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THE STRUCTURE OF THE ANTIBIOTIC HEDAMYCIN—III

^{13}C NMR SPECTRA OF HEDAMYCIN AND KIDAMYCIN†

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Abstract—The ^{13}C NMR spectra of hedamycin, kidamycin and some of their derivatives have been fully assigned. Proton coupling constants and ^{13}C NMR acetylation shifts indicate that the conformations of the highly substituted tetrahydropyran rings in solution are chair forms for ring E, as well as for ring F in isokidamycins, but a twist form for ring F in hedamycins and kidamycins.

Hedamycin (1) and Kidamycin (3) are antitumor active antibiotics produced by *Streptomyces* species. The structure of kidamycin was determined a few years ago by Furukawa *et al.*[2] using chemical and spectroscopic evidence as well as X-ray analyses of two derivatives. Séquin recently proposed a structure for hedamycin based upon a tight spectral comparison of hedamycin and kidamycin.[1] According to that work, both compounds are virtually identical with the exception of the substituent at C-2. Kidamycin features an olefinic side chain, whereas in hedamycin this substituent is saturated with the diepoxide structure shown in formula 1.

Since ^{13}C NMR spectroscopy has proved very useful for the investigation of biologically important compounds and biosynthetic studies, we now wish to present a detailed analysis of the ^{13}C NMR spectra of hedamycin, kidamycin and some derivatives.

Table 1 lists all the chemical shifts together with the multiplicities observed upon off-resonance decoupling. The assignments made reflect the shift differences expected from the differences in structure (hedamycin vs kidamycin), in degree of acetylation, and in configuration at C-6″ (kidamycin vs isokidamycin, the 6″-epimer of kidamycin). Due to the heavy substitution, ring F is in a twist conformation (at least in the crystals, as was revealed by X-ray analysis[2]). Acetylation of its 3″-OH group will most probably alter the conformation of ring F and give marked shifts for all carbons of ring F as well as for some carbons in ring D of the aromatic nucleus. The same is true, of course, for inversion of the C-6″ configuration.

Methyl groups. Assignment of the N-Me groups is straight forward. Those of ring F show marked shift differences between the different kidamycin derivatives as expected, whereas those belonging to ring E are hardly affected by structural changes in ring F.

Those Me resonances exhibiting different shifts in hedamycin and kidamycin must belong to the side chains at C-2. Thus the lines at 14.5 and 17.2 ppm in hedamycin (and at 14.2 and 17.2 ppm in its triacetate 2) must correspond to C-15 and C-19 respectively; the distinction between the two was made by specific proton decoupling (SPD)‡ of C-15 with hedamycin. The assignments made give further support to the diepoxide structure of the side chain, as the chemical shifts observed are in good agreement with the methyl shifts in the model compounds ovalicin,[3] aspertin[4] and aspyrone.[5] In kidamycin the lines at 12.1 and 14.9 ppm were assigned to carbons 15 and 17, respectively. Here the distinction was made from the observation of a *ca.* 7 Hz long range coupling for the line at 12.1 ppm vs the *ca.* 3.5 Hz exhibited by the 14.9 ppm resonance. Similar coupling constants and chemical shifts were found in tiglic acid. The assignments made are consistent with those for comparable methyl groups in vitamin A derivatives.[6]

The aromatic Me group, C-13, was assigned from SPD experiments with hedamycin. It shows a constant shift of *ca.* 24 ppm through the whole series of compounds as expected.

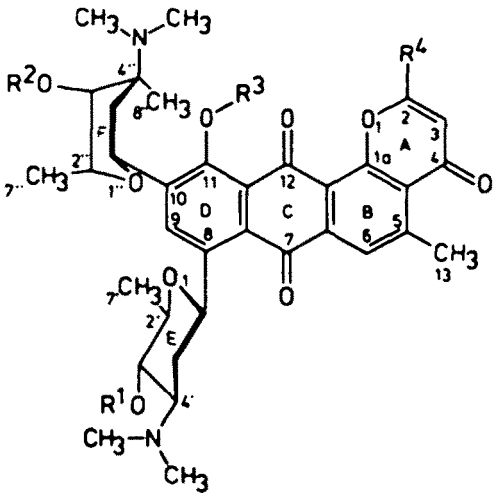
For C-8″ a shift of 12.3 ppm was found by SPD with hedamycin. This carbon is expected to be shifted upon acetylation of the ring F OH group and thus was assigned the resonances at 13.8 ppm in 4, 5 and 6. In the isokidamycin series, carbon 8″ (being an axial Me group) was assigned the Me resonance at highest field.

