MAGNETIC RESONANCE IN CHEMISTRY
Magn. Reson. Chem. **36**, 873–877 (1998)

Note

NMR proof of a piperidine to pyrrolidine ring contraction during nucleophilic substitution

Gabrijela Ambrožič, Simon Čeh and Andrej Petrič*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, SI-1000 Ljubljana, Slovenia

Received 3 March 1998; revised 10 May 1998; accepted 20 May 1998

ABSTRACT: Products formed in the reaction of 1-(6-acetyl-2-naphthyl)-4- [(4-methylphenyl)sulfonyloxy] methylpiperidine with spiperone ketal, 8-{3-[2-(4-fluorophenyl)-1,3-dioxolan-2-yl]propyl}-1-phenyl-1,3,8-triazaspiro[4.5] decan-4-one, at room and elevated temperatures were compared and the respective structure were assigned based on ^{1}H and ^{13}C NMR spectra. Piperidine to pyrrolidine ring transformation at elevated temperature is documented.

KEYWORDS: NMR; ^{13}C NMR; ^{1}H NMR; piperidine; pyrrolidine; rearrangement

INTRODUCTION

Exploring synthetic routes to new fluorescent probes based on the structure of 2-(1,1-dicyanopropenyl-2),6-dimethylaminonaphthalene (DDNP),[1] we utilized nucleophilic substitution of the 4-methylphenylsulfonyloxygroup by spiperone, a highly potent ligand for dopaminergic D_2 receptor, in its ketal protected form, 8-{3-[2-(4-fluorophenyl)-1,3-dioxolan-2-yl]propyl}-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one.[2] Of special interest was the reaction of 1-(6-acetyl-2-naphthyl)-4-[(4-methylphenyl)sulfonyloxy] methylpiperidine (**1**; R = Ts). Compound **1** reacted with spiperone ketal under phase-transfer conditions at room temperature to give two major fluorescent products, **2** and **3** (Scheme 1).[2] After a long reaction time the desired *N*-alkylated product **2** was isolated in a low yield.

To achieve a shorter reaction time, we performed the reaction in DMF at 80 °C in the presence of anhydrous potassium carbonate. The isolated major fluorescent product exhibited exactly the same molecular mass and composition as **2** and **3**, but different NMR spectra. Using modern 1D and 2D NMR techniques, the structure of this product (**4**) was elucidated.

RESULTS AND DISCUSSION

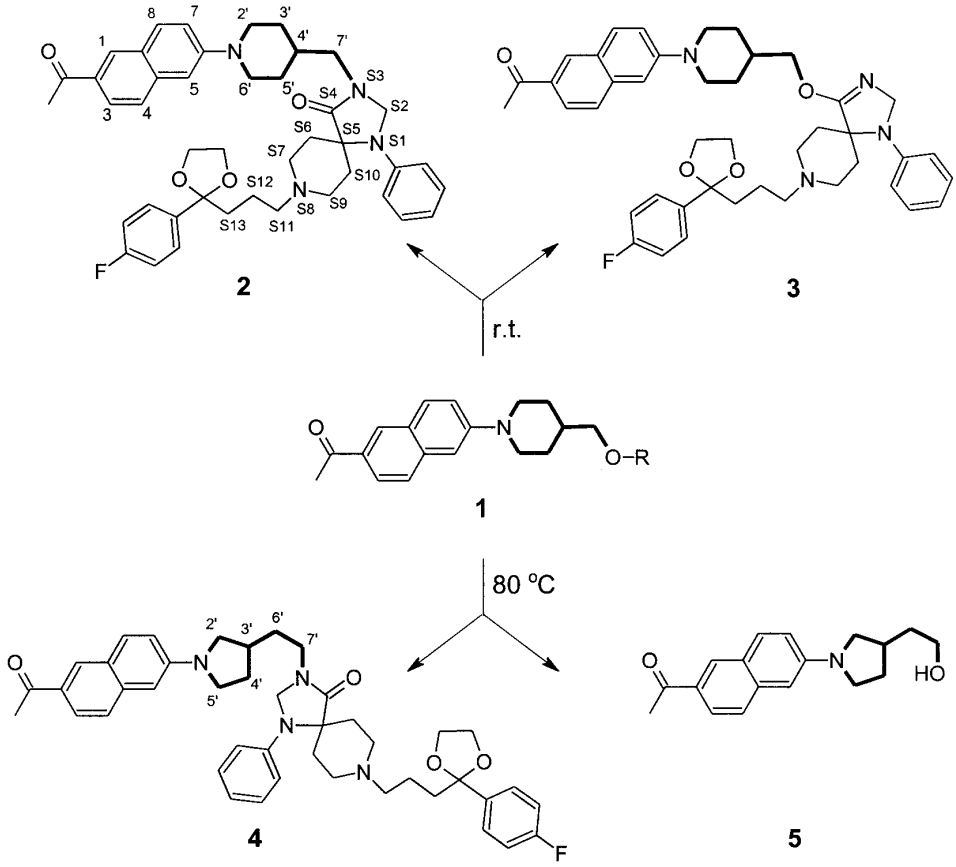
The molecular composition of **2**, **3** and **4**, as determined by high-resolution mass spectrometry (HRMS), was $C_{43}H_{49}FN_4O_4$, suggesting that in all three cases spiperone ketal substitution of the 4-methylphenylsulfonyloxy group in **1** (R = Ts) has occurred. NMR spectral assignments, especially ^{1}H, were not straightforward because of the overlapping signals in the aliphatic region. Nevertheless, we could distinguish between three subspectra, resulting from the acetylnaphthalene, spiperone ketal and the heterocyclic link between the two moieties.[2,3] As expected, parts of the spiperone ketal subspectrum, resulting from atoms in remote positions with respect to the imidazolinone ring, were not significantly affected by changes at the S3/S4 positions. On the other hand, major differences in chemical shifts for H-S2 in ^{1}H NMR spectra of **2** and **3** were indicative of the amide (**2**) and imide (**3**) structures.[2] The acetylnaphthalene subspectrum was the least sensitive to structural differences and did not offer much additional information about the structures. The most information on the respective structures was obtained from the heterocyclic link subspectra.

