

***N*-SUBSTITUTED 5,5-DIMETHYL-2,5-DIHYDRO-4*H*-ISOINDOL-4-ONES:  
SYNTHESIS AND NMR- INVESTIGATION<sup>#</sup>**

Helmut Spreitzer\*, Wolfgang Holzer, Günther Fülep, and Christiane Puschmann

Institute of Pharmaceutical Chemistry, University of Vienna, Pharmaziezentrum,

Althanstrasse 14, A-1090 Vienna, Austria

**Abstract** - The synthesis of novel *N*- substituted 5,5-dimethyl-2,5-dihydro-4*H*-isoindol-4-ones by reaction of 5,5-dimethyl-2,5-dihydro-4*H*-isoindol-4-one (**1**) with appropriate electrophiles (methyl iodide, 3,3-dimethylallyl bromide, 2-*N,N*-dimethylethyl chloride, ethyl 3-bromopropionate, benzoyl chloride, *N,N*-dimethylchloroformate, phenyl chloroformate) is described. Moreover, detailed nmr spectroscopic studies (<sup>1</sup>H, <sup>13</sup>C) with the title compounds are presented.

## INTRODUCTION

In contrast to the widespread occurrence of the indole skeleton as structural element of many natural products the isoindole system is part of only a very few naturally occurring compounds.<sup>1</sup> As we showed in an earlier study, the isoindole nucleus is accessible upon reaction of 6,6-dimethylcyclohexadienone with metallated tosylmethyl isocyanide leading to 5,5-dimethyl-2,5-dihydro-4*H*-isoindol-4-one (**1**).<sup>2</sup> The regioselectivity of this reaction can be explained by the typical charge distribution of hexadienones with the

<sup>#</sup> Dedicated with best personal wishes to Prof. Dr. H. Oelschläger on the occasion of his 75th anniversary

consequence of positive charge concentration at C-3, being characteristic for dienones,<sup>3</sup> and furthermore by sterical hindrance of the 6,6-dimethyl group which prevents an attack at C-5 and likewise favours an attack at C-3 of the dienone system. Whereas - in continuation to the above study<sup>2</sup> - investigations concerning the synthesis of potential pharmacologically active isoindoles employing this approach are in progress, in this work we describe the synthesis of novel *N*-substituted 5,5-dimethyl-2,5-dihydro-4*H*-isoindol-4-ones (**2**) - (**9**) (Scheme 1) by reaction of **1** with appropriate electrophiles. Furthermore, in view of the fact that there is only little <sup>13</sup>C nmr data material available for isoindoles,<sup>4</sup> detailed nmr spectroscopic studies with the title compounds are presented.

## RESULTS AND DISCUSSION

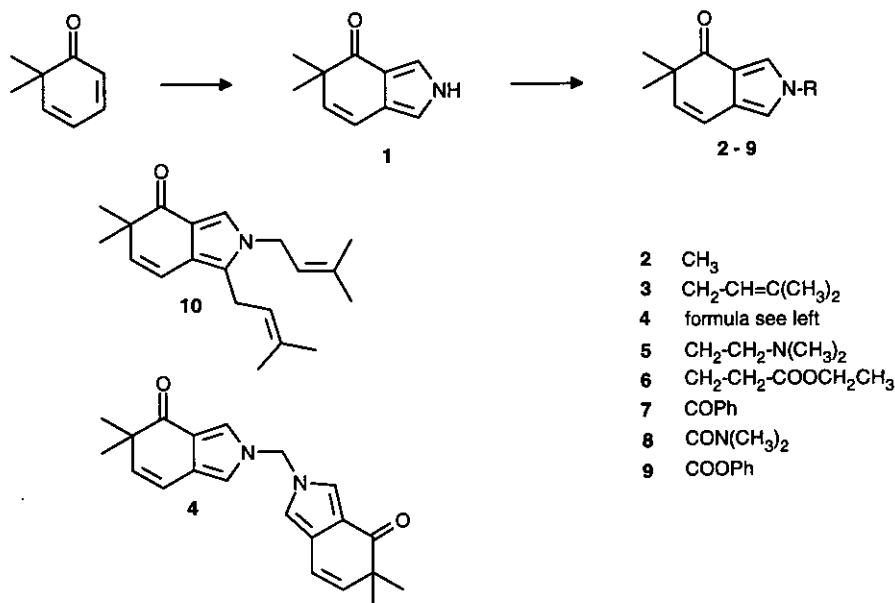
### Synthesis

For producing the desired *N*-alkyl-, *N*-acyl- as well as carboxylic acid derivatives of **1** we tried to find a generally applicable synthetic method. After some preliminary trials the phase transfer catalyzed *N*-acylation method of indoles (described by V.O. Illi<sup>5</sup>) seemed to be convincing. This method uses pulverized NaOH/Bu<sub>4</sub>N·HSO<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> and was developed to circumvent the problem of poly-acylation of the indole core. In a similar way, starting from **1** we thus obtained a series of selectively *N*-substituted alkyl-, aminoalkyl-, and carboxyalkyl products (**2**, **3**, **5**, **6**), and further the *N*-acyl-, urethan- and carbamate derivatives (**7** - **9**). Only the use of the highly reactive dimethylallyl bromide resulted in a mixture of *N*-substitution product (**3**) and the *C*-1,*N*-diallyl derivative (**10**). Finally, without addition of an electrophile the solvent CH<sub>2</sub>Cl<sub>2</sub> itself reacted with two equivalents of **1** to afford the bis-substituted methylene compound (**4**).

