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SYNTHESIS AND NMR STUDY OF ADAMANTANE DERIVATIVES

PÁL SOHÁR*
EGIS Pharmaceuticals, Spectroscopic Department. POB 100, H-1475, Budapest, Hungary

JÁNOS KUSZMANN and ÁGNES NÉDER
Institute for Drug Research, POB 82, H-1325, Budapest, Hungary.

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ABSTRACT - For the synthesis of modified aminoglycosides dimethyl biciclo[3,3,1]nonane-2,6-dione-3,7-dicarboxylate (1) was reduced with $LiAlH_4$ and subsequently mesylated to give the corresponding 2,6-dimesyloxy-3,7-dimethylene derivative 3. Diene 3 underwent addition and simultaneous cyclisation when treated with different reagents, yielding 1,3,4,8-tetrasubstituted adamantane derivatives 6,7 and 8. The steric arrangement of the different substituents in the new compounds was established by NMR investigation. Correlation between structure and the spectral data was studied, first of all the limits of the additivity of substituent effects in the C-13 NMR spectra. The additivity is valid for the non-substituted bridghead atoms and for the methylene carbons, but in the case of the substituted tertiary carbons a significant non-additivity was observed making the determination of the configuration possible.

INTRODUCTION

Adamantane derivatives are ideal models for studying the substituent effects by NMR methods[1,2,3] due to their rigid skeleton. During our search for biologically active compounds tetrasubstituted adamantane derivatives were synthesized and their structures were elucidated by IR, ^1H and ^{13}C NMR spectroscopy. The series of these derivatives enabled us to investigate the validity of the additivity of substituent effects, established on the mono- as well as on the 1,3- and 2,4-disubstituted derivatives, in these 1,3,4,8-tetrasubstituted analogs.

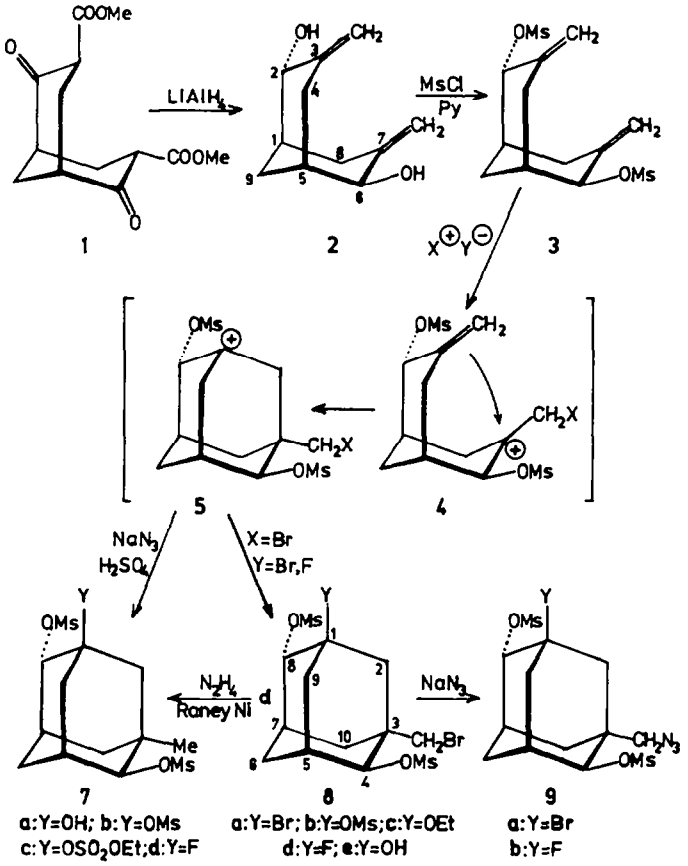
SYNTHESIS

Clarification of the mechanism of the resistance of bacteria against aminoglycoside antibiotics[4,5] has led to extensive research aiming at the modification of the different components of these antibiotics. Recently we started the synthesis of modified cyclitols which are essential components of many aminoglycosides. As starting material the known dimethyl bicyclo[3,3,1]nonane-2,6-dione-3,7-dicarboxylate (1) was used, which can easily be prepared from formaldehyde and methyl malonate followed by partial decarboxylation.[6]

For obtaining a polyhydroxylated derivative, 1 was reduced with lithium aluminium hydride, but the two primary hydroxyl groups formed were eliminated during this reaction, leading to the 2,6-dihydroxy-3,7-dimethylene derivative 2. This was con-

* Author to whom correspondence should be addressed

verted into its dimesylate 3 which was treated according to the literature[7] in chloroform with bromine, but instead of the expected dibromo-adamantane derivative 6a an inseparable mixture of several components was obtained. When dichloromethane was used as solvent in the same reaction, 6a was obtained as major product (66%) and the corresponding 1-mesyloxy (6b) and 1-ethoxy derivative (6c) could be isolated as byproducts. All these derivatives can originate from a common intermediate 5 which can be formed via 4 as postulated by Stetter et al.[7,8] The cyclic cation 5 can readily react with any nucleophile; consequently with ethanol, present as contaminant in the solvent, it gives 6c, and with methanesulfonic acid, which can be eliminated in a decomposition reaction from 4 or 5, it will form 6b.



When BrF was used in the addition reaction, in agreement with the polarity of this mixed halogen the 3-bromomethyl-1-fluoro compound 6d was obtained as the main component (54%) but - as the reagent was generated in situ from NBS and 70% aqueous hydrogen fluoride, water reacted as a nucleophile too, yielding the 1-hydroxy derivative 6e (29%). As a minor component the corresponding 1-ethoxy compound 6c (8%) could be isolated in this case, too.

