Synthesis of 3-substituted cyclopenta[*b*]indoles

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When reacting with I_2, 2-(cyclopent-2-enyl)anilines undergo cyclization into 3-iodo-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indoles in high yields. The minor reaction products were 3,5- or 3,7-diiodoindolines. Ammonolysis of 3-iodo-5-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole or its *N*-chloroacetyl derivative results in 3-amino-5-methyl-1,2,3,3a,4,8b-hexahydro- and 5-methyl-1,3a,4,8b-tetrahydrocyclopenta[*b*]indoles.

Key words: 2-(cyclopent-2-enyl)anilines, iodocyclization, 3-iodo-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indoles, elimination, 5-methyl-1,3a,4,8b-tetrahydrocyclopenta[*b*]indole, 3-amino-5-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole.

Cyclopenta[*b*]indole fragments are very common in nature, in particular, as components of some alkaloids.[1,2] In cyclopenta[*b*]indoles obtained from cyclopentanone phenylhydrazones[3] by acid-catalyzed[4] or photochemical[5,6] intramolecular cyclization of 2-cyclopentenylanilines, the cyclopentane fragment is not functionalized, thus limiting their use in further transformations. By contrast, the reaction of 2-(cyclopent-2-enyl)anilines with iodine can not only afford compounds of this series, but also provide conditions for their subsequent functionalization. Although halocyclization[7] is widely used in the preparation of various heterocycles, this reaction has been studied only for a limited set of 2-alkenylanilines.[8]

In the present work, we investigated the iodocyclization of 2-(cyclopent-2-enyl)anilines[9] and some transformations of the reaction products. The starting anilines can easily be prepared from commercial dicyclopentadiene.

Results and Discussion

The reaction of arylamine **1** with I_2 in nonpolar solvents (CCl_4, C_6H_6, or C_6H_{12}) results in 3-iodo-5-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole (**2**) in 85% yield. The yield of 3,7-diiodo-5-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole (**3**) is low (<1%). In polar solvents such as MeCN or EtOH, the reaction is more sluggish. Furthermore, full conversion of amine **1** into indoline **2** was achieved only upon addition of a new portion of I_2. The content of diiodide **3** in the reaction mixture was 6—7%. Taking into account the absence of stereo- and regioisomers of indoline **2**, we assume that electrophilic addition of iodine to the double bond of the alkenyl fragment results, *via* complex **4**, in intermediate **5** with subsequent intramolecular nucleophilic attack of the N atom on C(2′) and 5-*exo*-cyclization[10] (Scheme 1).

Analogously, monoiodo derivatives **8** and **9** were the major products (in 86 and 88% yield, respectively) in the reactions of amines **6** and **7** with I_2.

However, unlike the cyclization of arylamine **1** (where only one possible diiodide **3** is formed), the reactions of 6- (**6**) and 2-(cyclopent-2-enyl)-3-methylaniline (**7**) with I_2 in CCl_4 afford two isomeric diiodides, namely, 3,7-diiodo-6-methyl- (**10**) or 3,7-diiodo-8-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indoles (**11**) and 3,5-diiodo-6-methyl- (**12**) or 3,5-diiodo-8-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indoles (**13**), which represent *para*- and *ortho*-iodination products with respect to the —NH group, respectively, in 0.3—1% yields.

Indoline **2** reacted with chloroacetyl chloride to give compound **14**. When heated with zinc in ethanol,[11] the latter undergoes ring-opening (similar to that described earlier[12] for 1-acylamino-2-iodoalkanes) to form *N*-acetyl-6-(cyclopent-2-enyl)-2-methylaniline (**15**), which was identified by comparing with an authentic sample.[14]

Ammonolysis of iodide **2** in MeOH at 100 °C results in 3-amino-5-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole (**16**) in 83% yield and 5-methyl-1,3a,4,8b-tetrahydrocyclopenta[*b*]indole (**17**) in trace amounts. Under similar conditions, *N*-chloroacetyl-3-iodo-5-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole (**14**) also affords aminoindoline **16** (81%) and compound **17** (8%) (Scheme 2).

