Indolopyridines containing a bridgehead heteroatom
12.* Synthesis and reduction of 12-arylidene-5,6-dihydroindolo[2,1-*a*]isoquinolinium trifluoroacetates

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Condensation of 5,6-dihydroindolo[2,1-*a*]isoquinoline with aromatic aldehydes in trifluoroacetic acid afforded 12-arylidene-5,6-dihydroindolo[2,1-*a*]isoquinolinium trifluoroacetates. Hydrogenolysis of these salts on rhenium heptasulfide at elevated temperature and hydrogen pressure yielded indolo[2,1-*a*]isoquinolines, while reduction with sodium borohydride gave 12-arylmethylindoloisoquinolines. Photoluminescence was found for some indolo[2,1-*a*]isoquinolines.

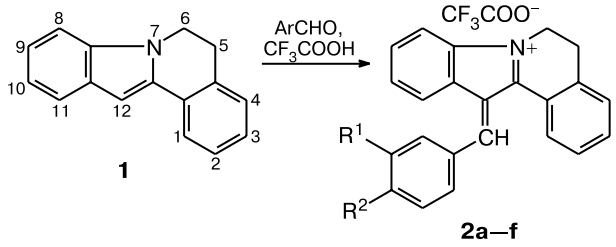
Key words: 5,6-dihydroindolo[2,1-*a*]isoquinolines, 12-arylidene-5,6-dihydroindolo[2,1-*a*]isoquinolinium trifluoroacetates, 12-benzylindolo[2,1-*a*]isoquinolines, reduction, hydrogenolysis, rhenium heptasulfide, sodium borohydride, photoluminescent properties.

In the preceding work,[1] we synthesized a number of 12-arylideneindolo[2,1-*a*]isoquinolinium acetates, trichloroacetates, and trifluoroacetates, which are potential luminophores. The present study is devoted to the synthesis of analogous quaternary salts containing a partially hydrogenated indolopyridine fragment, their reduction under various conditions, and the photoluminescent properties of the compound obtained.

Condensation of 5,6-dihydroindolo[2,1-*a*]isoquinoline (**1**) with some aromatic aldehydes in trifluoroacetic acid (TFA) at ~20 °C gave 12-arylidene-5,6-dihydroindolo[2,1-*a*]isoquinolinium salts **2a**—**f**, which were isolated as high-melting colored crystals (Scheme 1; Tables 1, 2). The yields of these products were 33 to 57%; *i.e.*, they are significantly lower than the yields of the previously synthesized[1] analogous aromatic salts **3a**—**c**. Apparently, this is associated with partial hydrogenation of the starting heterocycle **1**, which may be regarded as *N*-alkyl-2-arylindole and tends to oligomerize when protonated in acidic media.

Hydrogenation of nitrogen-containing fused aromatic compounds is known to be specifically affected by rhenium heptasulfide Re_2S_7.[2] Earlier,[3] we found that the exocyclic C=C bond in 9-arylideneazafluorenes can be

Scheme 1



2: $R^1 = R^2 = H$ (**a**); $R^1 = H$, $R^2 = OMe$ (**b**); $R^1 = H$, $R^2 = NO_2$ (**c**); $R^1 = OH$, $R^2 = OMe$ (**d**); $R^1 = R^2 = OMe$ (**e**); R^1, $R^2 = OCH_2O$ (**f**)

hydrogenated with Re_2S_7 as a heterogeneous catalyst. In this study, selective hydrogenation of quaternary salts **2** was attempted under analogous conditions (H_2, 140 atm, 250 °C). This reaction could be expected to yield a hexahydro derivative of type **A** (its cyclic framework is contained in alkaloids cryptaustoline and cryptowoline[4]). However, compound **2a** underwent hydrogenolysis to give product **1** in high yield (Scheme 2). The intermediate benzyl group in the β-position of the pyrrole ring is easily eliminated, which accounts for our failure to benzylate dihydro derivative **1** and indoloisoquinoline **4** with benzyl alcohol under analogous conditions of heterogeneous reductive alkylation.[5]

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Table 1. Characteristics of compounds **2a**—**f**, **5a**—**c**, and **6a**—**c**