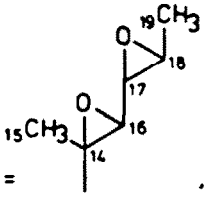
Assignment of C atoms 7′ and 7″ was possible in 4 from SPD experiments. The Me at ring E, C-7′, is expected to show almost no chemical shift variation with acetylation or change of the C-6″ configuration, whereas C-7″ at ring F will exhibit distinct shifts. From this, the line at *ca.* 18.9 ppm was attributed in all compounds to C-7′, the remaining Me resonance to C-7″.

Carbonyl carbons. The three lines at lowest field in the spectra correspond to the three CO groups, i.e. C-4, C-7 and C-12. They are easily assigned from comparison with anthraquinone,[7] 1-hydroxyanthraquinone, 5 - hydroxy - 1,4 - naphthoquinone (juglone)[8] and flavone.[9] The assignments made are confirmed by the shifts these lines experience upon acetylation of the phenol, by the *ca.*

†For the previous paper of this series see Ref. 1.

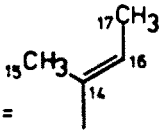
‡Specific proton decoupling experiments are based on the ^{1}H NMR assignments given earlier.[1,3]





1: hedamycin R^4 = , $R^1 = R^2 = R^3 = H$

2: R^4 = // , $R^1 = R^2 = R^3 = Ac$



3: kidamycin R^4 = , $R^1 = R^2 = R^3 = H$

4: R^4 = // , $R^1 = R^2 = R^3 = Ac$

5: R^4 = // , $R^1 = R^2 = Ac$, $R^3 = H$

6: R^4 = // , $R^1 = H$, $R^2 = R^3 = Ac$

3 Hz vicinal coupling with H-6 which is observed for C-7, and by the chemical shift difference of the C-4 resonance between hedamycin and kidamycin. In the compounds where the phenol is acetylated, C-12 has an extremely long spin-lattice relaxation time T_1 due to the absence of any protons in the neighbourhood. Care must be taken in selecting the experimental parameters to avoid saturation of the corresponding carbon resonance, which otherwise may easily be lost in the noise. The low relative intensity of this line at 181.2 ppm is illustrated by the ^{13}C NMR spectrum of 4 (Fig. 1).

sp^2-Carbons bonded to oxygen. The sp^2-carbons 1a, 2 and 11 are bonded to oxygen and therefore are expected to have resonances at rather low field. The C-11 line is readily detected by comparison with 1-hydroxyanthraquinone and juglone.[8] The assignment is supported by a 9.5 Hz coupling with H-9, which collapses when this proton is irradiated. This coupling also identifies the C-11 resonance in the acetylated derivatives. The upfield shift of *ca.* 14 ppm observed for this carbon upon acetylation of the phenol is comparable to the values found for 1-acetoxyanthraquinone and juglone acetate.[8] The lines for C-1a and C-2 are assigned from a comparison with flavone.[9] Of the three carbons, 1a, 2 and 11, C-2 is the one having the largest shift difference between hedamycin and kidamycin, as expected. The assignment of C-1a is further supported by the fact that the C-1a resonance is of rather low intensity (Fig. 1). This must be due to a long spin-lattice relaxation time, which can easily be rationalized by the absence of any neighboring protons that could effect dipole–dipole relaxation of C-1a.

Protonated sp^2-carbons. The protonated sp^2-carbons (C-3, C-6 and C-9, as well as C-16 in the kidamycins) are readily assigned from SPD-experiments.

Remaining quaternary sp^2-carbons. Of the remaining quaternary sp^2-carbons C-5 could be easily detected due to its splitting into a quartet by protons in the region of $\delta_H \approx 3$ ppm. This must be due to the Me protons of C-13. The same two-bond coupling was recently observed by Höfle[7] in a similar methylated anthraquinone. Furthermore, the shift of *ca.* 149 ppm found for C-5 corresponds well to the shifts found in model anthraquinones.[7]

C atoms 11a and 12a are expected to resonate at highest field in hedamycin and kidamycin due to the ortho oxygen functions. Again, 1-hydroxyanthraquinone and juglone can serve as model compounds. The line around 119 ppm shows the larger shift difference between hedamycin and kidamycin and therefore is assigned to carbon 12a, the line at 116 ppm remaining for C-11a. These assignments are confirmed by the 6 Hz