The structures of compounds **2**—**17** were determined based on data from NMR spectroscopy and elemental analysis. Thus the *cis*-arrangement of H(8b) and H(3a) protons in compounds **2**—**14**, **16**, and **17** was confirmed

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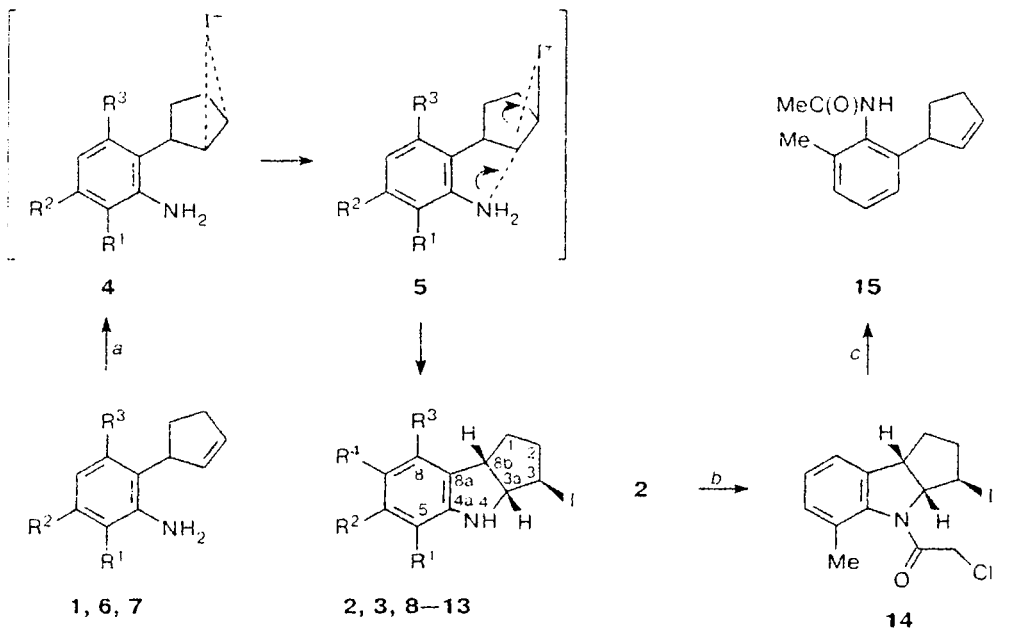
Scheme 1



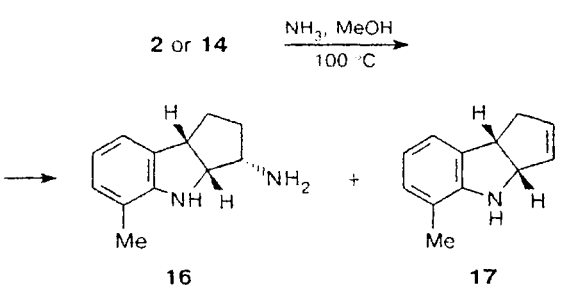
	1	2	3	6	7	8	9	10	11	12	13
R^1	Me	Me	Me	H	H	H	H	H	H	I	I
R^2	H	H	H	Me	H	Me	H	Me	H	Me	H
R^3	H	H	H	H	Me	H	Me	H	Me	H	Me
R^4		H	I			H	H	I	I	H	H

Reagents and conditions: (*a*) I_2, $NaHCO_3$, solvent (CCl_4, C_6H_6, C_6H_{12}, MeCN, or EtOH), 20 °C, 24—72 h; (*b*) $ClCH_2COCl$, K_2CO_3, CH_2Cl_2, 20 °C, 24 h; (*c*) Zn, EtOH, 80 °C, 5 h.

by large vicinal coupling constants ($^3J_{H(3a),H(8b)}$ = 8—9 Hz) (Table 1), which were determined by the double resonance method, and by the presence of an intramolecular nuclear Overhauser effect (NOE). Saturation of a signal for the H(3a) proton increases the signal intensity for H(8b) by 8.3%, whereas the signal for H(3) is not affected. This suggests the proximity of the H(3a) and H(8b) protons, which is only possible if they are axial, the five-membered rings are *cis*-fused, and the H(3a) and H(3) protons are *trans* to each other.