Compound	Yield (%)	M.p. /°C	R_f	IR, ν/cm^{-1}	Fluorescence UV*, λ_{max}/nm	MS, m/z (I_{rel} (%))	Found / Calculated (%) C	H	N	Molecular formula
2a	36	174—176	0.48	1690, 1590, 1530	388	—	71.5 71.3	4.4 4.3	3.2 3.3	$C_{25}H_{18}F_3NO_2$
2b	41	236—237	0.38	1700, 1600, 1510, 1310	385	—	68.7 69.2	4.1 4.4	2.9 3.1	$C_{26}H_{20}F_3NO_3$
2c	57	>300	0.45	1690, 1600, 1525, 1345	376	—	64.7 64.4	3.6 3.6	5.8 6.0	$C_{25}H_{17}F_3N_2O_4$
2d	35	208—210	0.22	1530, 1690, 1610, 1540	384	—	67.0 66.8	4.1 4.3	3.0 2.9	$C_{26}H_{20}F_3NO_4$
2e	41	218—220	0.20	1680, 1610, 1510	—	—	67.5 67.4	4.6 4.6	3.0 2.9	$C_{27}H_{22}F_3NO_4$
2f	33	200—202	0.25	1690, 1600, 1520	384	—	67.5 67.1	4.0 3.9	3.1 3.0	$C_{26}H_{18}F_3NO_4$
5a	65	168—170	0.75	—	—	307 $[M]^+$ (100), 230 (59)	89.5 89.9	5.3 5.5	4.3 4.6	$C_{23}H_{17}N$
5b	73	108—110	0.69	—	386	337 $[M]^+$ (100), 230 (61)	85.3 85.4	5.3 5.6	4.0 4.2	$C_{24}H_{19}NO$
5c	75	173—174	0.60	1540, 1351	382	352 $[M]^+$ (100), 217 (16)	77.9 78.4	4.3 4.5	7.9 8.0	$C_{23}H_{16}N_2O_2$
6a	55	160—162	0.72	—	—	309 $[M]^+$ (100), 236 (63)	88.9 89.3	6.1 6.2	4.3 4.5	$C_{23}H_{19}N$
6b	64	103—105	0.58	—	381	339 $[M]^+$ (100), 232 (49)	84.9 85.0	6.1 6.2	4.0 4.2	$C_{24}H_{21}NO$
6c	69	139—141	0.63	1535, 1345	378	364 $[M]^+$ (100), 232 (38)	77.9 78.0	5.0 5.1	7.6 7.9	$C_{23}H_{18}N_2O_2$

* For compounds **1**, **4**, and **3a**—**c**, λ_{max} = 368, 444, 452, 454, and 408 nm, respectively.

Sodium borohydride is known to reduce a pyridinium cation to dihydro- and tetrahydropyridine.[6] Reduction of the five-membered pyrrole ring in indole is also possible with this reagent.[7] For this reason, we attempted to reduce indoloisoquinoline **4** and quaternary salts **2** and **3** with $NaBH_4$.

It turned out that heterocycle **4** is not reduced with $NaBH_4$ either in water, ethanol, or acetic acid. In the presence of a stronger acid (TFA), reduction did occur to give 5,6-dihydroindoloisoquinoline **1** in 20% yield (see Scheme 2).

Quaternary salts **2** and **3** contain a positively charged >C=N$^+$< fragment incorporated both in the indolenine and pyridine rings; because of this, one could expect that the reactions of the starting salts with $NaBH_4$ in TFA would yield a tetrahydro derivative of type **B**. However,

