A New Alkaline Rearrangement of the Benzofuran Skeleton. One Step Transformation of 2-(2-Benzofuranyl)benzonitriles Into (*Z*)-Phenylmethyleneisoindolinones

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The alkaline hydrolysis of 2-(2-benzofuranyl)benzonitriles **2** by potassium hydroxide under reflux in ethanol stops at the corresponding amides **5**. Using other solvents (ethylene glycol or methoxyethanol) at higher temperatures, one can obtain either the amides **5**, the acids **1** or rearrangement products depending on the experimental conditions. The rearrangement products were identified as (*Z*)-phenylmethylenedihydroisoindolinones **6** resulting from opening of the furan ring. The structures of the compounds **6** were established by ^{1}H nmr spectroscopy (nOe) and X-ray crystallography.

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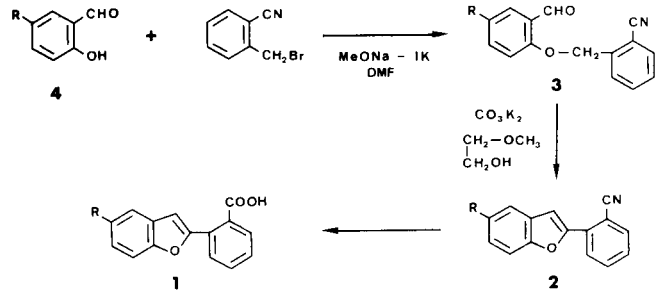
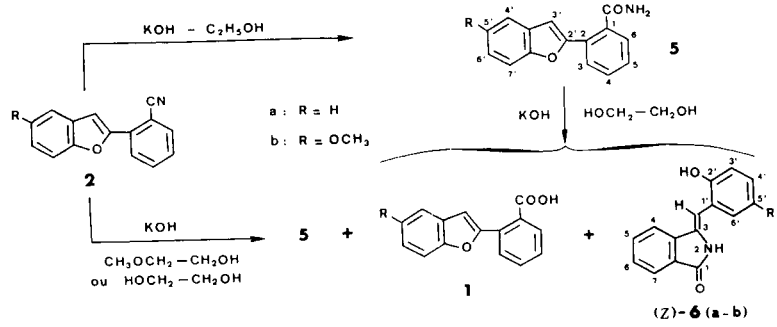
There have been a number of descriptions of opening the 1-2 bond of benzofuran derivatives in basic media. Degradation of benzofuran itself or 2-halogeno benzofurans by alcoholic potassium hydroxide [1-3] or sodium ethylate [3], 2-alkyl or 2-aryl benzofurans by sodium in liquid ammonia [4,5] or ethanol [6], or of organometallic derivatives of benzofuran [7-11] have all been reported. Other examples of opening the oxygen containing ring of benzofuran under alkaline conditions have involved compounds bearing an electron withdrawing group in the 3 position [12-20]. Some of these cleavage reactions provide a new route to nitrogen heterocycles, such as the isoxazoles [16,17], pyrazoles [17,19] or substituted pyrimidines [18-20].

In the course of a study of potential therapeutic agents based on 10*H*-benzo[*b*]indeno[2,1-*d*]furan-10-one, we prepared the unknown precursor 2-(2-benzofuranyl)benzoic acids **1** from the nitriles **2** which are readily synthesized by heterocyclization of the *o*-phenoxybenzaldehydes **3** (Scheme 1) using a classical method [21].

Scheme 1



Scheme 2



We found that hydrolysis of these nitriles in boiling ethanol in the presence of sodium or potassium hydroxide stopped at the corresponding amides **5**. Using more vigorous conditions, such as refluxing with potassium hydroxide in ethylene glycol as described by MacDowell and Wisowaty [22], gave the acids **1**, but in low yields due to production of varying amounts of isoindolinones **6** [23] (Scheme 2). We also established that the amides **5**, under the same conditions (potassium hydroxide, ethylene glycol) also led to acids **1** and isoindolinones **6**.

This unexpected transformation of the nitriles **2** and amides **5** provides a further illustration of alkaline opening of benzofurans, and a new example of transformation of a heterocyclic oxygen ring into a nitrogen heterocycle. We therefore examined in more detail the effects of i) the nature of the solvent (ethanol, methoxyethanol, ethylene glycol), and ii) the experimental conditions (reaction duration and temperature) on the reaction of the nitriles **2** with sodium or potassium hydroxide. Depending on the exact conditions, we were able to obtain: the amides **5**, the isoindolinones **6** and the acids **1** with varying amounts of amides and isoindolinones, which could be readily separated.

From these results (Table 1) it can be seen that the nature and proportions of products formed depended both on the solvent, and the reaction temperature and duration.

Refluxing the nitriles **2** in ethanolic solution of potassium hydroxide for 72 hours at 78° led to an almost quantitative yield of the amides **5**, whereas in methoxyethanol at the same temperature the reaction was markedly slower,

Table 1

Effects of Solvent and Temperature on the Transformation of Nitriles 2 (1 equivalent) by potassium hydroxide (2.7 equivalent)

Temperature °C	Reaction solvent	Reaction time	2		5		1		6	
			a	b	a	b	a	b	a	b
78	EtOH	72 h	0	6	92	81				
	$MeOCH_2$-CH_2OH	72 h	70	79	24	6				
	$HOCH_2$-CH_2OH	72 h	86	100	5	0				
124	$MeOCH_2$-CH_2OH	16 h	0	0	6	trace	trace	5	92	85
	$HOCH_2$-CH_2OH	16 h	13	51	39	19	28	13	trace	trace
		72 h	trace	trace	8	11	77	70	4	5
160	$HOCH_2$ -CH_2OH	16 h			0	0	72	65	14	26
198	$HOCH_2$-CH_2OH	1 h			5	trace	52	39	42	45

Table 2

Influence of Reaction Time on the Transformation of Nitriles 2 (1 equivalent) by Potassium Hydroxide (2.7 equivalents) under Reflux in Mehtoxyethanol and Ethylene Glycol

Reaction solvent	Reaction time	2		5		1		6	
		a	b	a	b	a	b	a	b
$MeOCH_2$–CH_2OH	1 h	7	12	78	58	trace	trace	14	15
	5 h	0	1	28	16	trace	trace	72	59
	16 h	0	0	6	trace	trace	5	92	85
$HOCH_2$–CH_2OH	5 min	18	31	64	45	4	2	4	3
	15 min	3	2	28	25	32	26	24	26
	30 min	trace	0	19	18	34	32	36	42
	1 h	0	0	5	trace	52	39	42	45
	2 h	0	0	0	0	56	37	38	41

and in ethylene glycol there was virtually no reaction.

Boiling the nitriles **2** in methoxyethanol with potassium hydroxide (124°) led to almost complete transformation into the isoindolinones **6** within 16 hours, whereas under the same reaction conditions in ethylene glycol, large amounts of unchanged nitrile were found along with the intermediate amides **5** and acids **1**. No isoindolinones were detected. The use of this latter solvent thus required a considerable increase in reaction temperature (160°) to produce the isoindolinones **6** along with large amounts of the acids **1**. Refluxing in ethylene glycol (198°) speeded up the reaction giving essentially the same products.