In the ^1H NMR spectrum of diamine **16**, $^3J_{H(3)H,H(3a)}$ = 6.3 Hz (see Table 1). Insofar as the reactions of iodide **2** and amide **14** with NH_3 yield only one stereoisomer **16**, the process probably follows the S_N2 mechanism. In the case of the S_Ni mechanism, amination could also result in a second stereoisomeric diamine. Hence, one can state that the H(3) and H(3a) protons have *cis*-configuration.

Scheme 2



Iodination of the aromatic ring is confirmed by the presence of characteristic signals at δ 79—87 for the I—C_{arom} atoms in the ^{13}C NMR spectra of compounds **3** and **10**—**13**.[14] The ^1H NMR spectra of indolines **3** and **10** show two one-proton singlets in the aromatic region, suggesting C(7)-substitution. In the ^1H NMR spectrum of compound **11**, analogous substitution is evidenced by the presence of two one-proton doublets from the H(5) and H(6) protons. C(5)-iodination was deduced from the presence of two doublets for aromatic protons in the ^1H NMR spectra of indolines **12** and **13**. In addition, the ^{13}C signal from the C(5) atom in indolines **10** and **11** is shifted upfield (δ 109.9 and 108.4, respectively) because of the α-effect of the NH group, while the spectra of heterocycles **12** and **13** show no signals in this region.

Thus, the reaction of 2-cyclopentenylanilines with I_2 under mild conditions results in 3-iodoindolines, whose ammonolysis gives 3-aminoindolines in high yields.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AM 300 instrument (300.13 and 75 MHz, respectively) in $CDCl_3$ with Me_4Si as the internal standard. IR spectra were

Table 1. ^{1}H NMR spectra of compounds **2**, **3**, **8**—**14**, **16**, and **17***

Compound	δ (*J*/Hz)										
	H(1a), H(1b)	H(2a), H(2b)	H(3)	H(3a)	H(8b)	H(5)	H(6)	H(7)	H(8)	CH_3, CH_2Cl	NH, NH_2
2	1.9—2.6 (m)		4.3 (m)	4.8 (d, *J* = 8.5)	4.0 (t, *J* = 8.5)	—	7.0 (d, *J* = 7.3)	6.7 (t, *J* = 7.3)	6.9 (d, *J* = 7.3)	2.1 (s)	3.9 (s)
3	1.7—2.6 (m)		4.3 (m)	4.8 (d, *J* = 8.4)	3.9 (t, *J* = 8.4)	—	7.1 (s)	—	7.2 (s)	2.0 (s)	3.8 (s)
8	1.9—2.6 (m)		4.3 (m)	4.6 (d, *J* = 8.3)	4.0 (t, *J* = 8.3)	6.5 s	—	7.2 (d, *J* = 8.1)	7.1 (d, *J* = 8.1)	2.2 (s)	3.9 (s)
9	1.9—2.6 (m)		4.3 (m)	4.8 (d, *J* = 8.7)	4.0 (t, *J* = 8.7)	6.4 (d, *J* = 8.0)	7.0 (m)	6.9 (d, *J* = 8.1)		2.4 (s)	3.9 (s)
10	1.6—2.5 (m)		4.1 (m)	4.7 (d, *J* = 8.8)	3.8 (t, *J* = 8.8)	6.4 (s)	—	—	7.3 (s)	2.2 (s)	4.1 (s)
11	1.6—2.5 (m)		4.2 (m)	4.7 (d, *J* = 9.2)	3.9 (t, *J* = 9.2)	6.1 (d, *J* = 8.2)	7.3 (d, *J* = 8.2)	—	—	2.2 (s)	4.1 (s)
12	1.6—2.5 (m)		4.2 (m)	4.7 (d, *J* = 9.0)	4.0 (dt, *J* = 9.0; 3.0)	—	—	7.1 (d, *J* = 8.0)	6.2 (d, *J* = 8.0)	2.2 (s)	4.1 (s)
13	1.6—2.5 (m)		4.2 (m)	4.7 (d, *J* = 8.9; 2.7)	3.9 (t, *J* = 9.2)	6.1 (d, *J* = 8.2)	7.3 (d, *J* = 8.2)	—	—	2.2 (s)	4.1 (s)
14	1.6—2.5 (m)		4.2 (m)	5.0 (dd, *J* = 7.8; 3.2)	3.9 (t, *J* = 7.8)	—		6.9—7.1 (m)		2.2 (s) 4.4 (d, *J* = 12.5)	
16	1.4—2.1 (m)		4.1 (dq, *J* = 6.3; 3.0)	4.3 (dq, *J* = 9.0; 6.3)	3.9 (dt, *J* = 9.0; 3.0)	—	7.0 (d, *J* = 7.4)	6.6 (t, *J* = 7.4)	6.9 (d, *J* = 7.4)	2.2 (s)	3.3 (br.s)
17	2.6 (dq, *J* = 2.1; 16.7) 2.9 (ddq, *J* = 1.8; 3.6; 8.4, 16.7)	5.7 (ddd, *J* = 2.1; 4.1; 5.9)	5.9 (ddd, *J* = 1.6; 3.6; 5.9)	4.9 (dd, *J* = 8.4; 1.6)	4.0 (t, *J* = 8.4)	—	6.9 (d, *J* = 7.4)	6.7 (t, *J* = 7.4)	7.0 (d, *J* = 7.4)	2.2 (s)	2.4—3.1 (br.s)

