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Synthesis of 5,7,11 b,12-Tetrahydro-isoindolo[2,1—b]isoquinolinium Methiodides and Their *Stevens* Rearrangement[1]

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The title compounds **5** were synthetized in two steps from the corresponding isoindolo[2,1—b]isoquinoline-5(7*H*)-ones **3**, obtained in high yields from 3-ethoxy-1*H*-isoindoles **2** and homophthalic anhydrides **1**. The *Stevens* rearrangement of **5** gave 2-methyl-2,3-dihydro-1*H*-isoindole-1-spiro-2′-indanes **6**.

[Keywords: Homophthalic anhydrides; Isoindolo[2,1—b]isoquinoline-5(7H)-ones; 2-Methyl-2,3-dihydro-1H-isoindole-1-spiro-2′-indanes; Stevens rearrangement; 5,7,11b,12-Tetrahydro-1H-isoindolo[2,1—b]isoquinolines]

Synthese von 5,7,11b,12-Tetrahydro-isoindolo[2,1—b]isochinolinium Methiodiden und ihre Stevens-Umlagerung

Die Titelverbindungen **5** wurden in zwei Stufen aus den entsprechenden Isoindolo[2,1—b]isochinolin-5(7*H*)-onen (**3**) dargestellt, die ihrerseits in hohen Ausbeuten aus 3-Ethoxy-1*H*-isoindolen (**2**) und Homophthalsäureanhydriden erhältlich sind. Die *Stevens*-Umlagerung von **5** führte zu 2-Methyl-2,3-dihydro-1*H*-isoindol-1-spiro-2′-indanen (**6**).

The isoindolo[2,1—b]isoquinoline-5(7*H*)-ones **3a**[2], **3b** and **3c** were obtained from the homophthalic anhydrides **1a**, **b** and the lactim ethers **2a**[3] and **2b** in yields of 74 to 75% as an extension of the recently described method for preparation of isoquinolinone derivatives[4]. From **3b**, **c** the 5,7,11 b,12-tetrahydro-isoindolo[2,1—b]isoquinolines **4b**[5] and **4c** were obtained in analogy to a known procedure[6] in yields of 84 to 85%. The compounds **4b** and **4c** were transformed into the corresponding diastereomeric mixtures of the methiodides **5b** and **5c**, which were resolved into the pure isomers (*cis*-**5**b, **c** and *trans*-**5b**, **c**) by fractional

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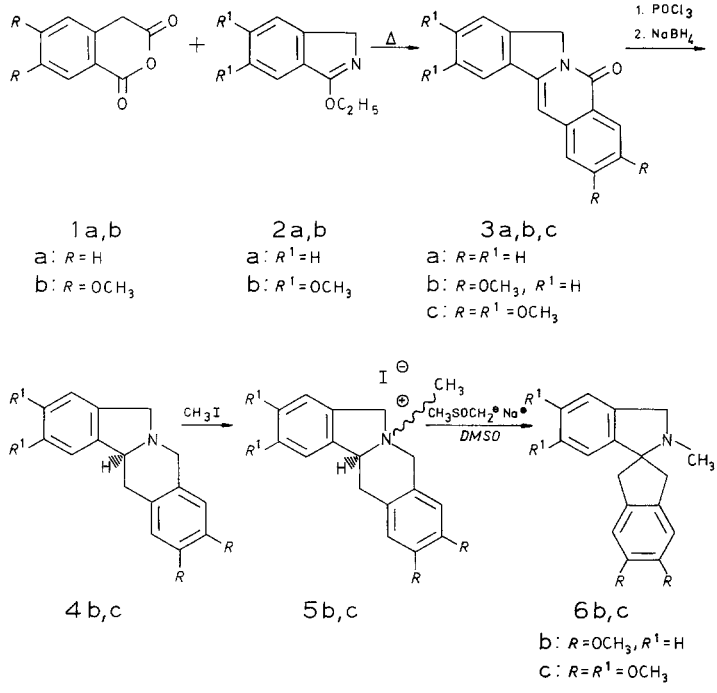
recrystallization. In agreement with[7], on the basis of the ^{1}H-NMR spectra, the *cis* configuration was ascribed to the isomers with higher, and *trans* configuration to the isomers with lower melting points respectively.

It is known, that the *Stevens* rearrangement of quaternary salts of the type **5** with phenyllithium results in the formation of pavine



structures in moderate yields[8,9]. It was shown recently, that dimsylsodium (*DMSO* + NaH) is an excellent reagent for the *Stevens* rearrangement[10]. The diastereomeric mixtures **5b** and **5c**, if treated with dimsylsodium—in analogy to the rearrangement of berbinium methiodides into spirobenzylisoquinolines[10]—gave rise to 2-methyl-2,3-dihydro-1*H*-isoindole-1-spiro-2′-indanes (**6b**, **c**) in yields of 50%.