### Nmr Spectroscopic Investigations

The <sup>1</sup>H nmr data of compounds (**1**) - (**10**) are collected in Table 1, Table 2 contains the <sup>13</sup>C chemical shifts, whereas Table 3 gives a survey of the <sup>13</sup>C,<sup>1</sup>H spin coupling constants determined. Complete and unambiguous assignments were performed on basis of different nmr techniques such as NOE difference

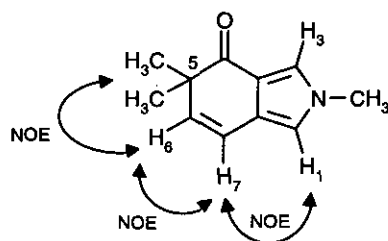
Scheme 1



experiments,<sup>6</sup> selective 1D-TOCSY<sup>7</sup> spectra, fully <sup>1</sup>H-coupled <sup>13</sup>C nmr spectra (gated decoupling), direct <sup>13</sup>C,<sup>1</sup>H shift correlations (HMQC)<sup>8</sup> and long-range INEPT spectra with selective DANTE excitation.<sup>9</sup> The <sup>13</sup>C,<sup>1</sup>H spin coupling constants were extracted from the gated decoupled <sup>13</sup>C nmr spectra, from <sup>13</sup>C satellite signals in the <sup>1</sup>H nmr spectra and, particularly, from two-dimensional long-range INEPT spectra<sup>10</sup> with selective excitation of unequivocally assigned proton resonances.

As an example, compound (2) may serve. Irradiation of the 5-(CH<sub>3</sub>)<sub>2</sub> resonance (1.21 ppm) in an NOE-difference experiment enhances the doublet signal of the spatially close H-6 proton (5.71 ppm, J = 9.6 Hz); reversely, perturbation of the H-6 resonance generates NOEs for the signals of 5-CH<sub>3</sub> and H-7 (Figure 1). This consecutively assigns the double doublet with 6.38 ppm (J = 9.6 Hz and 0.7 Hz) to be due to H-7. A further NOE difference experiment (strong NOE on the signal of H-1 upon irradiation of the H-7 resonance) allowed to distinguish between the signals of H-1 and H-3 (Figure 1).

Figure 1. Identification of H-6 and H-1 via NOE-difference experiments

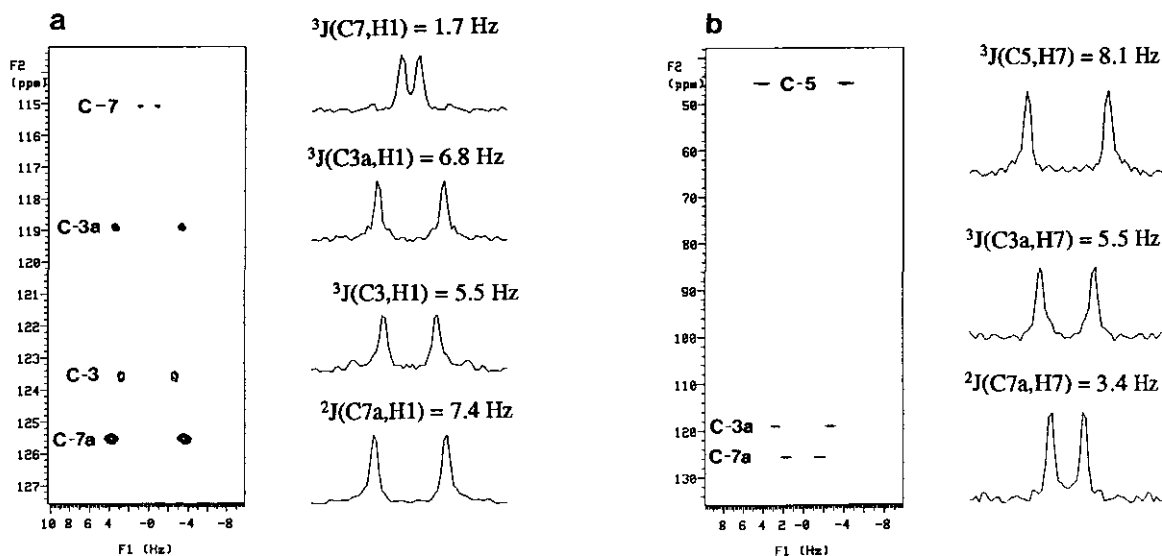
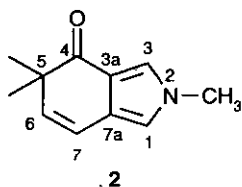