In the ^{1}H NMR spectra of compounds containing a 4-methylpiperidine structural element, a characteristic subspectrum, resulting from a chair conformation, could be recognized [Fig. 1(A)]. Such a subspectrum, already described for 4-piperidinemethanol [Fig. 1(B)] and some derivatives,[4] consisted of six well separated signals: two for equatorial and three for axial piperidine protons, and one for exocyclic methylene group protons. The respective areas of the signals reflected the symmetry of the 1,4-disubstituted piperidine moiety. Combining this information with the expected differences in chemical shifts for the doublet resulting from the exocyclic methylene group (NCH_2 *vs.* OCH_2), structures **2** and **3** were assigned to the two products, isolated in the reaction at room temperature.

In contrast to the spectra of **2** and **3**, the heterocyclic link spectrum of **4** [Fig. 1(C)] did not resemble that of the 1,4-disubstituted piperidine moiety. The characteristic doublet for the exocyclic methylene group was not

* *Correspondence to*: A. Petrič, Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, SI-1000 Ljubljana, Slovenia.
E-mail: andrej.petric@uni-lj.si
Contract/grant sponsor: US–Slovene Science and Technology Joint Fund; *Contract/grant number*: US-SLO 95/2-02.
Contract/grant sponsor: Ministry of Science and Technology of the Republic of Slovenia.

 CCC 0749-1581/98/110873–05 $17.50



Scheme 1. Compound **1** [R = H or Ts (4-methylphenylsulphonyl)] and its transformations. Numbering used in Tables 1–5.

present, and the areas of other pertinent signals did not correspond to a symmetric structure element. This indicated that during the reaction a skeletal rearrangement to an isomeric product must have occurred. Assignments are given in Tables 1–3.

Owing to overlap of the signals in the ^{1}H spectrum of **4**, we were unable to determine the structure of the heterocyclic link directly. A small amount of a side product was isolated from the reaction mixture. From its ^{1}H NMR and mass spectra we concluded that the molecule consisted only of the acetylnaphthalene moiety and a moiety containing 11 non-exchangeable protons. Of a total of 18 signals in the ^{13}C NMR spectrum, 12 were identified and ascribed to the acetylnaphthalene moiety. By a DEPT45 experiment we found that all of the remaining six signals belonged to protonated carbon atoms.