* The signals for the H(3a) protons of compounds **3** and **8**—**13** are broadened doublets, and those for the H(8b) proton of compounds **2**, **3**, and **8**—**14** are broadened triplets.

recorded on a UR-20 instrument. The course of the reaction was monitored using Silufol UV 254 plates. The yields and characteristics of all products are given in Tables 1—3.

General procedure for iodocyclization. A solution of arylamine **1**, **6**, or **7** (1.73 g, 10 mmol) and I_2 (2.54 g, 20 mmol) in 25 mL of a solvent (CCl_4, benzene, cyclohexane, MeCN, or EtOH) was stirred at 20 °C for 24—72 h. The course of the reaction was monitored by TLC (hexane—MeOH, 98 : 2). For MeCN or EtOH as the solvent, an additional portion of I_2 (2.5 g) was added after 24 h. After the starting amine disappeared, the reaction mixture was diluted with 100 mL of $CHCl_3$, washed with 5% $Na_2S_2O_3$ (3×100 mL) and water (2×20 mL), and dried with Na_2SO_4. The solvent was removed *in vacuo*. The residue was chromatographed on silica gel (10 g) in CCl_4.

***N*-Chloroacetyl-3-iodo-5-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole (14).** $ClCH_2COCl$ (2.26 g, 20 mmol) was

Table 2. ^{13}C NMR spectra ($CDCl_3$, δ) of compounds **2**, **3**, **8**—**14**, **16**, and **17**

Compound	C(1)	C(2)	C(3)	C(3a)	C(4a)	C(5)	C(6)	C(7)	C(8)	C(8a)	C(8b)	CH_3
2	33.6	35.6	37.2	73.9	148.5	119.2	131.7	122.1	128.6	118.0	46.0	16.7
3	31.6	35.5	36.2	73.9	141.8	117.9	130.7	80.0	134.5	126.3	45.6	16.5
8	33.2	35.7	36.8	74.3	149.7	116.1	130.3	122.9	129.7	125.1	46.2	20.4
9	33.4	35.1	35.9	74.7	140.4	109.3	121.6	125.2	134.8	116.2	44.5	17.4
10	33.6	36.2	35.6	74.5	150.5	109.9	140.2	86.3	134.4	132.6	45.1	28.2
11	32.4	36.1	35.4	74.7	150.1	108.4	138.1	87.5	137.0	132.3	45.4	24.3
12	32.3	35.3	35.2	73.3	151.8	87.5	140.4	122.1	134.2	131.3	47.6	23.9
13	32.1	35.9	35.5	73.1	152.8	83.8	139.0	135.9	136.8	119.9	46.3	18.1
14	30.0	31.0	36.6	75.3	139.5	121.0	127.9	130.0	136.2	126.0	45.5	20.5*
16	30.5	32.5	63.7	74.0	149.3	133.9	121.8	128.4	120.5	129.8	46.9	17.0
17	40.3	133.0	132.6	66.5	148.0	119.7	119.3	131.7	122.0	128.6	44.8	17.0