Table 1. ^{13}C NMR spectra of hedamycins, kidamycins and isokidamycins

Carbon	Hedamycin 1	Hedamycin triacetate 2	Kidamycin 3	Kidamycin triacetate 4	Kidamycin-3',3" diacetate 5	Kidamycin-11,3" diacetate 6	Isokidamycin 7	Isokidamycin triacetate 8
1a	156.1	155.0	155.7	154.9	155.7	154.9	155.6	155.0
2	166.3	165.7	163.7	163.6	163.7	163.6	163.6	163.7
3	110.0 d	110.5 d	108.7 d	108.7 d	108.7 d	108.7 d	108.7 d	108.8 d
4	178.7	178.7	179.2	179.6	179.3	179.7	179.2	179.7
4a	125.8*	126.0	125.8	125.8	125.8*	125.8	125.9*	125.9
5	149.7	148.3	149.6	148.1	149.6	148.2	149.4	148.2
6	125.9 d	125.0 d	125.4 d	124.4 d	125.3 d	124.4 d	125.3 d	124.5 d
6a	137.3	136.8	137.0	136.7	137.0	136.8	136.9	136.5
7	183.1	183.9	183.0	184.1	183.0	184.2	182.8	184.1
7a	126.2*	128.5	125.8	128.7	126.1*	128.7	125.6*	129.0
8	140.2	143.7	140.0	143.7	140.8	144.1*	140.0	143.7*
9	133.1 d	131.0 d	133.0 d	130.8 d	132.4 d	131.0 d	132.6 d	131.5 d
10	138.6	144.4	138.4	144.5	138.3	144.3*	139.0	143.3*
11	159.8	145.4	159.7	145.4	159.4	145.4	158.7	145.4
11a	116.1	127.1	116.0	127.0	115.8	127.0	115.4	127.3
12	188.0	181.0	188.1	181.2	187.9	181.3	187.7	181.2
12a	119.2	121.2	118.9	121.0	118.8	121.0	118.6	121.1
13	24.1 q	23.7 q	24.0 q	23.8 q	24.0 q	23.8 q	24.0 q	23.8 q
14	57.7	57.3	127.2	127.5	127.2	127.6	127.1	127.6
15	14.5 q	14.2 q	12.1 q	12.0 q	12.1 q	12.0 q	12.0 q	12.0 q
16	63.9 d	63.5 d	134.2 d	133.3 d	134.2 d	133.3 d	134.0 d	133.3 d
17	55.4 d	55.6 d	14.9 q	14.7 q	15.0 q	14.7 q	14.9 q	14.7 q
18	51.8 d	51.6 d						
19	17.2 q	17.2 q						
2'	77.3 d	75.5*d	77.3 d	75.7 d	75.7*d	77.8 d	77.6 d	75.6 d
3'	71.9 d	73.0 d	71.9 d	73.0 d	73.1 d	71.7 d	73.5 d	73.0 d
4'	67.4 d	64.8 d	67.4 d	64.8 d	64.8 d	67.6 d	67.6 d	64.7 d
5'	28.3 t	31.7 t	28.3 t	31.6 t	30.9 t	29.6 t	28.3 t	31.8 t
6'	75.2 d	75.4*d	75.2 d	75.5*d	75.3*d	75.6*d	75.6 d	75.4 d
7'	18.9 q	18.5 q	18.9 q	18.5 q	18.5 q	18.9 q	18.7 q	18.4 q
4'N(CH_3)$_2$	40.4 q	40.7 q	40.4 q	40.7 q	40.8 q	40.5 q	40.5 q	40.7 q
2"	67.3 d	70.3 d	67.2 d	70.2 d	69.9 d	70.2 d	72.3 d	71.8 d
3"	70.9 d	64.8 d	70.8 d	64.8 d	64.8 d	64.8 d	70.3 d	72.1*d
4"	57.3	57.9	57.4	57.9	57.7	57.9	58.7	57.6
5"	33.7 t	42.0 t	33.6 t	42.0 t	41.1 t	42.0 t	37.0 t	38.6 t
6"	69.6 d	75.8*d	69.5 d	75.7*d	76.3*d	75.8*d	71.0 d	71.4*d
7"	17.6 q	14.8 q	17.6 q	14.7 q	15.0 q	14.7 q	18.0 q	17.9 q
8"	12.3 q	13.8 q	12.3 q	13.8 q	13.7 q	13.8 q	10.9 q	12.0 q
4"N(CH_3)$_2$	36.8 q	39.1 q	36.8 q	39.1 q	39.4 q	39.2 q	36.7 q	37.6 q
acetyl-groups		170.5 170.2 169.1 21.3 q 21.2 q 21.1 q		170.5 170.2 168.9 21.3 q 21.1+q	170.4+ 21.2+q	170.3 168.9 21.1+q		171.0 170.6 169.1 21.3+q 20.9 q

Chemical shifts are δ_C-values in ppm from internal TMS.

