Chemistry of Heterocyclic Compounds, Vol. 37, No. 4, 2001

SYNTHESIS OF 14,15-DIHYDRO-8H-7a,15-METHANONAPHTH[1'2':6,7]-1,3-OXAZEPINO[3,2-*a*]INDOLE-14-CARBOXAMIDE DERIVATIVES

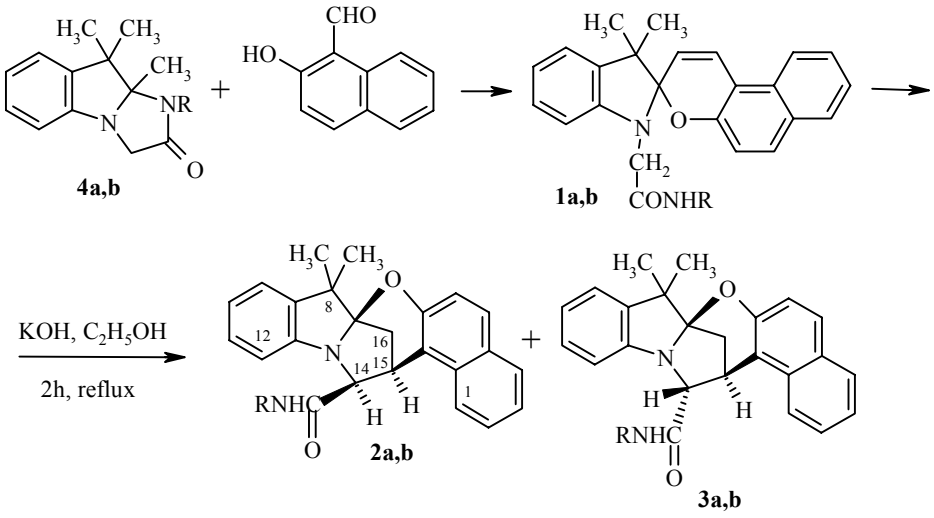
N. Kleiziene[1], V. Martynaitis[1], U. Berg[2], A. Sackus[1]

Keywords: imidazo[1,2-*a*]indole, indoline spiropyran, 7a,15-methanonaphth[1',2':6,7]oxazepino[3,2-*a*]-indole.

Since the discovery of the photochromism of indoline spiropyrans by Fischer and Hirshberg nearly 50 years ago [1], synthesis of this practically important class of heterocyclic compounds has been the target of many investigations. However, the chemical properties of indoline spiropyrans remain still poorly disclosed.

We report here that 1-(N-benzylcarbamoylmethyl)- and 1-(N-ethylcarbamoylmethyl)-2,3-dihydrospiro[1H-indole-2,2'-[2H]naphtho[2,1-*b*]pyrans] **1a,b** under treatment with a strong base easily rearrange to 7a,15-methanonaphth[1',2':6,7]-1,3-oxazepino[3,2-*a*]indole-14-carboxamide derivatives **2**, **3**.

The indoline spironaphthopyrans **1a,b** were synthesized by condensation of 1-benzyl- and 1-ethyl-9,9,9a-trimethyl-1,2,3,9a-tetrahydro-9H-imidazo[1,2-*a*]-indol-2-ones **4a,b** with 2-hydroxy-1-naphthaldehyde. The characteristic signals in the ^{1}H NMR spectrum of compounds **1a,b** represent the AB-pattern (^2J ~17.0 Hz) of diastereotopic NCH_2CO protons at ~3.7 ppm and a doublet (^3J ~10.5 Hz) of the vinyl proton in the area of 5.8-6.0 ppm.



1–4 a R = $CH_2C_6H_5$, **b** R = C_2H_5

[1] Department of Organic Chemistry, Kaunas University of Technology, LT-3028 Kaunas, Lithuania; e-mail: asackus@ctf.ktu.lt. [2] Department of Organic Chemistry 1, Department of Chemistry, Chemical Center, Lund University, Lund P.O.Box 124, 22100, Sweden.