Scheme 2

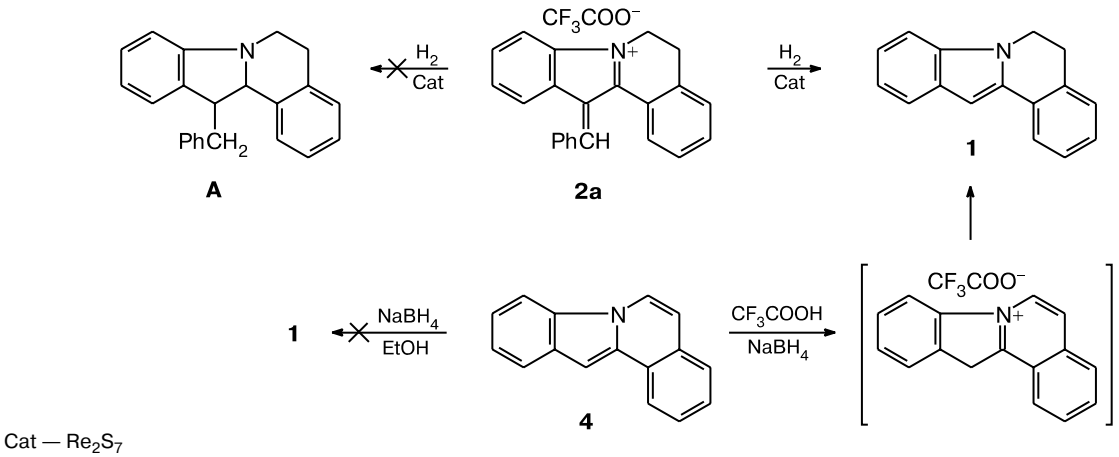

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Table 2. ^{1}H NMR spectra of compounds **2a—f**, **5a—c**, and **6a—c**

Compound	δ (*J*/Hz)			
	H(5)	H(6)	H arom.	Other protons
2a	3.15 (t, *J* = 6.0)	4.28 (t)	6.80—8.10 (m, 14 H)	—
2b	3.13 (t, *J* = 6.0)	4.25 (t)	6.80—8.10 (m, 12 H); 7.12 (s, 13 H)*	3.85, 3.91 (both s, 3 H, OMe, *E* : *Z* = 2 : 1)
2c	3.13 (t, *J* = 6.0)	4.30 (t)	8.16, 7.60 (both d, 2 H each, $C_6H_4NO_2$, *J* = 8.6); 6.60—7.45 (m, 8 H); 7.30 (s, 13 H)*	—
2d	3.05 (t, *J* = 6.0)	4.20 (t)	6.60—7.40 (m, 12 H)	3.90 (s, 3 H, OMe)
2e	3.14 (t, *J* = 6.0)	4.15 (t)	6.70—7.50 (m, 11 H); 7.00 (s, 13 H)*	3.65, 3.91 (both s, 3 H each, OMe)
2f	3.15 (t, *J* = 6.0)	4.28 (t)	6.70—7.40 (m, 11 H); 6.98 (s, 13 H)*	5.92 (s, 2 H, OCH_2O)
5a	6.65 (d, *J* = 7.6)	8.10 (d)*	7.15—8.12 (m, 13 H)	4.70 (s, 2 H, $C\underline{H}_2Ar$)
5b	6.63 (d, *J* = 7.4)	8.00 (d)*	6.70—8.00 (m, 12 H)	3.70 (s, 3 H, OMe); 4.60 (s, 2 H, $C\underline{H}_2Ar$)
5c	6.83 (d, *J* = 7.4)	8.30 (d)	6.90—8.20 (m, 12 H)	4.26 (s, 2 H, $C\underline{H}_2Ar$)
6a	3.18 (t, *J* = 6.0)	4.30 (t)	7.10—7.55 (m, 13 H)	4.50 (s, 2 H, $C\underline{H}_2Ar$)
6b	3.20 (t, *J* = 6.0)	4.28 (t)	6.90—7.70 (m, 12 H)	3.80 (s, 3 H, OMe); 4.46 (s, 2 H, $C\underline{H}_2Ar$)
6c	3.19 (t, *J* = 6.4)	4.32 (t)	7.11—7.45 (m, 10 H); 8.13 (d, 2 H, $C_6H_4NO_2$, *J* = 8.5)	4.57 (s, 2 H, $C\underline{H}_2Ar$)

* The signals overlap.

salts **3a—c** were reduced to 12-benzylindoloisoquinolines **5a—c** in good yields, with retained aromaticity of the polyfused framework (Scheme 3). Their structures were confirmed by UV and ^{1}H NMR spectra. Thus the UV spectrum of compound **5a** shows four absorption bands (λ_{max} = 290, 307, 362, and 370 nm) only slightly differing from those in the spectrum of parent tetracycle **4** (λ_{max} = 286, 305, 366, and 370 nm). This indicates the retained aromaticity of the indolizine fragment. Molecular formulas of compounds **5a—c** were confirmed by their mass spectra containing $[M]^+$ molecular ion peaks of maximum intensity. In all cases, salts **3** undergo side hydrogenolysis to give indoloisoquinoline **4** (3—5%) and its 5,6-dihydro derivative **1** (0.5—1%).

There were even better grounds to expect stable tetrahydro compounds of type **B** to form from 12-benzylidene-5,6-dihydro derivatives **2a—c** in the same system ($NaBH_4$—TFA) since one double bond in the starting reagent is already reduced. However, the reaction products were 12-benzyl-5,6-dihydroindoloisoquinolines **6a—c** in somewhat lower yields than for **5a—c**.

