Chemistry of Heterocyclic Compounds, Vol. 45, No. 6, 2009

SYNTHESIS OF 2-ALKYL-3-(INDOL-2(OR 3)-YL)-1,3-DIHYDROISOINDOL-1-ONES BY AMIDOALKYLATION

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2-Alkyl-3-(indol-3-yl)-1,3-dihydroisoindol-1-ones have been obtained in good yield on amidoalkylation of indoles with 2-alkyl-3-hydroxyphthalides in chloroform at room temperature in the presence of catalytic quantities of boron trifluoride etherate. When a substituent is present at position 3 of the indole, attack is directed to position 2 of the indole nucleus.

Keywords: 2-alkyl-3-hydroxyphthalides, 2-alkyl-3-(indol-3-yl)-1,3-dihydroisoindol-1-ones, indoles, amidoalkylation, rotational isomerism.

The amidoalkylation reaction is widely applied in synthetic organic chemistry [1]. In the indole series this reaction leads, depending on the structure of the substrate, the reactant, and the reaction conditions, to substitution in position 1 [2], 2 [3-5], or 3 [1-3] of the indole molecule, and in strongly acidic medium amidoalkylation is directed to position 5 or 6 [6].

We have found that both indole itself and its 1- and/or 2-substituted derivatives **1** react with 2-alkyl-3-hydroxyphthalides **2** in chloroform at room temperature in the presence of catalytic amounts of boron trifluoride etherate, and attack is directed to position 3 of the indole nucleus.

The obtained compounds **3** are stable crystalline substances, in the ^{1}H NMR spectra of which the signal of the proton in position 3 of the indole nucleus has disappeared and a signal for a benzhydryl proton appears. The properties and spectral characteristics of the obtained compounds are correlated in Tables 1 and 2.

In the ^{1}H NMR spectra of compounds **3a-d,h-j** a double set of portions of signals of comparable intensity was observed, and the greatest difference in values of the chemical shifts of the two sets of signals was observed for the protons in position 3 of the isoindolone and the methyl group in position 2 of the indole (see Table 2). In the spectra of compounds **3k-o** the intensity of the second set of signals was significantly less, and in the spectra of the remaining compounds only one set of signals was present. This doubling is impossible to explain by a competing attack at position 1 of indole, since it is also observed in the case of N-methyl derivatives of indole (compounds **3i-k,m,o**).

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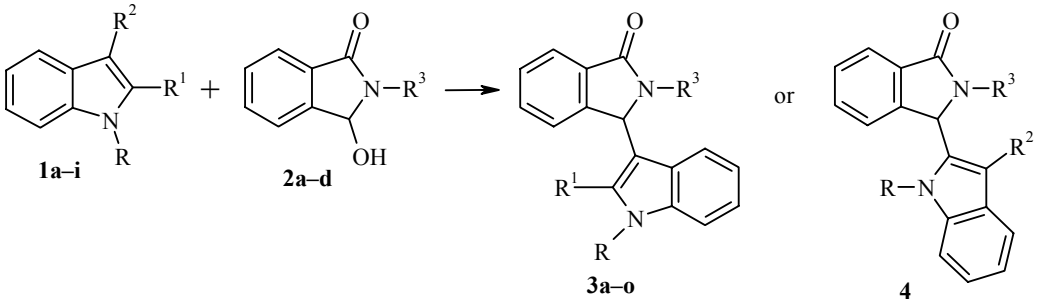
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 847-852, June, 2009. Original article submitted March 11, 2008.



