Chemistry of Indoles Carrying a Basic Function, Part 3[1)]

Synthesis of Spiro[cyclopropane-1,3′[3*H*]indol]-2′(1′*H*)-ones with Antihypoxic Effects

István Moldvai, Eszter Gács-Baitz, Mihály Balázs, Mária Incze, and Csaba Szántay*

Central Research Institute for Chemistry of the Hungarian Academy of Sciences, H-1525 Budapest, POB 17, Hungary

Key Words: *oxindoles; isatinylidenes; spiro-cyclopropanes; hypoxia; brain edema*

Summary

Hydroxyindolones (**1–6**, **15–16**) were transformed into isatinylidenes (**7**, **9–13**, **17–19**) by dehydration with 4-toluenesulfonic acid. The dimer-type compounds (**14**, **20**) were also isolated in a few cases. The obtained isatinylidenes were transformed into 3-spiro-cyclopropane-oxindoles (**21–32**) with dimethyloxosulfonium methylide. Compound **22** shows protective effects against hypobaric hypoxia and triethyltin induced brain edema.

Introduction

As advances in the medical treatment give rise to extended life expectancy, diseases that affect the growing population of elderly individuals will increase in prevalence. The typical symptoms of these diseases are connected with cognitive and neurological deficiencies. Several strategies have been employed to ameliorate these complex diseases. The applied drugs encompass vasoactive drugs like vincamine and its derivatives; "metabolic enhancers" like some ergot alkaloids; neurotransmitter precursors like *l*-DOPA, choline, and 5-hydroxytryptamine; transmitter metabolizing enzyme inhibitors like physostigmine, and neuropeptides such as adrenocorticotropic hormone and vasopressin-related peptides. The indole unit can often be found among the efficacious drugs indicating the importance of this family of compounds.

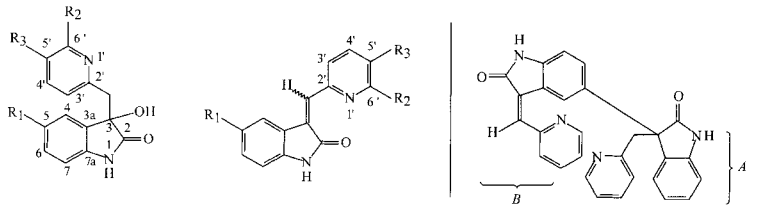
At the research level, indoles possessing a spiro C3 atom may display several types of biological activity[1]. Although some representatives with a cyclopropane moiety can be found in the literature[1], compounds containing nitrogen incorporated in a ring with a C_2-distance commensurable with tryptophan or tryptamine have not yet been described. As a part of our continued interest in searching for new routes leading to this type of compounds, we intended to prepare 3-spiro-cylopropane-oxindoles with a basic nitrogen function in order to establish their biological properties.

Chemistry

Synthesis of Isatinylidines

Isatinylidene derivatives served as starting materials for the synthesis of 3-spiro-cyclopropane-oxindoles. To obtain this type of compounds, Akkerman and Veldstra[2] first applied the Ladenburg reaction in preparing hydroxyindolone **1** (Scheme 1) as the main product (74%). In the side reaction isatinylidine **7** was formed in a small quantity (2%). By extending this method, nicotinic acid derivatives **8** and **11** were also prepared[2,3]. Using a different route, isatinylidine **7** was also obtained starting from oxindole and 2-pyridinecarboxyaldehyde[4]. In order to avoid using sensitive aldehyde analogues, the preparation of isatinylidenes from hydroxyindoles seemed to be promising. Based on the above mentioned method compounds **1–6** and **15–16** (Scheme 1 and 3) were prepared in a straightforward way. Several reagents[5] were tested unsuccessfully for the transformation of hydroxyindolones into isatinylidenes, but 4-toluenesulfonic acid proved to be suitable for the dehydration. Starting from hydroxyindolone **1**, isatinylidene **7** was obtained in 44% yield as yellow crystals. The *Z*-configuration for **7** was proved by NMR methods (see below), while the presence of the *E*-isomer could not be detected. However, in a dimeric minor product (**14**, 11%) the double bond in the isatinylidene unit has *E*-geometry.

The stereoselective formation of **7** can be interpreted by stereoelectronic factors. The Dreiding model of **1** indicates two preferred states of conformation for an E_2-type trans-axial water elimination (c_1 and c_2, see Scheme 2). Assuming the same steric arrangement of the carbonyl and the pyridyl



	R_1	R_2	R_3
1	H	H	H
2	Br	H	H
3	NO_2	H	H
4	Br	H	CO_2Me
5	Br	H	Me
6	Br	Me	H

	R_1	R_2	R_3	Z:E (%)
7	H	H	H	100:0
8	H	H	CO_2H	
9-E	Br	H	H	0:100
9-Z/E	Br	H	H	90:10
10	NO_2	H	H	0:100
11	Br	H	CO_2Me	13:87
12	Br	H	Me	100:0
13	Br	Me	H	100:0

14

Scheme 1: Structure of compounds **1–14**.

groups as that of the C4-H and pyridyl groups, the *Z*- and *E*-isatinylidenes are expected to be formed in the same ratio. The exclusive formation of the *Z*-isomer can be interpreted by the presence of an intramolecular hydrogen bond between

[1)] Part 2, See: I. Moldvai, Cs. Szántay Jr., Cs. Szántay, *Heterocycles* **1992**, *34*, 219–223.

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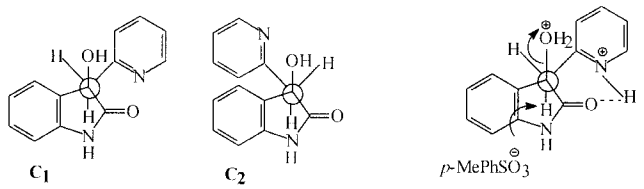


Scheme 2: Stereoselective formation of isatinylidenes.

the protonated pyridyl nitrogen and the carbonyl group in the transition state. The transition state thus requires lower energy level for the c_1 conformer, which determines the configuration of the double bond in the end product. The *Z*-isatinylidenes formed seem to be stable enough to avoid isomerization during the applied chemical reactions.

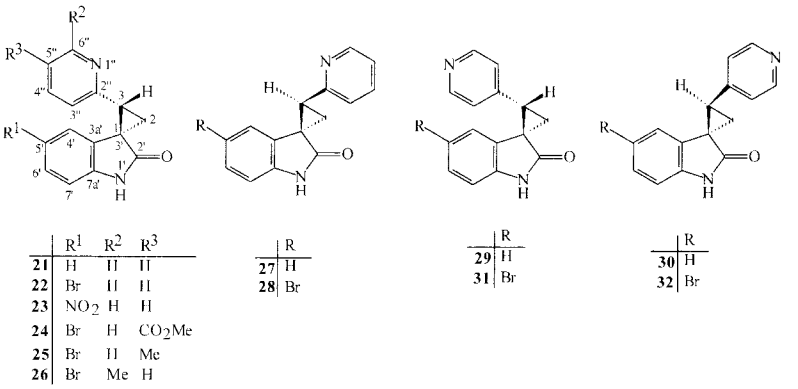
Starting from the C5-brominated hydroxyindolone derivative **2**, the dimerization is obviously prevented and only isatinylidene **9** can be isolated in a good yield (97%). However, the repeated dehydration of **2**, under the same conditions, gave **9** with varying configuration of the double bond. Sometimes the **9-*E*** isomer was formed exclusively, at other times the **9-*Z*** isatinylidene was dominant (**9** ***Z*:*E*** ≈ 90:10%). Moreover, it is to be noted that the **9-*Z*** isomer could be transformed into the 50:50% isomeric mixture by heating the deuterodimethyl sulfoxide solution (80 °C, 20 min) in the NMR tube. A similar, anomalous formation of isatinylidenes was established by an Italian group[6]. They found that isatinylidene derivatives having 2-pyridyl rings were formed as single isomers, while the 3-pyridyl compounds gave mixtures of two isomers. Hydroxyindolone **3** afforded isatinylidene **10** with *E*-configuration in 74% yield. In order to present further details for the stereoselectivity in the formation of isatinylidenes, modified pyridyl derivatives have also been prepared. Considering the biological interest, the Ladenburg reaction was repeated by reacting the 5-bromoisatin with methyl 6-methylnicotinate. At lower temperature (120 °C) hydroxyindolone **4** could be obtained (76% yield). When **4** was allowed to react with 4-toluenesulfonic acid, a hardly separable isatinylidene isomer mixture (**11**) was formed in 65% yield. In this product the *E*-isomer was dominant (*E*:*Z* ≈ 87:13%). Starting from compound **5**, the *Z*-isatinylidene **12** was isolated in 94% yield. The position of the methyl group did not affect the configuration of the double bond in the end product. The structure isomer **6** gave the same result (**13**; 79%). Considering the importance of the hydrogen bond in the transition state one can assume that, in addition to the intramolecular hydrogen bond (see Scheme 2), the nitrogen of the pyridyl group can also participate in an intermolecular hydrogen bond with the carbomethoxy group, changing considerably the transition state and resulting in an opposite stereoselectivity of the double bond.

