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SYNTHESIS AND CONVERSIONS OF POLYHEDRAL COMPOUNDS. 28*. SYNTHESIS OF 2-(NAPHTHYL-1') AND 2-(2′-HYDROXYNAPHTHYL-1') DERIVATIVES OF 5,7-DIALKYL-1,3-DIAZAADAMANTANES

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2-Naphthyl and 2-(2'-hydroxynaphthyl) derivatives of 5,7-dialkyl-1,3-diazaadamantanes were synthesized by the reaction of the corresponding 5,7-dialkyl-3,7-diazabicyclo[3.3.1]nonanes with naphthaldehyde or 2-hydroxynaphthaldehyde.

Keywords: 1,3-diazaadamantane, 3,7-diazabicyclo[3.3.1]nonane, naphthaldehydes, condensation.

We have previously reported on the anticancer activity of 2-indolyl- [2], 2-phosphoryl- [3], and 2-spiro-substituted [4] derivatives of 5,7-dimethyl-6-oxo-1,3-diazaadamantane. From the point of view of routes to new pharmacologically active compounds there is definite interest in the synthesis of 1,3-diazaadamantanes containing naphthyl groups in position 2, since it is known that derivatives of naphthalene possess a wide spectrum of biological activity.

We have previously synthesized the first example of this class – 2-(2'-hydroxynaphthyl-1')-5,7-dimethyl-6-oxo-1,3-diazaadamantane [5] which had anticancer activity relative to sarcoma 45 and 180 and Swedish leucosis, but had no visible toxicity in laboratory animals. In this connection we have carried out the synthesis of a series of 5,7-dialkyl-2-naphthyl-1,3-diazaadamantanes.

As starting materials we used the 1,3-diazaadamantanes **1a-e**, which contain various alkyl group in positions 5 and 7 [6]. Diazaadamantane **1f** was synthesized by reduction of the carbonyl group of compound **1e** with $LiAlH_4$ [7], whereas compound **1g** was prepared by reduction of the same carbonyl group by the Kishner reaction [7].

3,7-Diacetyl-1,5-dialkyl-3,7-diazabicyclo[3.3.1]nonanes **2a-d** were synthesized by reaction of acetyl chloride with the corresponding diazaadamantanes **1a-d**. Acid hydrolysis of the acetyl groups of compounds **2a-d** gave the 1,5-dialkyl-3,7-diazabicyclo[3.3.1]nonanes **3a-d** with free amino groups. The diazabicyclononanes **3a-g** (for synthesis of compounds **3e-g**, see [8, 1, 7] respectively) condensed under mild conditions at room temperature with 1-naphthaldehyde or 2-hydroxy-1-naphthaldehyde to give the corresponding 1,3-diaza-adamantanes **4a-i.**

* For comunication 27, see [1].

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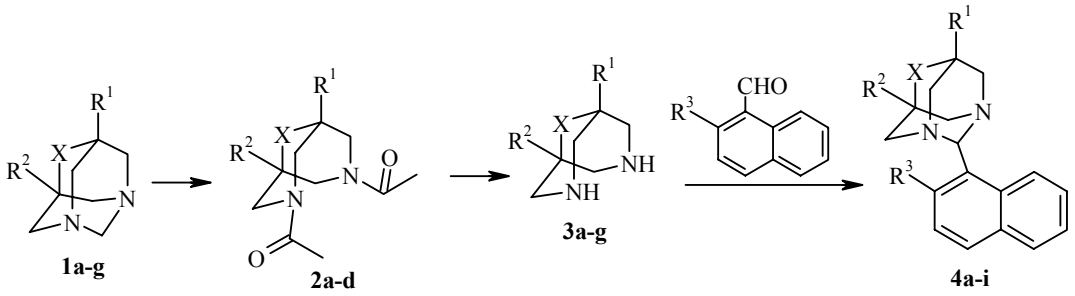

1a-g **2a-d** **3a-g** **4a-i**

1-3 a-d X = CO, **a** $R^1 = R^2 =$ *n*-Pr; **b** $R^1 = R^2 =$ *i*-Pr; **c** R^1 = Me, $R^2 =$ *n*-Pr; **d** R^1 = Me, $R^2 =$ *n*-Bu; **e** X = CO, $R^1 = R^2$ = Me; **f** X = CHOH, $R^1 = R^2$ = Me; **g** X = CH_2, $R^1 = R^2$= Me; **4 a-d** X = CO, R^3 = OH, **a** $R^1 = R^2 =$ *n*-Pr; **b** $R^1 = R^2 =$ *i*-Pr; **c** R^1 = Me, $R^2 =$ *n*-Pr; **d** R^1 = Me, $R^2 =$ *n*-Bu; **e-g** X = CO, R^3 = H, **e** $R^1 = R^2$ = Me, **f** $R^1 = R^2 =$ *n*-Pr, **g** R^1 = Me, $R^2 =$ *n*-Pr; **h** X = CHOH, $R^1 = R^2$ = Me, R^3 = H; **i** X = CH_2, $R^1 = R^2$ = Me, R^3 = OH