For the synthesis of 1-amino derivatives[9] a chloroform solution of the diene 3 was treated with HN_3, which was generated in situ from sodium azide with sulfuric acid. Under these conditions however the HN_3 is not dissociated enough to attack the intermediate cation (5, X=H), therefore only the 1-hydroxy- 7a, the 1-mesyloxy- 7b and the 1-ethoxysulfonate derivative 7c could be isolated, in yields of 24, 13 and 33%, respectively.

When the 3-bromomethyl-1-fluoro derivative 6d was treated with hydrazine hydrate as the hydrogen donor in the presence of Raney nickel,[10] the bromomethyl group was reduced selectively affording the 3-methyl derivative 7d in high yield. Treatment of the 6-type 3-bromomethyl compounds with sodium azide led to the corresponding

TABLE 1. ^{1}H NMR chemical shifts (δ_{TMS}=0 ppm) on compounds 6a-e, 7a-d and 8a,b in $CDCl_3$ solution at 250 MHz.

Compound	CH_2(2,6,9,10) m's (8H)[a]	H-5,7		CH_3(4,8-Ms)		CH_2/CH_3(3)		H-4,8	
		2xm[b] (2x1H)		2xs(2x3H)[c]		2xd/s(2/3H)[d]		2xd/2xt(2x1H)[e]	
6a	1.80$^{\alpha}$; 1.9-2.3$^{\beta}$; 2.80$^{\alpha}$	2.65		3.15[f]	3.18	3.14[f]	3.40	4.73	4.76
6b[g]	1.56$^{\alpha}$; 1.65-2.0$^{\beta}$; 2.37$^{\alpha}$	2.46	2.66	3.10	3.14	3.15	3.45	4.63	4.69
6c	1.75$^{\alpha}$; 1.8-2.1$^{\gamma}$; ∿2.2$^{\delta}$; ∿2.3$^{\alpha}$; 2.8$^{\alpha}$	2.75	2.80	3.09	3.15 3.16	3.19	3.45	4.72	5.05
6d	1.7-2.1$^{\varepsilon}$; ∿2.4$^{\alpha}$	2.55	2.73	3.09[h]	3.15	3.18	3.47	4.70[f]	4.72[f]
6e	1.64$^{\alpha}$; 1.7-1.9$^{\beta}$; 2.22$^{\alpha}$	2.45[i]	2.63	3.14		3.16	3.46	4.59	4.70
7a[g]	∿1.42$^{\alpha}$; 1.8-2.2$^{\beta}$; 2.72$^{\alpha}$	2.52	2.60	3.08	3.14	1.06		4.43[f]	4.93
7b	1.40$^{\alpha}$; 1.8-2.1$^{\zeta}$; 2.2-2.3$^{\delta}$; 2.76$^{\alpha}$	2.51	2.58	3.08	3.15	1.05		4.43	5.02
7c[j]	1.35$^{\alpha}$; 1.62$^{\alpha}$; 1.68$^{\delta}$; 1.8-1.95$^{\gamma}$; 2.15$^{\alpha}$	2.38	2.48	3.05	3.14	1.01		4.42	4.57
7d	1.36$^{\alpha}$; 1.75-2.00$^{\beta}$; ∿2.35$^{\alpha}$	2.45	2.58	3.06[h]	3.08	1.05		4.41	4.70
8a	1.68$^{\alpha}$; 1.9-2.3$^{\beta}$; 2.8$^{\alpha}$	2.52	2.59	3.11	3.19	3.12	3.36	4.69	4.76
8b	1.42$^{\alpha}$; 1.75-2.05$^{\beta}$; ∿2.4$^{\alpha}$	2.55	2.72	3.08[k]	3.10	3.16	3.42	4.62	4.73

a) Partly overlapped AB-type multiplets of the four methylene groups. The four lines of these AB spectra show further fine structures due to vicinal and long-range couplings. The upfield d is well separated from the others as well as the downfield ones arising probably from the skeletal protons in Pos. 10, anti to the 1-substituent and in Pos. 9, syn to the 3-substituent, respectively, Intensities: α) 1H, β) 6H, γ) 3H, δ) 2H, ε) 7H, ζ) 4H; - b) Quartet- or quintet-like signal (in case of 6d, 7d and 8b) with close, coalesced lines; - c) In case of compound 6c 3xs of 3-3H intensity, for 6e one s of 6H-intensity, in the spectrum of 7b the intensity of the signal at 3.08 ppm is 6H; - d) AB multiplet for 6a-e and 8a,b ^2J(A,B): 10.6 (6a,c,d,e), 12,3 (8a,b) and 10.3 Hz (6b), s with 3H-intensity for 7a-d; - e) 2xd split by 3.5 and 3.5 (6a), 3.4 and 3.3 (6b), 3.3 and 3.8 (6c), 3.4 and 3.4 (6e),? and 3.3 (7a), 3.0 and 3.5 (7b), 3.3 and 3.6 (7c) and 3.3 and 3.5 Hz (8a) or 2xt split by ∿3 (6d), 4.0 and 5.2 (dd split by 4.0 and 6.4 Hz, 7d) and 3.6 and 4.7 Hz (8b) resp.; - f) Overlapping signals; - g) CH_3(ethyl): 1.16 ppm, t, 6.9 Hz (6b) and 1.44 ppm, t, 7.2 Hz (7a); CH_2(ethyl): 3.49 (6b) and 4.40 ppm (7a); - h) Broadened line due to long-range through space interaction with the fluorine atom; - i) Overlapped with the OH-signal (intensity 2H); - j) OH: 2.22 ppm (1H), broad s, - k) d split by 0.7 Hz due to ^6J(F,H) coupling.