For further evidence, the 4-pyridyl derivatives (**15** and **16**; Scheme 3) were also examined.

Upon treatment of **15**[7] with 4-toluenesulfonic acid, three components were detected by TLC in the reaction mixture, which were separated by column chromatography. *E*-isatinylidene (**17**, 32%) and a dimer (**20**, 48%) have been obtained as main products. The *Z*-isomer **18** was formed as a minor product (5% yield). During the dehydration of the C5-bromo analogue **16**, isatinylidene **19** was formed (75% yield) as a mixture (*E*:*Z* ≈ 35:65 %). The lack of intramolecular hydrogen bonding in the transition states can be considered as a decisive factor for the composition of products.

Synthesis of 3-Spiro-cyclopropane-oxindoles

The isatinylidenes discussed above served as starting materials for the preparation of cyclopropane derivatives. Corey and Chaykovsky demonstrated[8] that dimethyloxosulfonium methylide reacts with α,β-unsaturated ketones resulting in cyclopropyl ketones. We assumed that this procedure can be extended to our isatinylidenes, i.e. they behave as Michael receptors having a structural element similar to the α,β-unsaturated ketones. Reacting isatinylidene **7** with dimethyloxosulfonium methylide (generated from trimethyl-sulfoxonium iodide with sodium hydride) in DMF (2 h, 0 °C → room temp.) 3-spiro-cyclopropane-oxindole **21** (Scheme 4.) was obtained as crystals in 43 % yield. Chromatography of the mother liquor afforded the other diastereoisomer **27** in traces (0.6%) beside **21** (5.9%).



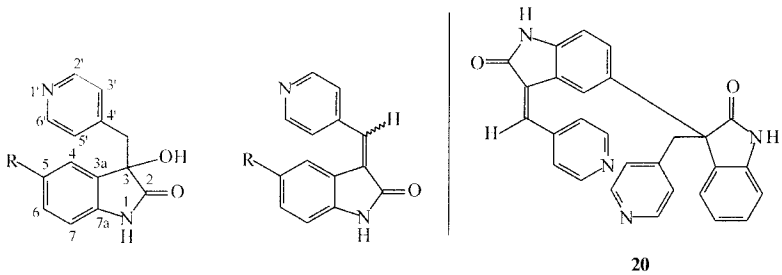
	R^1	R^2	R^3
21	H	H	H
22	Br	H	H
23	NO_2	H	H
24	Br	H	CO_2Me
25	Br	H	Me
26	Br	Me	H

	R
27	H
28	Br

	R
29	H
31	Br

	R
30	H
32	Br

Scheme 4: Structure of spiro compounds **21–32**.



	R
15	H
16	Br

	R	Z:E (%)
17	H	0:100
18	H	100:0
19	Br	65:35

20

Scheme 3: Structure of compounds **15–20**.

The reactions of α-pyridyl analogues **9–13** gave almost the same results. The main products were isolated by fractional crystallization (**9**→**22**, 50 %; **10**→**23**, 35%; **11**→**24**, 24%; **12**→**25**, 52 %; **13**→**26**, 52 %). The minor diastereomeric bromo derivative was also isolated (**28**, 5%).

As for the 4-pyridyl derivatives, *E*-isatinylidene **17** showed similar chemical behaviour to *Z*-isatinylidene **7**. The main isomer **29** was obtained in 43% yield, while the minor diastereoisomer **30** was isolated in about 1% yield. Bromo derivatives **31** and **32** were also prepared by the above procedure.

Structure Determination by NMR Methods

The ^{13}C NMR data of compounds **1–32** are collected in Tables **1–3**, the proton parameters are given in the experimental part (Tables **4–6**). Complete proton assignments were obtained by homonuclear decoupling experiments. For compounds **6**, **13**, **14**, and **26** correlation between identified protons and proton-bearing carbons was obtained by hetero-correlated (HETCOR) experiments, while long-range hetero-correlated (INEPT long-range) experiments afforded the assignment of quaternary carbons. The new structure found for **14** was corroborated also by applying a two-dimensional INEPT method[9], while the constitution of **20** was established by analogy with the thoroughly studied **14**.

The stereochemistry was mostly inferred from results of NOE difference experiments. *E* and *Z* isatinylidenes gave characteristically different NOE spectra. Irradiation of the olefinic proton (7.61 ppm) in the **9-*E*** isomer gave signal enhancement of the 3′-H proton only. Similarly, the selective saturation of the 4-H resonance (9.27 ppm) enhanced the 3′-H (7.76 ppm) and 6′-H (8.88 ppm) pyridyl resonances, and no NOE effect was observed between 4-H and the olefinic proton. On the contrary, in the **9-*Z*** isomer a sizeable NOE effect was expected between the above mentioned protons. Since these two protons appeared together in the proton spectrum of the $CDCl_3$ + DMSO-d_6 solution, the NOE connectivities, in agreement with expectations, were detected in deuteroacetonitrile solution (olefinic proton: 7.76 ppm, 4-H: 7.90 ppm).

While the chemical shift of the olefinic protons did not reflect *E*:*Z* isomerism (7.61 ppm in **9-*E*** and 7.66 ppm in **9-*Z***), some of the aromatic protons were considerably deshielded in comparison with the corresponding protons of the other isomer. The 9.10 ppm chemical shift value of 3′-H proton in the **9-*Z*** isomer can be attributed to the anisotropy effect of the carbonyl group. A similar value (9.05 ppm) was found for 3′-H in compound **7**, which, in agreement with the NOE results reveals the same (*Z*) stereochemistry of the double bond. The 4-H proton is significantly deshielded in **9-*E*** (9.27 ppm), and similarly large chemical shift values were found

Table 1: ^{13}C-NMR chemical shifts[a-b] of hydroxyindolones **1–6** and **15–16** in $CDCl_3$+DMSO-d_6. ([a]The δ values are in ppm from internal TMS. [b]Signals marked with identical symbols are interchangeable.)

	1	**2**	**3**	**4**	**5**	**6**	**15**	**16**
2-C	178.89	178.38	177.29	178.45	178.37	177.53	178.46	178.44
3-C	76.02	75.98	73.86	76.29	76.00	75.26	76.03	76.37
3a-C	130.95	133.26	129.98	132.92	133.41	132.52	130.38	132.57
4-C	124.29	127.45	118.40	127.45	127.42	126.62	124.35	127.41
5-C	121.38	113.37	140.45	114.49	113.34	112.82	121.31	113.88
6-C	128.79	131.33	122.80	132.05	131.28	130.54	128.98	131.81
7-C	109.71	111.27	107.75	111.82	111.24	110.58	109.52	111.55
7a-C	141.35	140.71	146.04	140.27	140.72	139.61	141.50	140.62
CH_2	44.51	44.64	42.15	44.07	44.12	42.46	42.92	43.29
2′-C	156.39	155.99	153.94	161.11	152.95	154.87	148.49	148.80
3′-C	124.65	124.58	124.06	124.42	123.95	120.69	125.53	125.63
4′-C	136.15	136.00	134.61	137.60	136.54	135.92	144.18	143.78
5′-C	121.74	121.75	120.20	124.48	130.83	120.63	125.53	125.63
6′-C	147.99	148.18	145.43	149.53	148.45	155.94	148.49	148.80
CO_2Me				165.50				
$CO_2\mathit{Me}$				52.38				
Me					17.81	23.20		

Table 2: ^{13}C-NMR chemical shifts[a–b] of isatinylidenes **7**, **9–14** and **17–20** in $CDCl_3$+DMSO-d_6. ([a]The δ values are in ppm from internal TMS. [b]Signals marked with identical symbols ($^{+,o,*}$) are interchangeable.)