In the HMQC spectrum (Table 4), three of these, at 32.1, 48.0 and 54.0 ppm, had cross peaks to two multiplets each in ^{1}H NMR spectrum, revealing ^{1}H chemical shifts of three pairs of magnetically non-equivalent methylene protons (2′, 4′ and 5′). The signals at 36.8 and

Table 1. Acetylnaphthalene subspectra assignment

	1[a] (R = H)		**1** (R = Ts)[b]	**2**	**3**	**4**		**5**	
Atom	^{13}C	^{1}H	^{1}H	^{1}H	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
*C*H$_3$CO—	26.3	2.68 (s)	2.67 (s)	2.67 (s)	2.67 (s)	26.4	2.65 (s)	26.7	2.66 (s)
CH$_3$*C*O—	197.0					197.6		198.0	
1	130.0	8.32 (d)	8.31 (d)	8.32 (d)	8.32 (d)	130.6	8.30 (d)	131.0	8.30 (d)
2	130.4					130.4		130.7	
3	123.8	7.94 (dd)	7.94 (dd)	7.94 (dd)	7.95 (dd)	124.7	7.91 (dd)	125.1	7.91 (dd)
4	126.1	7.66 (d)	7.65 (d)	7.65 (d)	7.66 (d)	125.8	7.59 (d)	126.2	7.59 (d)
4a	136.5					137.9		138.2	
5	107.8	7.10 (d)	7.06 (d)	7.08 (d)	7.11 (d)	104.4	6.71 (d)	104.9	6.71 (d)
6	150.7					147.5		147.9	
7	118.5	7.32 (dd)	7.27 (dd)	7.32 (dd)	7.32 (dd)	114.8	7.00 (dd)	116.5	6.99 (dd)
8	130.3	7.80 (d)	7.78 (d)	7.79 (d)	7.81 (d)	131.0	7.78 (d)	131.3	7.78 (d)
8a	124.8					124.8		125.2	

[a] In DMSO.
[b] Ts group: H-2, H-6 [7.81 (d)]; H-3, H-5 [7.36 (d)]; CH$_3$ [2.46 (s)].