Based on the complete assignment of protons, in an HMQC experiment the carbon signals of C-1, C-3, C-6- and C-7 (and of 2-CH<sub>3</sub> and 5-CH<sub>3</sub>) now could be unequivocally identified. Assignment of the signals of the quaternary carbons C-3a, C-4, C-5 and C7a was achieved via long-range INEPT experiments with selective DANTE excitation of the H-1, H-3, H-6, H-7, and 5-CH<sub>3</sub> resonance, respectively. The same techniques were also applied for the assignment of resonances of the substituent R, if necessary (e.g. compounds (3), (5), (6), (7), (9), (10)). Overlapping signals belonging to different spin systems were discriminated by selective 1D-TOCSY experiments (e. g. 1- and 2-substituents in compound (10) or Ph H-3,5 and isoindolone H-1 in structure (9)).

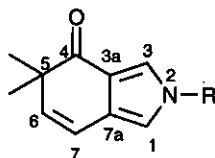
Whereas the direct <sup>13</sup>C, <sup>1</sup>H spin coupling constants could be easily extracted from the fully <sup>1</sup>H-coupled <sup>13</sup>C nmr spectra (or were determined considering the <sup>13</sup>C satellite signals in the <sup>1</sup>H nmr spectra), the unambiguous determination of many long-range couplings was not possible in this way owing to complicated splitting patterns and overlapping lines. Additionally, the unequivocal discrimination between coupling constants of similar magnitude from the gated decoupled spectra (e.g. <sup>3</sup>J(C3a,H1) versus <sup>2</sup>J(C3a,H3) for carbon atom C-3a) is a very difficult task. However, the absolute values of these coupling constants could be obtained employing two-dimensional long-range INEPT experiments with selective DANTE excitation of unequivocally assigned (and well separated) proton resonances. In Figure 2, two examples are demonstrated with *N*-methyl congener (2): upon selective excitation of the H-1 signal all carbon atoms which have a long-range coupling to H-1 (C-7a, C-3, C-3a, C-7) appear in the 2D (δ, J) spectrum (the <sup>3</sup>J coupling with NCH<sub>3</sub> is outside of the depicted part of the spectrum), the absolute values

of the coupling constants can be easily extracted from the appropriate 1D-traces (Figure 2a). Similarly, selective excitation of H-7 permits to determine  ${}^2J(C7a,H7)$ ,  ${}^3J(C3a,H7)$  and  ${}^3J(C5,H7)$  (Figure 2b).<sup>11</sup> It should be emphasized, that in those cases when coupling constants could be determined according to both of the above methods (gated decoupled spectra and 2D-( $\delta$ , J) spectra) a good correspondence between the obtained results was observed.

Figure 2. a) 2D ( $\delta$ , J) Long-range INEPT spectrum of **2** resulting from selective excitation of H-1 (optimized for J = 6 Hz); b) 2D ( $\delta$ , J) Long-range INEPT spectrum of **2** resulting from selective excitation of H-7 (optimized for J = 6 Hz).



The data in Tables 1 - 3 coarsely reflect the influence of the *N*-2 substituent R on the chemical shifts and spin coupling constants. Expectedly, the attachment of more electron withdrawing functional groups at *N*-2 (compounds (**7**) - (**9**)) leads to a deshielding of H-1 and H-3. Whereas the  ${}^{13}\text{C}$  chemical shifts of the

Table 1. <sup>1</sup>H-NMR Data of compounds (1) - (10) (solvent: CDCl<sub>3</sub>)

No.	<sup>1</sup> H-chemical shifts (δ, ppm)						coupling constants
	H-1	H-3	H-6	H-7	5-CH <sub>3</sub>	H of R	
1	6.69	7.39	5.74	6.47	1.25	10.21 (NH)	a
2	6.46	7.22	5.71	6.38	1.21	3.67 (2-Me)	b
3	6.49	7.28	5.70	6.38	1.21	4.44 (2-CH <sub>2</sub> ) <sup>e</sup> , 5.35 (=CH) <sup>ef</sup> , 1.77 ((E)-Me), 1.74 ((Z)-Me)	b
4	6.65	7.51	5.75	6.36	1.22	5.91 (2-CH <sub>2</sub> )	b
5	6.79	7.52	5.73	6.38	1.19	4.67 (2-CH <sub>2</sub> ) <sup>g</sup> , 3.54 (Me <sub>2</sub> NCH <sub>2</sub> ) <sup>g</sup> , 2.82 (NMe <sub>2</sub> )	b
6	6.53	7.28	5.70	6.36	1.20	4.19 (2-CH <sub>2</sub> ) <sup>h</sup> , 2.76 (COCH <sub>2</sub> ) <sup>h</sup> , 4.13 (OCH <sub>2</sub> ) <sup>i</sup> , 1.21 (Me) <sup>i</sup>	b
7	7.29	7.78	5.87	6.45	1.27	7.75 (Ph H-2,6), 7.52 (Ph H-3,5), 7.64 (Ph H-4)	b
8	6.89	7.58	5.77	6.38	1.22	3.07 (NMe <sub>2</sub> )	b
9	7.28	8.04	5.87	6.44	1.28	7.25 (Ph H-2,6), 7.44 (Ph H-3,5), 7.31 (Ph H-4)	b
10	-- <sup>c</sup>	7.25	5.65	6.41	1.22	4.38 (2-CH <sub>2</sub> ) <sup>j</sup> , 5.28 (=CH) <sup>jk</sup> , 1.77 ((E)-Me), 1.72 ((Z)-Me)	d