Assignments that were obtained from SPD experiments are underscored.

Multiplicities observed upon off-resonance decoupling are indicated by the usual abbreviations (d, t, q, no letter indicating singlets).

*Similar values within a column may be reversed.

†Signal corresponds to two carbon atoms.

coupling C-12a shows with H-6; C-11a shows no coupling at all. In the compounds where the phenol is acetylated, the C-12a resonance is at 121 ppm, again confirmed by the observed coupling. C-11a must experience a large downfield shift upon acetylation of the phenol (about 9 ppm is expected from comparison with juglone[9]) and is thus assigned the line at *ca.* 127 ppm in **2**, **4**, **6** and **8**. No long range coupling could be discerned for these lines. In addition, they have relatively low intensities in the spectra (Fig. 1) due to long spin-lattice relaxation times, as have the corresponding resonances in the spectra of **1**, **3**, **5** and **7**.

A comparison of the spectra of hedamycin and kidamycin shows that the line at 127.2 ppm in the kidamycin spectrum does not have its counterpart in hedamycin and therefore has to be attributed to C-14 of the olefinic side chain. Similarly the C-14 resonance was found at 127.5 ppm in the derivatives where the phenol is acetylated. The resonance shows a typical splitting into at least four lines, which is simplified when aliphatic protons are irradiated.

Estimation of the chemical shifts of carbons 8 and 10 by correcting the values in 1-hydroxyanthraquinone for the tetrahydropyran substituents[10] leads to the conclusion that the lines around 140 and 138 ppm must correspond to carbons 8 and 10. Of these two resonances the one showing no difference between kidamycin (**3**) and isokidamycin (**7**) is assigned to C-8. Similar arguments lead to the assignments of these same two carbons in the compounds **4** and **8**. They are confirmed

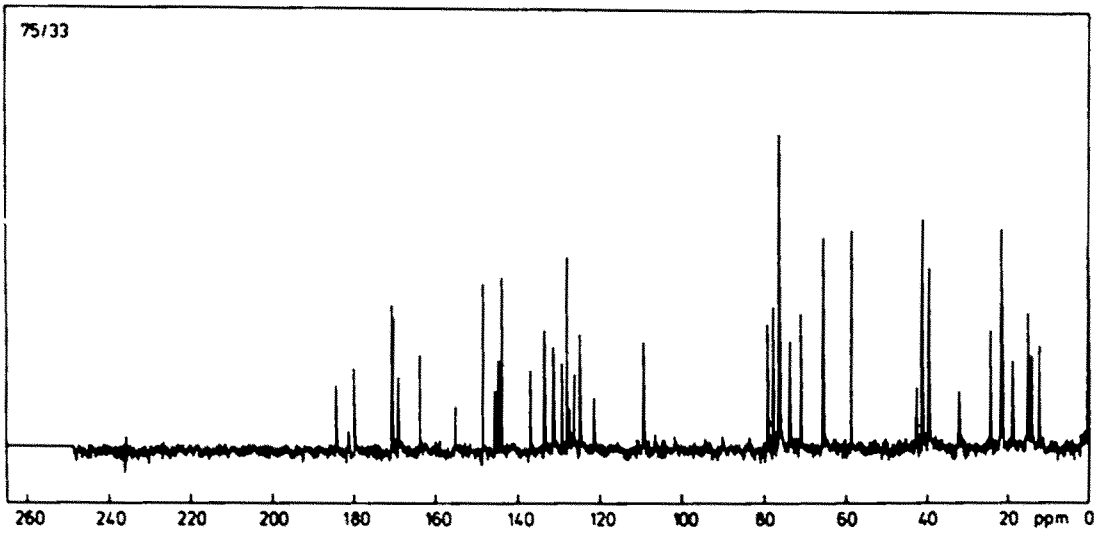
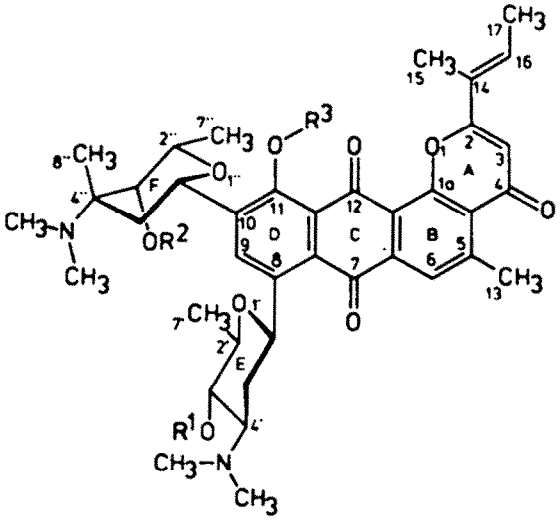