1a–i **2a–d** **3a–o** **4**

	R	R^1	R^2	R^3
1a	H	Me	H	
1b	Me	H	H	
1c	H	H	H	
1d	Me	Me	H	
1e	H	*p*-MeC_6H_4	H	
1f	Me	*p*-MeC_6H_4	H	
1g	H	*p*-ClC_6H_4	H	
1h	Me	Ph	H	
1i	H	H	Me	
2a				$(CH_2)_2CHMe_2$
2b				*c*-C_6H_{11}
2c				$(CH_2)_3OBu$
2d				CH_2CH_2Ph
3a	H	Me		$(CH_2)_2CHMe_2$
3b	H	Me		*c*-C_6H_{11}
3c	H	Me		$(CH_2)_3OBu$
3d	H	Me		CH_2CH_2Ph
3e	Me	H		$(CH_2)_2CHMe_2$
3f	H	H		$(CH_2)_2CHMe_2$
3g	H	H		$(CH_2)_3OBu$
3h	Me	Me		$(CH_2)_2CHMe_2$
3i	Me	Me		*c*-C_6H_{11}
3j	Me	Me		CH_2CH_2Ph
3k	H	*p*-MeC_6H_4		$(CH_2)_2CHMe_2$
3l	H	*p*-MeC_6H_4		*c*-C_6H_{11}
3m	Me	*p*-MeC_6H_4		$(CH_2)_2CHMe_2$
3n	H	*p*-ClC_6H_4		*c*-C_6H_{11}
3o	Me	Ph		*c*-C_6H_{11}
4	H	Me		CH_2CH_2Ph

It is known that in a series of indole derivatives a rearrangement of the Wagner-Meerwein type may take place in acidic media, occasionally under very mild conditions, as a result of which migration occurs of a group from position 3 to position 2 of indole, and a substituent from position 2 may transfer to position 3 [3]. To check this hypothesis we carried out the interaction of the isomeric 2-methylindole (**1a**) and 3-methylindole (**1i**), and also 1,2-dimethylindole (**1d**), with 3-hydroxy-2-phenylethylphthalide (**2d**). In the ^{1}H NMR spectra of the obtained compounds **3d,j** two sets of signals were observed, but in the spectrum of compound **4** there was only one set of signals. The spectra of isoindolones **3d** and **4** differed significantly from one another and contained no common signals (see Table 2). The sole signal for the methyl group in the spectrum of compound **4** was found at 2.15-2.45 ppm (br. s), and in the spectra of compounds **3d,j** the methyl group was displayed as two signals at 1.60-1.65 and 2.50-2.55 ppm. Therefore isomerization does not occur in the course of the reaction being studied.

TABLE 1. Characteristics of the Obtained Compounds **3, 4**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3a	$C_{22}H_{24}N_2O$	79.69 / 79.48	7.08 / 7.28	8.31 / 8.43	182-185	48
3b	$C_{23}H_{24}N_2O$	80.04 / 80.20	7.24 / 7.02	8.00 / 8.13	244-245	70
3c	$C_{24}H_{28}N_2O_2$	76.77 / 76.56	7.30 / 7.50	7.32 / 7.44	140-142	34
3d	$C_{25}H_{22}N_2O$	82.03 / 81.94	6.15 / 6.05	7.75 / 7.64	192-195	55
3e	$C_{22}H_{24}N_2O$	79.75 / 79.48	7.05 / 7.28	8.37 / 8.43	125-127	32
3f	$C_{21}H_{22}N_2O$	79.54 / 79.21	7.10 / 6.96	8.78 / 8.80	158-160	62
3g	$C_{23}H_{26}N_2O_2$	76.54 / 76.21	7.37 / 7.23	7.71 / 7.73	128-130	46
3h	$C_{23}H_{26}N_2O$	79.75 / 79.73	7.92 / 7.56	8.13 / 8.09	137-139	66
3i	$C_{24}H_{26}N_2O$	80.50 / 80.41	7.27 / 7.31	7.86 / 7.81	176-178	40
3j	$C_{26}H_{24}N_2O$	82.40 / 82.07	6.57 / 6.36	7.28 / 7.36	149-151	84
3k	$C_{28}H_{28}N_2O$	82.14 / 82.32	6.99 / 6.91	6.85 / 6.86	267-269	56
3l	$C_{29}H_{28}N_2O$	83.02 / 82.82	6.59 / 6.71	6.60 / 6.66	302-304	70
3m	$C_{29}H_{30}N_2O$	82.52 / 82.43	7.30 / 7.16	6.60 / 6.63	138-140	50
3n	$C_{28}H_{25}ClN_2O$	76.10 / 76.27	5.52 / 5.71	6.40 / 6.35	297-298	58
3o	$C_{29}H_{28}N_2O$	82.99 / 82.82	6.97 / 6.71	6.58 / 6.66	181-182	64
4	$C_{25}H_{22}N_2O$	82.02 / 81.94	6.28 / 6.05	7.64 / 7.64	198-201	54