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3-azidomethyl derivatives (8a, 8b) which can be regarded as precursors in the synthesis of aminocyclitol analogs.

IR AND ^{1}H NMR SPECTRA

The IR spectra are dominated by the absorption of the mesyloxy groups. These appear at 1327-1358 (sometimes split into two bands), at 1171-1177, at 905-984 (two or three bands) and at 845-865 and 519-536 cm^{-1} (sometimes two bands), respectively. The sulfate ester group of 7c gives additional bands at 1338, 1196, 941, 864 and 579 cm^{-1}, partly overlapping with these previously mentioned. Besides these, only the νOH band of 7a (3537 cm^{-1}) and the azide bands (2120 and 2108 cm^{-1}) of 8a and 8b are noteworthy.

The ^{1}H NMR data (Table 1) prove the constitution of the compounds. In each spectrum the methyl singlets of the mesyloxy groups can be detected at 3.05-3.15 and 3.08-3.19 ppm, respectively, and in the case of 6c and 7b the presence of a third mesyloxy group is observed. In the fluorinated derivatives 6d, 7d and 8b the signals at higher field are broadened or split into a doublet. Consequently these signals can be assigned to the mesyloxy groups at C-8, which are close enough to the fluorine atom for this to be responsible for this phenomenon via a ^6J(F,H) through space spin-spin coupling.[11a] On the other hand it is not possible to distinguish H-4 from H-8, as the ^3J(F,H-8) and ^5J(F,H-4) couplings are of the same magnitude, due to the favourable arrangement[11a] of the C-F and the C_4-H bonds (the dihedral angle is 180°), consequently both protons have triplet signals. These data

prove simultaneously the "equatorial" arrangement of the mesyloxy group at C-4 (endo arrengement to the C-F bond). As all NMR data point to a highly symmetrical arrangement of both mesyloxy groups, that at C-8 should be in an exo position with respect to the former. This means that the hypothetical structure of intermediate 2 with the double-chair conformation of the two fused sixmembered rings and the diequatorial arrangement of the two newly formed hyrdoxyl groups could be proved this way, too.

The H-4 and H-8 signals of all unfluorinated derivatives are doublets in the range of 4.41-4.73 and 4.57-5.05 ppm, respectively, due to $^3J(H_4,H_5)$ or $^3J(H_7,H_8)$ interactions. Taking into account the established additivity of the substituent effects in adamantane derivatives,[1,3b,d,12] the upfield signal can be attributed in all cases to H-4.

In compounds 6a-d and 8a,b the methylene group attached to C-3 gives an AB pattern with a coupling constant of 10.3-10.6 and 12.3 Hz, at 3.12-3.19 and 3.36-3.47 ppm, respectively, proving the presence of the bromomethyl and azidomethyl groups. In derivatives 7a-c the singlet of the C_3-methyl group appears at 1.01-1.06 ppm.

The signals of the bridgehead protons H-5,7 appear as quartets and in the fluorinated derivatives as quintets at 2.38-2.75 and 2.48-2.80 ppm, respectively. That means that some of the vicinal couplings - probably on account of the vicinity of the electron-withdrawing substituents[11b] - do not cause any significant splitting, whereas the $^4J(F,H)$-type interaction can always be detected. The shift difference of H-5,7 is < 0.2 ppm (0.11 ppm in average).

The multiplets of the four methylene groups overlap partly with each other as well as with the signals of H-5,7 (between 1.35 and 2.8 ppm). The individual pair of their protons are chemically non-equivalent, and the corresponding AB type multiplets show further fine structure due to vicinal and long-range interactions (see also footnote "a" to Table 1.).

^{13}C NMR SPECTRA

The ^{13}C NMR chemical shifts (Table 2) furnished a further proof of the steric arrangement of the mesyloxy groups. For this reason a firm assignment of all ten skeletal carbon atoms was necessary. 7 out of the 10 signals (C-2,3,5,6,7,9,10) appear in a very narrow range (between 31 and 43 ppm) and the two mesyl signals, furthermore the methylene signal of 6a-e and the third mesyl signal of 6c and 7b appeared in the same interval. For the assignment the following facts and methods were used:

a) By the DEPT measurements[13,14] the signals of methyl, methylene (C-2,6,9,10) methine (C-4,5,7,8) and quaternary (C-1,3) carbon atoms can be distinguished. From the methine carbons the C-4,8 and C-5,7 pairs coud easily be separated according to their very different chemical shifts and the same holds for C-1 and C-3.

b) With the help of the fluorine-carbon couplings[3j,15] the C-2,9 and C-6,10 signals could be traced for compounds 6d, 7d and 8b. The related lines of the overlapping doublets were identified when necessary by using solvent shifts.[11c]

c) Taking into account the corresponding data of the monosubstituted adamantane derivatives[1,2,16,17] and presuming the additivity of the substituent effects the theoretical shift values were calculated (Table 3).

d) Apart from the different substituents at C-1 and C-3 the investigated molecules possess C_2 symmetry in the proposed structures, therefore C-5 and C-7 are chemically nearly equivalent.