<sup>a</sup> <sup>4</sup>J(H1,H3) = 1.7 Hz; <sup>5</sup>J(H3,H7) = 0.7 Hz; <sup>3</sup>J(H6,H7) = 9.6 Hz.

<sup>b</sup> Typical spin coupling constants for compounds 2 - 9: <sup>4</sup>J(H1,H3) = 2.0 - 2.1 Hz; <sup>5</sup>J(H3,H7) = 0.6 - 0.8 Hz; <sup>3</sup>J(H6,H7) = 9.5 - 9.8 Hz.

<sup>c</sup> 1-Substituent: 3.34 (1-CH<sub>2</sub>), 5.15 (=CH), 1.72 ((E)-Me and (Z)-Me); coupling constants: <sup>3</sup>J(1-CH<sub>2</sub>,=CH) = 6.8 Hz; <sup>4</sup>J(=CH,Me) = 1.5 Hz.

<sup>d</sup> <sup>5</sup>J(H3,H7) = 0.6 Hz; <sup>3</sup>J(H6,H7) = 9.7 Hz.

<sup>e</sup> <sup>3</sup>J(2-CH<sub>2</sub>,=CH) = 7.3 Hz.

<sup>f</sup> <sup>4</sup>J(=CH,Me) = 1.4 Hz.

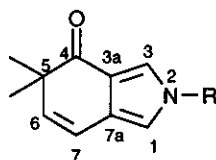
<sup>g</sup> <sup>3</sup>J(2-CH<sub>2</sub>,Me<sub>2</sub>NCH<sub>2</sub>) = 6.8 Hz.

<sup>h</sup> <sup>3</sup>J(2-CH<sub>2</sub>,COCH<sub>2</sub>) = 6.7 Hz.

<sup>i</sup> <sup>3</sup>J(OCH<sub>2</sub>,CH<sub>3</sub>) = 7.1 Hz.

<sup>j</sup> <sup>3</sup>J(2-CH<sub>2</sub>,=CH) = 6.9 Hz.

<sup>k</sup> <sup>4</sup>J(=CH,CH<sub>3</sub>) = 1.5 Hz.

Table 2.  $^{13}\text{C}$ -Chemical shifts ( $\delta$ , ppm, solvent:  $\text{CDCl}_3$ ) of compounds (1) - (10)

No.	C-1	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	5-CH <sub>3</sub>	C of R
1	113.8	120.8	118.8	201.6	45.7	137.4	115.6	124.9	26.0	--
2	117.1	123.6	119.0	199.5	45.5	137.9	115.2	125.6	26.0	36.8 (Me)
3	115.8	122.3	118.7	199.6	45.5	137.8	115.3	125.4	26.0	47.6 (2-CH <sub>2</sub> ), 118.7 (=CH), 138.5 (=CMe <sub>2</sub> ), 25.6 ((E)-Me), 17.9 ((Z)-Me)
4	115.3	122.5	120.3	199.9	45.7	138.8	114.9	126.6	26.0	62.6 (CH <sub>2</sub> )
5	116.9	122.4	120.1	199.9	45.7	138.4	115.1	126.1	26.0	45.0 (2-CH <sub>2</sub> ), 57.6 (Me <sub>2</sub> NCH <sub>2</sub> ), 43.7 (NMe <sub>2</sub> )
6	116.2	122.7	119.1	199.6	45.5	137.9	115.2	125.5	26.0	45.6 (2-CH <sub>2</sub> ), 35.9 (COCH <sub>2</sub> ), 170.4 (CO), 61.0 (OCH <sub>2</sub> ), 14.0 (CH <sub>3</sub> )
7	115.3	123.3	122.1	200.3	46.0	140.0	115.0	126.6	26.0	167.7 (CO), 131.9 (Ph C-1), 129.6 (Ph C-2,6), 128.8 (Ph C-3,5), 133.0 (Ph C-4)
8	115.6	121.9	120.3	200.0	45.8	138.9	114.9	125.1	26.0	153.5 (CO), 38.6 (NMe <sub>2</sub> )
9	114.8	122.1	122.3	199.8	45.9	139.8	114.8	126.6	26.0	148.4 (CO), 150.0 (Ph C-1), 120.9 (Ph C-2,6), 129.7 (Ph C-3,5), 126.8 (Ph C-4)
10	127.0 <sup>a</sup>	121.7	117.8	199.7	45.5	136.5	115.0	121.8	26.2	45.1 (2-CH <sub>2</sub> ), 119.2 (=CH), 137.6 (=CMe <sub>2</sub> ), 25.6 ((E)-Me), 17.9 ((Z)-Me)

