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# $^{13}$C NMR SUBSTITUENT EFFECTS IN TETRACYCLIC DITERPENOIDS

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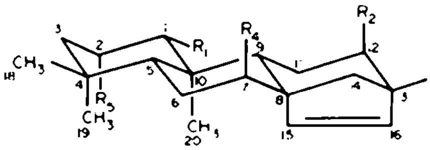
**Abstract**—The $^{13}$C NMR chemical shifts of *ent*-beyer-15-ene, and one hydroxy and four acetoxy derivatives are reported. The substituent effects of the acetoxy groups upon the saturated and olefinic carbon atoms are discussed. Conformational aspects of the molecules are considered in the light of these effects.

Substituent effects in $^{13}$C NMR spectroscopy have been found to be remarkably additive in closely related systems.[1] A factor that contributes very significantly to these substituent effects is steric interactions.[2] Thus, $^{13}$C NMR spectroscopy has become a very powerful method to determine the positions of substitution and the configuration at the substituted centres in polycyclic systems with a common skeleton. It is obvious, therefore, that this technique is going to play an increasingly important role in the field of natural products. It has even been suggested that $^{13}$C NMR spectroscopy is the appropriate method to establish the identity between synthetic and naturally occurring complex compounds.[3]

Recently we reported some preliminary data on the $^{13}$C NMR spectra of a series of tetracyclic diterpenoids with *ent*-beyerane and *ent*-beyer-15-ene skeletons.[4] We have now completed our work and would like to report on several substituent effects observed in these compounds.

## RESULTS AND DISCUSSION

Our first objective was to obtain the chemical shifts of the unsubstituted *ent*-beyer-15-ene, of which we had only a few milligrams. With this small quantity we were able to obtain a good proton noise-decoupled $^{13}$C NMR spectrum but a less satisfactory off-resonance decoupled spectrum. This made the full assignment of the lines rather difficult. The lines in the noise-decoupled spectrum of *ent*-beyer-15-ene were finally assigned by comparing the experimental chemical shifts with empirically estimated values. These values were obtained by taking the chemical shifts of the saturated derivative *ent*-beyerane[4] and correcting them for the effects of introducing a $\Delta^{15}$ double bond. As models for ascertaining these effects, we used the pair of compounds bicyclo-[3.2.1]-octane and $\Delta^6$-bicyclo-[3.2.1.]-octane[5] to evaluate the effects of introducing a $\Delta^{15}$ double bond in *ent*-beyerane on the chemical shifts of carbon atoms in rings C and D, and the pair 1-methyl-norbornane and 1-methyl-norbornene to determine the effects of the double bond on carbon atoms C-7 and C-17. Long-range effects of the double bond were considered to be negligible.



1 : $R_1 = R_2 = R_3 = R_4 = R_5 = H$
2 $R_1 = R_3 = H$, $R_2 = R_4 = OAc$
3 $R_1 = R_4 = H$, $R_2 = R_3 = OAc$
4 $R_1 = H$, $R_2 = R_3 = R_4 = OAc$
5 $R_4 = H$, $R_1 = R_2 = R_3 = OAc$
6 $R_1 = R_2 = R_3 = R_4 = H$, $R_5 = OH$

Table 1 shows the calculated values together with the experimental ones obtained from a very small sample of *ent*-beyer-15-ene. The agreement is reasonably good. This is further evidence of what has become gradually apparent during the last few years, namely, that $^{13}$C NMR spectra of derivatives with a common skeleton can be easily assigned once the chemical shift values for the parent compound are known (or vice versa), by a straightforward comparison of the experimental values with those calculated using simple models.

Table 2 contains the chemical shift data of all *ent*-beyer-15-ene derivatives studied in this work. Some of the substituent effects of the various acetoxyl groups in compounds **2**–**6** are discussed below.

*Acetoxyl group at C*-1. Table 3 shows some of the substituent effects due to an equatorial acetoxyl group at C-1. These effects were calculated by subtracting the chemical shift values of compound 3 from those of 5 for the corresponding carbon atoms. There are two points worth mentioning: the downfield shift of C-11 and the fact that the γ-effect on C-9 is negligible.

The spatial relationship between the substituent and C-11 is analogous to the one existing in *cis*-4-hydroxy-9-methyl-*trans*-decalin reported[7] as responsible for the 3.4 ppm downfield shift observed for the methyl group. The substituent effects of a hydroxyl and an acetoxyl group can justifiably be compared in this case, since the acetylation shifts on γ and δ effects have been found to be negligible.[8]

It has been reported[9] that in 1,3-diaxial dimethylcyclohexane derivatives there is no γ-effect of the C-3 methyl group on C-1. The interpretation given for this is that the carbon atom C-1 does not possess a hydrogen atom able to interact with the C-3 methyl group. Ap-

