

## Synthesis of 5,7,11 b,12-Tetrahydro-isoindolo[2,1—b]isoquinolinium Methiodides and Their Stevens Rearrangement<sup>1</sup>

Vassil I. Ognyanov<sup>a</sup>, Marietta A. Haimova<sup>b,\*</sup>, and Nikola M. Mollov<sup>a</sup>

<sup>a</sup> Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Sofia 1113

<sup>b</sup> Faculty of Chemistry, University of Sofia, 1126 Sofia, Bulgaria

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The title compounds **5** were synthesized 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(7*H*)-ones; 2-Methyl-2,3-dihydro-1*H*-isoindole-1-spiro-2'-indanes; Stevens rearrangement; 5,7,11 b,12-Tetrahydro-1*H*-isoindolo[2,1—b]isoquinolines]

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



## Experimental

All melting points are uncorrected. The IR spectra were recorded on a Specord 71-IR instrument using 1% chloroform solutions. The  $^1\text{H-NMR}$  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<sup>12</sup> (30 mmol) by alkylation with triethyloxonium tetrafluoroborate (60 mmol) in boiling dichloroethane analogously to the synthesis of **2a**<sup>3</sup>.

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<sup>4</sup>, and purified by recrystallization.

The methiodides **5b**, **c** were obtained as a crude diastereomeric mixtures in quantitative yields from **4b**, **c** (2 mmol) and methyl iodide (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 dimethylsodium. 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 dimethylsodium, 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<sup>10</sup>, 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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## References

- <sup>1</sup> Presented as a preliminary report at the 8th International Congress of Heterocyclic Chemistry, Graz, Austria (August 23-28, 1981).
- <sup>2</sup> *Godfrey J. C.*, *J. Org. Chem.* **24**, 581 (1959).
- <sup>3</sup> *Petersen S.*, *Tietze E.*, *Liebigs Ann. Chem.* **623**, 166 (1959).
- <sup>4</sup> *Haimova M. A.*, *Ognyanov V. I.*, *Mollov N. M.*, *Synthesis* **10**, 845 (1980).
- <sup>5</sup> *Kodama K.*, *J. Pharm. Soc. Japan* **63**, 54 (1943); *C. A.* **45**, 5169 b (1951).
- <sup>6</sup> *Kametani T.*, *Sugai T.*, *Shoji Y.*, *Honda T.*, *Saitoh F.*, *Fukumoto K.*, *J. Chem. Soc., Perkin Trans. II* **1977**, 1151.