Since the reaction in ethanol does not proceed beyond the stage of the amides **5**, we investigated the effect of reaction time only in the cases of boiling methoxyethanol and ethylene glycol (*cf.* Table 2).

It can be seen that in methoxyethanol, the transformation of nitriles **2** into the amides **5** was relatively rapid, and that instead of undergoing a classical hydrolysis, the amides were progressively and almost exclusively transformed into the isoindolinones **6**. In ethylene glycol, although the reaction was much faster (disappearance of nitrile within 30 minutes) due to the higher temperature, the yield of isoindolinones **6** was halved due to formation of the acids **1**.

These results suggested that the nitriles themselves do not undergo rearrangement, and that hydrolysis into the amides is the first step in the reaction. This is supported by the fact that the amides could be isolated from the reaction mixture without acidification, which indicated that they had not undergone ring opening, leading to products soluble in alkaline medium. In fact, the amides **5** led to the same species and in comparable proportions to those produced from the starting nitriles **2** (cf. Table 3).

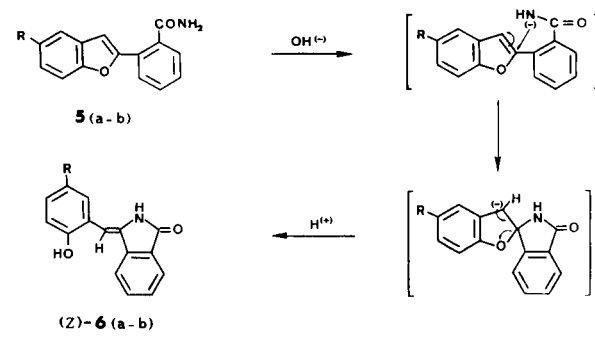
Table 3

Transformation of Amides 5 (1 equivalent) by potassium hydroxide (2.7 equialents) under Reflux in Methoxyethanol and Ethylene Glycol

Reaction solvent	Reaction time	5 a	5 b	1 a	1 b	6 a	6 b
$MeOCH_2$–CH_2OH	1 h	78	70	trace	1	13	22
	5 h	34	28	4	4	57	60
	16 h	9	3	10	trace	66	84
$HOCH_2$–CH_2OH	1 h	17	0	51	42	23	41

The reaction mechanism probably involves an initial hydrolysis of the nitriles **2** into the amides **5** followed by a spiro-type attack of the amide anion on the carbon in position 2 on the furan double bond. The intermediate undergoes a rearrangement leading to breakage of the oxygen carbon bond (Scheme 3).

Scheme 3



The spiro attack will thus depend on reaction conditions favoring formation of the intermediate anion from the amide **5**. In this respect, the anion could also be produced by the action of sodium amide under reflux in tetrahydrofuran, although only in the case of the amide **5b** bearing a methoxyl group on the 5 position. A mechanism involving initial opening of the benzofuran heterocycle seemed less likely. Hydrolysis of position isomers such as the 4-(2-benzofuranyl)benzonitriles led to the expected acids [24], their *para* structure effectively preventing the rearrangement. Moreover, the stability of the benzofuran skeleton in basic media is supported by the fact that 2-phenylbenzofuran itself remained unchanged under our experimental conditions. The mechanism is thus different from those governing opening of benzofuran derivatives with electron-withdrawing groups in the 3 position [12-20].

Since our main objective was to prepare the acids **1**, we investigated the optimum reaction conditions for this product (*cf.* Table 1). We found that refluxing in ethylene glycol for 72 hours at 124° led to lower yields of the isoindolinones - and consequently to better yields of acids **1** - than refluxing in methoxyethanol.

Thus the alkaline treatment of the nitriles **2** could be adjusted to lead to either a rearrangement of the benzofuran skeleton into the isoindolinone skeleton in a single step, or the normal, partial or total hydrolysis of nitriles 2.

Structural Studies.

NMR Analysis.

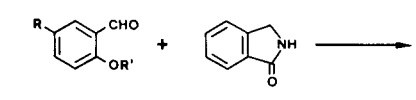
Although establishment of the structure of the acids **1** was straightforward, the identification of the unexpected isoindolinones **6** was complicated by the fact that they have the same empirical formula and molecular weight, and similar ir characteristics as the amide **5**.

The first indication of the occurrence of the rearrangement of the benzofuran structure to the isoindolinone system came from ^1H nmr analysis of the compounds **5** and **6**. In DMSO-d_6, there was a marked difference in the chemical shifts of the aromatic protons of the amides **5** and the isoindolinones **6**. In addition, only the isoindolinones have two different exchangeable protons (NH and OH). In deuteriochloroform, a singlet was observed for the isoindoli-

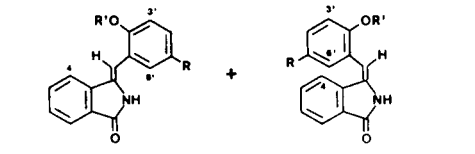
nones **6** at a higher field than that for the β protons of the furan ring of the amides **5**, indicating the existence of an ethylenic proton.

The structure of the isoindolinones **6** was confirmed by comparison with compounds synthesized by an unambiguous route (*cf.* Scheme 4), although of unreported configuration [25]. We therefore determined the configurations (*Z* or *E*) of the compounds produced by the rearrangement reaction described above.

Scheme 4



4a: R = R' = H
b: R = OCH_3, R' = H
c: R = H, R' = CH_3
d: R = OCH_3, R' = CH_3



(Z)-**6a**: R = R' = H
b: R = OCH_3, R' = H
c: R = H, R' = CH_3
d: R = OCH_3, R' = CH_3

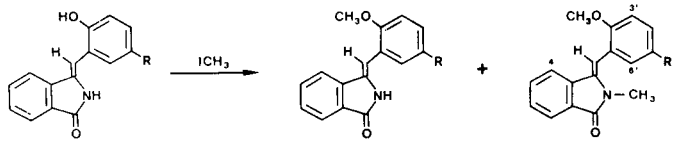
(E)-**6c**: R = H, R' = CH_3
d: R = OCH_3, R' = CH_3

The nOe difference determinations indicated that the hydroxylated isoindolinones **6a** and **6b** were in the *Z* form, whether derived from the nitriles **2** or amides **5**, or from condensation of phthalimidine with the *ortho*-hydroxylated aldehydes **4a** and **4b**. However, the isoindolinones **6c** and **6d** issued from condensation of the *ortho*-methoxylated aldehydes **4c** and **4d** were found in both *Z* and *E* forms.

For the compounds **6a-d** in the *Z* configuration, irradiation of the ethylenic proton led to an Overhauser effect on the H_4 proton and *vice versa*. This would be impossible with the (*E*)-isomer. These results were supported by further nOe studies on the *O,N*-dimethylated derivatives **7a** and **7b** that we prepared (Scheme 5). Irradiation of the H_4 protons led to an Overhauser effect on the ethylenic proton, which was not observed with the N- methyl derivative. In addition, the (*E*)-isoindolinone **7b** obtained by isomerization of (*Z*)-**7b** displayed an Overhauser effect on the ethylenic proton after irradiation of the *N*-methyl protons.