Table 1. Experimental and calculated $^{13}$C chemical shifts of *ent*-beyer-15-ene

| Carbon atom | $\delta^{a}_{exp}$ | $\delta_{calc}$ | Carbon atom | $\delta^{a}_{exp}$ | $\delta_{calc}$ |
|---|---|---|---|---|---|
| C-1 | 39.3 | 39.7 | C-11 | 20.5 | 19.8 |
| C-2 | 18.7 | 18.5 | C-12 | 33.7 | 32.4 |
| C-3 | 42.2 | 42.0 | C-13 | 43.6 | 43.5 |
| C-4 | 33.3 | 33.1 | C-14 | 61.3 | 63.1 |
| C-5 | 56.1 | 56.5 | C-15 | 135.2 | 136.8 |
| C-6 | 20.3 | 20.4 | C-16 | 136.1 | 140.8 |
| C-7 | 37.4 | 38.2 | C-17 | 25.0 | 24.1 |
| C-8 | 49.1 | 49.2 | C-18 | 33.8 | 33.7 |
| C-9 | 53.0 | 49.3 | C-19 | 22.0 | 21.9 |
| C-10 | 37.4 | 37.6 | C-20 | 15.1 | 15.1 |

[a] Chemical shifts in ppm downfield from TMS. Solvent deuteriochloroform. These data were obtained with a very small sample (aprox. 10 mg) and refer to a proton noise-decoupled spectrum only.

Table 2. $^{13}$C chemical shifts of the *ent*-beyer-15-ene derivatives **1**–**6**

| Carbon atom | **1** | **2** | **3** | **4** | **5** | **6**[a] |
|---|---|---|---|---|---|---|
| C-1 | 39.3 | 38.6 | 38.8 | 38.6 | 81.5 | 45.9 |
| C-2 | 18.7 | 18.3 | 18.4 | 18.3 | 24.9 | 67.5 |
| C-3 | 42.2 | 41.8 | 41.9 | 41.9 | 39.2 | 46.6 |
| C-4 | 33.3 | 32.5 | 33.1 | 32.5 | 32.9 | 32.6 |
| C-5 | 56.1 | 47.9 | 55.8 | 47.8 | 54.9 | 53.6 |
| C-6 | 20.3 | 25.1 | 20.0 | 25.2 | 19.7 | 20.4 |
| C-7 | 37.4 | 75.5 | 36.4 | 75.2 | 36.6 | 37.0 |
| C-8 | 49.1 | 52.7 | 48.3 | 52.0 | 48.6 | 48.9 |
| C-9 | 53.0 | 44.6 | 49.3 | 44.9 | 49.2 | 53.8 |
| C-10 | 37.4 | 36.8 | 36.9 | 36.9 | 41.6 | 37.3 |
| C-11 | 20.5 | 26.5 | 26.4 | 26.1 | 28.7 | 20.3 |
| C-12 | 33.7 | 73.0 | 68.9 | 68.4 | 68.8 | 33.1 |
| C-13 | 43.6 | 47.4 | 50.8 | 51.1 | 50.5 | 43.6 |
| C-14 | 61.3 | 49.6 | 49.2 | 44.9 | 48.9 | 61.2 |
| C-15 | 135.2 | 135.6 | 139.3 | 136.6 | 138.8 | 136.3 |
| C-16 | 136.1 | 137.3 | 131.4 | 133.1 | 131.9 | 134.9 |
| C-17 | 25.0 | 20.9 | 65.5 | 65.2 | 65.3 | 24.9 |
| C-18 | 33.8 | 33.2 | 33.5 | 33.2 | 32.9 | 33.4 |
| C-19 | 22.0 | 21.6 | 21.8 | 21.6 | 21.5 | 24.7 |
| C-20 | 15.1 | 13.7 | 14.2 | 13.7 | 10.5 | 18.1 |

[a] The chemical shift data of compound **6** have kindly been made available to us by Professor J.R. Hanson, to whom we are much indebted.

Table 3. Substituent effects of an equatorial acetoxyl group at C-1 (in ppm)

| Carbon atom | Δδ [a] |
|---|---|
| C-1 | +42.7 |
| C-2 | +6.5 |
| C-3 | -2.7 |
| C-5 | -0.9 |
| C-9 | -0.1 |
| C-10 | +4.7 |
| C-11 | +2.3 |
| C-20 | -3.7 |

[a] The numbers given are the chemical shift differences δ(5) - δ(3) for corresponding carbon atoms. A positive sign signifies a downfield shift.

parently, this is also applicable in our case (no γ-effect on C-9), since the carbon atom C-9 does not possess a hydrogen atom able to interact with the C-1 acetoxyl group.

*Acetoxyl group at C-7.* Table 4 shows some of the substituent effects due to an axial acetoxyl group at C-7, which were obtained by comparing the spectra of compounds **4** and **3**.