	7	**9**	**10**	**11**	**13**	**14**		**17**	**18**	**19**		**20**	
						Part A	*Part B*			*major*	*minor*	*Part A*	*Part B*
2-C	167.21	166.71	168.98	167.05	164.98	180.05	170.48	169.20	167.34	166.89	168.45	178.48	168.48
3-C	129.72	126.40^{o}	126.92	127.35	126.51	57.04	129.94	131.15	131.50	133.18	130.12	56.85	130.44*
3a-C	124.30	128.40^{o}	121.21	123.39	124.67	133.76	121.87	120.68	124.08	126.08	126.60	132.82	120.42
4-C	119.91*	122.96	123.24	129.18	121.18	125.79	127.03	121.56*	120.06*	123.08	125.67	125.20	121.82
5-C	121.32*	113.50	141.32	111.48	111.75	121.32	131.87	123.20*	121.83*	113.85	113.50	121.62	130.50*
6-C	129.64	132.00	128.69	131.68*	130.19	127.70	129.46	130.94	130.39	132.44*	130.43^{o}	128.23	129.45
7-C	109.70	111.37	108.91	109.68	109.62	109.55	109.76	110.66	110.09	111.57	112.14	109.80	110.30
7a-C	141.46	140.43	148.55	141.45	138.56	142.12	142.60	143.26	141.30	140.48	142.50^{+}	142.13^{+}	141.78^{+}
CH_2						45.22						42.08	
=CH	135.61	135.89	135.94*	131.58*	135.75		133.73	131.82	132.41	134.09*	133.37^{o}		131.91
2′-C	152.50	152.27	151.99	154.88	149.44	156.82	153.41	149.86	149.37	149.83	150.36	148.63	149.97
3′-C	126.48	126.60	126.23	126.43	122.18	123.74	127.68	123.24	124.92	124.84	122.52	125.19	122.76
4′-C	136.01	137.56	136.80*	136.05	134.82	135.55	136.58	143.49	141.34	140.76	142.47^{+}	144.93	142.69^{+}
5′-C	123.66	123.94	124.17	124.66	121.99	121.44	123.40	123.24	124.92	124.84	122.52	125.19	122.76
6′-C	149.08	149.35	148.94	148.10	155.71	148.40	149.53	149.86	149.37	149.83	150.36	148.63	149.97
$\underline{C}O_2Me$				162.89									
$CO_2\underline{Me}$				50.67									
Me					22.23								

Table 3: ^{13}C-NMR chemical shifts[a–e] of 3-spiro-cyclopropane-oxindoles **21–32**. ([a]The δ values are in ppm from internal TMS. [b]Signals marked with identical symbols are interchangeable. [c]In $CDCl_3$ solution. [d]In $CDCl_3$+DMSO-d_6 solution. [e]In $CDCl_3$+MeOD solution.)

	21[c]	**27**[d]	**22**[e]	**28**[d]	**23**[d]	**24**[d]	**25**[c]	**26**[c]	**29**[c]	**30**[c]	**31**[d]	**32**[d]
1-C/3′-C	35.71	34.06	35.76	33.81	33.88	36.70	35.74	35.84	33.65	34.28	33.20	34.00
2-C	21.23	21.86	21.59	21.68	19.58	21.61	21.83	21.58	21.41	21.99	20.95	21.46
3-C	38.03	39.09	37.80	39.21	36.76	38.24	38.40	38.51	34.54	36.95	34.30	36.30
2′-C	178.51	175.71	177.52	174.55	175.04	176.74	177.89	177.32	178.20	174.46	176.68	174.03
3a′-C	127.77	130.73	129.60	132.98	126.63	129.39	130.09	129.86	126.77	130.39	128.83	132.45
4′-C	121.81*	121.57*	124.93	121.87*	115.96	124.92	124.76	125.71	121.71*	122.21	123.10	121.46
5′-C	121.49*	118.51	114.23	113.36	139.77	113.60	114.19	113.36	120.72*	118.72	113.14	113.44
6′-C	126.77	126.83	129.67	129.22	121.93	129.55	129.37	128.90	127.21	127.34	129.37	129.38
7′-C	109.79	109.67	111.20	110.92	107.32	111.11	110.89	110.59	110.07	109.56	111.00	110.94
7a′-C	141.46	141.22	140.52	140.78	146.99	141.34	140.32	140.75	141.28	140.35	140.89	140.62
2″-C	154.89	154.69	153.91	154.28	152.08	159.28	151.34	153.45	149.56	149.37	149.55	148.76
3″-C	125.53	123.63	125.68	123.45	123.53	125.39	125.23	121.84	125.10	124.32	124.41	124.15
4″-C	136.34	135.84	137.59	135.62	134.87	137.31	137.15	136.39	144.59	143.28	143.38	143.17
5″-C	122.23*	122.00*	122.90	121.58*	120.75	124.38	132.07	121.37	125.10	124.32	124.41	124.15
6″-C	148.88	148.89	148.13	148.59	146.84	149.80	149.17	157.24	149.56	149.37	149.55	148.76
CO_2Me						165.48						
CO_2*Me*						52.35						
Me							18.21	24.06				

for compound **10** (10.15 ppm) and for the major isomer of **11** (9.19 ppm). The unusual values may be explained by the anisotropy effect of the 2-pyridyl ring assuming coplanarity between the two aromatic rings in the favoured rotational conformation of the pyridyl ring.

The proton spectra were quite different for the 4-pyridyl derivatives where we had both *E* and *Z* isomers for the unsubstituted (**17** and **18**) and for the 5-bromo compounds (**19** minor and **19** major, respectively). The chemical shifts of 4-H (7.40–7.64 ppm) and the olefinic protons (7.38–7.72 ppm) barely differed in the stereoisomers for both pairs. These values suggest that in the prefered conformation the 4-pyridyl ring is twisted away from coplanarity. Moreover, the presence of the bromine substituent in C-5 position does not affect the conformational behaviour of the 4-pyridyl derivatives (cf. **17** with **19** minor and **18** with **19** major).

Similarly to the spectral characteristics of substances **7–13** and **17–19**, different values were found also for the 4-H proton in the isatinylidene part of the dimers with 2-pyridyl (**14**) and 4-pyridyl (**20**) units (9.05 ppm and 7.39 ppm, respectively).

Considerably deshielded 4-H protons of further 2-pyridylisatinylidenes with *E*-configuration were also reported in the literature[6,10] (8.90 ppm in the 5,6-dimethoxy derivative and 9.10 ppm in the parent compound having unsubstituted A-ring). On the contrary, the chemical shift of 4-H proton in the *E*-isomer of 3-pyridyl derivatives was always ca. 7.4 ppm[6]. The different behaviour of 2-pyridylisatinylidenes in comparison with the 3-pyridyl and 4-pyridyl analogues may be explained by a secondary non-bonded interaction between the nitrogen and the "loose" proton at position 4, by which the coplanar arrangement of the aromatic rings in the 2-pyridyl derivatives is stabilized.

As the proton chemical shifts of the two diastereomeric 3-spiro-cyclopropane-oxindoles were rather similar, stereochemical elucidation of the substituted cyclopropyl ring required NOE measurements. For compound **21–26**, **29**, and **31** irradiation of the 3-H resonance gave NOE enhancement on the signal of 2_β-H only, furthermore, NOE connection was observed between 2_α-H and 4′-H protons. In the compounds with inverse stereochemistry (**27–28**, **30**, and **32**) irradiation of the 3-H proton resulted in signal enhancements of the resonances attributed to 4′-H and 2_α-H. All these findings established the steric arrangements as depicted in Scheme 4. Two further facts are in consonance with the given stereochemical assignment: a) the ca. 3–4 ppm shielding of 3a′-C in compounds **21**, **22**, **29**, and **31** (in comparison with the corresponding values of **27**, **28**, **30**, and **32**, respectively), b) the ca. 3 ppm shielding of 2′-C in compounds **27**, **28**, **30**, and **32** (vs **21**, **22**, **29**, and **31**, respectively). These upfield shifts are due to the *γ-gauche* effect of the 2-pyridyl or 4-pyridyl substituents.

