Monatshefte für Chemie 117, 1279—1286 (1986)

Monatshefte für Chemie
Chemical Monthly

Interpretation of ^{13}C NMR Spectra of 7-Substituted 9,11-Dideoxy-*PGF*$_1$ Analogues and Their Synthons

Witold Danikiewicz[a], **Tadeusz Jaworski***, and **Stefan Kwiatkowski**

Faculty of Chemistry, Technical University (Politechnika),
PL-00-662 Warsaw, Poland

(Received 29 April 1985. Accepted 17 June 1985)

A full interpretation of ^{13}C NMR spectra of the methyl esters of 7-hydroxy- and 7-oxo-9,11-dideoxy-*PGF*$_1$ analogues and their synthons is reported.

(Keywords: ^{13}C NMR of prostanoids; 7-Hydroxy prostaglandin analogues; 7-Oxo prostaglandin analogues)

Interpretation von ^{13}C-NMR-Spektren von 7-substituierten 9,11-Dideoxy-PGF$_1$-Analogen und deren Synthonen

Es wird eine vollständige Zuordnung der ^{13}C-NMR-Resonanzen von den Methylestern der 7-Hydroxy- und 7-Oxo-9,11-dideoxy-*PGF*$_1$-Analogen und ihrer Synthone beschrieben.

Introduction

^{13}C NMR spectroscopy has been used in prostaglandin research since 1973 when *Cooper* and *Fried*[1], and *Lukacs* et al.[2] have published the first papers concerning this problem. In the next years only a few papers devoted to ^{13}C NMR of prostanoids were published[3,4], but the spectra of some prostanoids and their synthons were published also as a documentation for synthetic studies, e.g.[5].

In a previous paper[6] we have described the synthesis of 7-oxo- and 7-hydroxy-9,11-dideoxy-*PGF*$_1$ methyl esters as model *PG* analogues with carbonyl or hydroxyl functions in the 7 position. Now we wish to report full interpretation of ^{13}C NMR spectra of those compounds and the synthons used for their preparation.

---

[a] Present address: Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, Poland.

Table 1.

Carbon	**1**	**2**	**3**	**4**	**5a**	**5b**
1	173.8	173.8	173.8	173.7	174.2	174.1
2	33.9	33.8	33.8	33.8	33.8	33.8
3	24.8	24.8^a	24.7	24.7	24.7	24.8
4	28.9	28.7	28.6	28.7	28.7	28.7
5	24.2	23.2	23.3	23.2	23.1	23.1
6	38.7	41.7	41.4	42.3	42.4	42.5
7	198.5	210.8	210.5	210.8	212.5	212.4
8	145.8	54.6	50.8	57.1	57.7	57.7
9	30.8	30.2	30.0	29.9	29.4	29.5
10	22.9	24.6^a	25.5	25.0^a	25.1^a	25.2^a
11	34.0	30.3	26.7	32.9	33.7	33.6
12	142.8	39.5	53.3	45.2	46.3	46.3
13	—	79.1	202.0	148.5	133.4^b	133.2^b
14	—	—	—	129.5	133.7^b	133.9^b
15	—	—	—	200.0	72.5	72.7
16	—	—	—	40.5	37.5	37.4
17	—	—	—	23.9^a	24.9^a	24.9^a
18	—	—	—	31.5	31.8	31.8
19	—	—	—	22.5	22.6	22.6
20	—	—	—	13.9	14.0	14.0
OCH_3	51.2	51.3	51.3	51.2	51.4	51.4
CH_2O $\vert$ > CH_2O	—	—	—	—	—	—

[a, b] Assignments in vertical columns may be interchanged.

[c] The spectra **11-I** and **11-II** were recorded for a mixture of two diastereoisomers. Two values for a particular carbon atom indicate that the chemical shifts for this carbon are different in each isomer; in the other case values are identical for both isomers.

Experimental

All compounds used in this study (**1**–**11**) were synthesized as described in our previous paper[6].

^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer for approx.