The above considerations led to the assignments given in Table 2. For comparison the measured and calculated data as well as their difference is given, too, for all theoretically possible arrangements of the mesyloxy groups at C-4,8 in Table 3. For the calculation the chemical shifts of the monosubstituted adamantanes were

TABLE 2. ^{13}C NMR chemical shifts (δ_{TMS} = 0 ppm) of compounds 6a-e, 7a-d and 8a,b, in $CDCl_3$ solution[a] at 20 MHz[b]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	$CH_{2/3}$[c]	CH_3(Ms)
6a	60.3	40.6	41.4	81.2	36.0[d]	33.1	35.8[d]	85.6	41.4	32.3	38.9	39.0, 38.85
6b[e]	72.7	34.1[d]	40.4	82.7	34.9[f]	33.1[d]	35.0[f]	84.0	33.5[d]	33.4[d]	39.8	38.7, 39.1
6c[g]	87.5	35.6[d]	40.1	82.9	36.8[f]	33.4[h]	36.2[f]	83.5	35.9[d]	33.4[h]	42.1	40.1, 40.8
6d	90.8	35.3	41.8	81.6	35.9	33.1	35.6	83.1	35.1	33.2	39.1	38.9[i], 38.6[j]
6e	78.7	37.3[d]	40.7	82.3	35.2[f]	33.6	34.7[f]	85.9	37.6[d]	33.3	39.6	38.7, 39.2
7a[e]	87.5	37.3	38.1	82.4	36.2[d]	33.3	36.0[d]	84.7	36.5[f]	34.1[f]	25.1	38.8, 38.8
7b[g]	86.8	38.0	38.0	82.5	36.1[d]	33.3	35.8[d]	84.7	36.5[f]	35.1[f]	25.2	39.0, 38.9
7c	68.8	40.1	37.0	86.3	35.5[d]	34.0	35.0[d]	86.5	37.3[f]	37.0[f]	25.2	38.8, 38.7
7d	91.1	37.5	38.2	85.4	36.2	33.6	36.0	83.6	35.3	36.8	25.0	38.8[i], 38.5[j]
8a	60.3	39.5	41.9	80.5	35.9[d]	33.1	35.7[d]	85.8	41.6	31.5	56.9	38.8, 38.6
8b	90.6	33.9	42.4	80.8	35.8	33.1	35.6	83.3	35.5	32.3	57.1	38.7[i], 38.6[j]

a) In case of 6c in DMSO-d_6; - b) The $^nJ(F,C)$ coupling constants of compounds 6d, 7d and 8b [in Hz] for the individual carbons are as follows: C-1: 195.0, 193.4, 194.3, C-2: 20.9, 18.8, 20.5, C-3: 9,9, 9.7, 9.8, C-4: 2.0, 2.0, 2.1, C-5: 9.5, 9.7, 9.5, C-6: 1.9, 1.8, 1.9, C-7: 4.6, 4.7, 5.2, C-8: 16.4, 16.4, 16.4, C-9: 18.4, 18.5, 19.6, C-10: 1.3, 0.9, 1.4, CH_2/CH_3(3): 4.3, 0.9, 2.0. The order of all carbon atoms corresponding to the spectral lines were proved by DEPT experiments for all compounds investigated; - c) CH_3 for compound 7a-d, CH_2 for all others; - d,f) Reversed assignment may be possible; - e) CH_3(ethyl); 15.8 (6b), 14.7 (7a); CH_2(ethyl): 56.5 (6b), 70.2 (7a); - g) CH_3(1-Ms): 42.6 (6c), 41.1 (7b); - h) Two overlapping lines; - i) CH_3(4-Ms), $^7J(C,F) < 0.5$ Hz; - j) CH_3(8-Ms), $^5J(C,F)$: 4.3 (6d), 4.7 (7d) and 4.5 Hz (8b).

used. The corresponding data of the 1-bromo-, 1-fluoro-, 1-hydroxy-, 1-bromomethyl and 1-methyladamantane are given in the literature.[1,2,15] The data of the 2-mesyloxy-adamantane are our own results. The substituent effect of the azidomethyl group was taken as equal to that of the bromomethyl substituent. For the ethoxy group the same difference was assumed as that obtained by comparing cyclohexanol with its O-methyl derivative, and for the 1-mesyloxy and 1-ethoxysulfonyl ester derivative the same difference was taken as that obtained by comparing the 2-hydroxy and 2-mesyloxy-adamantane.

The measured chemical shifts were first assigned to the skeletal carbons according to the order of the calculated values. Thereafter, if necessary, this order was changed taking into account the results of the DEPT measurements. At this stage we had to decide the assignments of pairs C-4,8, C-5,7 and the two mesyl-methyl carbons, and further that of the four methylene carbons C-2,6,9,10.

It is not possible to distinguish between the almost equivalent C-5,7 atoms ($\Delta\delta$: 0.1-0.6 ppm). The assignment of similar bridge atoms is still a topic of discussion in the literature[18] and for an unambigous decision special methods are necessary, e.g. shift reagents,[3a,19] relaxation-time measurements,[20] measurement of $^1J(^{13}C,^{13}C)$ couplings,[21] or the investigation of labelled compounds,[3g,18] etc.

In the case of the fluorine derivatives 6d, 7d and 8b the $^3J(F,C)$ coupling constant differs significantly for C-5 and C-7 (9.5, 9.7 and 9.5 for C-5 and 4.6, 4.7 and 5.2 Hz, for C-7, respectively). Presuming that the electron-withdrawing mesyloxy group, being attached to C_β of the F-C_α-C_β-C_γ chain, diminishes the coupling constant,[22] the upfield line can be attributed to C-5. The upfield shift caused by the hyperconjugative effect[23] of heteroatoms being in trans-periplanar arrangement to the C_γ atom was registered by Duddeck[3h,j] on several 2,4-disubstituted adamantanes and 4-substituted-2-adamantanone derivatives. This interaction is hindered along