For compounds (*Z*)-**6a**, (*Z*)-**6b**, (*Z*)-**7a** and (*Z*)-**7b**, irradiation of the N-H or the N-CH_3 protons also led to a weak Overhauser effect on the $H_{6'}$ protons. There was also a transfer of saturation on irradiation of exchangeable protons, indicated by simultaneous Overhauser effects on the 3' and 6' protons.

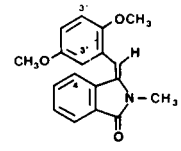
Scheme 5



(Z)-**6a**: R = H
b: R = OCH_3

(Z)-**6c**: R = H

(Z)-**7a**: R = H
b: R = OCH_3



(E)-**7b**

X-Ray Crystallographic Study.

The precise structure of (*Z*)-**6b** and (*Z*)-**6c** were established using X-ray crystallography. Crystal parameters and data-collection conditions are summarized in Tables 4-5. The final atomic coordinates for non-hydrogen atoms, bond lengths and bond angles are reported in Tables 6-8. The list of anisotropic thermal parameters, atomic coordinates for hydrogen atoms, the observed Fo and the calculated Fc structure factors are available on request. Figures 1 and 2 show the ORTEP drawings of both molecules projected on the isoindolinone ring. The molecules appear in the *Z*-configuration.

Bond lengths and angles of the substituted phenylmethylene groups are in agreement with those usually observed. However the angular distortion of the bond between the methoxy group and the aromatic nucleus (about 4°), caused by the bulkiness of the methyl group, should be emphasized. Moreover, the hydrogen atom borne respectively by the C(26) atom for (*Z*)-**6b** and the C(23) atom for (*Z*)-**6c** are in close contact with the methyl group.

Bond length and angles of the isoindolone ring are in complete agreement in both structures. The C(3)-C(10) and the C(1)-O(11) bond length values are normal for ethylenic and carbonyl bonds.

In both compounds the isoindolone ring is planar. The 3-(2-hydroxy-5-methoxyphenylmethylene) and the 3-(2-methoxyphenylmethylene) are quite planar with the C-atom of the methoxy group slightly out of the ring plane: 0.05 Å for the first molecule, 0.20 Å for the second molecule. The torsion angle around the C(10)-C(21) bond is close to 40° for (*Z*)-**6b** and only 16° for (*Z*)-**6c**.

The hydrogen bond network is different in structure (*Z*)-**6b** and (*Z*)-**6c**. In the first one, there are two intermolecular hydrogen bonds, of mean strength between: (i) the

hydroxyl of one molecule and the carbonyl of a symmetry-related molecule with d(0...0) = 2.724(4) Å and (ii) the NH of one molecule and the oxygen of the methoxy group of a symmetry-related molecule with d(N...O) = 2.974(4) Å. In the second one, there is only one intermolecular hydrogen bond, of mean strength, between the NH of one molecule and the carbonyl of a symmetry-related molecule with d(N...O) = 2.903(3) Å.

In both crystals, crystal cohesion essentially results from these hydrogen networks. Numerous Van der Waals interactions are also implicated in crystal cohesion, particularly in (*Z*)-**6c**. Because of the small torsion angle around the C(10)-C(21) bond in (*Z*)-**6c**, there are particularly short intramolecular distances in this structure, namely between: (i) O(32) of the methoxy group and the hydrogen borne by the C(10) bond with d(O...H) = 2.28(3) Å and (ii) the hydrogens borne by the N(2) and the C(26) atoms with d(H...H) = 2.00(5) Å.

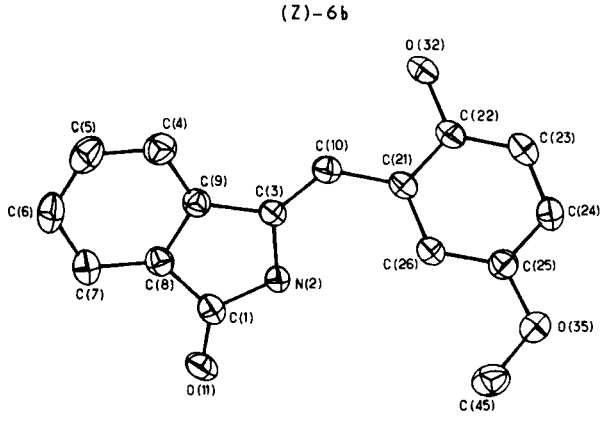


Figure 1

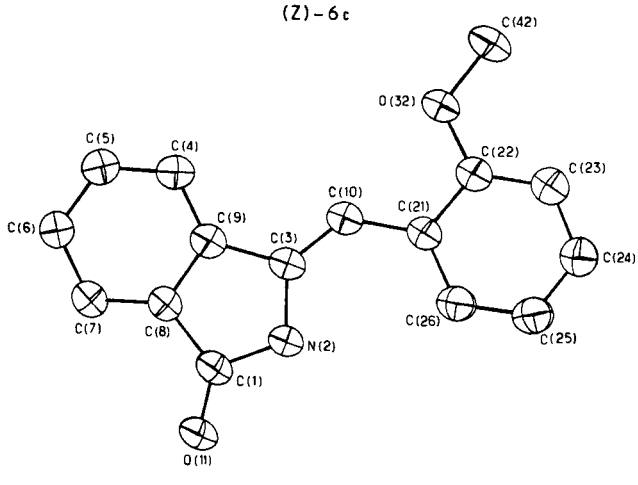


Figure 2

Table 4

Crystal Parameters

Compound	(Z)-**6b**	(Z)-**6c**
Formula	$C_{16}H_{13}NO_3$	$C_{16}H_{13}NO_2$
Molecular weight	267.3	251.3
Crystallization in	ethanol	ethanol
Color	yellow	yellow
crystal size	0.2 x 0.3 x 0.1 mm	0.3 x 0.4 x 0.15 mm
a	11.569(1) Å	7.124(2) Å
b	12.228(2) Å	10.508(2) Å
c	9.620(1) Å	9.510(2) Å
α	–	101.98(2)°
β	109.63 (1)°	104.22(1)°
γ	–	109.60(2)°
V	1282 Å^3	617 Å^3
Z	4	2
Space group	$P2_1/c$	$P\bar{1}$
ρ (calcd)	1.386	1.353
F (000)	560	264
μ (CuKα)	9.5 cm^{-1}	9.15 cm^{-1}

Table 5

Data Collection

Compound	(Z)-**6b**	(Z)-**6c**
Diffractometer	Nonius CAD-4	Nonius CAD-4
Monochromator	graphite	graphite
2 θ range	2-70°	1-75°
Scan type	ω - 2 θ	ω - 2 θ
Scan width Δω	(2 + 0.15 tg θ)°	(2. + 0.15 tg θ)°
Scan apperature	(1.3 + 0.7 tg θ)°	(1.3 + 0.2 tg θ)°
Unique reflections	2420	2434
Observed reflections*	1771	2125
Reliability factor R	0.052	0.058
Weighted R	0.051	0.053