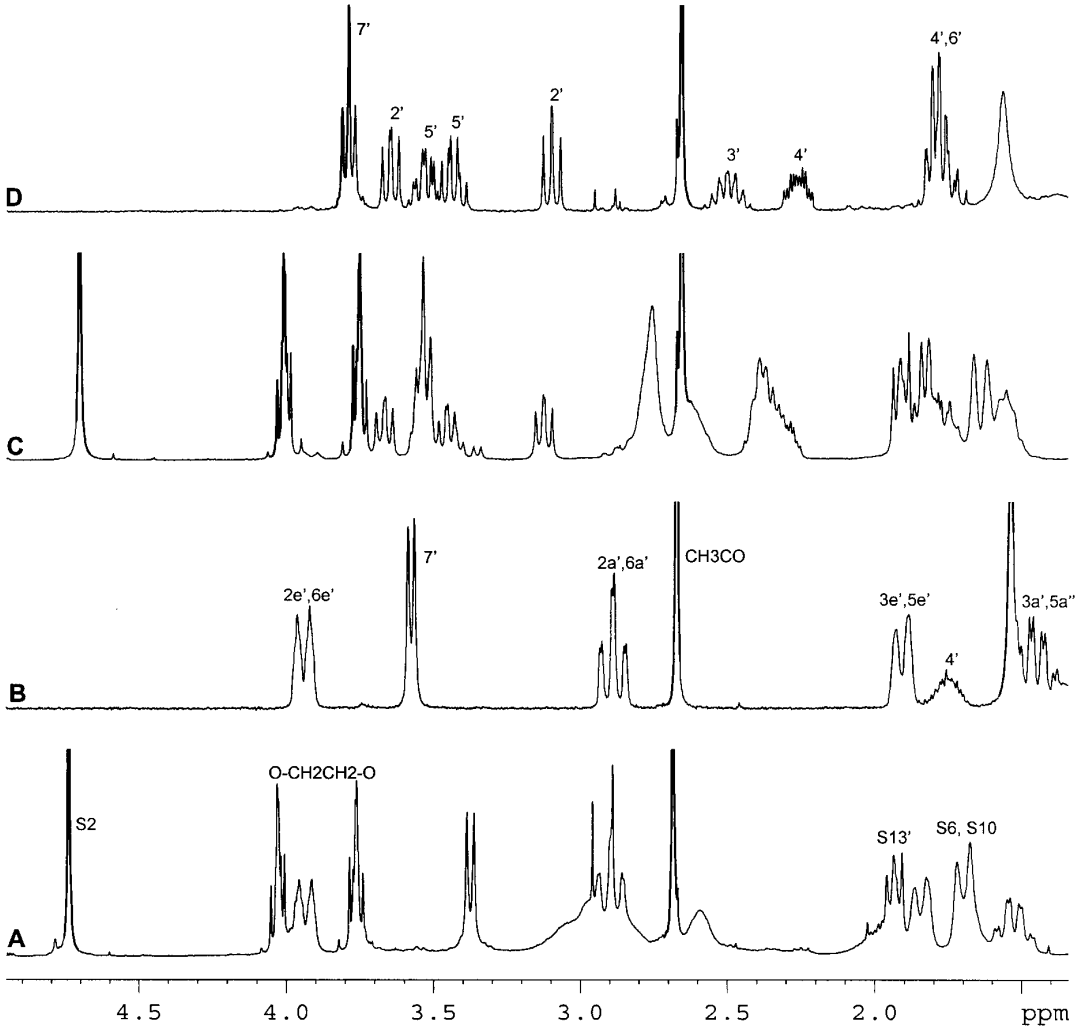


Figure 1. Partial ^{1}H spectra: (A) **2**; (B) **1** (R = H); (C) **4**; (D) **5**.

62.1 ppm were ascribed to two rotationally unrestricted exocyclic methylene groups (6′ and 7′) and the signal at 36.2 to a monoprotonated carbon atom (3′). Combining this with the information about the proton–proton coupling from a COSY45 spectrum (Table 5), we concluded that the molecule contained a hydroxyethyl group attached to the 3′ position in a pyrrolidine ring, and we assigned structure **5** to the isolated side product.

Table 2. Heterocyclic link moiety subspectra assignment

	1[a] (R = H)		**1** (R = Ts)	**2**	**3**	**4**		**5**	
Atom	^{13}C	^{1}H	^{1}H	^{1}H	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
2′	47.8	2.89 (ddd), 3.94 (bd)	2.83 (ddd), 3.87 (bd)	2.86 (bdd), 3.92 (bd)	2.95 (m), 3.92 (m)	53.3	3.13 (dd), 3.68 (dd)	54.0	3.10 (dd), 3.64 (dd)
3′	28.1	1.44 (bddd), 1.91 (bd)	1.40 (bddd) 1.85 (bd)	1.50 (bddd), 1.83 (bd)	1.48 (m), 1.84 (m)	36.5	2.37 (m)	36.2	2.50 (m)
4′	38.2	1.76 (m)	1.94 (m)	1.97 (m)	1.88 (m)	31.6	1.82 (m), 2.33 (m)	32.1	1.75 (m), 2.27 (m)
5′	28.1	1.44 (bddd), 1.91 (bd)	1.40 (bddd) 1.85 (bd)	1.50 (bddd), 1.84 (bd)	1.48 (m), 1.84 (m)	47.4	3.46 (m), 3.67 (m)	48.0	3.43 (ddd), 3.53 (ddd)
6′	47.8	2.89 (ddd), 3.94 (bd)	2.83 (ddd), 3.87 (bd)	2.86 (bdd), 3.92 (bd)	2.95 (m), 3.92 (m)	31.4	1.82 (m)	36.8	1.79 (m)
7′	65.6	3.58 (d)	3.92 (d)	3.35 (d)	4.19 (d)	39.8	3.53 (t)	62.1	3.79 (t)

[a] In DMSO.

Table 3. Spiperone subspectra assignment and coupling constants[a]