<sup>a</sup> Substituent at C-1: 23.6 (1-CH<sub>2</sub>), 121.1 (=CH), 132.9 (=CMe<sub>2</sub>), 25.5 ((E)-Me), 17.8 ((Z)-Me).

Table 3.  $^{13}\text{C}, ^1\text{H}$  Spin coupling constants (Hz) of compounds (1) - (10) (solvent:  $\text{CDCl}_3$ )

No.	$^1\text{J}(\text{C1},\text{H1})$	$^3\text{J}(\text{C1},\text{H3})$	$^3\text{J}(\text{C1},\text{H7})$	$^3\text{J}(\text{C3},\text{H1})$	$^1\text{J}(\text{C3},\text{H3})$	$^3\text{J}(\text{C3a},\text{H1})$	$^2\text{J}(\text{C3a},\text{H3})$	$^3\text{J}(\text{C3a},\text{H7})$	$^3\text{J}(\text{C4},\text{H6})$	$^3\text{J}(\text{C4},5\text{-CH}_3)$	$^2\text{J}(\text{C5},\text{H6})$	$^3\text{J}(\text{C5},\text{H7})$	$^2\text{J}(\text{C5},5\text{-CH}_3)$
1	187.3	7.0	2.2	6.3	188.3	6.6	6.9	5.5	6.7	3.7	3.1	8.2	3.8
2	186.1	6.3	2.0	5.5	187.6	6.8	6.7	5.5	6.5	3.7	3.1	8.1	3.8
3	186.0	6.3	2.0	5.4	187.6	6.8	6.7	5.5	6.6	3.7	3.0	8.1	3.8
4	187.5	5.9		5.2	189.1	6.9	6.3	5.5	6.7	3.8	3.0	8.1	3.8
5	187.8				188.2								
6	186.4	6.1		5.2	187.9	6.9	6.6	5.6	6.5	3.7		8.2	3.8
7	193.5	4.9		4.6	194.6								
8	191.5		1.8	4.9	192.6		5.5		6.7	3.8	3.1	8.1	3.8
9	194.9	4.6	2.0	4.3	196.5	7.4	6.1	5.6	6.7	3.8	2.9		3.8
10	--			--	187.6	--							

No.	$^1\text{J}(\text{C6},\text{H6})$	$^3\text{J}(\text{C6},5\text{-CH}_3)$	$^3\text{J}(\text{C7},\text{H1})$	$^1\text{J}(\text{C7},\text{H7})$	$^2\text{J}(\text{C7a},\text{H1})$	$^3\text{J}(\text{C7a},\text{H3})$	$^3\text{J}(\text{C7a},\text{H6})$	$^2\text{J}(\text{C7a},\text{H7})$	$^3\text{J}(5\text{-CH}_3,\text{H6})$	$^4\text{J}(5\text{-CH}_3,\text{H7})$	$^1\text{J}(5\text{-CH}_3)$	$^3\text{J}(5\text{-CH}_3,5\text{-CH}_3)$
1	159.2	4.3	1.6	161.3	7.6	5.8	11.7	3.4	2.4	0.8	129.0	5.1
2	158.9	4.3	1.7	161.1	7.4	6.2	11.7	3.4	2.4	0.8	128.9	5.1
3	158.8	4.2	1.9	160.8	7.3	6.3	11.7	3.4	2.4		129.0	5.2
4	159.4	4.3	1.7	162.1	7.0	6.3	11.9	3.5	2.4		129.0	5.1
5	159.4			162.0							129.1	
6	158.8	4.4	1.7	161.2	7.3	6.3	11.7	3.4	2.4	0.8	128.9	5.2
7	159.5	4.3	2.0	163.0							129.3	
8	159.3	4.3	1.9	162.4	7.2	6.7	11.9	3.5	2.5	0.8	129.1	5.1
9	159.6	4.4	2.0	163.1	7.2	7.0	12.0	3.5	2.4	0.7	129.3	5.1
10	158.6	4.2	--	159.1	--						128.7	

other couplings (nuclei of R involved):