Biological Characteristics of the New Compounds

Some of these compounds show prevention against hypoxic conditions, in particular compound **22** has characteristic effects. It can protect the effects of hypobaric hypoxia in spontaneously hypertensive rats (ED_{50}: 7.4 mg/kg), furthermore in a dose of 31.5 mg/kg p.o. it can produce almost complete protection against triethyltin induced brain edema [11]. Compound **22** shows moderate activity against hypobaric and asphyxic hypoxia, exhibits mild anticonvulsive effect, and it is moderately active in the inhibition of ^{45}Ca-uptake evoked by veratrine.

Acknowledgement

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Experimental Part

Mp('s): Boetius hot-stage apparatus, uncorrected.– IR spectra: Specord IR 75 and Nicolet 205 FT-IR spectrometers, KBr.– NMR spectra: Varian XL-100-15 and Varian XL-400 instruments, (100 and 400 MHz), $SiMe_4$ as an int. standard.– EI mass spectra: AEI-MS-902 spectrometer at 70 eV.

Preparation of hydroxyindolones

Hydroxyindolones **2–6** and **15–16** were prepared according to the literature[2] using the reagent (2- or 4-methylpyridine) as a solvent. The nicotinic acid derivative **4** was prepared in a melt reaction as an exception.

α-(2-Oxo-3-hydroxy-(5-bromo)indolinyl[3])-2-methylpyridine **2** *(general procedure)*

5-Bromoisatin monohydrate (48.8 g; 0.2 M) was suspended in 2-picoline (100 ml) and the mixture was refluxed for 3h. To the hot solution was added ethanol (50 ml), then the mixture was cooled to the room temperature. The crystals were filtered off, washed with ethanol (2 × 20 ml), dried to give **2** (50.9 g; 79.8 %).

α-(2-Oxo-3-hydroxy-(5-bromo)indolinyl[3])-2-methyl-(5-carbomethoxy)-pyridine **4** *(melt-reaction)*

5-Bromoisatin monohydrate (18.75 g; 83 mM) and 6-methylnicotinic acid methyl ester (29.25 g; 129 mM) were melted at 120 °C and the mixture was stirred at 120 °C for 4 h. After cooling, the obtained semisolid crystals were dissolved in a mixture of ethyl acetate and water (600+350 ml). After extraction, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 100 ml). The combined organic phase was washed with water (3 δ 200 ml) and dried (Na_2SO_4). The filtrate was concentrated to about 100 ml and the precipitated crystals were filtered off, washed with cold ethyl acetate (20 ml) and dried to yield **4** (21.95 g; 75.9%).

Synthesis conditions and physical constans for hydroxyindolones **1–6**, **15–16** were collected in Table 4. The following derivatives were also prepared:

α-(2-Oxo-3-hydroxy-(5-nitro)indolinyl[3])-2-methylpyridine **3**
α-(2-Oxo-3-hydroxy-(5-bromo)indolinyl[3]-2,5-dimethylpyridine **5**
α-2(Oxo-3-hydroxy(5-bromo)indolinyl[3]-2,6-dimethylpyridine **6**
α-2(Oxo-3-hydroxyindolinyl[3]-4-methylpyridine **15**
α-2(Oxo-3-hydroxy-(5-bromo)indolinyl[3]-4-methylpyridine **16**

Preparation of isatinylidines

Z-α-Isatinylidene-2-methylpyridine **7** *and 2,3-dihydro-5-(2,3-dihydro-2-oxo-3-(2-pyridylmethyl)-1H-indol-3-yl)-3-(2-pyridylmethylene)-1H-indol-2-one* **14** *(general procedure for preparing monomeric and dimeric compounds)*

4-Toluenesulfonic acid monohydrate (19 g; 0.1 M) was refluxed in benzene (400 ml) using a water-separating device for 1 h, then **1** (9.6 g; 40 mM) was added. The mixture was refluxed for 24 h. After cooling, the mixture was evaporated to dryness under reduced pressure. The residue was dissolved in a mixture of chloroform and water (280 ml/40 ml) and the pH was adjusted to 8 by adding concentrated aqueous ammonium hydroxide solution (10 ml).

Table 4: Synthesis conditions and physical constants for hydroxyindolones **1–6** and **15–16**.

Comp.	Yield (%)	M.p. (°C)	Formula (MW)	IR (ν_{max}) [cm^{-1}]	^{1}H-NMR (δ; ppm; [a]400 MHz, [b]100 MHz, [c]$CDCl_3$+DMSO-d_6, [d]$CDCl_3$)
1	see ref.[12]				[a,c] 3.18 + 3.38 (d each, 2H, J_{gem} = 14 Hz, CH_2), 5.20 (br. s, 1H, OH), 6.7–7.3 (m, 6H, 4-H, 5-H, 6-H, 7-H, 3′-H and 5′-H), 7.62 (m, 1H, *J* = 8.0 + 7.9 + 2 Hz, 4′-H), 8.48 (dd, 1H, *J* = 5 + 2 Hz, 6′-H), 9.81 (br. s, 1H, NH).
2	79.8	218–221	$C_{14}H_{11}BrN_2O_2$ (319.16)	3320, 1690, 1600, 1580, 1460	[a,c] 3.18 + 3.34 (d each, 2H, J_{gem} = 13.5 Hz, CH_2), 6.66 (br. s, 1H, OH), 6.65 (dd, 1H, *J* = 8 + 1 Hz, 7-H),6.93 (d, 1H, *J* = 2 Hz, 4-H), 7.17 (m, 1H, *J* = 7.5 + 4.9 + 1 Hz, 5′-H), 7.20 (m, 1H, *J* = 8 + 5 + 1 Hz, 3′-H), 7.22 (dd, 1H, *J* = 8 + 2 Hz, 6-H), 7.61 (m, 1H, *J* = 8 + 7.5 + 2 Hz, 4′-H), 8.39 (m, 1H, *J* = 4.9 + 2 + 1 Hz, 6′-H), 10.18 (br. s, 1H, NH).
3	63.1	219–220	$C_{14}H_{11}N_3O_4$ (285.25)	3380, 1740, 1705, 1620, 1595, 1510, 1480	[a,c] 3.24 + 3.42 (d each, 2H, J_{gem} = 13.5 Hz, CH_2), 6.95 (br. s, 1H, OH), 6.86 (d, 1H, *J* = 8 Hz, 7-H),7.2 (m, 2H, 3′-H and 5′-H), 7.63 (m, 1H, *J* = 8 + 7.5 + 2 Hz, 4′-H), 8.42 (m, 1H, *J* = 5 + 2 + 1 Hz, 6′-H), 10.95 (br. s, 1H, NH).
4	75.9	204–206	$C_{16}H_{13}BrN_2O_4$ (377.19)	3200, 1710, 1690, 1600, 1580, 1460, 1420	[a,c] 3.34 (s, 2H, CH_2), 3.95 (s, 3H, CO_2CH_3), 6.70 (d, 1H, *J* = 7.9 Hz, 7-H), 6.83 (br. s, 1H, OH), 7.03 (d, 1H, *J* = 1.9 Hz, 4-H), 7.27 (dd, 1H, *J* = 7.9 + 1.9 Hz, 6-H), 7.28 (d, 1H, *J* = 8 Hz, 3′-H), 8.21 (dd, 1H, J = 8 + 2 Hz, 4′-H), 8.94 (d, 1H, *J* = 2 Hz, 2′-H), 9.77 (br. s, 1H, NH).
5	56.4	218–220	$C_{15}H_{13}BrN_2O_2$ (333.18)	3350, 1700, 1620, 1600	[a,c] 2.27 (s, 3H, CH_3), 3.16 + 3.28 (d each, 2H, J_{gem} = 12.5 Hz, CH_2), 6.64 (br. s, 1H, OH),6.64 (d, 1H, *J* = 7.9 Hz, 7-H), 6.95 (d, 1H, *J* = 2.1 Hz, 4-H), 7.07 (d, 1H, *J* = 8 Hz, 3′-H), 7.22 (dd, 1H, *J* = 7.9 + 2.1 Hz, H-6), 7.39 (dd, 1H, *J* = 8 + 2.5 Hz, 4′-H), 8.21 (d, 1H, *J* = 2.5 Hz, 6′-H), 10.15 (br. s, 1H, NH).
6	70.8	185–187	$C_{15}H_{13}BrN_2O_2$ (333.18)	3300, 1710, 1610, 1600, 1590	[a,d] 2.50 (s, 3H, CH_3), 3.05 + 3.29 (d each, J_{gem} = 14.0 Hz, CH_2), 3.17 (s, 1H, OH), 6.71 (d, 1H, *J* = 8.2 Hz, 7-H), 6.80 (d, 1H, *J* = 2 Hz, 4-H), 6.98 (dd, 1H, *J* = 7.7 + 1 Hz, 3′-H), 7.08 (dd, 1H, *J* = 7.7 + 1 Hz, 5′-H), 7.24 (dd, 1H, *J* = 8.2 + 2 Hz, 6-H), 7.53 (t, 1H, *J* = 7.7 Hz, 4′-H), 9.2 (br. s, 1H, NH).
15	74.1	215–217	$C_{14}H_{12}N_2O_2$ (240.25)	3400, 1710, 1600, 1590	[b,c] 3.02 + 3.24 (d each, 2H, J_{gem} = 12.7 Hz, CH_2), 6.70 (dd, 1H, *J* = 7.9 + 1.3 Hz, 7-H),6.90 (br. s, 1H, OH), 7.02 (d, 2H, 3′-H and 5′-H), 7.0–7.4 (m, 3H, 6-H, 5-H and 4-H), 8.32 (d, 2H, 2′-H and 6′-H), 9.95 (br. s, 1H, NH).
16	90.6	234–236	$C_{14}H_{11}BrN_2O_2$ (319.16)	3400, 1700, 1605, 1595	[a,c] 3.06 + 3.22 (d each, 2H, J_{gem} = 12.5 Hz, CH_2), 6.38 (br. s, 1H, OH), 6.60 (d, 1H, *J* = 7.8 Hz, 7-H), 6.97 (m, 2H, 3′-H and 5′-H), 7.16 (d, 1H, *J* = 1.9 Hz, 4-H), 7.26 (dd, 1H, *J = 7.8 + 1.9 Hz, 6-H), 8.33 (m, 2H, 2′-H and 6′-H), 10.2 (br. s, 1H, NH).*