	2	3	4	
Atom	^{1}H	^{1}H	^{13}C	^{1}H
S2	4.71 (s)	4.97 (s)	63.5	4.71 (s)
S4			174.6	
S5			60.8	
S6	1.65 (m), 2.65 (m)	1.65 (m), 2.65 (m)	29.6	1.65 (m), 2.65 (m)
S7	2.75 (m)	2.75 (m)	49.6	2.75 (m)
S9	2.75 (m)	2.75 (m)	49.6	2.75 (m)
S10	1.65 (m), 2.65 (m)	1.65 (m), 2.65 (m)	29.6	1.65 (m), 2.65 (m)
S11	2.40 (t)	2.44 (t)	58.3	2.40 (m)
S12	1.55 (m)	1.55 (m)	21.3	1.55 (m)
S13	1.91 (t)	1.82 (m)	38.5	1.90 (m)
S14			110.1	
—OCH_2CH_2O—	3.75 (m), 4.20 (m)	3.75 (m), 3.92 (m)	64.6	3.76 (m), 4.02 (m)
Ph1			142.9	
Ph2,6	7.28 (m)	7.23 (m)	115.7	7.27 (m)
Ph3,5	6.90 (m)	6.80 (m)	129.3	6.90 (m)
Ph4	6.90 (m)	6.80 (m)	119.3	6.90 (m)
FPh1			138.5 (d)	
FPh2,6	7.43 (m)	7.41 (m)	127.6 (d)	7.42 (m)
FPh3,5	7.01 (m)	7.01 (m)	115.6 (d)	7.00 (m)
FPh4			162.5 (d)	

[a] **1** (R = H): (^{1}H) $J(1,3) = 1.9$ Hz; $J(3,4) = 8.9$ Hz; $J(5,7) = 2.3$ Hz; $J(7,8) = 9.0$ Hz; $J(2'a,2'e) = J(6'a,6'e) = 12.5$ Hz; $J(2'a,3'e) = J(5'e,6'a) = 2.6$ Hz; $J(2'a,3'a) = J(5'a,6'a) = 12.5$ Hz; $J(2'e,3'a) = J(5'a,6'e) = 4.0$ Hz; $J(3'a,3'e) = J(5'a,5'e) = 12.5$ Hz; $J(3'a,4'a) = J(4'a,5'a) = 12.5$ Hz; $J(4',7') = 6.4$ Hz.
1 (R = Ts): (^{1}H) $J(1,3) = 1.9$ Hz; $J(3,4) = 8.7$ Hz; $J(5,7) = 2.6$ Hz; $J(7,8) = 9.3$ Hz; $J(2'a,2'e) = J(6'a,6'e) = 12.4$ Hz; $J(2'a,3'e) = J(5'e,6'a) = 2.6$ Hz; $J(2'a,3'a) = J(5'a,6'a) = 12.4$ Hz; $J(2'e,3'a) = J(5'a,6'e) = 4.1$ Hz; $J(3'a,3'e) = J(5'a,5'e) = 12.4$ Hz; $J(4',7') = 6.4$ Hz; J(TPh2,TPh3) = J(TPh5,TPh6) = 8.7 Hz.
2: (^{1}H) $J(1,3) = 1.9$ Hz; $J(3,4) = 8.8$ Hz; $J(5,7) = 2.1$ Hz; $J(7,8) = 9.2$ Hz; $J(2'a, 2'e) = J(2'a,3'a) = J(5'a,6'a) = J(6'a,6'e) = 12.8$ Hz; $J(2'a,3'e) = J(5'e,6'a) = 2.4$ Hz; $J(2'e,3'a) = J(5'a,6'e) = 4.1$ Hz; $J(3'a,3'e) = J(5'a,5'e) = 12.4$ Hz; $J(4',7') = 7.3$ Hz; J(S12 = S13) = 7.9 Hz; J(—OCH2CH2O—) = 6.8 Hz.
3: (^{1}H) $J(1,3) = 2.1$ Hz; $J(3,4) = 8.8$ Hz; $J(5,7) = 2.1$ Hz; $J(7,8) = 9.1$ Hz; $J(2'a, 2'e) = J(6'a,6'e) = 12.4$ Hz; $J(2'a,3'e) = J(5'e,6'a) = 2.6$ Hz; $J(4',7') = 6.1$ Hz.
4: (^{1}H) $J(1,3) = 1.3$ Hz; $J(3,4) = 8.7$ Hz; $J(5,7) = 2.1$ Hz; $J(7,8) = 8.7$ Hz; $J(2'a, 2'e) = 8.5$ Hz; $J(2',3') = 8.3$ Hz; $J(4',5') = 7.1$ and 9.0 Hz; $J(5'a,5'e) = 9.0$ Hz; $J(6',7') = 7.3$ Hz; J(—OCH2CH2O—) = 6.9 Hz.
(^{13}C-F coupling) ^{1}J = 245.3 Hz; ^{2}J = 77.7 Hz; ^{3}J = 8.3 Hz; ^{4}J = 3.0 Hz.
5: (^{1}H) $J(1,3) = 1.9$ Hz; $J(3,4) = 8.8$ Hz; $J(5,7) = 2.3$ Hz; $J(7,8) = 9.0$ Hz; $J(2'a, 2'e) = 9.3$ Hz; $J(2',3') = 7.5$ and 8.3 Hz; $J(4',5') = 3.0$, 7.2 and 9.0 Hz; $J(5'a,5'e) = 9.0$ Hz; $J(3',6') = 1.5$ Hz; $J(6',7') = 6.4$ Hz.