Table 1. Physicochemical Characteristics of Compounds **2-4**

Com-pound	Empirical formula	Found, N % / Calculated, N %	mp, °C	R_f*	IR spectrum, ν, cm^{-1}	Yield, %
2a	$C_{17}H_{28}NO_3$	9.30 / 9.09	155-156	0.77	1700 (CO), 1640-1610 (CO amide)	80.2
2b	$C_{17}H_{28}N_2O_3$	9.42 / 9.09	182-183	0.68	1710 (CO), 1650-1610 (CO amide)	66.4
2c	$C_{15}H_{24}N_2O_3$	9.80 / 10.00	185-186	0.57	1700 (CO), 1640-1610 CO amide)	72.1
2d	$C_{16}H_{26}N_2O_3$	9.34 / 9.05	187-188	0.51	1700 (CO), 1650-1620 (CO amide)	73.2
3a	$C_{13}H_{24}N_2O$	12.10 / 12.50	66-68	0.76	3330-3090 (NH), 1690 (CO)	69.0
3b	$C_{13}H_{24}N_2O$	12.35 / 12.50	98-99	0.54	3360-3100 (NH), 1690 (CO)	45.2
3c	$C_{11}H_{20}N_2O$	14.05 / 14.29	74-75	0.56	3360-3090 (NH), 1690 (CO)	53.1
3d	$C_{12}H_{22}N_2O$	13.08 / 13.33	61-63	0.78	3360-3100 (NH), 1690 (CO)	55.1
4a	$C_{24}H_{30}N_2O_2$	7.80 / 7.41	163-164	0.46	1700 (CO), 1611, 1580, 1510 (arom.)	74.1
4b	$C_{24}H_{30}N_2O_2$	7.63 / 7.41	181-182	0.32	1700 (CO), 1610, 1570, 1510 (arom.)	72.1
4c	$C_{22}H_{26}N_2O_2$	8.41 / 8.00	174-175	0.33	1700 (CO), 1610, 1580, 1510 (arom.)	65.7
4d	$C_{23}H_{28}N_2O_2$	7.79 / 7.69	163-165	0.24	1695 (CO), 1610, 1570, 1500 (arom.)	71.4
4e	$C_{20}H_{22}N_2O$	8.75 / 9.15	132-133	0.24	1690 (CO), 1590, 1500 (arom.)	65.8
4f	$C_{24}H_{30}N_2O$	8.05 / 7.74	99-100	0.25	1690 (CO), 1540, 1500 (arom.)	68.4
4g	$C_{22}H_{28}N_2O$	9.00 / 8.33	135-137	0.30	1700 (CO), 1590, 1540, 1500 (arom.)	52.2
4h	$C_{20}H_{24}N_2O$	8.71 / 9.09	82-83	0.23	3340-3280 (OH), 1600, 1560, 1500 (arom.)	47.5
4i	$C_{20}H_{24}N_2O$	9.30 / 9.09	191-192	0.27	1600, 1580, 1500 (arom.)	57.1

* R_f values were obtained in the following systems: 7:3 propanol-water, developed with iodine vapor (compounds **2a-d**); butanol-saturated NH_3, developed with ninhydrin (compounds **3a-d**); 1:1 benzene-petroleum ether, developed with ninhydrin (compounds **4a-i**).