Fig. 1. 22.63 MHz ^{13}C NMR spectrum of kidamycin triacetate (4) in $CDCl_3$.



7: isokidamycin $R^1 = R^2 = R^3 = H$

8: $R^1 = R^2 = R^3 = Ac$

when 4 and 6 are compared: the line assigned to C-8 is shifted upon de-acetylation of ring E, whereas the one corresponding to C-10 remains in place. The assignments made are consistent with the shifts expected for the acetylation of the phenol.[8]

The line at *ca.* 137 ppm shows only a minor dependence on acetylation, epimerization at C-6" or the nature of the C-2 side chain. No long range coupling was discernible whatsoever. Among the three quaternary sp^2-carbons not yet assigned, C-4a and C-7a both have protons three bonds away and thus are expected to show vicinal coupling, whereas C-6a has only a proton two bonds away. Since $^2J_{CH}$ is usually much smaller than $^3J_{CH}$ and therefore hardly resolved,[7] the resonance at *ca.* 137 ppm was attributed to C-6a. Again the chemical shift is consistent with what was found by Höfle for similar compounds.[7]

The excellent agreement of the chemical shifts of the C atoms 1a, 2, 3, 4 and 6 in kidamycin with the values observed in flavone[9] suggests that with the aid of this latter model compound the line at 125.8 ppm, which shows constant chemical shifts throughout the whole series, can be assigned to carbon 4a.

The last line not yet assigned, with a chemical shift of *ca.* 126 ppm in compounds 1, 3, 5 and 7 and *ca.* 128.7 ppm in the derivatives with acetylated phenolic OH group, must—by exclusion—belong to C-7a.

C-2 *Side chain of hedamycin.* Hedamycin shows four resonances in addition to those seen in the kidamycin spectrum in the range of 50–60 ppm. These four lines can be attributed to the side chain at C-2 of hedamycin. In off-resonance decoupled spectra the C-14 resonance is readily detected as a singlet. Assignment of C-16 was made by SPD, and C atoms 17 and 18 could be distinguished by measurement of the residual splittings of the corresponding carbon resonances in SPD experiments where proton signals adjacent to those of H-17 and H-18 were irradiated. Assignment of the side chain carbon resonances in 2 was then straightforward, since no appreciable acetylation shifts are expected.

Tetrahydropyran carbons. The two methylene groups of the tetrahydropyran rings, C-5' and C-5", are easily assigned from off-resonance decoupled spectra. They can be distinguished by the rather large shifts the C-5" resonance experiences upon acetylation of the antibiotic or change of the C-6" configuration. Furthermore, C-5", which has an additional β-carbon (C-8"), is expected to resonate at lower field than C-5'.

The assignment of C-4" is also straightforward, as it gives a singlet in off-resonance decoupled spectra.

Extensive SPD experiments with kidamycin triacetate (4) resulted in unambiguous assignments of all remaining tetrahydropyran carbons of this compound, with the exception of C-6' and C-6", which could not be distinguished. Assignments for the carbons of rings E and F in 2 and 5, for ring F in 6 and for ring E in 8 were then straightforward.

In hedamycin and kidamycin, SPD revealed the C-2" resonance as well as the two signals for C-6' and C-6" together.

SPD experiments with isokidamycin triacetate (8)

confirmed the assignments made by comparison with compound 4 for C atoms 2', 4' and 6'. In addition, the resonance of C-2" could be assigned unambiguously. The remaining two lines at 72.1 and 71.4 ppm must correspond to C-3" and C-6".