Having done this, we compared the ^{1}H spectrum of the product, which we isolated in the reaction of **1** (R = Ts) with spiperone ketal at 80 °C [Fig. 1(C)] with the spectrum of **5** [Fig. 1(D)]. In addition to the additional signals corresponding to the spiperone moiety in **5** and the expected upfield position of the signal for the 7′-methylene group in **4** (CH_2CH_2N) in comparison with the analogous group in **5** (CH_2CH_2O), the two spectra were found to be almost identical (Tables 1–3).

Table 4. Compound **5** aliphatic region HMQC correlations

Atom		Cross peaks
2′	54.0	3.10 (H-2′a), 3.64 (H-2′e)
3′	36.2	2.50 (H-3′)
4′	32.1	1.75 (H-4′a), 2.27 (H-4′e)
5′	48.0	3.43 (H-5′a), 3.53 (H-5′e)
6′	36.8	1.79 (H-6′)
7′	62.1	3.79 (H-7′)

Table 5. Compound **5** COSY45 correlations

F_1	ppm	Cross peaks
CH_3CO	2.66 (s)	—
H-1	8.3 (d)	7.91 (H-3)
H-3	7.91 (dd)	8.30 (H-1), 7.59 (H-4)
H-4	7.59 (d)	7.91 (H-3)
H-5	6.71 (d)	6.99 (H-7)
H-7	6.99 (dd)	6.71 (H-5), 7.78 (H-8)
H-8	7.78 (d)	6.99 (H-7)
H-2′a	3.10 (dd)	3.64 (H-2′e), 2.50 (H-3′)
H-2′e	3.64 (dd)	3.10 (H-2′a), 2.50 (H-3′)
H-3′	2.50 (m)	3.64 (H-2′e), 1.75 (H-4′a)
H-4′a	1.75 (m)	2.50 (H-3′), 2.27 (H-4′e), 3.43 (H-5′a), 3.53 (H-5′e)
H-4′e	2.27 (m)	1.75 (H-4′a), 3.43 (H-5′a)
H-5′a	3.43 (ddd)	1.75 (H-4′a), 2.27 (H-4′e), 3.53 (H-5′e)
H-5′e	3.53 (ddd)	2.27 (H-4′e), 3.43 (H-5′a)
H-6′	1.79 (m)	2.50 (H-3′), 3.79 (H-7′)
H-7′	3.79 (t)	1.79 (H-6′)

CONCLUSION

Depending on the reaction conditions, spiperone ketal reacted with 1-(6-acetyl-2-naphthyl)-4 -[(4-methylphenyl)sulfonyloxy] methylpiperidine to give isomeric products exhibiting the same molecular composition and mass. ^{13}C and complex ^{1}H spectra were assigned using ^{1}H, ^{13}C, DEPT, COSY and HMQC experiments, and the respective structures of the products were determined. It was found that the reaction at room temperature lead to a mixture of *O*- and *N*-alkylated spiperone ketal with the 4-methylpiperidine moiety left intact. At elevated temperature a rearrangement occurred during which the 4-methylpiperidine fragment was transformed into a 3-ethylpyrrolidine moiety. The mechanism of this rearrangement and possible applications are under investigation.