TABLE 3. Calculated carbon chemical shifts (δ) of compounds 6a–d, 7a–c and 8a,b and the shift differences (Δδ) between the calculated and observed values (in ppm) for all possible orientation of the 4,8-mesyloxy-substituents

Compound		C-1		C-2			C-3		C-4	C-5		C-6			C-7		C-8	C-9			C-10		
		a	b	a	b/d	c	a	d		a	d	a	b/d	c	a	b		a	d	b	a	b	d
6a, 8a		69.1	69.4	41.1	46.3	51.5	42.1	42.4	88.1	37.6	37.3	33.8	28.6	23.4	37.6	37.3	97.6	43.3	38.1	48.5	32.7	27.5	37.9
6b		80.9	81.2	33.7	38.9	44.1	39.8	40.1	89.0	35.5	35.0	35.8	30.6	25.4	35.3	35.0	90.2	34.8	29.6	40.0	33.8	28.6	39.0
6c		84.9	85.2	36.9	42.1	47.3	41.4	41.7	89.0	36.9	36.6	35.8	30.6	25.4	36.9	36.6	93.4	38.0	32.8	43.2	33.8	28.6	39.0
6d, 8b		94.9	95.2	34.7	39.9	45.1	41.4	41.7	88.6	36.9	36.6	34.3	29.1	23.9	36.9	36.6	91.2	36.9	31.7	42.1	33.2	28.0	38.4
6e	δ	72.3	72.6	37.4	42.6	47.8	40.5	40.8	88.7	36.0	35.7	34.4	29.2	24.0	36.0	35.7	93.9	38.5	33.3	43.7	33.3	28.1	38.5
7a,b		85.2	85.5	40.5	45.7	50.9	37.9	38.2	92.6	37.2	36.9	34.7	29.5	24.3	37.2	36.9	93.4	38.0	32.8	43.2	37.2	32.0	42.4
7c		72.6	72.9	41.0	46.2	51.4	37.0	37.3	92.3	36.3	36.0	34.4	29.2	24.0	36.3	36.0	93.9	38.5	33.3	43.7	36.9	31.7	42.1
7d		95.2	95.5	38.3	43.5	48.7	37.9	38.2	92.2	37.2	36.9	34.3	29.1	23.9	37.2	36.9	91.2	35.8	30.6	41.0	36.6	31.4	41.8
6a		-8.8	-9.1	-0.5	-5.7	-10.9	-0.7	-1.0	-6.9	-1.6	-1.3	-0.7	4.5	9.7	-1.8	-1.5	-12.0	-1.9	3.3	-7.1	-0.4	4.8	-5.6
6b		-8.2	-8.5	-0.6	-4.8	-10.0	0.6	0.3	-6.3	-0.4	-0.1	-2.7	2.5	7.7	-0.3	0.0	- 6.2	-1.3	3.9	-6.5	-0.4	4.8	-5.6
6c		2.6	2.3	-1.3	-6.5	-11.7	-1.3	-1.6	-6.1	-0.1	0.2	-2.4	2.8	8.0	-0.7	-0.4	- 9.9	-2.1	3.1	-7.3	-0.4	4.8	-5.6
6d		-4.1	-4.4	-0.6	-4.6	- 9.8	0.4	0.1	-7.0	-1.0	-0.7	-1.2	4.0	9.2	-1.3	-1.0	- 8.1	-1.8	3.4	-7.0	0.0	5.2	-5.2
6e		-3.4	-3.7	-0.1	-5.3	-10.5	0.2	-0.1	-6.4	-0.8	-0.5	-0.8	4.4	9.6	-1.3	-1.0	- 8.0	-0.9	4.3	-6.1	0.0	5.2	-5.2
7a	Δδ	2.3	2.0	-3.2	-8.4	-13.6	0.2	-0.1	-10.2	-1.0	-0.7	-1.4	3.8	9.0	-1.2	-0.9	- 8.7	-1.5	3.7	-6.7	3.1	2.1	-8.3
7b		1.6	1.3	-2.5	-7.7	-12.9	0.1	-0.2	-10.1	-1.1	-0.8	-1.4	3.8	9.0	-1.4	-1.1	- 8.7	-1.5	3.7	-6.7	-2.1	3.1	-7.3
7c		-3.8	-4.1	-0.9	-6.1	-11.3	0.0	-0.3	-6.0	-0.8	-0.5	-0.4	4.8	10.0	-1.3	-1.0	- 7.4	-1.2	4.0	-6.4	0.1	5.3	-5.1
7d		-4.1	-4.4	-0.8	-6.0	-11.2	0.3	0.0	-6.8	-1.0	-0.7	-0.7	4.5	9.7	-1.2	-0.9	- 7.6	-0.5	4.7	-5.7	0.2	5.4	-5.0
8a		-8.8	-9.1	-1.6	-6.8	-12.0	-0.2	-0.5	-7.6	-1.7	-1.4	-0.7	4.5	9.7	-1.9	-1.6	-11.8	-1.7	3.5	-6.9	-1.2	4.0	-6.4
8b		-4.3	-4.6	-0.8	-3.9	- 9.1	1.0	0.7	-7.8	-1.1	-0.8	-2.0	3.2	8.4	-1.3	-1.0	- 7.9	-1.4	3.8	-6.6	-0.1	5.1	-5.3
$\Delta\delta^{e}$		4.5	4.9	1.2	6.0	11.2	0.5	0.4	7.4	1.0	0.7	1.3	3.9	9.1	1.3	0.9	8.8	1.4	3.8	6.5	0.7	4.5	5.9

a) C-1,4 and C-3,8 substituent pairs are both in syn position;
b) C-1,4 and C-3,8 substituent pairs are in anti and syn position, respectively;
c) C-1,4 and C-3,8 substituent pairs are both in anti position;
d) C-1,4 and C-3,8 substituent pairs are in syn and anti position, respectively;
e) Mean value of the shift differences.

the C_1-C_8-C_7 chain by the 8-mesyloxy substituent, resulting in the upfield shift of C-5 compared to C-7.