In isokidamycin (7) the assignments of C atoms 2', 4' and 6' as well as 2" and 6" could be made from SPD experiments. These assignments found for C-2', C-4' and C-6' lead to the corresponding assignments in compounds 6, 3 and 1, where the carbons of ring E are expected to exhibit similar shifts. The last line in 6 not yet assigned (71.7 ppm) must then belong to C-3', the same being true for the other compounds with non-acetylated ring E. By exclusion the assignments for carbons 6" and 3" in 1 and 3, as well as for 3" in 7 can then be made.

Very recently Kondo *et al.* have reported on the structure and ^{13}C NMR spectra of the closely related compounds neopluramycin and pluramycin A and their diacetates.[11] Neopluramycin was found to be kidamycin 3"-acetate (and thus its diacetate is identical with 4), while pluramycin A seems to be the 3"-acetate of a hedamycin derivative with a 17,18 double bond instead of the epoxide. The assignments given for these compounds correspond by and large with those reported here. Yet there are some discrepancies; the most severe ones are discussed below.

(a) The assignments of the two side chain Me groups, C-15 and C-17, in neopluramycin and its diacetate must be reversed. (b) Kondo *et al.* have not observed the resonance of C-12 in the spectra of their fully acetylated compounds, most certainly because the experimental conditions used were inappropriate. As a consequence, C-12 was assigned a line at 170.6 ppm, which, in fact, is one of the acetyl resonances. Then, the signal at 163.7 ppm was attributed to an acetyl group in neopluramycin diacetate whereas the corresponding resonance in pluramycin A diacetate is reported at 167.4 ppm. These two values are not consistent and we cannot see any reason, why these two CO resonances should show such a large shift difference, the corresponding Me groups having the same chemical shifts within 0.1 ppm. (c) The resonances of C-11 and C-2 are not correctly assigned. (d) Carbon 1a is claimed to experience a huge upfield shift of *ca.* 10 ppm upon acetylation of the phenol. We can hardly see a reason for this and suggest that the assignment of C-1a in the fully acetylated compounds be revised. (e) An extreme upfield acetylation shift of *ca.* 10 ppm is also proposed for C-10, which is hardly believable when compared with the *ca.* 12 ppm downfield shift given for C-11a (which we consider to be correct). Here too, the assignments for neopluramycin diacetate and pluramycin A diacetates must be revised. (f) Furthermore, Kondo *et al.* have reported reversed assignments for the two tetrahydropyran methylene groups. Our assignments are based on the comparison with the isokidamycins and partially acetylated kidamycins and are unambiguous. (g) Finally, the lines around 65 ppm are not due to C-6" but rather to C-3" as we have shown by an SPD experiment.

DISCUSSION

The ^{13}C NMR assignments made shed light on the conformations the two highly substituted tetrahydropyran rings adopt in solution.

Ring E was shown[2] to be in the chair conformation 9 in the crystal. All substituents are equatorial. There is no doubt that the same arrangement will also be the preferred one in solution. This assumption is supported by ^1H- and ^{13}C NMR data. Proton–proton coupling constants have been measured in hedamycin at 270 MHz; they indicate a trans diaxial arrangement of all the protons at ring E.[12] The ^{13}C NMR acetylation shifts observed for the C atoms of the same tetrahydropyran ring are compiled in Table 2. For C-3', bearing the OH group, and its neighbors C-2' and C-4' the observed acetylation shifts correspond with respect to their signs to what is expected from the acetylation data of *trans*-4-t-butylcyclohexanol.[13] They are furthermore in reasonable agreement (sign and magnitude) with the acetylation shifts measured for β-D-glucose,[14] which are smaller by about a factor two than the shifts observed in the carbocyclic t-butylcyclohexanol. Since the most stable conformations of both these model compounds are chair forms with equatorial OH groups, we conclude that ring E also assumes the chair conformation 9 in solution.