EXPERIMENTAL

Spectra

NMR spectra were obtained on a Bruker Avance DPX 300 instrument operating at 300.130 MHz (^{1}H) or 75.471 MHz (^{13}C) $CDCl_3$ (unless stated otherwise) in 5 mm o.d. tube at 302 K. The sample solutions were prepared using between 3 and 10 mg of the solute and 0.6

ml of the solvent. One-dimensional spectra were acquired using 30° pulses, 32K (^{1}H) or 64K (^{13}C) data points and processed with an exponential window function (0.3 Hz and 1 Hz line broadening for ^{1}H and ^{13}C, respectively) and no zero filling. The DEPT spectrum was obtained with a 45° flip angle (DEPT45) to reveal all protonated carbon atom signals. The COSY45[5,6] spectrum was acquired as a 1024 × 128 data matrix with eight transients per increment with a 2 s delay between the transients. The data were processed after zero filling in F_1 as a 512 × 256 matrix. The FID resolution was 2.9 and 17.8 Hz in F_2 and F_1, respectively. The HMQC[7] spectrum was acquired as a 1024 × 128 data matrix with 16 transients per increment and a 0.5 s delay between the transients. The data were processed as a 1024 × 256 matrix with zero filling in both dimensions. The delay d_7 for the BIRD pulse was optimized for maximum suppression of the ^{12}C–H signals. The respective FID resolution was 2.4 (F_2) and 52.6 Hz (F_1). The spectra were referenced to internal TMS at $\delta = 0$ ppm.

Compounds

To prepare 1-[6-{3-(2-[8-{3-[2-(4-fluorophenyl)-1,3-dioxolan-2-yl]propyl}-1-oxo-4-phenyl-2,4,8-triazaspiro [4.5]dec-2-yl]ethyl) tetrahydro-1*H*-1-pyrrolyl}-2-naphthyl]-1-ethanone (**4**) and 1-{6-[3-(2-hydroxyethyl) tetrahydro-1*H*-1-pyrrolyl]-2-naphthyl}-1-ethanone (**5**), A mixture of **1**[2] (R = Ts; 146 mg, 0.3 mmol), spiperone ketal[8] (153 mg, 0.3 mmol), anhydrous potassium carbonate (220 mg) and *N*,*N*-dimethylformamide (DMF, 7.5 ml) was heated with stirring at 80 °C for 88 h. After cooling, ethyl acetate (100 ml) was added and the solution was washed with brine (3 × 50 ml), dried and evaporated *in vacuo* to yield 229 mg of an orange oil. Products **4** (80 mg, 22%) and a small amount of **5** were isolated by radial chromatography (2 mm silica, 1% methanol in dichloromethane). Compound **4**: HRMS, calculated for $C_{43}H_{49}N_4O_4F$ (M^+), 704.3738; found, 704.3710. Compound **5**: HRMS, calculated for $C_{18}H_{21}NO_2$ (M^+), 283.1580; found, 283.1572.

Radial chromatography was performed on a Chromatotron (Harrison Research, Palo Alto, CA. The rotors were coated as recommended by Harrison Research using Merck silica gel G (Cat. No. 7749-3). HR mass spectra were measured by Dr B. Kralj at the National Center for Mass Spectrometry of the Republic of Slovenia.

Acknowledgements

This work was supported by the US–Slovene Science and Technology Joint Fund in cooperation with the US Department of Energy and the Ministry of Science and Technology of the Republic of Slovenia (Project No. US-SLO 95/2-02) and in part by the Ministry of Science and Technology of the Republic of Slovenia.

REFERENCES

1. A. Jacobson, A. Petrič, A. Sinur and J. R. Barrio, *J. Am. Chem. Soc.* **118**, 5579 (1996).
2. A. Petrič, T. Špes and J. R. Barrio, *Monatsh. Chem.* in press.
3. A. Petrič, A. F. Jacobson and J. R. Barrio, *Bioorg. Med. Chem. Lett.* in press.
4. A. Petrič and J. R. Barrio, *J. Heterocycl. Chem.* **31**, 545 (1994).
5. W. P. Aue, E. Bartholdi and R. R. Ernst, *J. Chem. Phys.* **64**, 2229 (1976).
6. K. Nagayama, A. Kumar, K. Wüthrich and R. R. Ernst, *J. Magn. Reson.* **40**, 321 (1980).
7. A. Bax and G. A. Morris, *J. Magn. Reson.* **42**, 501 (1981).
8. W. G. Scharpf, US Pat. 3,839,342 (1974); *Chem. Abstr.* **82**, 43416 (1975); D. O. Kiesewetter, W. C. Eckelman, R. M. Cohen, R. D. Finn and S. M. Larson, *Appl. Radiat. Isot.* **37**, 1181 (1986).