The structures of the compounds synthesized were confirmed by elemental analysis, the molecular masses determined by mass spectrometry (compounds **4a,e,f,i**), and by analysis of their IR and ^{1}H NMR spectra (Tables 1-3). In the ^{1}H NMR spectra of compounds **4**, the signals may be combined into three groups: 1) the signals of the aromatic protons, 2) the signals of the protons of the diazaadamantane skeleton, and 3) the signals of the side chains. The signals of the protons of the diazaadamantane unit in compounds **2-4** (Tables 2 and 3) basically appear as four doublets in the 3.8-2.8 ppm region. As a result of the influence of the amide groups, the chemical shifts of these protons in compounds **2** are shifted to weaker field (4.94-2.67 ppm). The doubling of the

Table 2. ^{1}H NMR Spectra of 3,7-diazabicyclo[3.3.1]nonanes **2** and **3**

Compound	Chemical shifts, δ, ppm (*J*, Hz)	
	Skeletal protons (CH_2–N)	Remaining protons
2a	4.94 (2H, dd, *J* = 13.5, *J* = 2.8); 4.07 (2H, dd, *J* = 13.2, *J* = 2.8); 3.24 (2H, dd, *J* = 13.2, *J* = 2.7); 2.67 (2H, dd, *J* = 13.5, *J* = 2.7)	2.03 (6H, s, $2COCH_3$); 1.27-1.45 (8H, m, $4CH_2$); 0.97 (6H, t, *J* = 6.8, $2CH_3$)
2b	4.94 (2H, dd, *J* = 13.5, *J* = 2.7); 4.05 (2H, dd, *J* = 13.2, *J* = 2.7); 3.29 (2H, dd, *J* = 13.2, *J* = 2.7); 2.71 (2H, dd, *J* = 13.5, *J* = 2.7)	2.14 (2H, sp, *J* = 6.9, 2CH); 2.05 (6H, s, $2COCH_3$); 0.96 (12H, d, *J* = 6.9, $4CH_3$)
2c	4.94 (2H, ddd, *J* = 13.4, *J* = 11.2, *J* = 2.8); 4.09 (2H, ddd, *J* = 13.4, *J* = 4.2, *J* = 2.8); 3.24 (2H, ddd, *J* = 13.4, *J* = 9.2, *J* = 2.8); 2.67 (2H, ddd, *J* = 13.4, *J* = 4.2, *J* = 2.8)	2.04 (6H, s, $COCH_3$); 1.28-1.46 (4H, m, $2CH_2$); 0.98 (3H, t, *J* = 6.8, CH_3); 0.97 (3H, s, CH_3)
3a	3.26 (4H, br. d, *J* = 12.5); 2.75 (4H, br. d, *J* = 12.5)	2.88 (2H, br. s, 2NH); 1.19-1.24 (8H, m, $4CH_2$); 0.88-0.93 (6H, m, $2CH_3$)
3b	3.28 (4H, br. d, *J* = 12.2); 2.77 (4H, br. d, *J* = 12.2)	2.70 (2H, br. s, 2NH); 2.00 (2H, sp, *J* = 6.9, 2CH); 0.82 (12H, d, *J* = 6.9, $4CH_3$)
3c	3.29 (2H, br. d, *J* = 12.5); 3.23 (2H, br. d, *J* = 12.5); 2.78 (2H, br. d, *J* = 12.5); 2.76 (2H, br. d, *J* = 12.5)	2.98 (2H, br. s, 2NH); 1.20-1.25 (4H, m, $2CH_2$); 0.91 (3H, m, CH_3); 0.76 (3H, s, CH_3)
3d	3.28 (2H, br. d, *J* = 12.5); 3.22 (2H, br. d, *J* = 12.5); 2.76 (2H, br. d, *J* = 12.5); 2.77 (2H, br. d, *J* = 12.5)	2.90 (2H, br. s, 2NH); 1.11-1.36 (6H, m, $3CH_2$); 0.91 (3H, t, *J* = 7.0, CH_3); 0.76 (3H, s, CH_3)

Table 3. ^{1}H NMR Spectra of 1,3-diazaadamantanes **4**

Compound	Chemical shifts, δ, ppm (*J*, Hz)			
	Aromatic protons	Skeletal protons		Protons of alkyl groups
		N–CH–N	CH_2–N	
1	2	3	4	2
4a	12.59 (1H, s, OH); 9.10 (1H, dd, *J* = 8.7, *J* = 1.3, H-8′); 7.64 (1H, dd, *J* = 8.0, *J* = 1.7, H-5′); 7.64 (1H, d, *J* = 8.8, H-4'); 7.26 (1H, ddd, *J* = 8.7, *J* = 6.7, *J* = 1.7, H-7'); 7.18 (1H, ddd, *J* = 8.0, *J* = 6.7, *J* = 1.3, H-6′); 6.94 (1H, d, *J* = 8.8, H-3′)	5.79, s	3.74 (2H, dd, *J* = 13.2, *J* = 3.2); 3.30 (2H, br. d, *J* = 13.2); 3.27 (2H, br. d, *J* = 13.5); 2.94 (2H, br. d, *J* = 13.0)	1.37 (4H, m, $2CH_2$); 1.13 (4H, m, $2CH_2$); 0.99 (3H, m, CH_3); 0.80 (3H, m, CH_3)