An unexpectedly large downfield acetylation shift of 3.4 ppm was observed for the methylene group of ring E, C-5'. We do not think, that this originates from a steric effect within the tetrahydropyran ring but rather from an alteration of the torsion angle about the C-6'/C-8 bond, which would bring the methylene C-5' into different positions relative to the aromatic nucleus and the CO group C-7. An additional contribution to the downfield acetylation shift of C-5' comes from esterification of the phenolic OH group. This contribution is +0.7 to +1.3 ppm as can be seen from a comparison of 4 and 5 or

Table 2. ^{13}C NMR acetylation shifts $\Delta\delta_C$ for the carbon atoms of ring E in hedamycins, kidamycins and isokidamycins

	C-2'	C-3'	C-4'	C-5'	C-6'	C-7'	$N(CH_3)_2$
observed $\Delta\delta_C$ [a]	-1.5 to -2.0	+1.1 to +1.5	-2.6 to -2.9	+3.3 to +3.5	-0.2 to +0.6	-0.3 to -0.4	+0.2 to +0.3
$\Delta\delta_C$ [b] in trans-4-t-butylcyclohexanol (equatorial OH) [13]	-3.7	+2.7	-3.7	-0.1	0		
$\Delta\delta_C$ [b] in β-D-glucose [14]	-1.8	+1.5	-1.8	-0.2			

[a] $\Delta\delta_C = \delta_C$(triacetate) − δ_C(parent antibiotic)

[b] $\Delta\delta_C = \delta_C$(ROAc) − δ_C(ROH)

6 and 3. The other carbons of ring E are, in general, only negligibly influenced by the acetylation of the phenol. The net shift of C-5′ due to acetylation of the OH group at C-3′ is +2.6 ppm as calculated from 5 and 3. Thus the two contributions seem to be additive.

Ring F in the isokidamycin series prefers a chair conformation in the crystal[2] with the two largest substituents, aryl and dimethylamino, in equatorial positions and the OH group and the tertiary Me group (C-8″) as axial substituents (*cf* 10). The observed acetylation shifts (Table 3) for C-2″, C-3″ and C-4″ are again in agreement as far as the sign is concerned with the values for *cis*-4-t-butylcyclohexanol, a model compound with an axial OH group. Their magnitude is much smaller than the shifts observed for the cyclohexanol, as was already noticed for ring E (and for glucose). The fact, that the upfield shifts for C-2″ and C-4″ are smaller in magnitude than the downfield shift of C-3″ suggests that ring F has in solution a chair conformation featuring an axial OH group. An equatorial OH would have caused the downfield acetylation shift of C-3″ to be larger than the shifts for C-2″ and C-4″ as is the case for ring E and for the two equatorial model alcohols (Table 2).

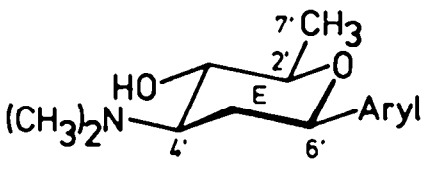
Ring F was shown[2] to have the twist conformation 11 in the crystal, with the aryl and dimethylamino substituents pseudoequatorial, OH and tertiary Me (C-8″) pseudoaxial and with the secondary Me group (C-7″) in an isoclinal position. One would, however, expect the most stable conformation to be one, where the geminal substituents are in isoclinal positions.[15] Thus, conformation 12 with dimethylamino group and tertiary Me in isoclinal positions and with aryl and secondary Me pseudoequatorial would seem more favorable; in this arrangement only one substituent, OH, would be pseu-

Table 3. ^{13}C NMR acetylation shifts $\Delta\delta_C$ for the carbon atoms of ring F in hedamycins, kidamycins and isokidamycins

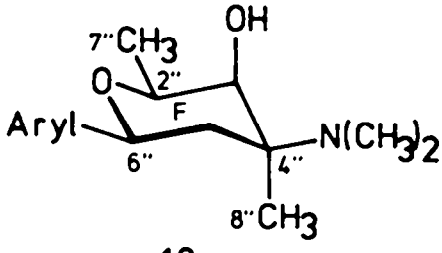
	C-2″	C-3″	C-4″	C-5″	C-6″	C-7″	C-8″	$N(CH_3)_2$
$\Delta\delta_C$[a] observed in isokidamycins	−0.5	+1.1 to +1.8	−1.1	+1.6	+0.4 to +1.1	−0.1	+1.1	+0.9
$\Delta\delta_C$[a] observed in hedamycins and kidamycins	+2.7 to +3.0	−6.0 to −6.1	+0.1 to +0.9	+7.5 to +8.4	+5.8 to +6.8	−2.4 to −2.8	+1.4 to +1.9	+2.3 to +2.6
$\Delta\delta_C$[b] in cis-4-t-butylcyclohexanol (axial OH) [13]	−2.7	+3.7	−2.7	+0.8	−0.5			
$\Delta\delta_C$[b] in trans-4-t-butylcyclohexanol (equatorial OH) [13]	−3.7	+2.7	−3.7	−0.1	0			