Probably in this case we are dealing with inhibition of internal rotation around the indole C-3 and isoindolone C-3 σ-bond. In reality in the spectra of the compounds in which there is no substituent in position 2 of the indole nucleus (**3e-g**) steric difficulties are insignificant and we are observing the sole set of signals in the spectra. If there is a bulky aryl group in position 2 of the indole (compounds **3k-o**), rotation is impeded or impossible, and probably as a result of significant steric hindrance one of the possible rotational isomers exists preferentially. Consequently the intensity of the signals of the second rotational isomer in the ^{1}H NMR spectra is small. In the presence of a methyl group in position 2 of the indole (compounds **3a-d,h-j**) the existence of both rotational isomers is possible, but the internal rotation is hindered or impossible, and both rotational isomers are clearly displayed in the spectra in comparable amounts.

There was no temperature dependence in the spectra of compounds **3a,b,d,h,j** obtained in DMSO-d_6 at temperatures of 20, 40, and 60°C, therefore the barrier to rotation around the σ-bond from C-3 in the indole to C-3 in the indolone is fairly high.

We were unsuccessful in reacting 2-(*m*- and *p*-nitrophenyl)indoles under the given conditions due to their low reactivity, and in the case of 2-(*m*- and *p*-methoxyphenyl)indoles the reaction products proved to be contaminated to a significant extent by starting indoles due to the low solubility of the reaction products and of the starting materials.