After extraction, the organic phase was washed with water (2 × 20 ml, 3 × 50 ml), dried (Na_2SO_4). In the course of drying crystals were formed. The precipitated crystals were filtered off, washed with hot water (2 × 50 ml), dried to give **7** (2.35 g). [MS (*m/z*; %): 222(90, M^+), 221(100), 194(62), 192 (14.2), 166(7.8), 145(8.4), 116(6.8), 111(9.9), 110.5(8.5), 97(13.3, M–125). For the other physical constants, see: Table 5.] The organic mother liquor was evaporated to about 150 ml and the formed crystals were filtered off, washed with ether (20 ml) to give again **7** (1.26 g). The filtrate was evaporated to dryness under reduced pressure. The residue (5 g) was crystallized from methanol (10 ml) to give a mixture of **7** and **14** (3.53 g). This product was refluxed in a mixture of chloroform and methanol (30 ml/30 ml). After cooling, the precipitated crystals were filtered off, washed with the above mixture of solvents (10 ml), then with ether (10 ml) to give pure **14**. [MS (*m/z*; %): 445(20.6), 444.156(59.3, M^+), 443(3.7), 366(4.9), 365(5.7, M–79), 355(2.6), 354(9.1), 353(100, M–92), 338(4, M–106), 334(2.8, M–110), 324(3.4 M–120), 296(3.8, M–148), 281(2.6, M–163), 222(6.5, M–222), 221(3.4), 117(22.8), 105 (13.9), 32(18.1), 28(57.1). For the other physical constants, see: Table 5.] In the course of evaporation of the mother liquor besides of the mixture of **7** and **14** (0.87 g), an additional amount of pure **7** (0.34 g) was also obtained.

Table 5: Synthesis conditions and physical constants for isatinylidenes **7, 9–14, 17–20**.