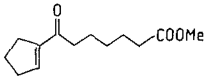
^{13}C *NMR chemical shifts*

6	**7**	**8**	**9a**	**9b**	**10**	**11-I**[c]	**11-II**[c]
173.9	173.8	173.9	174.1	174.2	173.7	174.2	174.2
33.9	33.9	34.0	34.1	34.0	33.7	34.0	34.0
24.9[a]	24.9	25.0	24.9[a]	24.9[a]	24.7	[d]	[e]
28.7	28.1	28.4	28.4	28.4	28.8	29.2	29.2
23.5	23.4	23.5	23.5	23.5	23.2	[d]	[e]
35.8	36.3	36.4	36.5	36.4	42.1	36.3 35.3	36.1 35.5
113.0	112.4	113.2	113.8	113.7	210.8	76.4 72.7	76.4 72.8
48.6	48.5	52.3	52.0	51.7	57.0	52.1 51.3	52.2 51.4
29.4	29.4	29.5	29.5	29.5	29.9	[d]	[e]
24.8[a]	25.3	25.0[a]	25.3[a]	25.2[a]	25.0	[d]	[e]
31.2	27.1	33.7	34.6	34.5	32.8	34.3 33.8	34.3 34.0
38.9	52.9	43.8	43.6	43.5	45.1	46.9 45.1	47.2 45.0
81.0	203.0	152.1	131.4[b]	131.1[b]	149.9	132.9 132.6	133.0 132.5
—	—	128.3	136.9[b]	137.1[b]	130.3	137.0 135.6	137.1 135.4
—	—	200.7	73.0	73.0	197.9	73.0 71.6	72.8 71.6
—	—	40.0	37.6	37.5	27.1	37.4	37.5 37.3
—	—	24.2[a]	25.0[a]	25.0[a]	—	[d]	[e]
—	—	31.6	31.9	31.9	—	31.8	31.8
—	—	22.5	22.7	22.7	—	22.6	22.6
—	—	13.9	14.0	14.0	—	14.0	14.0
51.3	51.2	51.2	51.3	51.4	51.3	51.4	51.4
65.0	65.0	65.2	65.2	65.2	—	—	—
65.5	65.7	65.5	65.5	65.4			

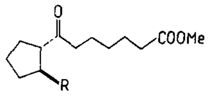
[d] Group of five partially overlapping signals between 24.34 and 25.87 ppm.
[e] As above, 24.17–25.82 ppm.

10–20% *v*/*v* $CDCl_3$ solutions using *TMS* as an internal standard. For all compounds noise-band decoupled and single frequency off-resonance decoupled spectra were recorded.

Chemical shift values for investigated compounds (in ppm relative to *TMS* = 0 ppm) are collected in Table 1.

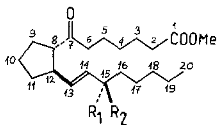


1



2 $R = CH_2NO_2$

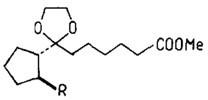
3 $R = CHO$



4 $R_1, R_2 = O$

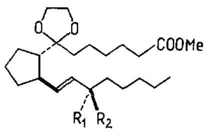
5a $R_1 = OH, R_2 = H$

5b $R_1 = H, R_2 = OH$



6 $R = CH_2NO_2$

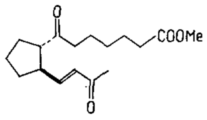
7 $R = CHO$



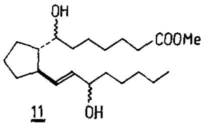
8 $R_1, R_2 = O$

9a $R_1 = OH, R_2 = H$

9b $R_1 = H, R_2 = OH$



10



11

Results and Discussion

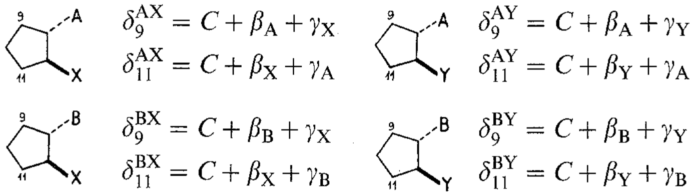
Chemical shifts of the "upper" chain with the carbonyl group in position 7 were estimated using methyl 7-oxooctanoate as a model compound. Because the ^{13}C NMR spectrum of this compound was not published, the chemical shifts of its carbon atoms were calculated in two independent ways, starting from methyl hexanoate or 2-heptanone spectra[7] and using acetyl group or methoxycarbonyl group increments, respectively[8]. Chemical shifts of the "upper" chain carbon atoms in the 7-ethylenedioxy derivatives were estimated in a similar manner.