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Table 1

Product	Yield [%]	mp [°C] (solvent)	IR [cm <sup>-1</sup> ]	Molecular formula <sup>a</sup>	<sup>1</sup> H-NMR (δ, ppm) (J in Hz)
<b>2b</b>	81.3	106-107 (ether- <i>n</i> -C <sub>6</sub> H <sub>14</sub> )	1610	C <sub>12</sub> H <sub>15</sub> NO <sub>3</sub> (221.2)	1.53 (t, <i>J</i> = 7.4, 3 H, CH <sub>3</sub> ); 3.95 (s, 6 H, 2 OCH <sub>3</sub> ); 4.53 (q, <i>J</i> = 7.4, 2 H, OCH <sub>2</sub> ); 4.54 (s, 2 H, H-1); 7.03 (s, 1 H, H-7); 7.06 (s, 1 H, H-4)-CDCl <sub>3</sub> /80 MHz.
<b>3a</b>	74.8	193-195 <sup>b</sup> (C <sub>6</sub> H <sub>6</sub> - <i>n</i> -C <sub>6</sub> H <sub>14</sub> )	1665	C <sub>16</sub> H <sub>17</sub> NO (233.2)	5.05 (s, 2 H, H-7); 6.85 (s, 1 H, H-12); 7.0-7.9 (m, 7 H arom.); 8.43 (apparent d, 1 H, H-4)-CDCl <sub>3</sub> /80 MHz.
<b>3b</b>	75	245-247 (CHCl <sub>3</sub> -CH <sub>3</sub> OH)	1660	C <sub>18</sub> H <sub>15</sub> NO <sub>3</sub> (293.3)	3.90 + 3.95 (2s, 6 H, 2 OCH <sub>3</sub> ); 4.95 (s, 2 H, H-7); 6.68 + 6.75 (2s, 1 H arom + H-12); 7.1-7.8 (m, 5 H arom.)-CDCl <sub>3</sub> /80 MHz.
<b>3c</b>	74.2	248-250 (CHCl <sub>3</sub> -CH <sub>3</sub> OH)	1665	C <sub>20</sub> H <sub>19</sub> NO <sub>5</sub> (353.4)	4.10 + 4.15 + 4.20 (3s, 12 H, 4 OCH <sub>3</sub> ); 5.45 (s, 2 H, H-7); 7.28 + 7.38 + 7.53 + 7.70 + 7.90 (5s, 4 H arom. + H-12)-CF <sub>3</sub> CO <sub>2</sub> H/80 MHz.
<b>4b</b>	84.8	154-156 <sup>c</sup> (C <sub>2</sub> H <sub>5</sub> OH)	2716 2770 2785	C <sub>18</sub> H <sub>19</sub> NO <sub>2</sub> (281.3)	2.6-4.4 (m, 7 H, 3 CH <sub>2</sub> + H-11 b); 3.83 (s, 6 H, 2 OCH <sub>3</sub> ); 6.58 + 6.77 (2s, 2 H, H-1 + H-4); 7.19 (s, 4 H arom.)-CDCl <sub>3</sub> /80 MHz.
<b>4c</b>	84.3	175-177 (C <sub>2</sub> H <sub>5</sub> OH)	2720 2770 2790	C <sub>20</sub> H <sub>23</sub> NO <sub>4</sub> (341.4)	2.6-4.3 (m, 7 H, 3 CH <sub>2</sub> + H-11 b); 3.86 (s, 12 H, 4 OCH <sub>3</sub> ); 6.57 + 6.73 + 6.80 + 6.85 (4s, 4 H arom.)-CDCl <sub>3</sub> /100 MHz.
<i>cis-5b</i>		231-232 <sup>d</sup> (CH <sub>3</sub> OH)	1615	C <sub>19</sub> H <sub>23</sub> NO <sub>2</sub> I (423.3)	2.50 (s, 3 H, NCH <sub>3</sub> ); 2.5-3.8 (m, 2 H, H-12); 3.47 + 3.50 (2s, 6 H, 2 OCH <sub>3</sub> ); 4.2-4.9 (m, 5 H, CH <sub>2</sub> NCH <sub>3</sub> + H-11 b); 6.47 + 6.57 (2s, H-1 + H-4); 6.9-7.3 (m, 4 H arom.)-CF <sub>3</sub> CO <sub>2</sub> H/100 MHz.