Table 3. (continued)

1	2	3	4	2
4b	12.63 (1H, s, OH); 9.10 (1H, br. d, *J* = 8.7, H-8'); 7.65 (1H, dd, *J* = 8.0, *J* = 1.7, H-5'); 7.64 (1H, *J* = 8.8, H-4'); 7.26 (1H, ddd, *J* = 8.7, *J* = 6.8, *J* = 1.7, H-7'); 7.18 (1H, ddd, *J* = 8.0, *J* = 6.8, *J* = 1.2, H-6'); 6.95 (1H, d, *J* = 8.8, H-3')	5.76, s	3.81 (2H, br. d, *J* = 13.2); 3.33 (2H, br. d, *J* = 13.2); 3.30 (2H, br. d, *J* = 13.2); 2.99 (2H, br. d, *J* = 13.2)	2.06 (1H, sp, *J* = 7.0, CH); 1.74 (1H, sp, *J* = 7.0, CH); 0.98 (6H, d, *J* = 7.0, $2CH_3$); 0.75 (6H, d, *J* = 7.0, $2CH_3$)
4c*	12.57 (1H, s, OH); 9.10 (1H, br. d, *J* = 8.7, H-8′); 7.64 (1H, br. d, *J* = 8.0, *J* = 1.7, H-5′); 7.64 (1H, d, *J* = 8.8, H-4'); 7.26 (1H, ddd, *J* = 8.7, *J* = 6.8, *J* = 1.7, H-7'); 7.17 (1H, ddd, *J* = 8.0, *J* = 6.8, *J* = 1.3, H-6′); 6.94 (1H, d, *J* = 8.8, H-3′)	5.80, s	3.76 (2H, dd, *J* = 13.3, *J* = 3.2); 3.32 (2H, br. d, *J* = 13.3); 3.27 (2H, br. d, *J* = 13.0); 2.92 (2H, br. d, *J* = 13.0)	1.38 (4H, m, $2CH_2$); 1.0 (3H, m, CH_3); 0.72 (3H, s, CH_3)
4d*[2]	12.57 (1H, s, OH); 9.10 (1H, d, *J* = 8.8, H-8'); 7.64 (1H, dd, *J* = 8.1, *J* = 1.7, H-5'); 7.64 (1H, d, *J* = 8.8, H-4'); 7.27 (1H, m, H-7'); 7.17 (1H, m, H-6′); 6.95 (1H, d, *J* = 8.8, H-3')	5.81, s, 5.80, s	3.76 (1H, dd, *J* = 13.2, *J* = 3.2); 3.74 (1H, dd, *J* = 13.2, *J* = 3.2); 3.23-3.35 (4H, m); 2.97 (1H, br. d, *J* = 13.1); 2.92 (1H, br. d, *J* = 13.1)	1.30-1.45 and 1.08-1.23 (6H, both m, $3CH_2$); 0.97 and 0.82 (3H, both t, *J* = 6.9, $CH_2C\underline{H}_3$); 0.96 and 0.72 (3H, both s, CH_3)
4e	8.90 (1H, dd, *J* = 7.6, *J* = 2.3, H-8'); 7.77-7.84 (3H, m); 7.35-7.48 (3H, m)	5.60, s	3.70 (2H, dm, *J* = 13.2); 3.36 (2H, dm, *J* = 13.4); 3.27 (2H, dm, *J* = 13.2); 2.84 (2H, br. d, *J* = 13.1)	0.96 (3H, s, CH_3); 0.69 (3H, s, CH_3)
4f	8.88 (1H, br. d, *J* = 8.1, H-8'); 7.77-7.84 (3H, m); 7.47 (1H, d, *J* = 7.7); 7.34-7.44 (2H, m)	5.62, br. s	3.71 (2H, dd, *J* = 13.1, *J* = 2.8); 3.36 (2H, br. d, *J* = 13.1); 3.28 (2H, d, *J* = 12.9); 2.86 (2H, d, *J* = 13.1)	1.39 (4H, m, $2CH_2$); 1.06-1.18 (4H, m, $2CH_2$); 0.99 (3H, m, CH_3); 0.81 (3H, t, *J* = 6.3, CH_3)
4g	8.90 (1H, dd, *J* = 7.2, *J* = 2.6, H-8′); 7.81-7.90 (3H, m); 7.41-7.51 (3H, m)	5.63, br. s	3.73 (2H, dd, *J* = 13.2, *J* = 3.2); 3.45 (2H, dd, *J* = 13.2, *J* = 3.2); 3.40 (2H, d, *J* = 13.0); 2.90 (2H, d, *J* = 13.0)	1.35-1.52 (4H, m, $2CH_2$); 1.02 (3H, t, *J* = 6.7, CH_3); 0.77 (3H, s, CH_3)
4h	8.91 (1H, dd, *J* = 7.7, *J* = 1.9, H-8′); 7.67-7.77 (3H, m); 7.41 (1H, d, *J* = 7.7); 7.29-7.38 (2H, m)	5.25, br. s	4.42 (1H, d, *J* = 5.0, OH); 3.49 (1H, dd, *J* = 12.8, *J* = 3.2); 3.30 (1H, dd, *J* = 13.1, *J* = 2.5); 3.23 (1H, br. d, *J* = 4.5, H-6); 2.91-3.06 (5H, m); 2.65 (1H, dt, *J* = 13.1, *J* = 1.5)	0.78 (3H, s, CH_3); 0.52 (3H, s, CH_3)
4i	13.52 (1H, s, OH); 9.17 (1H, d, *J* = 8.8, H-8′); 7.59 (1H, dd, *J* = 8.0, *J* = 1.7, H-5′); 7.57 (1H, d, *J* = 8.8, H-4′); 7.22 (1H, ddd, *J* = 8.8, *J* = 6.8, *J* = 1.7, H-7′); 7.13 (1H, ddd, *J* = 8.0, *J* = 6.7, *J* = 1.4, H-6'); 6.88 (1H, d, *J* = 8.8, H-3′)	5.49, s	3.35 (2H, d, *J* = 12.8); 3.04 (2H, d, *J* = 12.8); 2.94 (2H, d, *J* = 12.7); 2.61 (2H, d, *J* = 12.7); 1.58 (2H, br. s, 2H-6)	0.80 (3H, s, CH_3); 0.57 (3H, s, CH_3)