Comp.	Yield (%) M.p. (°C) Formula (MW)	IR (ν_{max}) [cm^{-1}]	NMR (δ; ppm; [a)]400 MHz, [b)]100 MHz, [c)]$CDCl_3$+DMSO-d_6, [d)]$CDCl_3$)
7	44.4 % 196–198 °C $C_{14}H_{10}N_2O$ (222.25)	3400, 1680, 1600, 1550, 1450, 1445, 1360	[a,c)] 6.87 (m, 1H, *J* = 8 + 1.5 + 1 Hz, 7-H), 7.01 (m, 1H, *J* = 8 + 7.5 + 1.5 Hz, 5-H), 7.23 (m, 1H, *J* = 8 + 7.5 + 1.5 Hz, 6-H), 7.29 (m, 1H, *J* = 8 + 5 + 1 Hz, 5′-H), 7.56 (m, 1H, *J* = 8 + 1.5 + 1 Hz, 4-H), 7.66 (s, 1H, =CH),7.80 (m, 1H, *J* = 8 + 8 + 2 Hz, 4′-H), 8.69 (m, 1H, *J* = 5 + 2 + 1 Hz, 6′-H), 9.05 (m, 1H, *J* = 8 + 1 + 1 Hz, 3′-H), 10.16 (br. s, 1H, NH).
14	10.8 % 300–302 °C $C_{28}H_{20}N_4O_2$ (444.15)	3380, 1700, 1600, 1580, 1470, 1410, 1280, 760, 735	[a,c)] *Part A*: 3.64 + 3.95 (d each, 2H, *J* =13 Hz, CH_2), 6.77 (m, 1H, *J* = 7.5 + 1 + 1 Hz, 7-H), 6.94 (m, *J* = 8 + 7.2 + 1 Hz, 5-H),6.97 (m, 1H, *J* = 8 + 1 + 1 Hz, 3′-H), 6.98 (m, *J* = 8 + 5 + 5 + 1 Hz, 5′-H), 7.13 (m, 1H, *J* = 8 + 7.5 +1 Hz, H-6),7.14 (m, 1H, *J* = 7.2 + 1 + 1 Hz, 4-H), 7.38 (m, 1H, *J* = 8 + 8 + 1.6 Hz, 4′-H) , 8.27 (m, 1H, *J* = 5 + 1.6 + 1 Hz, 6′-H),9.87 (br. s, 1H, NH); *Part B*: 6.89 (dd, 1H, *J* = 8.5 + 0.5 Hz, H-7), 7.22 (m, 1H, *J* = 8 + 5 + 1 Hz, 5′-H) ,7.54 (m, 1H, *J* = 7.8 + 1 + 1 Hz, 3′-H), 7.55 (dd, 1H, *J* = 8.5 + 2.5 Hz, 6-H), 7.56 (s, 1H, =CH), 7.74 (m, 1H, *J* = 8 + 7.8 + 2 Hz 4′-H), 8.48 (m, 1H, *J* = 5 + 2 + 1 Hz, 6′-H), 9.05 (dd, 1H, *J* = 2.5 + 0.5 Hz, 4-H), 10.15 (br. s, 1H, NH).
9-*E*	97.0 % 250–252 °C $C_{14}H_9BrN_2O$ (301.14)	1720, 1680, 1620, 1610, 1580, 1450, 1440, 1420, 1310, 1300, 1200, 1100	[a,c)] 6.81 (d, 1H, *J* = 8.2 Hz, 7-H), 7.37 (dd, 1H, *J* = 8.2 + 2 Hz, 6-H), 7.43 (m, 1H, *J* = 7.8 + 4.8 + 1 Hz, 5′-H), 7.61 (s, 1H, =CH), 7.76 (dd, 1H, *J* = 7.8 + 1 Hz, 3′-H), 7.90 (m, 1H, *J* = 7.8 + 7.8 + 1 Hz, 4′-H), 8.88 (dd, 1H, *J* = 4.8 + 1 Hz, 6′-H), 9.27 (d, 1H, *J* = 2 Hz, 4-H), 10.62 (br. s, 1H, NH).
9-*Z*	97.0 % 242–246, then 250–252 °C $C_{14}H_9BrN_2O$ (301.14)	1690, 1610, 1580, 1470, 1430, 1200	[a,c)] 6.78 (dd, 1H, *J* = 8.1 + 1 Hz, 7-H), 7.32 (dd, 1H, *J* = 8.1 + 2 Hz, 6-H), 7.33 (m, 1H, *J* = 8 + 5 + 1 Hz, 5′-H), 7.65 (dd, 1H, *J* = 2 + 1 Hz, 4-H), 7.66 (s, 1H, =CH), 7.83 (m, 1H, *J* = 8.1 + 8 + 1.8 Hz, 4′-H), 8.71 (m, 1H, *J* = 5 + 1.8 + 0.9 Hz, 6′-H), 9.10 (m, 1H, *J* = 8.1 + 1 + 0.9 Hz, 3′-H), 10.42 (br. s, 1H, -NH).
10	74.8 % <260 °C $C_{14}H_9N_3O_3$ (267.23)	3100, 1700, 1620, 1520	[a,c)] 7.04 (d, 1H, *J* = 8 Hz, 7-H), 7.52 (m, 1H, *J* = 7.5 + 5 + 1.3 Hz, 5′-H), 7.74 (s, 1H, =CH), 7.93 (m, 2H, 4′-H and 3′-H), 8.22 (dd, 1H, *J* = 8.8 + 2.7 Hz, 6-H), 8.95 (dd, 1H, *J* = 5 + 1.5 Hz, 6′-H), 10.15 (d, 1H, *J* = 2.7 Hz, 4-H), 11.28 (br. s, 1H, NH).
11	64.7 % undefined $C_{16}H_{11}BrN_2O_3$ (359.18)	3400, 1700, 1600, 1580	[a,c)] *major isomer*: 3.98 (s, 3H, CO_2CH_3), 6.87 (d, 1H, *J* = 8.1 Hz, 7-H), 7.45 (dd, 1H, *J* = 8.1 + 2 Hz, 6-H), 7.67 (s, 1H, =CH), 7.95 (d, 1H, *J* = 8.2 Hz, 3′-H), 8.42 (dd, 1H, *J* = 8.2 + 2.4 Hz, 4′-H), 9.19 (d, 1H, *J* = 2 Hz, 4-H), 9.37 (d, 1H, *J* = 2.4 Hz, 6′-H), 10.62 (br. s, 1H, NH).
12	94.0 % 188–197 °C $C_{15}H_{11}BrN_2O$ (315.17)	3100, 1720, 1700	[a,c)] 2.42 (s, 3H, CH_3), 6.82 (d, 1H, *J* = 8.2 Hz, 7-H), 7.40 (dd, 1H, *J* = 8.2 + 2 Hz, 6-H), 7.84 (dd, 1H, *J* = 8.2 + 1.7 Hz, 4′-H), 7.87 (s, 1H, =CH), 7.93 (d, 1H, *J* = 2 Hz, 4-H), 8.65 (d, 1H, *J* = 1.7 Hz, 6′-H), 8.84 (dd, 1H, *J* = 8.2 + 1.7 Hz, 3′-H), 10.97 (br. s, 1H, NH).
13	79.3 % 227–236 °C $C_{15}H_{11}BrN_2O$ (315.17)	3100, 1730, 1700	[a,d)] 2.55 (s, 3H, CH_3), 6.77 (d, 1H, *J* = 8.2 Hz, 7-H), 7.21 (dd, 1H, *J* = 7.8 + 1 Hz, 5′-H), 7.33 (dd, 1H, *J* = 8.2 + 1.2 Hz, 6-H), 7.67 (s, 1H, =CH), 7.72 (dd, 1H, *J* = 7.7 + 7.8 Hz, 4′-H), 7.77 (d, 1H, *J* = 1.2 Hz, 4-H), 8.83 (d, 1H, *J* = 7.7 Hz, 3′-H), 9.1 (br. s, 1H, NH).
17	32.0 % 227–230 °C $C_{14}H_{10}N_2O$ (2.25)	3400, 1690, 1600, 1580, 1450, 1400, 1395, 1310	[a,c)] 6.83 (m, 1H, *J* = 8 + 7.5 + 1.5 Hz, 5-H), 6.91(m, 1H, *J* = 8 + 1.5 + 1 Hz, 7-H), 7.23 (m, 1H, *J* = 8 + 7.5 + 1.5 Hz, 6-H), 7.40 (m, 1H, *J* = 8 + 1.5 + 1 Hz, 4-H), 7.59 (s, 1H, =CH), 7.58 (d, 2H, 3′-H and H-5′), 8.76 (d, 2H, 2′-H and 6-H′), 10.2 (br. s, 1H, NH).
18	5.1 % 167–171 °C $C_{14}H_{10}N_2O$ (222.25)	1680, 1600, 1590, 1460, 1410, 1380, 1280, 1205	[a,c)] 6.87 (m, 1H, *J* = 8 + 1.5 + 1 Hz, 7-H), 7.02 (m, 1H, *J* = 8 + 7.5 + 1.5 Hz, 5-H), 7.26 (m, 1H, *J* = 8 + 7.5 + 1.5 Hz, 6-H), 7.38 (s, 1H, =CH), 7.52 (m, 1H, *J* = 8 + 1.5 + 1 Hz, 4-H), 8.08 (d, 2H, 3′-H and 5′-H), 8.70 (d, 2H, 2′-H and 6′-H), 9.56 (br. s, 1H, NH).
20	48.0 % 200–203 °C $C_{28}H_{20}N_4O_2$ (444.15)	3380, 1700, 1600, 1580, 1450, 1390, 1300, 1290, 800, 730, 725	[a,c)] *Part A*: 3.30 + 3.46 (d each 2H, *J* = 13 Hz, CH_2), 6.68 (m, 1H, *J* = 7.5 + 1 + 1 Hz, 7-H), 6.81 (d, 2H, 3′-H and 5′-H), 6.96 (m, 1H, *J* = 8 + 7.5 + 1 Hz, 5-H), 7.11 (m, 1H, *J* = 7.5+ 1 + 1 Hz, 4-H), 7.13 (m, 1H, *J* = 8 + 7.5 + 1 Hz, 6-H), 8.20 (d, 2H, 2′-H and 6′-H), 10.09 (br. s, 1H, NH); *Part B*: 6.91 (dd, 1H, *J* = 8.5 + 0.5 Hz, 7-H), 7.39 (dd, 1H, *J* = 2.5 + 0.5 Hz, 4-H), 7.39 (2H, 3′-H and 5′-H), 7.49 (s, 1H, =CH), 7.55 (dd, 1H, *J* = 8.5 + 2 Hz, 6-H), 8.55 (d, 2H, 2′-H and 6′-H), 10.55 (br. s, 1H, NH).
19	74.8 % undefined $C_{14}H_9BrN_2O$ (301.14)	3400, 1700, 1605, 1595, 1560, 1460	[a,c)] *major isomer*: 6.76 (d, 1H, *J* = 8 Hz, 7-H), 7.40 (s, 1H, =CH), 7.40 (dd, 1H, *J* = 8 + 2 Hz, 6-H), 7.64 (d, 1H, *J* = 2 Hz, 4-H), 7.98 (m, 2H, 3′-H and H-5′-H), 8.04 (br. s, 1H, NH), 8.73 (m, 2H, 2′-H and 6-H′); *minor isomer*: 6.78 (d, 1H, *J* = 8 Hz, 7-H), 7.38 (dd, 1H, *J* = 8 + 2 Hz, 6-H), 7.48 (m, 2H, 3′-H and 5′-H), 7.54 (d, 1H, *J* = 2 Hz, 4-H), 7.72 (s, 1H, =CH), 8.12 (br. s, 1H, NH), 8.79 (m, 2H, 2′-H and 6′-H).

Table 6: Synthesis conditions and physical constants for 3-spirocyclopropyl-oxindoles **21–32**.