The assignment of the methyl signal to the 8-mesyloxy group is unambigous in the case of 6d, 7d and 8b due to the prevailing ^5J(F,C) coupling of 4.3, 4.7 and 4.5Hz, respectively. Similarly, it was presumed for all other compounds that the upfield signal belongs to the 8-mesyloxy group, but because of the small shift difference (max. 0.7 ppm, on average 0.23 ppm), the possibility of a reversed assignment cannot be ruled out.

Using the difference in the carbon-fluorine couplings it is easy to distinguish the two mesyloxy substituted carbon atoms C-4,8. The ^2J(F,C) 16.4 Hz coupling belongs to C-8, while the ^4J(F,C) = 2.0, 2.0 and 2.1 Hz splittings belong to C-4. As the character of the neighbouring substituents is not changed in the other investigated derivatives, it can be assumed that in all cases the upfield line belongs to C-4. This further supported by the fact that in 8a C-4 is hardly shifted compared to 8b (Δδ: 0.3 ppm), and neither in the case of the 6a,d pair (Δδ: 0.4 ppm), whereas these differences of the C-8 shifts are much more significant (in both cases Δδ: 2.5 ppm),due to the fluoro-bromo exchange.

Similarly the methylene carbons C-2,9 can be distinguished from C-6,10 by the large ^2J(F,C) coupling (18.4-20.9 Hz) prevailing in the derivatives 6d, 7d and 8b, compared to the small ^4J(F,C) couplings (0.9-1.9 Hz). In accordance with the literature[3j] the ^2J(F,C) coupling constant of C-2, being flanked by two substituted carbon atoms, has the larger value. In the case of the 1-bromo-substituted derivatives 6a,8a the C-2,9 lines are shifted downfield[11d] (40.6 and 41.4 ppm in 6a and 39.5 and 41.6 ppm in 8a) compared to the fluoro analogs (33.9-35.5 ppm), due to the larger β-effect[24] of the bromo substituent. At the same time the shift of the C-6,10 lines is practically unaffected by this substituent change.

There was no difficulty in locating the line of C-2 and C-6 in derivatives 7a-c. Due to the additive β-effects of the 1,3-substituents, the C-2 line shifted downfield compared to the other methylene signals. The C-6 signal which is isolated from the substituents, remained relatively unchanged at the highest fields in compounds 7a-c. This assignment is supported in the fluoro derivatives by its larger ^4J(F,C) coupling (1.8-1.9, Hz) compared to that of C-10 (0.9-1.4 Hz, respectively). This coupling is transmitted in the case of C-6 *via* C_1-C_8-C_7 and C_1-C_9-C_5 bond-chains and in the case of C-10 *via* C_1-C_8-C_7 and C_1-C_2-C_3. While the first line is identical for both carbons, in the second one the electron-withdrawing 3-substituent will reduce the coupling.[22] The smaller β-effect of the azidomethyl group in 8b compared to the bromomethyl substituent in 6d results in an upfield shift of the C-10 lines by 0.9 ppm. The same holds for the 6a-8a pair. In 6c the two lines overlap and in 6b and 6e the too small difference in the chemical shifts (0.3 ppm) makes the assignment impossible.

For the differentiation between the lines of C-2 and C-9 the ^2J(F,C) coupling in 6d, 7d and 8b, as well as the effect of the 3-substituent was used. The latter should partly increase the coupling[3j] between the fluorine and the C-2 atom and partly it should cause a stonger downfield shift of the C-2 line. The assignments given in Table 2 were made according to these considerations.

The calculated and measured data are in good agreement except for the atoms C-1,4,8. The average deviation is less than 1 ppm for C-2,3,5,6,10 and less than 2 ppm for C-7,9. The individual deviations are in only seven cases larger than 2 ppm (2.0-3.2 ppm) for these carbons and only in those derivatives (6b,c and 7a,b) for which no substituent-effects are known from monosubstituted adamantanes. The unexpected large upfield shift of C-4,8 (on average -8.3 and -10.0 ppm, respectively) must be due to the steric compression shift[25] induced by the neighbourhood of the bulky substituents. This was verified by the extremely large effect

measured for C-1 and C-8 of the 1-bromo derivatives 6a and 8a (-8.8, -12.0 and -8.8, -11.8 ppm, respectively). The large upfield shift (-8.2 ppm) in the case of compound 6b is probably a consequence of having used an inappropriate substituent constant.

All C,F coupling constants were in the expected range,[2,15,26] except the through-space $^5J(F,C)$ coupling and the unusually small $^3J(F,C)$ coupling of C-7, already mentioned. The $^1J(F,C)$ couplings are however larger than usual (195.0, 193.4 and 194.3 Hz in 6d, 7d and 8b) instead of 179-191 Hz, which can not be explained by hyperconjugative effects as suggested for 1,3-[15] and 1,4- disubstituted[3j] adamantanes. In our case the large coupling constants must be due to the presence of the 8-mesyloxy group, consequently inductive interactions have to be taken into consideration.

The steric arrangement of the mesyloxy groups at C-4,8 was further confirmed by the fact, that in all other but the assigned configurations the difference between the calculated and observed shifts would be substantially larger for the carbons in "1,3-positions" to these substituents, i.e. for C-2,6,9,10. Instead of the mean deviation of 0.9, 1.4, 1.8 and 0.9 ppm the deviation would be 6.0, 3.8, 7.0 and 4.3 or 6.0, 3.8, 3.4 and 6.1 ppm if one, and 11.2, 9.0, 1.8 and 0.9 when both mesyloxy groups would occupy the opposite configuration.