*I > 2.5 σ (I)

Table 6

Atomic Coordinates (x 10^4) with Standard Deviations and Equivalent Isotropic Temperature Factors, B_{eq}. for Non-hydrogen Atoms

Compound (Z)-**6b**

	x	y	z	B_{eq} ($Å^2$)
C(1)	1822(3)	1330(3)	847(3)	2.6
N(2)	2218(2)	1020(2)	2300(2)	2.4
C(3)	1240(3)	920(3)	2858(3)	2.3
C(4)	-1099(3)	1169(3)	1483(3)	3.0
C(5)	-1953(3)	1437(3)	125(3)	3.7
C(6)	-1590(3)	1702(3)	-1080(3)	3.7
C(7)	-365(3)	1671(3)	-970(3)	3.1
C(8)	481(3)	1409(3)	385(3)	2.4
C(9)	132(3)	1172(3)	1609(3)	2.3
C(10)	1334(3)	653(3)	4237(3)	2.5
O(11)	2512(2)	1501(2)	127(2)	3.1
C(21)	2450(3)	296(3)	5409(3)	2.4
C(22)	2689(3)	630(3)	6860(3)	2.7
C(23)	3739(3)	276(3)	796(3)	3.2
C(24)	4549(3)	-428(3)	7652(3)	3.2
C(25)	4304(3)	-787(3)	6213(3)	2.7
C(26)	3274(3)	-433(3)	5097(3)	2.5
O(32)	1859(2)	1319(2)	7140(2)	3.5
O(35)	5166(2)	-1501(2)	6010(2)	3.4
C(45)	4938(3)	-1954(3)	4578(3)	3.6
C(1)	7673(3)	9626(2)	10955(2)	4.0
N(2)	7497(3)	8451(2)	9898(2)	3.8
C(3)	5629(3)	7255(2)	9607(2)	3.5
C(4)	2655(3)	7068(2)	10784(2)	4.0
C(5)	2007(3)	7840(2)	11767(3)	4.4
C(6)	3238(4)	9283(2)	12568(3)	4.6
C(7)	5157(3)	9970(2)	12392(2)	4.3
C(8)	5788(3)	9193(2)	11398(2)	3.7
C(9)	4556(3)	7761(2)	10584(2)	3.4
C(10)	4890(3)	5926(2)	8644(2)	3.6
O(11)	9171(2)	10808(1)	11417(2)	5.1
C(21)	5784(3)	5284(2)	7628(2)	3.5
C(22)	4464(3)	3966(2)	6475(2)	3.8

Table 6 (continued)

Compound (Z)-**6c**

	x	y	z	B_{eq} ($Å^2$)
C(23)	5216(3)	3337(2)	5454(3)	4.4
C(24)	7320(4)	3976(2)	5576(3)	4.8
C(25)	8673(3)	5236(2)	6722(3)	4.7
C(26)	7906(3)	5882(2)	7724(3)	4.2
O(32)	2414(2)	3392(1)	6452(2)	4.6
C(42)	1085(4)	2002(2)	5402(3)	5.5

EXPERIMENTAL

Chemistry.

Melting points - uncorrected - were determined on a Kofler hot stage. The ir spectra were recorded with a Perkin Elmer 1710 spectrophotometer. The ^1H nmr spectra were obtained at 90 MHz (using a Varian EM 390 instrument) or at 250 MHz (with a Bruker WN250) with TMS as internal standard; chemical shifts are expressed in ppm (s = singulet, bs = broad singulet, d = doublet, bd = broad doublet, dd = doublet of doublet, dm = doublet of multiplet, td = triplet of doublet, bt = broad triplet, sh = shoulder). Mass spectra were measured at 70 eV using Nermag R10-10C apparatus.

General Procedure for Cyanobenzaldehydes **3**.

To a freshly prepared solution of sodium methylate (1.3 g of sodium in 25 ml methanol), 50 mmoles of the required salicylaldehyde in 30 ml of dimethylformamide were added dropwise. After 30 minutes, a few crystals of potassium iodide were added, then, in 10 minutes, a solution of 2-bromomethylbenzonitrile (10.78 g, 0.055 mole) in 30 ml of dimethylformamide. The stirred mixture was kept boiling for 2 additional hours. After cooling, the preparation was diluted with water and extracted with ethyl acetate. The organic layer was then washed and dried over sodium sulfate. After solvent removal under vacuum, the crude product was eluted with dichloromethane on a short silica gel column.

[[(1-Formyl-2-phenyl)oxy]methyl]benzonitrile (**3a**).

This compound was obtained from toluene-petroleum ether in a 89% yield, mp = 110°; ^1H nmr (DMSO-d_6): 90 MHz δ 5.40 (s, 2H, OCH_2), 7.00-7.90 (m, 8H arom), 10.40 (s, CHO).

Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.71; H, 4.70; N, 5.91.

[[(1-Formyl-5-methoxy-2-phenyl)oxy]methyl]benzonitrile (**3b**).

This compound was obtained (toluene-cyclohexane) in a 91% yield, mp = 78°; ^1H nmr (DMSO-d_6): 90 MHz δ 3.77 (s, 3H, OCH_3), 5.36 (s, 2H, OCH_2), 7.16-7.96 (m, 7H, arom), 10.40 (s, CHO).

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.96; H, 4.90; N, 5.27.

Table 7

Bond Lengths and angles of (Z)-**6b**

Bond Lengths (Å) with Standard Deviations

C(1)	-N(2)	1.370(4)	C(10)	-C(21)	1.467(5)
C(1)	-C(8)	1.466(5)	C(21)	-C(22)	1.390(5)
C(1)	-C(11)	1.238(4)	C(21)	-C(26)	1.409(5)
N(2)	-C(3)	1.411(4)	C(22)	-C(23)	1.385(5)
C(3)	-C(9)	1.465(5)	C(22)	-O(32)	1.370(4)
C(3)	-C(10)	1.335(5)	C(23)	-C(24)	1.376(5)
C(4)	-C(5)	1.387(5)	C(24)	-C(25)	1.388(5)
C(4)	-C(9)	1.388(6)	C(25)	-C(26)	1.379(5)
C(5)	-C(6)	1.397(6)	C(25)	-O(35)	1.387(5)
C(6)	-C(7)	1.386(5)	O(35)	-C(45)	1.425(4)
C(7)	-C(8)	1.380(5)			
C(8)	-C(9)	1.397(5)			