2:  $^3\text{J}(\text{C1},2\text{-CH}_3) = 3.2$ ;  $^3\text{J}(\text{C3},2\text{-CH}_3) = 3.5$ ;  $^1\text{J}(2\text{-CH}_3) = 139.5$ ;  $^3\text{J}(2\text{-CH}_3,\text{H1}) = 1.7$ ;  $^3\text{J}(2\text{-CH}_3,\text{H3}) = 2.5$ . 3:  $^3\text{J}(\text{C1},2\text{-CH}_2) = 3.1$ ;  $^3\text{J}(\text{C3},2\text{-CH}_2) = 3.4$ ;  $^3\text{J}(2\text{-CH}_2,\text{H1}) = 1.7$ ;  $^3\text{J}(2\text{-CH}_2,\text{H3}) = 2.2$ ;  $^1\text{J}(2\text{-CH}_2) = 138.8$ ;  $^2\text{J}(2\text{-CH}_2,=\text{CH}) = 3.1$ ;  $^2\text{J}(=\text{CH},2\text{-CH}_2) = 5.5$ ;  $^1\text{J}(=\text{CH}) = 157.0$ ;  $^3\text{J}(\text{Me}_2\text{C},2\text{-CH}_2) = 5.1$ ;  $^2\text{J}(\text{Me}_2\text{C},\text{CH}_3) = 6.6$ ;  $^3\text{J}((E)\text{-Me},=\text{CH}) = 6.9$ ;  $^1\text{J}((E)\text{-Me}) = 126.1$ ;  $^3\text{J}((E)\text{-CH}_3,(Z)\text{-CH}_3) = 4.4$ ;  $^3\text{J}((Z)\text{-Me},=\text{CH}) = 8.1$ ;  $^1\text{J}((Z)\text{-Me}) = 126.0$ ;  $^3\text{J}((Z)\text{-CH}_3,(E)\text{-CH}_3) = 4.2$ . 4:  $^3\text{J}(\text{C1},2\text{-CH}_2) = 3.5$ ;  $^3\text{J}(\text{C3},2\text{-CH}_2) = 3.7$ ;  $^3\text{J}(2\text{-CH}_2,\text{H3}) = 2.8$ ;  $^1\text{J}(2\text{-CH}_2) = 153.2$ . 5:  $^1\text{J}(2\text{-CH}_2) = 142.1$ ;  $^1\text{J}(\text{Me}_2\text{NCH}_2) = 143.9$ ;  $^1\text{J}(\text{NCH}_3) = 144.1$ . 6:  $^3\text{J}(2\text{-CH}_2,\text{H1}) = 1.6$ ;  $^3\text{J}(2\text{-CH}_2,\text{H3}) = 2.0$ ;  $^1\text{J}(2\text{-CH}_2) = 141.7$ ;  $^2\text{J}(2\text{-CH}_2,\text{COCH}_2) = 4.7$ ;  $^2\text{J}(\text{COCH}_2,2\text{-CH}_2) = 3.4$ ;  $^1\text{J}(\text{COCH}_2) = 129.9$ ;  $^2\text{J}(\text{COO},\text{COCH}_2) = 7.4$ ;  $^1\text{J}(\text{OCH}_2) = 147.8$ ;  $^2\text{J}(\text{OCH}_2,\text{CH}_3) = 4.4$ ;  $^2\text{J}(\text{CH}_3,\text{OCH}_2) = 2.6$ ;  $^1\text{J}(\text{CH}_3) = 127.7$ . 8:  $^3\text{J}(\text{CON},\text{NCH}_3) = 3.3$ ;  $^1\text{J}(\text{NCH}_3) = 139.2$ ;  $^3\text{J}(\text{NCH}_3,\text{NCH}_3) = 3.3$ . 10:  $^3\text{J}(\text{C3},2\text{-CH}_2) = 3.8$ ;  $^1\text{J}(2\text{-CH}_2) = 138.2$ ;  $^1\text{J}(1\text{-CH}_2) = 126.4$ .



isoindolone system are only slightly affected, some  $^{13}\text{C},^1\text{H}$  spin coupling constants are sensitive to a variation of the *N*-2-substituent. Thus,  $^1\text{J}(\text{C}1,\text{H}1)$  and  $^1\text{J}(\text{C}3,\text{H}3)$  (and to a smaller extent also  $^1\text{J}(\text{C}7,\text{H}7)$ ) increase with increasing electron-withdrawing properties of R, whereas - in contrast -  $^3\text{J}(\text{C}1,\text{H}3)$  and  $^3\text{J}(\text{C}3,\text{H}1)$  decrease.