* Data for the dominant diastereomer (84%).

*[2] Data cited for the two approximately equal diastereomers.

signals in the ^{1}H NMR spectra of compounds **4c** and **4d** (Table 3) indicate the formation of two diastereomeric pairs, since only the signals of the diazaadamantane unit and the side groups are doubled. From the intensities of the signals in each pair, the ratio of the diastereomers in compound **4c** is equal to 84:16 (the data in Table 3 refer to the major isomer) and 55:45 in **4d**.

EXPERIMENTAL

IR spectra of nujol mulls were recorded on a UR-20 spectrometer, ^{1}H NMR spectra of DMSO solutions with TMS as internal standard were recorded on Varian Mercury-300 (300 MHz) instrument. Molecular masses were determined on an MX-1321A mass spectrometer with direct insertion of the sample into the ion source and an ionization energy of 50 eV. The course of reactions and purity of substances were monitored by TLC on Silufol UV-254 plates.

3,7-Diacetyl-1,5-dialkyl-9-oxo-3,7-diazabicyclo[3.3.1]nonanes 2a-d. Acetyl chloride (1.96 g, 25 mmol) was added dropwise with stirring over 1 h at room temperature to a mixture of diazaadamantane **1** (10 mmol), sodium bicarbonate (2.1 g, 25 mmol), benzene (20 ml), and water (5 ml). Stirring was continued for a further hour and the benzene layer was separated. After evaporation of the benzene the residual oil was crystallized with ether. The crystals formed were filtered off, washed with ether, and dried (Tables 1 and 2).

1,5-Dialkyl-9-oxo-3,7-diazabicyclo[3.3.1]nonanes 3a-d. Diazabicyclononane **2** (10 mmol) and 5 N HCl (30 ml) were boiled for 5 h and then neutralized with NaOH carefully with cooling to pH 8-9.The crystals formed were filtered off, dried, and recrystallized from ethyl acetate (Tables 1 and 2).

The synthesis of the diazabicyclononanes **3e-g** are described respectively in papers [8, 1, 7].

2-(Naphthyl-1′)- and 2-(2′-Hydroxynaphthyl-1′)-5,7-dialkyl-1,3-diazaadamantanes 4a-i. A solution of the corresponding diazabicylononane **3** (10 mmol) and the naphthaldehyde (10 mmol) in ethanol (20 ml) was stirred at room temperature for 5-6 h and left overnight, the crystals which formed were filtered off and recrystallized twice from ethanol (Tables 1 and 3).

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