There are not many references in the literature to substituent effects on olefinic carbon atoms, except for some norbornene derivatives[9,10] and these are not applicable to our case. In compound **4** there is an *anti*-periplanar γ-effect[11] on C-15, which does not greatly differ from other effects of this type on saturated carbon atoms. There is also a remarkable δ-effect (Δδ = +1.7 ppm) on C-16 which seems to comply with the observation made in connection with acyclic olefins that when the transmission of an effect takes place through a π-bond there is a sign reversal of the effect.[12] The γ-gauche effects observed for C-5, C-9 and C-14 (Δδ = −8.0, −4.4 and −4.3 ppm) seem to indicate a certain amount of "puckering" of C-7 in compound **4**. In terms of the torsion angle,[11] it would mean $\Phi_{C-5,C-6} > 56°$.

*Acetoxyl groups at C-12 and C-17.* The combined effects of the acetoxyl groups at C-12 and C-17 can be calculated by subtracting the chemical shift values of compound **1** from those of **3** for the corresponding carbon atoms. Since it is possible to obtain the substituent effects of the acetoxyl group at C-17 by subtracting the chemical shifts of compound **2** from those of **4**, the substituent effects due to each of the two groups can be deduced on the assumption that these are additive. Table 5 shows these results.

The data reported in Table 5 provide new examples of γ and δ effects on olefinic carbon atoms. The results agree well with our previous comments. γ-effects are consistently shielding, while a remarkable deshielding δ-effect is also in operation. A dependence of both effects on conformational factors is apparent. There is an indication of a certain degree of flattening of ring C in the low values observed for the γ-gauche effect of the axial acetoxyl group at C-12 on carbon atoms C-9 and C-14. This is consistent with the postulated[11] deformation of the chair ring of [3.2.1]-bicyclo octane as a result of the presence of a two-atom bridge and with the results obtained from X-ray diffraction studies[14] of glaucarubin *p*-bromobenzoate. In accordance with this glaucarubin studies torsion angles of $\Phi_{C-11,C-12} \approx 50°$ and $\Phi_{C-12,C-13} \approx 65°$ would be quite reasonable and well in agreement with the reported substituent effects of −4.0 and −7.4 ppm (see Table 5). The pronounced α-effect (Δδ = +39.8 ppm) observed for C-12 seems to confirm a departure of the acetoxyl group from a pure axial position.

Some of the substituent effects described above closely agree with the values obtained from compound **6** (see Table 6), for instance, the *syn*-diaxial effect of the hydroxyl group at C-2 on carbon atoms C-19 and C-20, and the negligible γ-gauche effects on C-4 and C-10.

Table 4. Substituent effects of an axial acetoxyl group at C-7 (in ppm)

| Carbon atom | Δδ [a] |
|---|---|
| C-5 | -8.0 |
| C-6 | +5.2 |
| C-7 | +38.8 |
| C-8 | +3.7 |
| C-9 | -4.4 |
| C-14 | -4.3 |
| C-15 | -2.7 |
| C-16 | +1.7 |

[a] The numbers given are the chemical shift differences δ(4) - δ(3) for corresponding carbon atoms. A positive sign signifies a downfield shift.

Table 5. Substituent effects of an axial acetoxyl group at C-12, Δδ, and an acetoxyl group at C-17, Δδ' (in ppm)

| Carbon atom | Δδ [a] | Δδ' |
|---|---|---|
| C-9 | -4.0 | +0.3 |
| C-11 | +6.3 | -0.4 |
| C-12 | +39.8 | -4.6 |
| C-13 | +3.5 | +3.7 |
| C-14 | -7.4 | -4.7 |
| C-15 | +3.1 | +1.0 |
| C-16 | -0.5 | -4.2 |
| C-17 | -3.8 | +44.3 |

[a] The Δδ' values are the chemical shift differences δ(4) - δ(2) for corresponding carbon atoms. The Δδ values were obtained by subtracting the Δδ' values from the differences δ(3) - δ(1) for corresponding carbon atoms.

Table 6. Substituent effects of an axial hydroxyl group at C-2 (in ppm)

| Carbon atom | $\Delta\delta$ [a] |
|---|---|
| C-1 | +6.6 |
| C-2 | +48.8 |
| C-3 | +4.4 |
| C-4 | −0.7 |
| C-5 | −2.5 |
| C-10 | −0.1 |
| C-19 | +2.7 |
| C-20 | +3.0 |

[a] The $\Delta\delta$ values are the chemical shift differences $\delta(\mathbf{6}) - \delta(\mathbf{1})$ for corresponding carbon atoms.

## EXPERIMENTAL

*NMR spectra.* $^{13}$C NMR spectra were obtained at 25.2 MHz in the Fourier mode using a Varian XL-100-15-FT spectrometer in conjunction with a Varian 620/L 16K memory computer. Spectra of the compounds were determined in $CDCl_3$ solutions (which also provided the lock signal) with $Me_4Si$ added as internal reference. All samples were contained in precision-ground 5 mm o.d. tubes. Measurement conditions were as follows: pulse width, 45 μsec (approx. 30°); acquisition time, 0.8 sec.

*Materials.* Compounds 3, 4 and 5 are acetylated derivatives of the corresponding natural diterpene alcohols previously reported by us.[15,16] Compounds 1 and 2 have been prepared from *ent*-beyer-15-ene-7,12,17-triol by methods described before.[16]

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