<i>trans</i> - <b>5b</b>	160-162 (CH <sub>3</sub> OH— ether)	1615	C <sub>19</sub> H <sub>22</sub> NO <sub>2</sub> I (423.3)	2.6-3.7 (m, 2 H, H-12); 3.06 (s, 3 H, NCH <sub>3</sub> ); 3.47 + 3.53 (2 s, 6 H, 2 OCH <sub>3</sub> ); 4.23 + 4.54 (2 s, 4 H, CH <sub>2</sub> NCH <sub>2</sub> ); 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 <sub>3</sub> CO <sub>2</sub> H/100 MHz.
<i>cis</i> - <b>5c</b>	252-254 (CH <sub>3</sub> OH)	1615	C <sub>21</sub> H <sub>26</sub> NO <sub>4</sub> I (483.3)	2.56 (s, 3 H, NCH <sub>3</sub> ); 2.5-3.8 (m, 2 H, H-12); 3.52 + 3.54 + 3.56 (3 s, 12 H, 4 OCH <sub>3</sub> ); 4.2- 4.9 (m, 5 H, CH <sub>2</sub> NCH <sub>2</sub> + H-11 b); 6.42 + 6.55 + 6.64 + 6.73 (4 s, 4 H arom.)-CF <sub>3</sub> CO <sub>2</sub> H/ 100 MHz.
<i>trans</i> - <b>5c</b>	144-146 (CH <sub>3</sub> OH)	1615	C <sub>21</sub> H <sub>26</sub> NO <sub>4</sub> I (483.3)	2.6-3.8 (m, 2 H, H-12); 3.05 (s, 3 H, NCH <sub>3</sub> ); 3.48 + 3.52 + 3.54 (3 s, 12 H, 4 OCH <sub>3</sub> ); 4.24 + 4.48 (2 s, 4 H, CH <sub>2</sub> NCH <sub>2</sub> ); 4.76 (t, J = 6, 1 H, H-11 b); 6.41 + 6.51 + 6.58 + 6.64 (4 s, 4 H arom.)-CF <sub>3</sub> CO <sub>2</sub> H/100 MHz.
<b>6b</b>	120-122 ( <i>n</i> -C <sub>6</sub> H <sub>14</sub> )	1615	C <sub>19</sub> H <sub>21</sub> NO <sub>2</sub> (295.4)	2.42 (s, 3 H, NCH <sub>3</sub> ); 3.08 (q, J <sub>gem</sub> = 16, 4 H, H-1' + H-3'); 3.83 (s, 6 H, 2 OCH <sub>3</sub> ); 3.93 (s, 2 H, CH <sub>2</sub> N); 6.7-7.2 (m, 6 H arom.)- CDCl <sub>3</sub> /100 MHz.
<b>6c</b>	164-166 (C <sub>6</sub> H <sub>6</sub> — <i>n</i> -C <sub>8</sub> H <sub>14</sub> )	1615	C <sub>21</sub> H <sub>25</sub> NO <sub>4</sub> (355.4)	2.42 (s, 3 H, NCH <sub>3</sub> ); 3.14 (q, J <sub>gem</sub> = 16, 4 H, H-1' + H-3'); 3.78 (s, 2 H, CH <sub>2</sub> N); 3.86 (s, 12 H, 4 OCH <sub>3</sub> ); 6.43 (s, 1 H, H-7); 6.80 (s, 3 H arom.)-CDCl <sub>3</sub> /100 MHz.

<sup>a</sup> Elemental analyses are in full agreement with the calculated values.

<sup>b</sup> Ref.<sup>2</sup> mp. 193-194 °C (C<sub>6</sub>H<sub>6</sub>—*n*-C<sub>6</sub>H<sub>14</sub>).

<sup>c</sup> Ref.<sup>5</sup> mp. 154-156 °C (C<sub>2</sub>H<sub>5</sub>OH—H<sub>2</sub>O).

<sup>d</sup> Ref.<sup>5</sup> mp. 231-232 °C (CH<sub>3</sub>OH).

<sup>e</sup> Calculated overall yield from **4b**, **c**.

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- <sup>7</sup> Brewster J. H., Jones R. S., *J. Org. Chem.* **34**, 354 (1969).
- <sup>8</sup> Wittig G., Tenhaeff H., Schoch W., Koenig G., *Liebigs Ann. Chem.* **572**, 1 (1951).
- <sup>9</sup> Ito K., Furukawa H., Iida T., Lee K.-S., Soine T., *J. Chem. Soc. Chem. Commun.* **1974**, 1037.
- <sup>10</sup> Kano S., Yokomatsu T., Ono T., Takahagi Y., Shibuya S., *Chem. Pharm. Bull.* **25**, 2510 (1977).
- <sup>11</sup> Rice K. C., Ripka W. C., Reden J., Brossi A., *J. Org. Chem.* **45**, 60 (1980).
- <sup>12</sup> Kametani T., Honda T., Inoue H., Fukumoto K., *J. Chem. Soc., Perkin Trans. I* **1976**, 1221.