TABLE 2. ^{1}H NMR Spectra of Compounds **3, 4** at 20°C

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
3a	0.8-0.9 (6H, 2d, *J* ≈ 7, CH(C<u>H</u>$_3$)$_2$); 1.3-1.5 (2H, m, CCH$_2$C); 1.5-1.6 (1H, m, C<u>H</u>(CH$_3$)$_2$); 1.65, 2.65 (3H, 2s, ~1:4, CH$_3$); 2.7-2.9 (1H, m, NCH$_2$); 3.6-3.8 (1H, m, NCH'$_2$); 5.8, 6.1 (1H, 2s, ~ 4:1, H-3); 6.2-7.8 (8H, m, arom.); 11.0 (1H, br. s, NH)
3b	0.8-2.0; 1.7 (10 + 0.6H, br. m, 5CH$_2$ + high field portion CH$_3$C); 2.7 (2.4H, s, low field portion CH$_3$C); 3.6-3.8 (1H, br. m, NC<u>H</u>(CH$_2$)$_5$); 5.9, 6.15 (1H, 2 s, ~4:1, H-3); 6.3-7.8 (8H, m, arom.); 10.9 (1H, br. s, NH)
3c	0.85 (3H, t, *J* ≈ 7, CH$_3$); 1.1-1.5 (4H, m, 2CH$_2$); 1.5-1.85, 1.7 (~2.5H, m, CH$_2$ + high field portion H-3); 2.6 (~2.5H, s, low field portion CH$_3$); 2.8-3.0 (1H, m, NCH$_2$); 3.2-3.4 (4H, m, 2CH$_2$O); 3.6-3.9 (1H, m, NCH'$_2$); 5.8, 6.1 (1H, 2s, ~5:1, H-3); 6.2-7.8 (8H, m, arom.); 11.0 (1H, br. s, NH)
3d	1.65, 2.5 (3H, 2s, ~1:5, CH$_3$C); 2.7 (1H, m, C<u>H</u>$_2$C$_6$H$_5$); 3.0 (1H, m, C<u>H</u>'$_2$C$_6$H$_5$); 3.4 (1H, m, NCH$_2$); 3.9 (1H, m, NCH'$_2$); 5.5, 5.8 (1H, 2s, ~5:1, H-3); 6.2 - 7.9 (13H, m, arom.); 10.8 (1H, br. s, NH)
3e	0.8-0.9 (6H, 2d, *J* ≈ 7, CH(C<u>H</u>$_3$)$_2$); 1.4 (2H, m, CCH$_2$C); 1.5 (1H, m, C<u>H</u>(CH$_3$)$_2$); 2.7-2.9 (1H, m, NCH$_2$); 3.7-3.8 (1H, m, NCH'$_2$); 3.85 (3H, s, CH$_3$N); 5.85 (1H, s, H-3); 6.55-7.8 (9H, m, arom.)
3f	0.8-0.9 (6H, 2d, *J* ≈ 7, CH(C<u>H</u>$_3$)$_2$); 1.4 (2H, m, CCH$_2$C); 1.45-1.6 (1H, m, C<u>H</u>(CH$_3$)$_2$); 2.7-2.9 (1H, m, NCH$_2$); 3.7-3.9 (1H, m, NCH'$_2$); 5.85 (1H, s, H-3); 6.5-7.8 (9H, m, arom.); 11.1 (1H, br. s, NH)
3g	0.85 (3H, t, *J* ≈ 7, CH$_3$,); 1.1-1.5 (4H, m, 2CH$_2$); 1.5-1.85 (2H, m, CH$_2$); 2.8-3.0 (1H, m, NCH$_2$); 3.2-3.4 (4H, m, 2CH$_2$O); 3.6-3.9 (1H, m, NCH'$_2$); 5.9 (1H, s, H-3); 6.5-7.8 (9H, m, arom.); 11.1 (1H, br. s, NH)
3h	0.8, 0.9 (6H, 2d, *J* ≈ 7, CH(C<u>H</u>$_3$)$_2$); 1.4 (2H, m, CCH$_2$C); 1.5 (1H, m, C<u>H</u>(CH$_3$)$_2$); 1.7, 2.7 (3H, 2s, ~1:4, CH$_3$C); 2.75 (1H, m, NCH$_2$); 3.75 (1H, m, NCH'$_2$); 3.6, 3.8 (3H, 2 s, ~ 1:4, CH$_3$N); 5.9, 6.1 (1H, 2 s, ~4:1, H-3); 6.2-7.8 (8H, m, arom.)
3i	0.8-2.0; 1.7 (10 + 0.6H, br. m + s, 5CH$_2$ + high field portion CH$_3$C); 2.7 (2.4H, s, low field portion CH$_3$C); 3.6, 3.8 (3H, 2s, ~1:4, CH$_3$N); 3.7 (1H, br. m, NC<u>H</u>(CH$_2$)$_5$); 5.9, 6.15 (1H, 2s, ~4:1, H-3); 6.3-7.8 (8H, arom.)
3j	1.6, 2.55 (3H, 2s, ~1:4, CH$_3$C), 2.65-2.8 (1H, m, C<u>H</u>$_2$C$_6$H$_5$), 2.85-3.0 (1H, m, C<u>H</u>'$_2$C$_6$H$_5$), 3.05-3.2 (1H, m, NCH$_2$), 3.6-3.85 (3H, 2s, ~1:4, CH$_3$N), 3.85-3.95 (1H, m, NCH'$_2$), 5.7, 6.0 (1H, 2s, H-3); 6.2-7.8 (13H, m, arom.)
3k	0.6-0.7 (6H, 2t, *J* ≈ 7, CH(C<u>H</u>$_3$)$_2$); 0.85-1.2 (2H, m, CCH$_2$C); 1.2-1.4 (1H, m, C<u>H</u>(CH$_3$)$_2$); 2.45 (3H, s, CH$_3$); 2.55-2.65 (1H, m, NCH$_2$); 3.55-3.75 (1H, m, NCH'$_2$); 5.9, 6.2 (1H, 2 s, ~6:1, H-3); 6.3-7.9 (12H, m, arom.); 11.4 (1H, br. s, NH)
3l	0.7-1.6 (10H, br. m, 5CH$_2$); 2.4 (3H, s, CH$_3$); 3.6-3.8 (1H, br. m, NC<u>H</u>(CH$_2$)$_5$); 5.95, 6.2 (1H, 2s, ~ 40:1, H-3); 6.4-7.8 (12H, m, arom.); 11.3 (1H, br. s, NH)
3m	0.7-0.8 (6H, 2d, *J* ≈ 7, CH(C<u>H</u>$_3$)$_2$); 0.9-1.2 (2H, m, CCH$_2$C); 1.2-1.4 (1H, m, C<u>H</u>(CH$_3$)$_2$); 2.45 (3H, s, CH$_3$C); 2.55-2.7 (1H, m, NCH$_2$); 3.7 (3H, s, CH$_3$N); 3.7-3.8 (1H, m, NCH'$_2$); 5.55, 6.1 (1H, 2s, ~20:1); 6.3-7.8 (12H, m, arom.)
3n	0.7-1.6 (10H, br. m, 5CH$_2$); 3.6-3.8 (1H, br. m, NC<u>H</u>(CH$_2$)$_5$); 5.95, 6.25 (1H, 2 s, ~20:1, H-3); 6.4-7.8 (12H, m, arom.); 11.4 (1H, br. s, NH)
3o	0.8-1.7 (10H, br. m, 5CH$_2$); 3.6-3.8 (4H, br. m + s, NC<u>H</u>(CH$_2$)$_5$) + CH$_3$); 5.6, 6.25 (1H, 2 s, ~40:1), 6.5-7.8 (13H, br. m, arom.)
4	2.15-2.45 (3H, br. s, CH$_3$); 2.7-2.8 (1H, m, C<u>H</u>$_2$C$_6$H$_5$); 2.9-3.0 (1H, m, C<u>H</u>'$_2$C$_6$H$_5$); 3.05-3.15 (1H, m, NCH$_2$); 3.95-4.1 (1H, m, NCH'$_2$); 5.7 (1H, s, H-3); 6.9-7.8 (13H, m, arom.); 10.3 (1H, br. s, NH)