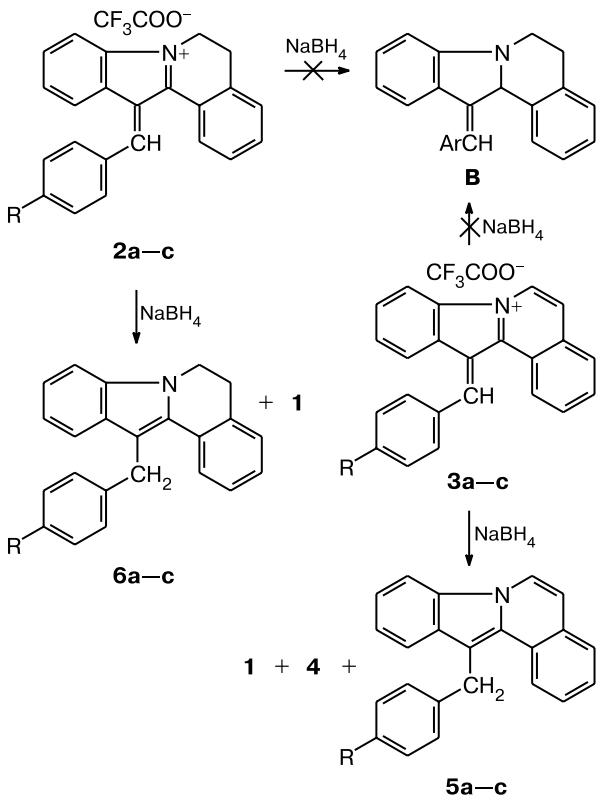
Accompanying reductive elimination of the benzyl group gave compound **1** in ≤5% yield.

Thus, the exocyclic C(12)=C(13) bond conjugated with the pyrrolenine ring in quaternary salts **2** and **3** undergoes unusual reduction with sodium borohydride, which enables us to propose a new two-step route for arylmethylation of the pyrrole ring in indolizine derivatives.

Fluorescence was found for compounds **1**, **2a—d,f**, **3a—c**, **4**, **5b,c**, and **6b,c** (see Table 1). The frameworks of **3—5** are completely aromatic, and their fluorescence maxima appears at 382—454 nm; having a longer π-conjugation chain, arylidene salts **3a—c** fluoresce in the longer-wavelength range (λ_{max} = 408—454 nm) compared to 12-benzylindoloisoquinolines **5b,c** (λ_{max} = 382—386 nm).

The π-conjugation chain in salts **3a,b** is longer than in compound **4**; hence it is not surprising that a fluorescence band experiences a bathochromic shift from λ_{max} = 444 nm in **4** to λ_{max} = 452 and 454 nm in **3a,b**, respectively. This is not the case of nitrobenzylidene trifluoroacetate **3c**, which fluoresces in the shorter-wavelength range (λ_{max} = 408 nm). The NO_2 group is known to often affect fluorescent properties specifically.[8] The hypsochromic shift of the fluorescence band for compound **3c** is probably due to strong electron-withdrawing properties of the excited NO_2 group; as a result, the electron density in the $S_0 \rightarrow S_1$ transition can be displaced in the opposite direction to the charge transfer from the C(12) atom. Apparently, a competition between these two processes loosens the double bond between the *para*-nitrobenzylidene and dibenzo-

Scheme 3



3, 5, 6: R = H (**a**), OMe (**b**), NO_2 (**c**)

indolizine fragments, which in turn reduces π-conjugation in the molecule. When the trifluoroacetate anion in salt **3c** is replaced by an acetate or trichloroacetate one, the fluorescence bands experience a significant shift (λ_{max} = 377 and 446 nm, respectively) attributed to the degree of dissociation of these salts in solution.

The spectra of 5,6-dihydro compounds **2** and **6** show fluorescence maxima in the shorter-wavelength range (λ_{max} = 368—388 nm) compared to aromatic analogs **3** and **5** and mainly have a diffuse vibrational structure. Apparently, both effects are due to the presence of a $-CH_2-CH_2-$ bridge, which breaks one of the π-conjugation chains. In addition, molecules **2** and **6** become less planar in the excited state in ethanol, as evidenced by a diffuse character of their fluorescence spectra.

