ir: ν 1595, 1495, 1365, 1095, 775, 740, 700; ^{1}H-nmr: δ 1.00 (t, J = 7.3, 3H), 1.41-1.56 (m, 2H), 1.73-1.85 (m, 2H), 4.33 (t, J = 7.6, 2H), 6.79 (s, 1H), 7.07-7.57 (m, 8H), 8.04 (d, J = 7.9, 1H); ^{13}C-nmr: δ 13.8 (q), 20.2 (t), 30.0 (t), 43.2 (t), 113.7 (d), 122.1 (d), 124.5 (d), 128.2 (d), 128.6 (d), 129.2 (d), 129.3 (d), 130.8 (d), 132.5 (s), 134.3 (s), 137.4 (s), 139.8 (s), 188.8 (s).

Anal. Calcd. for $C_{19}H_{19}NS$ (293.422): C, 77.79; H, 6.53; N, 4.77. Found: C, 77.52; H, 6.51; N, 4.79.

3-Benzylidene-2-phenylisoindoline-1-thione (**52**).

This compound had mp 166-167°; ir: ν 1595, 1495, 1355, 1335, 775, 760, 740, 710, 700; ^{1}H-nmr: δ 6.36 (s, 1H), 7.20-7.55 (m, 13H), 8.14 (d, J = 7.6, 1H); ^{13}C-nmr: δ 115.6 (d), 122.2 (d), 124.9 (d), 128.2 (d), 128.5 (d), 129.0 (d), 129.2 (d), 129.4 (d), 129.7 (d), 131.4 (d), 132.3 (s), 134.2 (s), 136.8 (s), 137.4 (s), 142.5 (s), 190.4 (s).

Anal. Calcd. for $C_{21}H_{15}NS$ (313.41): C, 80.49; H, 4.83; N, 4.47. Found: C, 80.26; H, 4.80; N, 4.49.

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