Comp.	Yield (%) M.p. (°C) Formula (MW)	IR (ν_{max}) [cm^{-1}]	NMR (δ; ppm; [a]400 MHz, [b]$CDCl_3$ + DMSO-d_6, [c]$CDCl_3$)
21	43.0 % 170–172 °C $C_{15}H_{12}N_2O$ (236.26)	3450, 1710, 1620, 1590	[a,b] 2.22 (dd, 1H, *J* = 9 + 4 Hz, 2β-H), 2.66 (dd, 1H, *J* = 8 + 4 Hz, 2α-H), 3.34 (dd, 1H, *J* = 9 + 8 Hz, 3-H), 6.65 (dd, 1H, *J* = 7.5 + 1.5 Hz, 4′-H), 6.73 (td, 1H, *J* = 7.5 + 1 Hz, 5′-H) 6.90 (dd, 1H, *J* = 7.5 + 1 Hz, 7′-H), 7.07 (td, 1H, *J* = 7.5 + 7.5 + 1.5 Hz, 6′-H), 7.17 (m, 1H, *J* = 7.5 + 5 +1.5 Hz, 5″-H), 7.23 (m, 1H, *J* = 7.5 + 1.5 + 1.5 Hz, 3″-H), 7.57 (td, 1H, *J* = 7.5 + 7.5 + 2 Hz, 4″-H), 8.63 (m, 1H, *J* = 5 + 2 + 1 Hz, 6″-H), 8.81 (br. s, 1H, NH).
27	≈ 1 % 199–201 °C $C_{15}H_{12}N_2O$ (236.26)	3450, 1705, 1620, 1595	[a,b] 2.09 (dd, 1H, *J* = 9 + 5 Hz, 2α-H) 2.49 (dd, 1H, *J* = 8.5 + 5 Hz, 2β-H), 3.29 (dd, 1H, *J* = 9 + 8.5 Hz, 3-H), 6.81 (dt, 1H *J* = 7.5 + 1 + 1 Hz, 7′-H), 6.93 (m, 1H, *J* = 7.5 + 1.5 + 1 Hz, 4′-H), 6.99 (td, 1H, *J* = 7.5 + 7.5 + 1 Hz, 5′-H), 7.14 (m, 2H, 6′-H and 5″-H), 7.38 (m, 1H, *J* = 7.5 + 1.5 + 1 Hz, 3″-H), 7.63 (td, 1H, *J* = 8 + 7.5 + 2 Hz, 4″-H), 8.50 (m, 1H, *J* = 5 + 2 + 1 Hz, 6″-H), 9.30 (br. s, 1H, NH).
22	49.9 % 199–203 °C $C_{15}H_{11}BrN_2O$ (315.15)	3400, 1680, 1650, 1570, 1450	[a,b] 2.27 (dd, 1H, *J* = 9 + 4.5 Hz, 2β-H), 2.63 (dd, 1H, *J* = 8 + 4.5 Hz, 2α-H), 3.36 (dd, 1H, *J* = 9 + 8 Hz, 3-H), 6.78 (d, 1H, *J* = 8 Hz, 7′-H), 6.79 (d, 1H, *J* = 2 Hz, 4′-H), 7.19 (dd, *J* = 8 + 2 Hz, 6′-H), 7.29 (m, 2H, 3″-H and 5″-H), 7.70 (td, 1H, *J* = 7.5 + 2 Hz, 4″-H), 8.70 (m, 1H, J = 5 + 2 + 1 Hz, 6″-H), 9.65 (br. s, 1H, NH).
28	5.0 % 231–232 °C $C_{15}H_{11}BrN_2O$ (315.15)	3375, 1705, 1685, 1620, 1580	[a,b] 2.11 (dd, 1H, *J* = 9 + 5 Hz, 2α-H), 2.49 (dd, 1H, *J* = 8 + 5 Hz, 2β-H), 3.28 (dd, 1H, *J* = 9 + 8 Hz, 3-H), 6.81 (d, 1H, *J* = 8 Hz, 7′-H), 7.07 (d, 1H, *J* = 2 Hz, 4′-H), 7.16 (m, 1H, *J* = 7.5 + 5 + 1.2 Hz, 5″-H), 7.27 (dd, 1H, *J* = 8 + 2 Hz, 6′-H), 7.37 (m, 1H, *J* = 7.5 + 1.2 Hz, 3″-H), 8.50 (m, 1H, *J* = 5 + 2 + 1 Hz, 6″-H), 9.79(br. s, 1H, NH).
23	34.8 % >260 °C $C_{15}H_{11}N_3O_3$ (281.26)	2800, 1710, 1590, 1510	[a,b] 2.16 (dd, 1H, *J* = 8.5 + 4.0 Hz, 2β-H), 2.76 (dd, 1H, *J* = 8 + 4 Hz, 2α-H), 3.28 (dd, 1H, *J* = 8 + 8.5 Hz, 3-H), 6.95 (d, 1H, *J* = 7.5 Hz, 7′-H), 7.25 (m, 1H, *J* = 7.5 + 5 + 1.5 Hz, 5″-H), 7.40 (dd, 1H, *J* = 7.5 + 1.5 Hz, 3″-H), 7.68 (td, 1H, *J* = 7.5 + 7.5 + 2 Hz, 4″-H), 7.83 (d, 1H, *J* = 2.5 Hz, 4′-H), 7.99 (dd, 1H, J = 7.5 + 2.5 Hz, 6′-H), 8.62 (dd, 1H, J = 5 + 2 Hz, 6″-H), 1 1.25 (br. s, 1H, NH).
24	23.9 % 228–231 °C $C_{17}H_{13}BrN_2O$ (373.20)	3420, 1720, 1615, 1600	[a,b] 2.23 (dd, 1H, *J*= 8.8 + 4.3 Hz, 2β-H), 2.67 (dd, 1H, *J* = 8.0 + 4.3 Hz, 2α-H), 3.26 (dd, 1H, *J* = 8.8 + 8.0 Hz, 3-H), 3.95 (s, 3H, CH_3),6.78 (d, 1H, *J* = 8.2 Hz, 7′-H), 7.13 (d, 1H, *J* = 2.0 Hz, 4′-H), 7.17 (dd, 1H, *J* = 8.2 + 2.0 Hz, 6′-H), 7.35 (d, 1H, *J* = 8 Hz, 3″-H), 8.20 (dd, 1H, *J* = 8 + 2.1 Hz, 4″-H), 9.22 (d, 1H, J = 2.1 Hz, 6″-H), 10.25 (br. s, 1H, NH).
25	58.3 % 226–228 °C $C_{16}H_{13}BrN_2O$ (329.19)	3300, 1700, 1620	[a,c] 2.24 (dd, 1H, *J*= 9 + 4 Hz, 2β-H), 2.26 (s, 3H, CH_3), 2.61 (dd, 1H, *J* = 8.5 + 4 Hz, 2α-H), 3.33 (dd, 1H, *J* = 9 + 8.5 Hz, 3-H), 6.72 (d, 1H, *J* = 8.1 Hz, 7′-H), 6.89 (d, 1H, *J* = 2.0 Hz, 4′-H), 7.14 (d, 1H, *J* = 8.0 Hz, 3″-H), 7.17 (dd, 1H, *J* = 8.1 + 2.0 Hz, 6′-H), 7.42 (dd, 1H, *J* = 8 + 2 Hz, 4″-H), 8.45 (d, 1H, *J* = 2 Hz, 6″-H), 9.46 (br. s, 1H, NH).
26	52.3 % 190–192 °C $C_{15}H_{11}BrN_2O$ (315.15)	3300, 1700, 1620	[a,c] 2.21 (dd, 1H, *J* = 9.0 + 4.2 Hz, 2β-H), 2.64 (dd, 1H, *J* = 7.9 + 4.2 Hz, 2α-H), 2.63 (s, 3H, CH_3), 3.23 (dd, 1H, *J* = 9.0 + 7.9 Hz, 3-H), 6.72 (d, 1H, *J* = 8.2 Hz, 7′-H), 7.02 (dd, 1H, *J* = 7.6 + 1 Hz, 3″-H), 7.04 (dd, 1H, *J* = 7.6 + 1 Hz, 5″-H), 7.14 (dd, 1H, *J* = 8.2 + 2.1 Hz, 6′-H), 7.28 (d, 1H, *J* = 2.1 Hz, 4′-H), 7.47 (t, 1H, *J* = 7.6 + 7.6 Hz, 4″-H), 8.6 (br. s, 1H, NH).
29	29.4 % 201–204 °C $C_{15}H_{12}N_2O$ (236.26)	3400, 1680, 1600	[a,c] 2.03 (dd, 1H, *J*= 8 + 4.9 Hz, 2α-H), 2.26 (dd, 1H, *J* = 9 + 4.9 Hz, 2β-H), 3.28 (dd, 1H, *J* = 9.0 + 8.0 Hz, 3-H), 6.01 (dd, 1H, *J* = 7.7 + 1.3 Hz, 4′-H), 6.72 (m, 1H, *J* = 7.7 + 7.7 + 1.1 Hz, 5′-H), 6.97 (dd, 1H, *J* = 7.9 + 1.1 Hz, 7′-H), 7.13 (m, 1H, *J* = 7.9 + 7.7 + 1.3 Hz, 6′-H), 7.21 (d, 2H, 3″-H and 5″-H), 8.59 (d, 2H, 2″-H and 6″-H), 8.91 (br. s, 1H, NH).
30	≈ 1 % 215–216 °C $C_{15}H_{12}N_2O$ (236.26)	3400, 1680, 1600	[a,c] 2.14 (dd, 1H, *J* = 8.9 + 5.2 Hz, 2α-H), 2.40 (dd, 1H, *J* = 8.8 + 5.2 Hz, 2β-H), 3.05 (dd, 1H, *J* = 9.0 + 8.0 Hz, 3-H), 6.91 (dd, 1H, *J* = 7.8 + 1 Hz, 7′-H), 6.98 (dd, 1H, *J* = 7.5 + 1.3 Hz, 4′-H), 7.08 (m, 1H, *J* = 7.5 + 7.5 + 1 Hz, 5′-H), 7.25 (m, 1H, *J* = 7.8 + 7.5 + 1.3 Hz, 6′-H),7.26 (d, 2H, 3″-H and 5″-H), 8.53 (d, 2H, 2″-H and 6″-H), 7.65 (br. s, 1H, NH).
31	16.1 % 224–227 °C $C_{15}H_{11}BrN_2O$ (315.15)	3400, 1690, 1600	[a,c] 2.03 (dd, 1H, *J* = 8 + 4.9 Hz, 2α-H), 2.26 (dd, 1H, *J* = 9 + 4.9 Hz, 2β-H), 3.28 (dd, 1H, *J* = 9.0 + 8.0 Hz, 3-H),6.01 (dd, 1H, *J* = 7.7 + 1.3 Hz, 4′-H), 6.72 (m, 1H, *J* = 7.7 + 7.7 + 1.1 Hz, 5′-H),6.97 (dd, 1H, *J* = 7.9 + 1.1 Hz, 7′-H), 7.13 (m, 1H, *J* = 7.9 + 7.7 + 1.3 Hz, 6′-H), 7.21 (d, 2H, 3″-H and 5″-H), 8.59 (d, 2H, 2″-H and 6″-H), 8.91 (br. s, 1H, NH).
32	2.5 % 218–220 °C $C_{15}H_{11}BrN_2O$ (315.15)	3400, 1675, 1595	[a,c] 2.15 (s, 1H, *J* = 8.9 + 5 Hz, 2α-H), 2.34 (dd, 1H, *J* = 8.6 + 5 Hz, 2β-H), 3.08 (dd, 1H, *J* = 8.9 + 8.6 Hz, 3-H),6.83 (d, 1H, *J* = 8 Hz, 7′-H), 7.10 (d, 1H, *J* = 2 Hz, 4′-H), 7.26 (d, 2H, 3″-H and 5″-H), 7.30 (dd, 1H, *J* = 8 + 2 Hz, 6′-H), 8.48 (d, 2H, 2″-H and 6″-H), 10.22 (br. s, 1H, NH).