## EXPERIMENTAL

Melting points were detected on a Reichert-Kofler hot-stage microscope and are uncorrected. The IR spectra were recorded on a Perkin-Elmer FTIR 1605 spectrophotometer. Mass spectra were obtained on a Hewlett Packard 5890A/5970B-MSD instrument or Shimadzu QP 1000 spectrometer. All NMR spectra were recorded on a Varian Unityplus 300 spectrometer (299.95 MHz for  $^1\text{H}$ , 75.43 MHz for  $^{13}\text{C}$ ) from  $\text{CDCl}_3$  solutions at 28°C. The solvent signal was used as an internal standard which was related to tetramethylsilane with  $\delta$  7.26 ppm ( $^1\text{H}$ ) and  $\delta$  77.0 ppm ( $^{13}\text{C}$ ). The digital resolutions were 0.25 Hz/data point for the  $^1\text{H}$ -NMR spectra, 0.56 Hz/data point for the broadband decoupled  $^{13}\text{C}$ -NMR spectra, 0.33 Hz/data point for the fully  $^1\text{H}$ -coupled  $^{13}\text{C}$  NMR spectra. The resolution for the 2D ( $\delta,\text{J}$ ) spectra was 0.63 Hz, the experiments were optimized for a long-range  $^{13}\text{C},^1\text{H}$  coupling constant of 4 - 6 Hz. Column chromatographic separations were performed by medium-pressure liquid chromatography (MPLC) on Merck LiChrorep Si 60, 0.040 - 0.063 mm.

### General procedure

To a well-stirred solution of 644 mg (4 mmol) of **1**, 15 mg (0.044 mmol) of tetrabutylammonium hydrogen sulfate and 400 mg (10 mmol) of finely powdered NaOH in dichloromethane (10 - 15 ml) was added dropwise under  $\text{N}_2$ -atmosphere a solution of 6 mmol reagent (methyl iodide, 3,3-dimethylallyl bromide, 2-*N,N*-dimethylethyl chloride, ethyl 3-bromopropionate, benzoyl chloride, *N,N*-dimethylchloroformate, phenyl chloroformate) dissolved in 10 ml of dichloromethane. After the appropriate reaction time (see following table) the reaction mixture was filtered, dried with anhydrous  $\text{MgSO}_4$  and concentrated *in vacuo*. The

crude products were purified by flash chromatography; solvent  $\text{CH}_2\text{Cl}_2$  (1 and 2) or ethyl acetate/light petroleum 1/3 (3-9).

	reaction time	temp.	yield (%) <sup>a)</sup>	mp (°C) <sup>b)</sup>
2	20 h	20°C	51	88-89
3	75 min	0°C	20	50-52
4	48 h	20°C	30	240-245
5	24 h	20°C	68	oil
6	48 h	20°C	61	53-55
7	75 min	20°C	60	oil
8	1 h	20°C	89	101-103
9	2 h	20°C	75	oil

<sup>a)</sup> Yields after recrystallization.

<sup>b)</sup> Solid products were recrystallized from ethyl acetate/light petroleum.

#### 2,5,5-Trimethyl-2,5-dihydro-4H-isoindol-4-one (2)

Ir (KBr):  $\text{cm}^{-1}$  1640 (C=O), 1523 (C=C); ms: m/z (%) 175 ( $\text{M}^+$ , 100), 161 (10), 160 (100), 146 (39), 132 (59), 131 (36), 117 (20), 91 (11). *Anal.* Calcd for  $\text{C}_{11}\text{H}_{13}\text{NO}$ : C, 75.40; H, 7.48; N, 7.99. Found: C, 75.13; H, 7.26; N, 8.17.

#### 5,5-Dimethyl-2-(3-methyl-2-butenyl)-2,5-dihydro-4H-isoindol-4-one (3)

Ir (KBr):  $\text{cm}^{-1}$  1641 (C=O), 1518 (C=C); ms: m/z (%) 229 ( $\text{M}^+$ , 100), 214 (30), 161 (52), 146 (76), 132 (36), 118 (27), 117 (27), 69 (30). *Anal.* Calcd for  $\text{C}_{15}\text{H}_{19}\text{NO}$ : C, 78.56; H, 8.35; N, 6.11. Found: C, 78.33; H, 8.32; N, 6.17.

#### 2,2'-Methylenebis-(5,5-dimethyl-2,5-dihydro-4H-isoindol-4-one) (4)

Ir (KBr):  $\text{cm}^{-1}$  1646 (C=O), 1520 (C=C); ms: m/z (%) 334 ( $\text{M}^+$ , 28), 174 (62), 72 (57), 71 (31), 69 (34), 60 (100), 58 (50), 56 (60). *Anal.* Calcd for  $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2$ : C, 75.42; H, 6.63; N, 8.38. Found: C, 75.21; H, 6.44; N, 8.23.

2-(2-Dimethylaminoethyl)-5,5-dimethyl-2,5-dihydro-4H-isoindol-4-one (5)

Ir (KBr):  $\text{cm}^{-1}$  1646 (C=O), 1522 (C=C); ms:  $m/z$  (%) 232 ( $M^+$ , 8), 130 (2), 117 (1), 77 (2), 59 (100), 58 (20). *Anal.* Calcd for  $C_{14}H_{20}N_2O$ : C, 72.38; H, 8.68; N, 12.06. Found: C, 72.16; H, 8.66; N, 12.01. The hydrochloride melted at 224-226°C (acetone).