From all these facts the general conclusion can be drawn, that in the ^{13}C NMR spectra of 1,2-disubstituted adamantane derivatives a significant non-additivity of substituent effects can be expected, first of all with the substituted tertiary carbons and, in the case of bulky substituents, also with the quaternary carbons. The orientation of the substituents at tertiary carbon atoms can be unambiguously established by the upfield shift caused by the steric compression of the protons, being in 1,3-diaxial arrangement with these substituents.

EXPERIMENTAL

The H-1 NMR spectra were recorded in $CDCl_3$ solution in a 5 mm tube at room temperature, on a Bruker WM-250 FT-spectrometer controlled by an Aspect 2000 computer at 250.13 MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measuring parameters of the H-1 NMR spectra were as follows: sweep width 5 kHz, pulse width 1 μs (∿20° flip angle), acquisition time 1.64 s, number of scans 16 or 32, computer memory 16 K. Lorentzian exponential multiplication for signal-to-noise enhancement (LB: 0.7 Hz) was applied.

The C-13 NMR spectra were run in $CDCl_3$ or DMSO-d_6 in 5 or 10 mm tubes at room temperature, on a Bruker WP 80-SY FT-spectrometer with an Aspect 2000 computer at 20.14 MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measuring parameters were: sweep width 5 kHz, pulse width 3.5 μs (∿30° flip angle), acquisition time 1.64 s, number of scans 1K-32K computer memory 16K. Complete proton noise decoupling (∿1.5 W) and Lorentzian exponential multiplication for signal-to-noise enhancement were used (1.0 Hz).

DEPT[13] spectra were run in a standard way,[14] using only the $\theta=135^\circ$ pulse to separate CH/CH_3 and CH_2 lines phased "up and down", respectively. Typical acquisition data were: number of scans 128-12 K, relaxation delay for protons 3 s, 90° pulse widths 10.8 and 22.8 μs for ^{13}C and ^1H, respectively. The estimated value for J(C,H) resulted in a 3.7 ms delay for polarization.

For t.l.c. Kieselgel HF_{254} was used with benzene-THF 4:1 (A) and 10:1 (B), and with benzene-ethanol 5:1 (C) and 10:1 (D) as solvent. For detection iodine vapour was applied. For column chromatography Kieselgel 40 (63-200 μm) was used with benzene-THF 6:1 (E) and 25:1 (F) and with benzene-ethanol 10:1 (G) as solvent. Organic solutions were dried over Na_2SO_4 before evaporation. Mp's were determined on a Boetius hot stage.

2,6-Dimesyloxy-3,7-dimethylene-bicyclo[3,3,1]nonane (3).

To a stirred slurry of $LiAlH_4$ (6 g) in dry THF (120 ml) a solution of diester 1[6] (8 g) in dry THF (80 ml) was added at 80 °C during a period of 2 h. Thereafter stirring was continued for 1.5 h when all the starting material (R_F 0.8, C) has been consumed. The excess of the hydride was decomposed by giving gradually water (50 ml) to the cooled slurry, which was then made neutral with M sulfuric acid (∿80 ml). The insoluble inorganic material was filtered off, the filtrate was evaporated yielding the crude dihydroxy compound 2 (4.2 g; R_F 0.6, C) as semisolid material. This was used without further purification for the next step. To a solution of crude 2 (4 g) in dry pyridine (20 ml) mesyl chloride (8 ml) was added

gradually at 0 °C. The reaction mixture was kept at room temperature for 2 h and was then poured into water. The crude diester was filtered, washed with water, dried and recrystallized from ethyl acetate to give pure 3 (3.6 g, 48.5%), m.p. 125-127 °C. Found: C, 46.3; H, 6.1; S, 19.0%. Calc. for $C_{13}H_{20}O_6S_2$: C, 46.4; H, 6.0; S, 19.1%).

Reaction of 3 with bromine. To a stirred solution of 3 (2.5 g) in CH_2Cl_2 (100 ml) a solution of bromine (1.3 g) in CH_2Cl_2 (15 ml) was added during 30 min. Stirring was continued for 1.5 h, then the solution was evaporated and the residue (4.1 g) was separated by column chromatography (solvent E).

The fractions having R_F 0.8 (A) gave on evaporation and recrystallization of the residue from ethanol 1-bromo-3-bromomethyl-4,8-dimesyloxy-adamantane (6a, 2.45 g, 66.3 %), m.p. 136-137 °C. (Found: C, 31.3; H, 4.0; Br, 29.8 %. Calc. for $C_{13}H_{20}Br_2O_6S_2$: C, 31.4; H, 4.0; Br, 32.1 %).

The fractions having R_F 0.65 (A) gave on evaporation and recrystallization from ethanol 3-bromomethyl-1-ethoxy-4,8-dimesyloxy-adamantane (6c, 0.25 g, 7.3 %), m.p. 132-133° (Found: C, 39.2; H, 5.4; Br, 17.15%. Calc. for $C_{15}H_{25}BrO_7S_2$: C, 39.4, H, 5.45; Br, 17.25%).

The fractions having R_F 0.5 (A) gave on evaporation and recrystallization from ethanol 3-bromomethyl-1,4,8-trimesyloxy-adamantane (6b, 0.5 g, 13.05%), m.p. 159-161 °C. (Found: C, 32.7; H, 4.5; Br, 15.5; %. Calc. for $C_{14}H_{23}BrO_9S_3$: C, 32.8; H, 4.5; Br,15.6%).