0009-3122/01/3704-0517$25.00©2001 Plenum Publishing Corporation

Heating of compounds **1a,b** in ethanol with potassium hydroxide gave a mixture of diastereomeric compounds **2a,b** and **3a,b**. Both isomers could be cleanly separated by crystallization and the structures elucidated by analysis of ^{1}H and ^{13}C NMR spectra and application of 2-D NMR experiments (COSY and NOESY). The distinction of *cis*-**2a,b** and *trans*-**3a,b** was based upon vicinal *J*-values of the pyrrolidine ring. For example, the H–C(14)–C(15)–H coupling constants are ^{3}J = 5.1 Hz in *cis*-**2a** and 0 Hz in *trans*-**3a**. The dihedral angles obtained from MM3 optimized structures are 37.5° for *cis*-**2a** and 88.8° for *trans*-**3a**. The Karplus equation in the version of Bothner-By [2] in this case gives the coupling constants as 7.51 and 1.98 Hz, respectively. Similar values were found for the *cis*-**2b** and *trans*-**3b** diastereomers. The quantitative discrepancy is probably due to the effect of the substituents and the cyclopentane bond angle deformation as these molecules have very rigid ring structures.

(7a*R,14*S**,15*S**)-14,15-Dihydro-8,8-dimethyl-8H-7a,15-methanonaphth[1',2':6,7]-1,3-oxazepino-[3,2-*a*]indole-14-(N-benzylcarboxamide) (*cis*-2a) and Its (7a*R**,14*R**,15*S**)-Isomer (*trans*-3a).** A mixture of 1-benzylimidazo[1,2-*a*]indol-2-one **4a** [3] (1.53 g, 5 mmol) and 2-hydroxy-1-naphthaldehyde (0.86 g, 5 mmol) in acetic acid (8 ml) was heated at 100°C for 5 h; then the mixture was poured into 5% sodium acetate (100 ml) and extracted with ether (2 × 15 ml). The organic layer was separated, washed with water (20 ml), and dried with $MgSO_4$; the solvent was evaporated and the residue crystallized from ethanol. The obtained compound **1a** (1.22 g, 2.65 mmol) was dissolved in ethanol (10 ml), and finely powdered potassium hydroxide (0.44 g, 8 mmol) was added to the solution. The mixture was refluxed for 2 h and then allowed to reach room temperature. The precipitated crystals of *cis*-**2a** were collected by suction filtration, washed with water to remove sodium hydroxide, and recrystallized from ethanol. After filtration, the ethanol filtrate was poured into water and extracted with ether. The organic layer was washed with water and dried over $CaCl_2$. The solvent was evaporated under reduced pressure and the residue crystallized from ethanol to afford *trans*-**3a**. *cis*-**2a**, yield 0.33 g (27%); mp 203-204°C. IR spectrum, cm^{-1}: 1670 (C=O), 3375 (N–H). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ: 1.52 (3H, s, CH_3); 1.53 (3H, s, CH_3); 2.21 (1H, dd, *J* = 11.1, 0.6 Hz, 16-H); 2.28 (1H, dd, *J* = 11.1, 3.9 Hz, 16-H); 3.82 (1H, dd, *J* = 4.2, 15.0 Hz, ½ NCH_2); 4.18 (1H, d, *J* = 5.1 Hz, 14-H); 4.26 (1H, dd, *J* = 8.1, 15.0 Hz, ½ NCH_2); 4.54-4.57 (1H, m, 15-H); 6.28-8.12 ppm (16H, m, Ar-H, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ: 23.91 (CH_3), 27.13 (CH_3), 33.80 (C-16), 37.89 (C-15), 43.25 (NCH_2), 45.54 (C-8), 79.56 (C-14), 110.14 (C-7a), 111.20 (CH), 118.06 (C), 118.31 (CH), 122.72 (CH), 123.22 (CH), 123.74 (CH), 124.36 (CH), 127.48 (4CH), 128.74 (CH), 128.89 (2CH), 128.95 (CH), 129.79 (CH), 130.01 (C), 132.30 (C), 138.23 (C), 139.50 (C), 150.00 (C), 150.98 (C), 170.95 ppm (C=O). Found, %: C 80.99; H 6.03; N 5.88. $C_{31}H_{28}N_2O_2$. Calculated, %: C 80.84; H 6.12; N 6.08. *trans*-**3a**, yield 0.39 g (32%); mp 192-193°C. IR spectrum: 1645 (C=O), 3315 cm^{-1} (N–H). ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ: 1.25 (3H, s, CH_3); 1.64 (3H, s, CH_3); 2.18 (1H, d, *J* = 11.0 Hz, 16-H); 2.57 (1H, dd, *J* = 4.2, 11.0 Hz, 16-H); 4.36 (1H, dd, *J* = 5.1, 14.4 Hz, ½ NCH_2); 4.48 (1H, s, 14-H); 4.49 (1H, d, *J* = 4.2 Hz, 15-H); 4.54 (1H, dd, *J* = 4.5, 14.4 Hz, ½ NCH_2); 6.09 (1H, br t, NH); 6.28 (1H, d, *J* = 7.5 Hz, 12-H); 6.76-7.63 (12H, m, Ar-H); 7.76 (1H, d, *J* = 7.65 Hz, 4-H); 8.07 ppm (1H, d, *J* = 8.4 Hz, 1-H). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ: 21.42 (CH_3), 28.68 (CH_3), 29.12 (C-16), 42.46 (C-15), 44.24 (NCH_2), 45.28 (C-8), 68.42 (C-14), 107.78 (C-7a, C-12), 119.43 (CH), 120.14 (CH, C), 121.89 (CH), 123.51 (CH), 123.95 (CH), 127.52 (CH), 128.15 (CH), 128.28 (CH), 128.49 (2CH), 129.29 (CH), 129.41 (3CH), 129.49 (CH), 131.26 (C), 138.38 (C), 142.12 (C), 142.46 (C), 151.49 (C), 170.68 ppm (C=O). Found, %: C 80.99; H 6.03; N 5.87. $C_{31}H_{28}N_2O_2$. Calculated, %: C 80.84; H 6.12; N 6.08.