Bond Angles (°) with Standard Deviations

N(2)	-C(1)	-C(8)	106.5(3)	C(3)	-C(10)	-C(21)	126.4(3)
N(2)	-C(1)	-O(11)	124.1(3)	C(10)	-C(21)	-C(22)	120.8(3)
C(8)	-C(1)	-O(11)	129.4(3)	C(10)	-C(21)	-C(26)	120.6(3)
C(1)	-N(2)	-C(3)	112.1(2)	C(22)	-C(21)	-C(26)	118.6(3)
N(2)	-C(3)	-C(9)	105.2(3)	C(21)	-C(22)	-C(23)	120.2(3)
N(2)	-C(3)	-C(10)	126.2(3)	C(21)	-C(22)	-O(32)	117.5(3)
C(9)	-C(3)	-C(10)	128.6(3)	C(23)	-C(22)	-O(32)	122.3(3)
C(5)	-C(4)	-C(9)	117.8(3)	C(22)	-C(23)	-C(24)	121.1(3)
C(4)	-C(5)	-C(6)	121.3(3)	C(23)	-C(24)	-C(25)	119.1(3)
C(5)	-C(6)	-C(7)	121.0(3)	C(24)	-C(25)	-C(26)	120.7(3)
C(6)	-C(7)	-C(8)	117.5(3)	C(24)	-C(25)	-O(35)	115.1(3)
C(7)	-C(8)	-C(9)	122.0(3)	C(26)	-C(25)	-O(35)	124.2(3)
C(1)	-C(8)	-C(7)	130.1(3)	C(25)	-O(35)	-C(45)	118.2(3)
C(1)	-C(8)	-C(9)	107.9(3)	C(21)	-C(26)	-C(25)	120.2(3)
C(4)	-C(9)	-C(8)	120.4(3)				
C(3)	-C(9)	-C(4)	131.3(3)				
C(3)	-C(9)	-C(8)	108.3(3)				

Table 8

Bond Lengths and angles of (Z)-**6c**

Bond Lengths (Å) with Standard Deviations

C(1)	-N(2)	1.368(4)	C(10)	-C(21)	1.455(4)
C(1)	-C(8)	1.461(4)	C(21)	-C(22)	1.413(4)
C(1)	-O(11)	1.237(3)	C(21)	-C(26)	1.400(4)
N(2)	-C(3)	1.407(3)	C(22)	-C(23)	1.377(4)
C(3)	-C(9)	1.466(4)	C(22)	-O(32)	1.373(3)
C(3)	-C(10)	1.344(4)	C(23)	-C(24)	1.385(4)
C(4)	-C(5)	1.377(4)	C(24)	-C(25)	1.379(4)
C(4)	-C(9)	1.387(4)	C(25)	-C(26)	1.380(4)
C(5)	-C(6)	1.397(4)	O(32)	-C(42)	1.426(4)
C(6)	-C(7)	1.385(4)			
C(7)	-C(8)	1.378(4)			
C(8)	-C(9)	1.390(4)			

Bond Angles (°) with Standard Deviations

N(2)	-C(1)	-C(8)	106.7(2)	C(3)	-C(9)	-C(8)	108.6(2)
N(2)	-C(1)	-O(11)	124.9(3)	C(4)	-C(9)	-C(8)	120.1(2)
C(8)	-C(1)	-O(11)	128.4(3)	C(3)	-C(10)	-C(21)	131.0(3)
C(1)	-N(2)	-C(3)	112.1(2)	C(10)	-C(21)	-C(22)	119.0(2)
N(2)	-C(3)	-C(9)	104.9(2)	C(10)	-C(21)	-C(26)	124.1(2)
N(2)	-C(3)	-C(10)	129.8(2)	C(22)	-C(21)	-C(26)	116.9(2)
C(9)	-C(3)	-C(10)	125.3(2)	C(21)	-C(22)	-C(23)	121.2(3)
C(5)	-C(4)	-C(9)	118.5(3)	C(21)	-C(22)	-O(32)	115.1(2)
C(4)	-C(5)	-C(6)	121.5(3)	C(23)	-C(22)	-O(32)	123.7(2)
C(5)	-C(6)	-C(7)	120.3(3)	C(22)	-C(23)	-C(24)	119.9(3)
C(6)	-C(7)	-C(8)	118.1(3)	C(23)	-C(24)	-C(25)	120.4(3)
C(1)	-C(8)	-C(7)	130.4(3)	C(24)	-C(25)	-C(26)	119.6(3)
C(1)	-C(8)	-C(9)	107.7(2)	C(21)	-C(26)	-C(25)	121.9(3)
C(7)	-C(8)	-C(9)	121.8(3)	C(22)	-O(32)	-C(42)	116.9(2)
C(3)	-C(9)	-C(4)	131.4(2)				

General Procedure for Nitriles **2**.

A solution of aldehyde-ethers **3** (0.1 mole) and potassium carbonate (27.6 g, 0.2 mole) in 300 ml of methoxyethanol was refluxed for 2 hours under stirring, then cooled and diluted in 3 liters of water. The precipitate thus obtained was collected and washed until neutral.

2-(2-Benzofuranyl)benzonitrile (**2a**).

This compound was obtained from cyclohexane in a 90% yield, mp = 73°; ir (potassium bromide): ν cm^{-1} 2220 (CN); ^1H nmr (DMSO-d_6): 90 MHz δ 7.20-8.20 (m, 9H, arom).

Anal. Calcd. for $C_{15}H_9NO$: C, 82.18; H, 4.14; N, 6.39. Found: C, 81.99; H, 4.20; N, 6.54.

2-(5-Methoxy-2-benzofuranyl)benzonitrile (**2b**).

This compound was obtained (toluene) in a 81% yield, mp = 153°; ir (potassium bromide): ν cm^{-1} 2226 (CN); ^1H nmr (deuterio-

acetone): 90 MHz δ 3.86 (s, 3H, OCH_3), 6.98 (dd, 1H, $H_{6'}$, J = 2.5 Hz, J = 9 Hz), 7.26 (d, 1H, $H_{4'}$, J = 2.5 Hz), 7.66 (s, 1H, $H_{3'}$), 7.43-8.20 (m, 5H, arom).

Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 76.79; H, 4.43; N, 5.60.

General Procedure for Amides **5**.

A solution of 4 mmoles of nitriles **2** and potassium hydroxide (0.6 g, 0.0108 mole) in ethanol (50 ml), was refluxed for 72 hours with stirring. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer, washed with water and dried, was evaporated under vacuum. Column-chromatography of the residue on silica gel (eluent: dichloromethane, then dichloromethane-methanol 99:1) enables to separate the amide from the unreacted starting material eluting first.

2-(2-Benzofuranyl)benzamide (**5a**).

This compound was obtained from toluene in a 90% yield, mp = 90°; ir (potassium bromide): ν cm^{-1} 3365 and 3175 (NH_2), 1643 (CO); ^1H nmr (DMSO-d_6): 90 MHz δ 7.10-8.00 (m, 9H, arom and NH_2); (deuteriochloroform): 90 MHz δ 7.06-7.93 (m, 9H, arom), 5.86 (sh, 2H, NH_2); ms: m/z 237.

Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 76.26; H, 4.89; N, 5.60.

2-(5-Methoxy-2-benzofuranyl)benzamide (**5b**).