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Bruker AM 360 instrument (360 MHz) in DMSO-d$_6$, internal standard was TMS. A check on the progress of reactions was effected by TLC on Merck Silicagel 60 F_{254} plates.

The initial 2-alkyl-3-hydroxyphthalides **2a-d** were obtained by the procedure of [7].

Preparation of Compounds 3 and 4 (General Method). A small excess (~5%) of 2-alkyl-3-hydroxyphthalide **2a-d** was added to a solution or suspension of indole **1a-i** (1 mmol) in $CHCl_3$ (10ml) at room temperature in one batch with stirring. Boron trifluoride etherate (~10 mol %) was then added. The suspension of the initial indole, if still present, dissolved after several minutes, the solution became colored, and water separated as an emulsion. The mixture was stirred for 2-3 h, then left overnight. If the reaction product separated as a solid it was filtered off, washed with $CHCl_3$, with alcohol, with ether, and dried. Otherwise the reaction mixture was passed through a layer of silica gel (Merck, for column chromatography, 0.035-0.070 nm, pore diameter 6 nm, 500 m^2/g) (eluent $CHCl_3$), the eluate was evaporated in vacuum, the residue was triturated with ether (in the case of N-methylindoles with hexane), the solid was filtered off, washed with ether or hexane, and dried.

REFERENCES

1. H. E. Zaugg, *Synthesis*, 85 (1984).
2. V. G. Kartsev, in: V. G. Kartsev and G. A. Tolstikov (editors), *Chemistry and Biological Activity of Synthetic and Natural Compounds. Nitrogen Heterocycles and Alkaloids*, Vol. 1, [in Russian], Iridium Press, Moscow (2001), p. 97.
3. L. A. Sviridova, S. V. Afanas'eva, G. A. Golubeva, P. B. Terent'ev, and Yu. G. Bundel', *Khim. Geterotsikl. Soedin.*, 1207 (1990). [*Chem. Heterocycl. Comp.*, **26**, 1008 (1990)].
4. H. Heaney and K. F. Shuhaibar, *Synlett*, 47 (1995).
5. V. Bocchi, G. Casnati, and G. Gardini, *Tetrahedron Lett.*, 683 (1971).
6. A. Muminov, A. G. Yudin, E. Ya. Zinchenko, N. N. Romanova, and A. N. Kost, *Khim. Geterotsikl. Soedin.*, 1218 (1985). [*Chem. Heterocycl. Comp.*, **21**, 1012 (1985)].
7. R. Scheffold and P. Dubbs, *Helv. Chim. Acta*, **50**, 798 (1967).