Reaction of 3 with BrF. To a stirred solution of 3 (4 g) in dichloro methane (80 ml) 70% aqueous HF (12.7 g) and NBS (6 g) was added at 0 °C. Stirring was continued for 1 h, then the solution was poured onto ice and was made neutral with solid sodium carbonate. The separated organic solution was washed with water, dried and evaporated. The residue (8.8 g) was separated by column chromatography (solvent G).

The fractions having R_F 0.8 (D) gave on evaporation and recrystallization from ethanol 3-bromomethyl-1-fluoro-4,8-dimesyloxy-adamantane (6d, 2.8 g, 54.2 %), m.p. 163-165 °C. (Found: C, 35.9; H, 4.55; Br, 18.5; F, 4.5 %). Calc. for $C_{13}H_{20}BrFO_6S_2$: C, 35.9; H, 4.6; Br, 18.25; F, 4.4 %).

The fractions having R_F 0.6 (D) gave on evaporation and recrystallization from ethanol 6b (0.5 g, 8.25 %) identical with that already described.

The fractions having R_F 0.4 (D) gave on evaporation and recrystallization from ethanol 3-bromomethyl-1-hydroxy-4,8-dimesyloxy-adamantane (6e, 1.5 g, 29.2 %), m.p. 167-168 °C. (Found: C, 35.9; H, 4.5; Br, 18.8 %. Calc. for $C_{13}H_{21}BrO_7S_2$: C, 35.95; H, 4.6; Br, 18.35 %).

Reaction of 3 with NH_3. To a vigorously stirred and ice cooled solution of 3 (1 g) in $CHCl_3$ (20 ml) NaN_3 (0.3 g) and subsequently conc. sulphuric acid (1.5 ml) was added slowly. Stirring was continued for 30 min. at room temperature, then the reaction mixture was poured onto ice. The organic solution was washed with water, dried, evaported and the residue separated by column chromatography (solvent E).

The fractions having R_F 0.65 (A) gave on evaporation and recrystallization from ethanol 1-ethoxy-sulfonyloxy-4,8-dimesyloxy-3-methyl-adamantane (7c, 0.38 g, 33.45%), m.p. 147-149 °C. (Found: C, 38.9; H, 5.4; S, 20.1 %. Calc. for $C_{15}H_{26}O_{10}S_3$: C, 39.0, H, 5.6; S, 20.65 %).

The fractions having R_F 0.5 (A) gave on evaporation and recrystallization from ethanol 1,4,8-trimesyloxy-3-methyladamantane (7b, 0.17 g, 13.25 %), m.p. 146-147 °C. (Found: C, 38.6; H, 5.4; S, 22.15 %. Calc. for $C_{14}H_{24}O_9S_3$: C, 38.9; H, 5.6; S, 22.2 %).

The fractions having R_F 0.35 (A) gave on evaporation and recrystallization from ethanol 1-hydroxy-4,8-dimesyloxy-3-methyl-adamantane (7a, 0.25 g, 23.85 %), m.p. 153-154 °C. (Found: C, 44.1; H, 6.2; S, 18.1 %. Calc. for $C_{13}H_{22}O_7S_2$: C, 44.1; H, 6.2; S, 18.15%).

1-Fluoro-3-methyl-4,8-dimesyloxy-adamantane (7d). To a stirred solution of 6d (0.3 g) in ethanol (10 ml) Raney Ni (1 g) and subsequently hydrazine hydrate (0.5 ml) was added. When the evolution of gas ceased, the slurry was heated on a steam bath for 15 min. The cooled mixture was filtered and the catalyst was separately washed with $CHCl_3$. The ethanolic filtrate was evaporated and the residue was dissolved in the $CHCl_3$ solution, washed with water and evaporated. The residue gave on recrystallization from ethanol pure 7d (0.23 g, 93.7 %), R_F 0.3 (B), m.p. 152-154 °C. (Found: C, 43.45; H, 5.5; F, 5.3; S, 18.05 %. Calc. for $C_{13}H_{21}FO_6S_2$: C, 43.6; H, 5.9; F, 5.3; S, 18.1 %).

3-Azidomethyl-1-bromo-4,8-dimesyloxy-adamantane (8a). A solution of dibromide 6a (3.5 g) and NaN_3 (1.2 g) in DMF (100 ml) was stirred at 120 °C for 3 h. The residue of the evaporated solution was partitioned between $CHCl_3$ and water, the organic solution was washed with water, dried and evaporated. The residue was purified by column chromatography (solvent F), to give after evaporation and recrystallization from ethanol pure 8a (2.62 g, 81.3 %), R_F 0.5 (B), m.p. 136-137 °C.(Found: C, 34.1; H, 4.3; Br, 17.2; N, 8.9 %. Calc. for $C_{13}H_{20}BrN_3O_6S_2$: C, 34.1; H, 4.4; Br, 17.4; N, 9.0 %).

3-Azidomethyl-1-fluoro-4,8-dimesyloxy-adamantane (8b). A solution of 6d (3 g) and NaN_3 (1 g) in DMF (90 ml) was stirred at 120 °C for 6 h and was then proceeded as described for 8a to give pure 8b (2.46 g, 89.5 %), R_F 0.3 (E), m.p. 137-138 °C. (Found: C, 39.1; H, 4.95; F, 4.85; N, 10.25 %), Calc. for $C_{13}H_{20}FN_3O_6S_2$: C, 39.3; H, 5.05; F, 4.8; N, 10.55%).

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