This compound was obtained from toluene in a 81% yield, mp = 163°; ir (potassium bromide): ν cm^{-1} 3193 (NH_2), 1630 and 1613 (CO); ^1H nmr (DMSO-d_6): 90 MHz δ 3.80 (s, 3H, OCH_3), 6.90 (dd, 1H, $H_{6'}$, J = 2.7 Hz, J = 8 Hz), 7.13 (d, 1H, $H_{3'}$, J = 0.9 Hz), 7.17 (d, 1H, $H_{4'}$, J = 2.7 Hz), 7.36-7.60 (m, 3H, arom and NH_2), 7.30-8.00 (m, 2H, arom); (deuteriochloroform): 90 MHz δ 3.80 (s, 3H, OCH_3), 5.90 (sh, NH_2), 6.83 (dd, 1H, $H_{6'}$, J = 2.5 Hz, J = 9 Hz), 7.00 (m, 2H, $H_{3'}$, $H_{4'}$), 7.30-7.90 (m, 5H, arom); ms: m/z 267.

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.78; H, 4.92; N, 5.22.

Rearrangement of Nitriles **2**.

The various experimental conditions orientating the reaction to yield either acids **1** or amides **5**, or isoindolinones **6** are indicated in Tables 1 and 2. We fully describe below one of the methods used to separate each of the compounds.

2-(2-Benzofuranyl)benzoic Acid (**1a**), 2-(2-Benzofuranyl)benzamide (**5a**) and 2,3-Dihydro-3-(2-hydroxyphenylmethylene)-1*H*-isoindol-1-one ((*Z*)-**6a**).

A solution of nitrile **2a** (1.1 g, 0.005 mole) and potassium hydroxide (0.75 g, 0.0135 mole) in ethylene glycol (10 ml) was refluxed for 15 minutes with stirring, then poured into water (100 ml).

The resulting solid was collected, dried and chromatographed on silica gel. The unreacted starting nitrile (3%) was thus eluted first (dichloromethane), and, further, the above-described amide **5a** was obtained in a 28% yield (eluent: dichloromethane-methanol, 99:1).

The alkaline filtrate was then acidified. The resulting precipitate was collected, washed until neutral, then treated for 30 minutes with a solution of 10 mmoles of sodium bicarbonate in 100 ml water in order to dissolve the acid **1a**. The insoluble isoindolinone (*Z*)-**6a** [24] was then collected by filtration (yield = 24%), mp = 242° (ethanol); ir (potassium bromide): ν cm^{-1} 3317 (NH), 1674 (CO); ^1H nmr (DMSO-d_6): 250 MHz δ 6.80 (s, 1H, ethylenic CH), 6.87 (m, 1H, $H_{5'}$), 6.92 (m, 1H, $H_{3'}$), 7.15 (m, 1H, $H_{4'}$), 7.55 (d, 1H, $H_{6'}$), 7.55 (td, 1H, H_6, J = 7.4 Hz), 7.70 (t, 1H, H_5, J = 1.2 Hz, J = 7.6 Hz), 7.76 (dd, 1H, H_7, J = 7.5 Hz), 8.02 (dm, 1H, H_4, J = 7.7 Hz), 10.04 (bs, 1H, OH), 10.45 (bs, 1H, NH); (deuteriochloroform): 90 MHz δ 6.56 (s, 1H, ethylenic CH), 6.90-7.40 (m, 4H, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$), 7.45-8.03 (m, 4H, H_4, H_5, H_6, H_7), 9.23 (bs, 1H, NH), 9.70 (bs, 1H, OH); ms: m/z 237.

Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.61; H, 4.68; N, 5.68.

The filtrate containing the sodium salt of the acid **1a** was acidified with 1*N* hydrochloric acid, and extracted with ethyl acetate. The organic layer, washed with water and dried, was evaporated under vacuum. Acid **1a** was thus obtained from toluene in a 32% yield, mp = 132°; ir (potassium bromide): ν cm^{-1} 1702 (CO); ^1H nmr (DMSO-d_6): δ 7.10 (s, 1H, $H_{3'}$), 7.16-7.86 (m, 8H, arom); ms: m/z 238.

Anal. Calcd. for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23. Found: C, 75.56; H, 4.14.

2-(5-Methoxy-2-benzofuranyl)benzoic Acid (**1b**) and 2,3-Dihydro-3-(2-hydroxy-5-methoxyphenylmethylene)-1*H*-isoindol-1-one (*Z*)-(**6b**).

Using the above technique, but with a two-hour reaction time, complete transformation of nitrile **2b** and amide **5b** succeeds, resulting in a mixture totally soluble in water, which was further treated as formerly. The following compounds were thus separated:

The Isoindolinone (*Z*)-**6b**.

This compound was obtained in a 41% yield, mp = 232° (ethanol); ir (potassium bromide): ν cm^{-1} 3285 (NH), 1676 (CO); ^1H nmr (DMSO-d_6): 250 MHz δ 3.78 (s, 3H, OCH_3), 6.75 (dd, 1H, $H_{4'}$, J = 2.9 Hz, J = 8.7 Hz), 6.76 (s, 1H, ethylenic CH), 6.85 (d, 1H, $H_{3'}$, J = 8.8 Hz), 7.05 (d, 1H, $H_{6'}$, J = 2.9 Hz), 7.56 (td, 1H, H_6, J = 0.5 Hz), 7.67-7.78 (m, 2H, H_5 and H_7), 8.01 (d, 1H, H_4, J = 7.8 Hz), 9.58 (bs, 1H, OH), 10.53 (bs, 1H, NH); (deuteriochloroform): 90 MHz δ 3.80 (s, 3H, OCH_3), 6.46 (s, 1H, ethylenic CH), 6.80 (m, 2H, $H_{3'}$ and $H_{4'}$), 7.10 (bs, 1H, $H_{6'}$), 7.50-8.05 (m, 4H, H_4, H_5, H_6, H_7), 10.30 (bs, 1H exchangeable); ms: m/z 267.

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.60; H, 5.12; N, 4.99.

The Acid **1b**.

This compound was obtained in a 37% yield, mp = 156° (toluene); ir (potassium bromide): ν cm^{-1} 1686 (CO); ^1H nmr (DMSO-d_6): δ 3.80 (s, 3H, OCH_3), 6.86 (dd, 1H, $H_{6'}$, J = 3 Hz, J = 9 Hz), 7.03 (s, 1H, $H_{3'}$), 7.16 (d, 1H, $H_{4'}$, J = 3 Hz), 7.45-7.86 (m, 5H, arom).

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.99; H, 4.79.

Univocal Synthesis of Isoindolinones **6** by Condensation of Aldehydes **4** with Phthalimidine.

Method A.

A 2.5 *N* sodium hydroxide solution (10 ml) containing salicylaldehydes **4a** or **4b** (0.02 mole) and phthalimidine (2.66 g, 0.02 mole) was refluxed for 7 hours. The hot reactional mixture was poured into 50 ml of 2*N* hydrochloric acid. The precipitated product was collected, washed with water, dried, and recrystallized

from ethanol. The above-described isoindolinones (*Z*)-**6a** and (*Z*)-**6b** were obtained in respective yields of 76% and 56%.

Method B.

To 10 ml of a (1:1) hydroalcoholic 1*N* sodium hydroxide, phthalimidine (2.66 g, 0.02 mole) and 0.022 mole of 2-methoxybenzaldehyde **4c** or 2,5-dimethoxybenzaldehyde **4d** were added. After refluxing for 4 hours, 40 ml of water was added, and the mixture was cooled to 5°, before undergoing the following treatments to separate the various compounds obtained.