Experimental

Compounds were isolated and purified by crystallization and column chromatography on L-60 silica gel (40/100). The purity of the products was checked by TLC on Silufol UV-254 plates in heptane—ether (1 : 1); spots were visualized with iodine vapor. ^{1}H NMR spectra were recorded on a Bruker WP-250 instrument (250 MHz) in $CDCl_3$ with Me_4Si as the internal standard. IR spectra were recorded on a UR-20 instrument (in pellets with KBr). Mass spectra were obtained with an MKh-1303 spectrometer (ionizing voltage 70 eV). Fluorescence spectra were measured on a Shimadzu RF-540 spectrofluorometer. Ethanol was used as a solvent; its purity was checked by UV absorption and fluorescence spectra. The concentration of solutions of the compounds studied in EtOH was ~10^{-6} mol L^{-1}.

12-Arylidene-5,6-dihydroindolo[2,1-*a*]isoquinolinium trifluoroacetates 2a—f (general procedure). Trifluoroacetic acid (10 mL) and an aromatic aldehyde (4.6 mmol) were successively added to a stirred, ice-cooled solution of 5,6-dihydroindoloisoquinoline **1** (4.6 mmol) in 25 mL of THF. The reaction mixture was kept at ~20 °C for 6 h. The solvents were removed *in vacuo*, and the residue was recrystallized from EtOH and purified by chromatography on SiO_2. The characteristics of trifluoroacetates **2a—f** are given in Tables 1 and 2.

Reduction of indolo[2,1-*a*]isoquinoline 4 in a $NaBH_4$—CF_3COOH system. Sodium borohydride (0.46 g, 12 mmol) was added in 0.1-g portions over 20 min to a vigorously stirred ice-cooled mixture of indoloisoquinoline **4** (0.65 g, 2.9 mmol) in 15 mL of anhydrous THF and 5.8 mL of TFA. The reaction mixture was stirred at ~20 °C for 6 h. The solvent and the excess of TFA were removed *in vacuo*. The residue was treated with a saturated aqueous solution of $NaHCO_3$. The product was extracted with $CHCl_3$ (4×10 mL), and the extract was dried over anhydrous Na_2SO_4. The chloroform was removed, and the oily residue was purified by column chromatography on SiO_2 to give 5,6-dihydroindoloisoquinoline **1** (0.13 g, 20%). Product **1** is identical in spectroscopic characteristics with an authentic sample.[9]

Hydrogenation of 12-benzylideneindoloisoquinolinium trifluoroacetate 2a over Re_2S_7. The reaction was carried out according to the known procedure.[9] Rhenium heptasulfide (0.05 g), salt **2a** (0.5 g, 1.2 mmol), and benzene (10 mL) were placed in a reaction vessel. Hydrogenation was performed at 250 °C and a hydrogen pressure of 140 atm for 2 h. Purification and separation of the catalyzate on SiO_2 gave nonsubstituted 5,6-dihydroindoloisoquinoline **1** (0.25 g, 96%). Product **1** is identical in characteristics with an authentic sample.[9]

Reduction of 12-arylideneindoloisoquinolinium trifluoroacetates 3a—c and their 5,6-dihydro analogs 2a—c in a $NaBH_4$—CF_3COOH system. The synthesis of 12-benzylindolo[2,1-*a*]isoquinolines 5a—c and 12-benzyl-5,6-dihydroindolo[2,1-*a*]isoquinolines 6a—c (general procedure). Trifluoroacetic acid (1 mL, 1.54 g, 13.5 mmol) was added dropwise to a stirred, ice-cooled suspension of an indoloisoquinolinium salt (**3a—c** or **2a—c**) (0.5 mmol) and $NaBH_4$ (0.073 g, 1.92 mmol) in 5 mL of anhydrous THF. The reaction mixture was stirred at ~20 °C for 6 h. The solvent and the excess of TFA were removed *in vacuo*. The residue was neutralized with a saturated solution of $NaHCO_3$, and the product was extracted with $CHCl_3$ (5×10 mL). The combined extracts were dried over anhydrous Na_2SO_4. The solvent was removed, and the residue was crystallized from EtOH or purified by column chromatography on SiO_2 in ether—hexane (1 : 1). 12-Benzylindoloisoquinolines **5a—c** or **6a—c** were isolated as slightly colored crystals. Side hydrogenolysis of compounds **3a—c** gave indoloisoquinolines **1** and **4** in 0.5—1% and 3—5% yields, respectively; the yield of indoloisoquinoline **4** from compounds **2a—c** was ~5%.

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