* δ 42.5 (CH_2Cl); 164.7 (CO).

Table 3. Yields, R_f, m.p.,[a] IR spectra, and elemental analysis data for compounds **2**, **3**, **8**—**14**, **16**, and **17**

Compound	Yield (%)	R_f [m.p.]	IR, ν/cm^{-1} NH, NH_2	Found / Calculated (%) C	H	I	Cl	N	Molecular formula
2	85[b]	0.5	3420	47.91 48.18	4.23 4.72	42.20 42.43	—	4.37 4.68	$C_{12}H_{14}IN$
3	7[b]	0.6	3420	31.39 31.91	2.82 3.08	59.46 59.71	—	2.76 3.30	$C_{12}H_{13}I_2N$
8	86[b]	0.5	3420	47.79 48.18	4.42 4.72	41.90 42.43	—	4.25 4.68	$C_{12}H_{14}IN$
9	88[b]	0.5	3420	47.88 48.18	4.30 4.72	41.96 42.43	—	4.18 4.68	$C_{12}H_{14}IN$
10	1[b]	0.6	3417	31.46 31.91	2.79 3.08	59.23 59.71	—	2.70 3.30	$C_{12}H_{13}I_2N$
11	1[b]	[88 °C] (CCl_4)[c]	3420	31.38 31.91	2.90 3.08	59.29 59.71	—	2.86 3.30	$C_{12}H_{13}I_2N$
12	0.3[b]	0.8	3422	31.42 31.91	2.85 3.08	59.22 59.71	—	2.72 3.30	$C_{12}H_{13}I_2N$
13	0.3[b]	0.8	3410	31.50 31.91	2.84 3.08	56.26 59.71	—	2.66 3.30	$C_{12}H_{13}I_2N$
14	91	0.3	—	44.48 44.76	3.70 4.02	33.57 33.78	9.12 9.44	3.37 3.73	$C_{14}H_{15}ICINO$
16	83	0.2	3475	76.23 76.55	8.34 8.57	—	—	14.41 14.88	$C_{12}H_{16}N_2$
17	8[d]	0.4	3390	83.91 84.18	7.52 7.64	—	—	7.92 8.18	$C_{12}H_{13}N$

[a] Indolines were obtained as dark viscous masses (except for iodide **11**).
[b] Obtained in MeCN for **3** and in CCl_4 for **2** and **8**—**13**.
[c] Solvent.
[d] From amide **14**.

added at 20 °C for 20 min to a mixture of indoline **2** (2.99 g, 10 mmol) and K_2CO_3 (3.76 g, 20 mmol) in 50 mL of CH_2Cl_2. The reaction mixture was stirred at 20 °C for 5 h and filtered, and the precipitate was washed on the filter with 20 mL of CH_2Cl_2. The filtrate was washed successively with water (1×50 mL), 10% $NaHCO_3$ until CO_2 ceased to evolve, and again water (2×50 mL) and dried with $MgSO_4$. The solvent was removed *in vacuo* to give amide **14** as a brown oil.

Ammonolysis of iodides. Indoline **2** (or **14**) (1 mmol) and a 16% solution of ammonia in methanol (15 mL) were heated in an autoclave at 100 °C for 24 h. On cooling, the solvent was removed, and the residue was dissolved in $CHCl_3$ (30 mL) and washed with 5% $NaHCO_3$ (1×20 mL) and water (20 mL). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The reaction products were isolated by chromatography on silica gel (10 g) in CCl_4—MeOH (9 : 1).

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