(*Z*) and (*E*)-2,3-Dihydro 3-(2-methoxyphenylmethylene)-1*H*-isoindol-1-one (**6c**).

Starting from aldehyde **4c**, the yellow solid precipitating at the end of the reaction (Method B) was collected, washed with water and dried. The two isoindolinone isomers (*Z*)-**6c** and (*E*)-**6c** were thus obtained (total yield 93%) in a 3:1 ratio according to nmr integration of the ethylenic protons signals. Recrystallization of the former mixture from ethanol enabled us to separate the majority of the isomer (*Z*)-**6c** [24], mp = 163°; ir (potassium bromide): ν cm^{-1} 3199 (NH), 1689 (CO); ^1H nmr (DMSO-d_6): 90 MHz δ 3.86 (s, 3H, OCH_3), 6.76 (s, 1H, ethylenic CH), 6.90-7.50 (m, 4H, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$), 7.50-7.84 (m, 3H, H_5, H_6, H_7), 8.00 (dt, 1H, H_4, J = 7.5 Hz), 10.46 (bs, 1H, NH); (deuteriochloroform): 250 MHz δ 3.90 (s, 3H, OCH_3), 6.63 (s, 1H, ethylenic CH), 6.95 (dm, 1H, $H_{3'}$, J = 0.8 Hz, J = 8.2 Hz), 7.02 (bt, 1H, $H_{5'}$), 7.29 (bt, 1H, $H_{4'}$), 7.41 (d, 1H, $H_{6'}$, J = 7.6 Hz), 7.47 (t, 1H, H_6), 7.59 (t, 1H, H_5), 7.80 (bd, 1H, H_4, J = 7.7 Hz), 7.85 (bd, 1H, H_7, J = 7.2 Hz), 8.52 (bs, 1H, NH); ms: m/z 251.

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.28; H, 5.36; N, 5.60.

The second isomer could be isolated by column chromatography (silica gel) of the evaporated solid from the ethanolic recrystallization mother-liquors. Elution with dichloromethane enabled us to isolate the slower migrating isomer (*Z*)-*6c*, mp 198-200°; ir (potassium bromide): ν cm^{-1} 3417 (NH), 1698 (CO); ^1H nmr (DMSO-d_6): 90 MHz δ 3.80 (s, 3H, OCH_3), 6.50 (s, 1H, ethylenic CH), 6.86-7.83 (m, 8H, arom), 10.56 (bs, 1H, NH); (deuteriochloroform): 90 MHz δ 3.83 (s, 3H, OCH_3), 6.65 (s, 1H ethylenic CH), 6.98 (m, 2H, $H_{3'}$, $H_{5'}$), 7.25-7.63 (m, 5H, H_4, H_5, H_6, $H_{4'}$, $H_{6'}$), 7.88 (bd, 1H, H_7, J = 7.5 Hz), 9.20 (bs, 1H, NH); ms: m/z 251. This compound is fairly unstable at room temperature and light; it is then partly transformed into its (*Z*)-isomer.

(*Z*) and (*E*)-2,3-Dihydro-3-(2,5-dimethoxy-phenylmethylene)-1*H*-isoindol-1-one (**6d**).

Starting from the aldehyde **4d**, the crude product of the reaction (method B), obtained in a 89% yield is a mixture of both isomers (*Z*)-**6d** and (*E*)-**6d**. Integration of the ethylenic protons signals of the mixture ^1H nmr spectrum indicated a *Z*/*E* ratio of 80/20.

Compound (*Z*)-**6d** was separated by recrystallization (ethanol) of the crude product of the reaction, mp 170°; ir (potassium bromide): ν cm^{-1} 3437 (NH), 1715 (CO); ^1H nmr (DMSO-d_6): 90 MHz δ 3.80 (bs, 6H, 2 OCH_3), 6.73 (s, 1H, ethylenic CH), 6.88 (dd, 1H, $H_{4'}$, J = 2.3 Hz, J = 7.5 Hz), 6.96 (d, 1H, $H_{3'}$, J = 7.5 Hz), 7.10 (d, 1H, $H_{6'}$, J = 2.3 Hz), 7.40-7.83 (m, 3H, H_5, H_6, H_7), 8.00 (bd, 1H, H_4, J = 1.8 Hz), 10.53 (bs, 1H, NH); (deuteriochloroform): 250 MHz δ 3.80 and 3.86 (2s, 6H, 2 OCH_3), 6.57 (s, 1H, ethylenic CH), 6.83 (dd, 1H, $H_{4'}$, J = 2.8 Hz, J = 8.9 Hz), 6.89 (d, 1H, $H_{3'}$, J = 8.9 Hz), 6.96 (d, 1H, $H_{6'}$, J = 2.8 Hz), 7.48 (td, 1H, H_6, J = 1 Hz, J = 7.6 Hz), 7.60 (td, 1H, H_5, J = 1.2 Hz, J = 7.6 Hz), 7.80 (bd, 1H, H_4, J = 7.7 Hz), 7.85 (bd, 1H, H_7, J = 7.6 Hz), 8.62 (bs, 1H, NH).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.57; H, 5.38; N, 4.94.

Separation of compound (*E*)-**6d** succeeded after two consecutive column chromatographies on silica gel of the residue obtained by evaporation of the (*Z*)-**6d** mothers-liquors. The first chromatography (eluent:dichloromethane) afforded a crude compound. The second purification, performed under the same conditions, furnished the analytically pure crystal product, mp 168°; ir (potassium bromide): ν cm^{-1} 3171 (NH), 1696 (CO); ^1H nmr (DMSO-d_6): 90 MHz δ 3.70 and 3.73 (s, 6H, 2 OCH_3), 6.46 (s, 1H, ethylenic CH), 7.03 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{6'}$), 7.53 (m, 3H, H_4, H_5, H_6), 7.73 (m, 1H, H_7), 10.55 (bs, 1H, NH); (deuteriochloroform): 90 MHz δ 3.76 and 3.80 (s, 6H, 2 OCH_3), 6.60 (s, 1H, ethylenic CH), 6.86 (m, 2H, $H_{3'}$, $H_{4'}$), 7.08 (bs, 1H, $H_{6'}$), 7.33-7.70 (m, 3H, H_4, H_5, H_6), 7.86 (m, 1H, H_7), 9.00 (bs, 1H, NH); ms: m/z 281.

Methylation of Isoindolinones (*Z*)-**6a-b**.

A solution of hydroxylated isoindolinone (*Z*)-**6a-b** (0.0042 mole), methyl iodide (1.5 g, 0.0105 mole) and potassium carbonate (1.45 g, 0.0105 mole) in 2-butanone (20 ml) was refluxed for 6 hours under stirring. After cooling, the mineral salts were collected and the solvent was evaporated. The residue was taken up in dichloromethane, washed with water, dried, and the solution was evaporated under reduced pressure.

2,3-Dihydro-2-methyl-3-(2-methoxyphenylmethylene)-1*H*-isoindol-1-one (*Z*)-**7a** and 2,3-Dihydro-3-(2-methoxyphenylmethylene)-1*H*-isoindol-1-one (*Z*)-**6c**.