Z- and E-α-(5-Bromo-isatinylidene-2-methylpyridine **9** *(general procedure for C5-substituted derivatives)*

Compound **2** (15.9 g; 50 mM) and 4-toluenesulfonic acid monohydrate (38 g; 0.2 M) in benzene (1000 ml) were refluxed for 24 h using a water-separating device. After cooling, the mixture was evaporated to dryness under reduced pressure. The residue was dissolved in a mixture of water and methanol (300+50 ml) and aqueous sodium hydroxide solution (8 g NaOH/160 ml water) was dropped. The formed yellow crystals were filtered off, washed with water (3 × 100 ml), methanol (30 ml) and dried to give **9** (14.5 g; 97.0 %).

Synthesis conditions and physical for isatinylidenes **7**, **9**–**14**, and **17**–**20** are listed in Table 5.

Z-α-(5-Nitro)isatinylidene-2-methylpyridine **10**
(E/Z)-α-(5-Bromo)isatinylidene-2-methyl(5-carbomethoxy)pyridine **11**
Z-α-(5-Bromo)isatinylidene-2-methyl-(5-methyl)pyridine **12**
Z-α-(5-Bromo)isatinylidene-2,6-dimethylpyridine **13**
E-Isatinylidene-4-methylpyridine **17**
Z-Isatinylidene-4-methylpyridine **18**
2,3-Dihydro-5-(2,3-dihydro-2-oxo-3-(4-pyridylmethyl)-1H-indol-3-yl)-3-(4-pyridylmethylene)-1H-indol-2-one **20**

Preparation of 3-spirocyclopropyl-oxindoles

(±)-1,3-l (2-Pyridyl)-spiro[cyclopropane-1,3′[3H]-indol]-2′(1′H)-one **21** *and (±)-1,3-ul (2-Pyridyl)-spiro[cyclopropane-1,3′[3H]-indol]-2′(1′H)-one* **27** *(typical procedure)*

Sodium hydride (2.0 g) was washed with hexane and dried, then dissolved in DMF (80 ml). The solution was cooled at 0–5 °C and trimethyloxosulfonium iodide (6.8 g; 30 mM) was added in portionwise (5 min) under an N_2 atmosphere. Stirring was continued for 15–20 min. The mixture was cooled continuously and **7** (4.44 g; 20 mM) was added in portionwise, then was stirred for 2 h allowing the bath to room temperature. After adding water (20 ml) in dropwise, the mixture was evaporated to dryness under reduced pressure. The residue was dissolved in a mixture of ethyl acetate and water (100+50 ml). After extraction, the organic phase was washed with water (2 × 50 ml) and dried (Na_2SO_4). The filtrate was evaporated under reduced pressure. The residue (4.5 g) was dissolved in hot acetone (15 ml), cleared with active carbone, filtered and the filtrate was kept in refrigerator overnight. The obtained crystals were filtered off, washed with cold acetone (5 ml), dried to yield **21** (2.02 g, 43 %). [MS (*m/z*, %): 237(16.4), 236(100, M^+), 235(14.9), 220(8.6), 219(51.4), 208(18.7), 207(30.2), 206(9.7), 205(6.0), 131(6.1), 130(43.0), 117(7.1), 104(5.5), 103(16.4), 74 (13.0), 73(13.8), 69(13.9), 60 (10.2). For the other physical constants, see: Table 6.]

In the course of the chromatography of the mother liquor on silica (eluent: chloroform+methanol, 19/1) an additional amount of **21** (0.28 g; 5.9 %) was obtained beside the minor isomer **27**(30 mg, 0.6 %). [MS (*m/z*, %): 236 (100, M^+), 219(47.2), 207(29.6), 130(27.0). For the other physical constants, see: Table 6.]

The following derivatives were also prepared and the physical constants are listed in Table 6.

(±)-1,3-l (2-Pyridyl)-spiro[cyclopropane-1,3′-(5-bromo)[3H]-indol]-2′(1′H)-one **22**

[MS (*m/z*, %): 315(34.4, M^+), 314(100), 299(64.2), 287(45.9), 234(12.2), 218(32.1), 208(53.5), 191(20.7), 178(9.1), 165(9.1), 129(14.3), 117(12.2), 103(58.1), 93(36.7), 89(35.4)].

(±)-1,3-ul (2-Pyridyl)-spiro[cyclopropane-1,3′-/5-bromo/[3H]-indol]-2′(1′H)-one **28**
(±)-1,3-l (2-Pyridyl)-spiro[cyclopropane-1,3′-(5-nitro)[3H]-indol]-2′(1′H)-one **23**
(±)-1,3-l ((5-Carbomethoxy)2-pyridyl)-spiro[cyclopropane-1,3′-(5-bromo)[3H]-indole]-2′(1′H)-one **24**
(±)-1,3-l ((5-Methyl)2-pyridyl)-spiro[cyclopropane-1,3′-(5-bromo)[3H]-indol]-2′(1′H)-one **25**
(±)-1,3-l ((6-Methyl)2-pyridyl)-spiro[cyclopropane-1,3′-(5-bromo)[3H]-indol]-2′(1′H)-one **26**
(±)-1,3-l (4-Pyridyl)-spiro[cyclopropane-1,3′[3H]-indol]-2′(1′H)-one **29**
(±)-1,3-ul (4-Pyridyl)-spiro[cyclopropane-1,3′[3H]-indol]-2′(1′H)-one **30**
(±)-1,3-l (4-Pyridyl)-spiro[cyclopropane-1,3′-(5-bromo)[3H]-indol]-2′(1′H)-one **31**
(±)-1,3-ul (4-Pyridyl)-spiro[cyclopropane-1,3′-(5-bromo)[3H]-indol]-2′(1′H)-one **32**

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