Ethyl 3-(5,5-dimethyl-4-oxo-4,5-dihydro-4H-isoindol-2-yl)propionate (6)

Ir (KBr):  $\text{cm}^{-1}$  1731, 1640 (C=O), 1527 (C=C); ms:  $m/z$  (%) 261 ( $M^+$ , 100), 246 (94), 218 (17), 161 (23), 158 (39), 144 (30), 130 (33). *Anal.* Calcd for  $C_{15}H_{19}NO_3$ : C, 68.94; H, 7.33; N, 5.36. Found: C, 68.82; H, 7.34; N, 5.30.

2-Benzoyl-5,5-dimethyl-4,5-dihydro-4H-isoindol-4-one (7)

Ir (KBr):  $\text{cm}^{-1}$  1706, 1670 (C=O), 1524 (C=C); ms:  $m/z$  (%) 265 ( $M^+$ , 47), 220 (1), 160 (6), 132 (3), 117 (4), 105 (100), 77 (33), 51 (8). *Anal.* Calcd for  $C_{17}H_{15}NO_2$ : C, 76.96; H, 5.70; N, 5.28. Found: C, 76.56; H, 5.73; N, 5.06.

5,5-Dimethyl-4-oxo-4,5-dihydro-4H-isoindole-2-N,N-dimethylcarboxamide (8)

Ir (KBr):  $\text{cm}^{-1}$  1692, 1655 (C=O), 1533 (C=C); ms:  $m/z$  (%) 232 ( $M^+$ , 29), 217 (8), 160 (5), 132 (4), 130 (2), 117 (5), 77 (5), 72 (100). *Anal.* Calcd for  $C_{13}H_{16}N_2O_2$ : C, 67.22; H, 6.94; N, 12.06. Found: C, 67.37; H, 7.17; N, 12.04.

5,5-Dimethyl-4-oxo-4,5-dihydro-4H-isoindole-2-carboxylic acid phenylester (9)

Ir (KBr):  $\text{cm}^{-1}$  1770, 1760 (C=O), 1588, 1490 (C=C); ms:  $m/z$  (%) 281 ( $M^+$ , 100), 266 (80), 237 (6), 222 (8), 194 (5), 161 (8), 146 (9), 77 (22). *Anal.* Calcd for  $C_{17}H_{15}NO_3$ : C, 72.58; H, 5.37; N, 4.98. Found: C, 72.41; H, 5.59; N, 4.70.

1,2-Bis-(3-methyl-2-butenyl)-5,5-dimethyl-2,5-dihydro-4H-isoindol-4-one (10)

Compound **10** was obtained as by-product (5 % yield) in the preparation of **4**. Ir (KBr): 1636 (C=O), 1522 (C=C); ms:  $m/z$  (%) 297 ( $M^+$ , 100), 282 (57), 254 (14), 229 (14), 214 (90), 161 (16), 160 (12), 158 (11). *Anal.* Calcd for  $C_{20}H_{27}NO$ : C, 80.76; H, 9.15; N, 4.71. Found: C, 80.34; H, 9.28; N, 4.78.

## REFERENCES AND NOTES

1. K. J. Herd, 'Methoden der Organischen Chemie/(Houben-Weyl): 1H- und 2H-Isoindole', Vol. E6b<sub>1</sub>, ed. by R. P. Kreher, Georg Thieme Verlag, Stuttgart · New York, 1994, p. 455.
2. H. Spreitzer and St. Mustafa, *Chem. Ber.*, 1990, **123**, 413.
3. W. Regel and W. von Philipsborn, *Helv. Chim. Acta*, 1968, **51**, 867.
4. D. J. Chadwick, 'Comprehensive Heterocyclic Chemistry: Pyrroles and Their Benzo Derivatives', Vol. 4, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, p. 172.
5. V. O. Illi, *Synthesis*, 1979, 387.
6. D. Neuhaus and M. P. Williamson, 'The Nuclear Overhauser Effect in Structural and Conformational Analysis', VCH Publishers, New York, 1989.
7. H. Kessler, U. Anders, G. Gemmecker, and S. Steuernagel, *J. Magn. Reson.*, 1989, **85**, 1; F. Inagaki, I. Shimada, D. Kohda, A. Suzuki, and A. Bax, *J. Magn. Reson.*, 1985, **62**, 109.
8. A. Bax and S. Subramanian, *J. Magn. Reson.*, 1986, **67**, 565.
9. A. Bax, *J. Magn. Reson.*, 1984, **57**, 314.
10. T. Jippo, O. Kamo, and K. Nagayama, *J. Magn. Reson.*, 1986, **66**, 344.
11. The coupling constant  $^3J(C1,H7)$  appears at a lower level of the contour plot.

Received, 30th April, 1996