The mixture resulting from the methylation of (*Z*)-**6a** was chromatographed on silica gel (eluent, dichloromethane), thus enabling to separate respectively (order of elution).

The isoindolinone (*Z*)-**7a** was obtained in a 18% yield, mp 127° (cyclohexane); ir (potassium bromide): ν cm^{-1} 1705 (CO); ^1H nmr (DMSO-d_6): 90 MHz δ 2.93 (s, 3H, N-CH_3), 3.85 (s, 3H, OCH_3), 6.80 (s, 1H, ethylenic CH), 6.95-7.83 (m, 7H, arom), 8.03 (dd, 1H, H_4, J = 7.5 Hz); (deuteriochloroform): 250 MHz δ 3.05 (s, 3H, N-CH_3), 3.86 (s, 3H, OCH_3), 6.70 (s, 1H, ethylenic CH), 6.92 (d, 1H, $H_{3'}$, J = 8.3 Hz), 6.98 (bt, 1H, $H_{5'}$), 7.23 (bd, 1H, $H_{6'}$, J = 7 Hz), 7.32 (bt, 1H, $H_{4'}$), 7.46 (td, 1H, H_6, J = 1 Hz, J = 7.3 Hz), 7.57 (td, 1H, H_5, J = 1.2 Hz, J = 7.6 Hz), 7.77 (bd, 1H, H_4, J = 7.6 Hz), 7.84 (bd, 1H, H_7, J = 7.3 Hz); ms: m/z 265.

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.65; H, 5.76; N, 5.23.

The isoindolinone (*Z*)-**6c** was obtained in a yield of 34% as described above.

2,3-Dihydro-2-methyl-3-(2,5-dimethoxyphenylmethylene)-1*H*-isoindol-1-one (*Z*)-**7b**.

Under the above-mentioned conditions, methylation of (*Z*)-**6b** only leads to an *O*,*N*-dimethylated isoindolinone (*Z*)-**7b**. This compound was obtained in a 63% yield after column-chromatography on silica gel (eluent, dichloromethane), mp 134° (cyclohexane); ir (potassium bromide): ν cm^{-1} 1719 (CO); ^1H nmr (DMSO-d_6): 90 MHz δ 2.94 (s, 3H, N-CH_3), 3.73 and 3.76 (2s, 6H, 2 OCH_3), 6.78 (s, 1H, ethylenic CH), 6.80-7.00 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{6'}$), 7.43-7.82 (m, 3H, H_5, H_6, H_7), 8.00 (bd, 1H, H_4, J = 7.5 Hz); (deuteriochloroform): 250 MHz δ 3.07 (s, 3H, N-CH_3), 3.76 and 3.80 (2s, 6H, 2 OCH_3), 6.65 (s, 1H, ethylenic CH), 6.80 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{6'}$), 7.44 (td, 1H, H_6, J = 0.9 Hz, J = 7.3 Hz), 7.55 (td, 1H, H_5, J = 1.2 Hz, J = 7.6 Hz), 7.75 (bd, 1H, H_4, J = 7.6 Hz), 7.82 (bd, 1H, H_7, J = 7.4 Hz); ms: m/z 295.

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.85; H, 5.77; N, 4.54.

When exposed a certain time to light, a large proportion of the derivative (*Z*)-**7b** in solution was transformed into its isomer (*E*)-**7b**. Many recrystallizations from cyclohexane were necessary to isolate this compound, mp 140°; ir (potassium bromide): ν cm^{-1} 1710 (CO); ^1H nmr (DMSO-d_6): 90 MHz δ 3.30 (s, 3H, N-CH_3), 3.70 and 3.73 (2s, 6H, 2 OCH_3), 6.48 (s, 1H, ethylenic CH), 7.00 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{6'}$), 7.30-7.53 (m, 3H, H_4, H_5, H_6), 7.75 (bd, 1H, H_7, J = 2 Hz, J = 7 Hz); (deuteriochloroform): 250 MHz δ 3.39 (s, 3H, N-CH_3), 3.74 and 3.78 (2s, 6H, 2 OCH_3), 6.42 (s, 1H, ethylenic CH), 6.90 (m, 2H, $H_{3'}$, $H_{4'}$), 7.05 (bs, 1H, $H_{6'}$), 7.32 (bt, 1H, H_6), 7.39 (bt, 1H, H_5), 7.48 (d, 1H, H_4, J = 7.7 Hz), 7.82 (d, 1H, H_7, J = 7 Hz); ms: m/z 295.

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.98: H, 5.87; N, 4.50.

Rearrangement of Amide **5b** by Sodium Amide.

To a suspension of sodium amide (0.82 g, 0.021 mole) in tetrahydrofuran (10 ml), a solution of amide **5b** (1.87 g, 0.007 mole) in tetrahydrofuran (25 ml) was added dropwise, under argon. The reaction mixture was then refluxed for 9 hours, with stirring. The solution was cooled, poured into water and acidified. The precipitated product was collected, washed with water until neutral and dried, yielding 63% of the above-described isoindolinone (*Z*)-**6b**.

Crystallography.

A single crystal of, respectively, (*Z*)-**6b** and (*Z*)-**6c** was mounted on a CAD-4 diffractometer. Cell parameters and their esd's were obtained by a least-square fit of 25 measured reflections with $20° < 2\theta < 40°$. Crystal parameters are listed in Table 4 and the main characteristics of data collection are listed in Table 5.

The 1,−3,−2; 3,2,−1 and −2,2,1 reflections were used as standards for (*Z*)-**6b**; the 0,−2,−3; −2,6, 4 and −4,0,0 were used as standards for (*Z*)-**6c**. There was no intensity decrease of those reflections during the data collections. No correction of absorption was made for (*Z*)-**6b** owing to the small size of the crystal used, but it was performed for crystal of compound (*Z*)-**6c**.

Both structures were solved by direct methods using the MULTAN 80 package [27] for (*Z*)-**6b** compound and the MITHRIL package [28] for compound (*Z*)-**6c**. The C, N and O parameters were refined with first isotropic, then anisotropic temperature factors. Hydrogen atoms were located from a different Fourier synthesis; the refinement was resumed using isotropic temperature factors for H atoms. Refinements converged at the following R reliability factors and R_w weighted reliability factors:

$$R = 0.052,\ R_w = 0.052 \text{ for } (Z)\text{-}\mathbf{6b}.$$

$$R = 0.058,\ R_w = 0.053 \text{ for } (Z)\text{-}\mathbf{6c}.$$

The minimization scheme was as follows: the sum $\Sigma w(Fo\text{-}Fc)^2$ was minimized with:

$$w = \frac{w_o}{1 + w_o\,[a(|F_o|-b)]^2}$$

where $w_o^{1/2} = 2\,Fo/\sigma(Fo^2)$, a = 0.1 and b = 10.

Final $(\Delta/\sigma)_{max} = 0.7$; residual electronic densities were less than 0.35 and −0.2 e.$Å^{-3}$ for both compounds; diffusion factors are from Cromer and Waber [29] for C, N, O atoms, from Steward, Davidson and Simpson [30] for hydrogens.

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