The *Stevens* rearrangement of the diastereomeric mixture **5c** with phenyllithium in diethyl ether or higher boiling inert solvents failed, leading only to the formation of traces of **6c** and the pavine alkaloid (±)-argemonine. The latter was isolated and identified by a direct comparison with an authentic sample[11].

Experimental

All melting points are uncorrected. The IR spectra were recorded on a Specord 71-IR instrument using 1% chloroform solutions. The ^{1}H-NMR spectra were taken on a Tesla BS-487-C (80 MHz) or Jeol JNM-PS-100 spectrometers with *TMS* as internal standard.

The 5,6-dimethoxy-3-ethoxy-1*H*-isoindol (**2b**) was obtained from 5,6-dimethoxy-2,3-dihydro-1*H*-isoindol-1-one[12] (30 mmol) by alkylation with triethyloxonium tetrafluoroborate (60 mmol) in boiling dichloroethane analogously to the synthesis of **2a**[3].

The isoindolo[2,1—b]isoquinoline-5(7*H*)-ones **3a**, **b**, **c** were obtained from **1a**, **b** (2 mmol) and **2a**, **b** (2.2 mmol) in dry chlorobenzene analogously to[4], and purified by recrystallization.

The methiodides **5b**, **c** were obtained as a crude diastereomeric mixtures in quantitative yields from **4b**, **c** (2 mmol) and methyliodide (10 mmol) in dry benzene. *Cis*-**5b** and cis-**5c** were obtained after two recrystallizations of **5b** and **5c** from dry methanol. From the combined mother liquors after evaporation of the solvent, *trans*-**5b** was isolated by fractional recrystallization from dry methanol—dry ether, and *trans*-**5c** from dry methanol.

The 2-methyl-2,3-dihydro-1*H*-isoindole-1-spiro-2′-indanes **6b**, **c** were obtained by treatment of **5b** or **5c** with dimsylsodium. From **4b** or **4c** (2 mmol) were prepared as above crude diastereomeric mixtures **5b** or **5c**, which were dissolved in dry dimethylsulfoxide (12 ml). The so obtained solution was added dropwise during 15 min at room temperature into a stirred solution of dimsylsodium, prepared by heating at 75 °C of stirred mixture of sodium hydride (0.04 mol) and dry dimethylsulfoxide (12 ml) under dry nitrogen. After stirring for 3 h at room temperature and work-up[10], the crude product was purified by a column chromatography on silica gel with ether—*n*-hexane or ether—methanol. Experimental data are summarized in the Table.

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Table 1

Product	Yield [%]	mp [°C] (solvent)	IR [cm^{-1}]	Molecular formula[a]	^{1}H-NMR (δ, ppm) (J in Hz)
2b	81.3	106-107 (ether-n-C_6H_{14})	1610	$C_{12}H_{15}NO_3$ (221.2)	1.53 (t, $J = 7.4$, 3H, CH_3); 3.95 (s, 6H, 2 OCH_3); 4.53 (q, $J = 7.4$, 2H, OCH_2); 4.54 (s, 2H, H-1); 7.03 (s, 1H, H-7); 7.06 (s, 1H, H-4)-$CDCl_3$/80 MHz.
3a	74.8	193-195[b] (C_6H_6-n-C_6H_{14})	1665	$C_{16}H_{11}NO$ (233.2)	5.05 (s, 2H, H-7); 6.85 (s, 1H, H-12); 7.0-7.9 (m, 7H arom.); 8.43 (apparent d, 1H, H-4)-$CDCl_3$/80 MHz.
3b	75	245-247 ($CHCl_3$-CH_3OH)	1660	$C_{18}H_{15}NO_3$ (293.3)	3.90 + 3.95 (2s, 6H, 2 OCH_3); 4.95 (s, 2H, H-7); 6.68 + 6.75 (2s, 1H arom + H-12); 7.1-7.8 (m, 5H arom.)-$CDCl_3$/80 MHz.
3c	74.2	248-250 ($CHCl_3$-CH_3OH)	1665	$C_{20}H_{19}NO_5$ (353.4)	4.10 + 4.15 + 4.20 (3s, 12H, 4 OCH_3); 5.45 (s, 2H, H-7); 7.28 + 7.38 + 7.53 + 7.70 + 7.90 (5s, 4H arom. + H-12)-CF_3CO_2H/80 MHz.
4b	84.8	154-156[c] (C_2H_5OH)	2716 2770 2785	$C_{18}H_{19}NO_2$ (281.3)	2.6-4.4 (m, 7H, 3 CH_2 + H-11b); 3.83 (s, 6H, 2 OCH_3); 6.58 + 6.77 (2s, 2H, H-1 + H-4); 7.19 (s, 4H arom.)-$CDCl_3$/80 MHz.
4c	84.3	175-177 (C_2H_5OH)	2720 2770 2790	$C_{20}H_{23}NO_4$ (341.4)	2.6-4.3 (m, 7H, 3 CH_2 + H-11b); 3.86 (s, 12H, 4 OCH_3); 6.57 + 6.73 + 6.80 + 6.85 (4s, 4H arom.)-$CDCl_3$/100 MHz.
cis-**5b**		231-232[d] (CH_3OH)	1615	$C_{19}H_{22}NO_2I$ (423.3)	2.50 (s, 3H, NCH_3); 2.5-3.8 (m, 2H, H-12); 3.47 + 3.50 (2s, 6H, 2 OCH_3); 4.2-4.9 (m, 5H, CH_2NCH_2 + H-11b); 6.47 + 6.57 (2s, H-1 + H-4); 6.9-7.3 (m, 4H arom.)-CF_3CO_2H/100 MHz.