[a] $\Delta\delta_C = \delta_C$(triacetate) − δ_C(parent antibiotic)

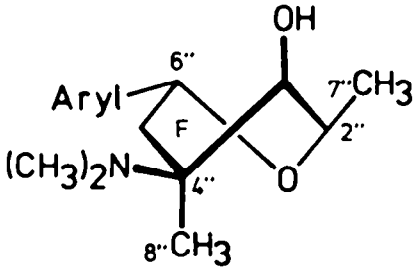
[b] $\Delta\delta_C = \delta_C$(ROAc) − δ_C(ROH)



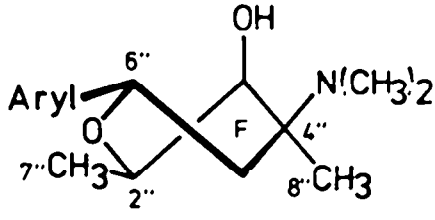
9



10



11



12

doaxial. However, there the OH group has an unfavorable isoclinal-pseudoequatorial interaction (dihedral angle of *ca.* 35°) with the bulky dimethylamino group, whereas such a steric relationship in 11 is between the OH and the less voluminous secondary Me group. From the Karplus equation the following ^1H–^1H coupling constants would be expected for conformation 11:† H-2″/H-3″: 5 Hz, H-5a″/H-6″: 8 Hz, H-5b″/H-6″: 5 Hz, and for conformation 12:‡ 1, 9 and 1 Hz. The values of 3, 7 and 5 Hz determined for bedamycin[12] seem to indicate conformation 11 rather than 12. They also rule out a chair conformation with equatorial aryl substituent, since in such a case the coupling of the axial H-6″ with the axial proton at C-5″ would have to be 10–13 Hz. Yet such a chair conformer would anyway be expected to be less favorable due to the axial arrangement of the dimethylamino group it would involve.[2] The ^{13}C NMR shifts induced in the C atoms of ring F upon acetylation (Table 3) show no resemblence whatsoever with the values for cyclohexanols with equatorial or axial OH groups. Furthermore the magnitude of these shifts is much larger than what was observed in ring E or in ring F of the isokidamycins. Again, the methylene group (C-5″) is shifted massively downfield (this time by *ca.* 8 ppm) and again about 1 ppm of this shift is due to the acetylation of the phenol as can be seen from a comparison of 4 and 5. Much larger shifts than observed for ring E are also found for C-2″, C-3″, C-6″ as well as for the secondary Me (C-7″) and the N-Me groups. These enormous acetylation shifts can only be interpreted in terms of a drastic change of conformation of ring F upon acetylation. We therefore conclude that ring F in non-acetylated bedamycins and kidamycins prefers the flexible twist conformation 11 in solution, which can be altered upon acetylation to relieve strain.

EXPERIMENTAL

All ^{13}C NMR spectra were recorded on a Bruker WH 90 spectrometer at 22.635 MHz with 8k/4k data points and usually a spectral width of 6000 Hz, thus giving a resolution of 1.46 Hz per point or 0.065 ppm per point. Some of the spectra were accumulated as 8k FID's, which—after elongation of the data table with 8k blanks—were Fourier transformed to give 8k real spectra with a resolution of 0.73 Hz or 0.032 ppm per point. The solvent, which also served for the internal lock signal, was $CDCl_3$ with TMS as internal standard. The samples (40–100 mg or 22–40 mg) were dissolved in the solvent (0.35 ml or 0.17 ml) and measured at ambient probe temperature (28°) in 5 mm tubes or microcells, respectively.

Broad band proton decoupling was effected with a noise modulated frequency of 5 W power, centered at *ca.* 7 ppm δ_H. For off-resonance decoupling the unmodulated decoupling frequency was set at −4 or +14 ppm δ_H (power 5 W). In specific proton decoupling (SPD) experiments the decoupler power was reduced to 0.15–0.4 W. Fully proton coupled spectra were recorded either with the decoupler switched *off* or using the gated decoupling technique (decoupler *off* during data acquisition, *on* between pulses).

Hedamycin (1) was a gift of Prof. A. I. Scott. Its triacetate (2) was made from 1 with Ac_2O in pyridine.[16] Kidamycin (3), its derivatives 4, 5 and 6 as well as isokidamycin (7) and its triacetate 8 have been described earlier.[2]

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†Assuming dihedral angles of 35, 155 and 35°.

‡Assuming dihedral angles of 60, 180 and 60°.

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