(7a*R,14*S**,15*S**)-14,15-Dihydro-8,8-dimethyl-8H-7a,15-methanonaphth[1',2':6,7]-1,3-oxazepino-[3,2-*a*]indole-14-(N-ethylcarboxamide) (*cis*-2b) and Its (7a*R**,14*R**,15*S**)-Isomer (*trans*-3b)** were synthesized from **4b** [3] (1.22 g, 5 mmol) by a similar method as compounds **2a, 3a**. *cis*-**2b**, yield 0.24 g (12%); mp 248-249°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ: 0.08 (3H, t, *J* = 6.9 Hz, $CH_2\underline{CH_3}$); 1.54 (3H, s, 8-CH_3); 1.59 (3H, s, 8-CH_3); 2.20-2.28 (2H, m, 16-H_2); 2.51-2.62 (1H, m, 0.5CH_2CH_3); 2.91-3.02 (1H, m, 0.5$CH_2\underline{CH_3}$); 4.08 (1H, d, *J* = 4.9 Hz, 14-H); 4.49-4.53 (1H, m, 15-H); 6.51-8.06 ppm (11H, m, Ar–H, NH). Found, %: C 78.55; H 6.47; N 6.69. $C_{26}H_{26}N_2O_2$. Calculated, %: C 78.36; H 6.57; N 7.02. *trans*-**3b**, yield 0.96 g (48%); mp 194-195°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ: 1.05 (3H, t, *J* = 7.2 Hz, $CH_2\underline{CH_3}$); 1.25 (3H, s, 8-CH_3);

1.64 (3H, s, 8-CH_3); 2.15 (1H, d, *J* = 11.3 Hz, 16-H); 2.53 (1H, dd, *J* = 4.0, 11.3 Hz, 16-H); 3.20-3.34 (2H, m, $\underline{CH_2}CH_3$); 4.41 (1H, s, 14-H); 4.46 (1H, m, 15-H); 5.75 (1H, br. s, NH); 6.24-8.08 ppm (10H, m, Ar-H). Found, %: C 78.10; H 6.63; N 7.08. $C_{26}H_{26}N_2O_2$. Calculated, %: C 78.36; H 6.57; N 7.02.

REFERENCES

1. E. Fischer and Y. Hirshberg, *J. Chem. Soc.,* 4522 (1952).
2. A. A. Bothner-By, *Adv. Magn. Res.,* No. 1, 195 (1965).
3. A. A. Sackus and J. A. Degutis, *Chem. Heterocycl. Comp. Engl. Transl.*, **24**, 41 (1988).