trans-**5 b**		160–162 (CH_3OH—ether)	1615	$C_{19}H_{22}NO_2I$ (423.3)	2.6–3.7 (m, 2 H, H-12); 3.06 (s, 3 H, NCH_3); 3.47 + 3.53 (2 s, 6 H, $2\,OCH_3$); 4.23 + 4.54 (2 s, 4 H, CH_2NCH_2); 4.88 (t, $J = 6$, 1 H, H-11 b); 6.55 + 6.67 (2 s, 2 H, H-1 + H-4); 6.7–7.2 (m, 4 H arom.)-CF_3CO_2H/100 MHz.
cis-**5 c**		252–254 (CH_3OH)	1615	$C_{21}H_{26}NO_4I$ (483.3)	2.56 (s, 3 H, NCH_3); 2.5–3.8 (m, 2 H, H-12); 3.52 + 3.54 + 3.56 (3 s, 12 H, $4\,OCH_3$); 4.2–4.9 (m, 5 H, CH_2NCH_2 + H-11 b); 6.42 + 6.55 + 6.64 + 6.73 (4 s, 4 H arom.)-CF_3CO_2H/100 MHz.
trans-**5 c**		144–146 (CH_3OH)	1615	$C_{21}H_{26}NO_4I$ (483.3)	2.6–3.8 (m, 2 H, H-12); 3.05 (s, 3 H, NCH_3); 3.48 + 3.52 + 3.54 (3 s, 12 H, $4\,OCH_3$); 4.24 + 4.48 (2 s, 4 H, CH_2NCH_2); 4.76 (t, $J = 6$, 1 H, H-11 b); 6.41 + 6.51 + 6.58 + 6.64 (4 s, 4 H arom.)-CF_3CO_2H/100 MHz.
6 b	50[e]	120–122 (n-C_6H_{14})	1615	$C_{19}H_{21}NO_2$ (295.4)	2.42 (s, 3 H, NCH_3); 3.08 (q, $J_{gem} = 16$, 4 H, H-1′ + H-3′); 3.83 (s, 6 H, $2\,OCH_3$); 3.93 (s, 2 H, CH_2N); 6.7–7.2 (m, 6 H arom.)-$CDCl_3$/100 MHz.
6 c	50.2[e]	164–166 (C_6H_6—n-C_6H_{14})	1615	$C_{21}H_{25}NO_4$ (355.4)	2.42 (s, 3 H, NCH_3); 3.14 (q, $J_{gem} = 16$, 4 H, H-1′ + H-3′); 3.78 (s, 2 H, CH_2N); 3.86 (s, 12 H, $4\,OCH_3$); 6.43 (s, 1 H, H-7); 6.80 (s, 3 H arom.)-$CDCl_3$/100 MHz.

[a] Elemental analyses are in full agreement with the calculated values.
[b] Ref.[2] mp. 193–194 °C (C_6H_6—n-C_6H_{14}).
[c] Ref.[5] mp. 154–156 °C (C_2H_5OH—H_2O).
[d] Ref.[5] mp. 231–232 °C (CH_3OH).
[e] Calculated overall yield from **4 b, c**.

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