The interpretation of the "lower" chain signals was based on the literature values for natural prostaglandins[1,2] and for 15-oxo derivatives[3]. There is no problem with assignments of the carbon atoms 15–20 because any changes in the ring or in the "upper" chain do not affect significantly the chemical shifts of these atoms. The situation is different for the vinyl carbons 13 and 14 because in this case a large effect of the substituent in position 7 on the chemical shifts of the carbons 13 and 14 is observed (for example: 133.4 and 133.7 ppm for ketone **5 a** and 131.4 and 136.9 ppm for its ethylene acetal **9 a**). In natural prostaglandins the higher chemical shift value is assigned to the atom 14 but for 7-substituted derivatives this assignment may be reverse. The discussion given above concerns compounds with the hydroxyl function in position 15, because for 15-oxo derivatives the assignment of the chemical shift values for carbon atoms 13 and 14 is obvious.

Assignments of the chemical shifts for ring carbon atoms were done in the following way: Shifts of the 8 and 12 carbon atoms (the only doublets in the aliphatic region) were assigned using estimated α and β increments for substituents attached to these atoms. The chemical shift of the atom 10 is very similar in all the investigated spectra (24.7 to 25.5 ppm) due to the very similar γ-increments of all substituents present in these compounds. Because in this region also signals of the carbon atoms 3 and 17 are observed, the discrimination of them is impossible without special studies.

The last two unassigned signals in the spectra are those of the 9 and 11 carbon atoms. A differentiation between them was possible using a simple linear additivity model involving β and γ increments of the substituents ("upper" chain and "lower" chain or its precursor). In this model the chemical shift values of the carbon atoms 9 and 11 can be described by the equations explained in Scheme 1.

Scheme 1



$$\delta_9^{AX} = C + \beta_A + \gamma_X \qquad \delta_9^{AY} = C + \beta_A + \gamma_Y$$
$$\delta_{11}^{AX} = C + \beta_X + \gamma_A \qquad \delta_{11}^{AY} = C + \beta_Y + \gamma_A$$
$$\delta_9^{BX} = C + \beta_B + \gamma_X \qquad \delta_9^{BY} = C + \beta_B + \gamma_Y$$
$$\delta_{11}^{BX} = C + \beta_X + \gamma_B \qquad \delta_{11}^{BY} = C + \beta_Y + \gamma_B$$

A and B designate the "upper" chain with carbonyl (A) and acetal (B) groups in position 7, and X and Y—"lower" chain or its precursor. By subtracting the appropriate equations the following relations are obtained:

$$\left.\begin{aligned} \delta_9^{AX} - \delta_9^{BX} &= \beta_A - \beta_B \\ \delta_9^{AY} - \delta_9^{BY} &= \beta_A - \beta_B \end{aligned}\right\} \quad \Rightarrow \quad \delta_9^{AX} - \delta_9^{BX} = \delta_9^{AY} - \delta_9^{BY}$$

$$\left.\begin{aligned} \delta_{11}^{AX} - \delta_{11}^{BX} &= \gamma_A - \gamma_B \\ \delta_{11}^{AY} - \delta_{11}^{BY} &= \gamma_A - \gamma_B \end{aligned}\right\} \quad \Rightarrow \quad \delta_{11}^{AX} - \delta_{11}^{BX} = \delta_{11}^{AY} - \delta_{11}^{BY}$$

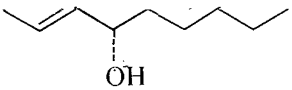
Because of the great simplification of the model those relations are only roughly fulfilled, so the criterion for the best assignment of the δ_9 and δ_{11}

values is the minimum value of the differences R_1 and R_2:

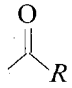
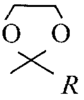
$$R_1 = |(\delta_9^{AX} - \delta_9^{BX}) - (\delta_9^{AY} - \delta_9^{BY})|$$

$$R_2 = |(\delta_{11}^{AX} - \delta_{11}^{BX}) - (\delta_{11}^{AY} - \delta_{11}^{BY})|$$

Using this criterion as an algorithm for a computer program two sets of the chemical shifts can be obtained. One of them must be assigned to the carbon 9 and the second to the carbon 11 in the investigated series of compounds. The next step was an estimation of the δ_9 and δ_{11} values in compounds **3** (X = CHO) and **5 a**

(X = ).

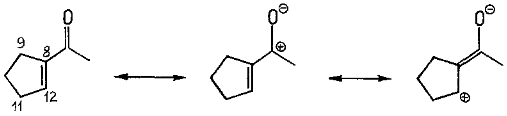
These substituents are characterized by the large difference between their β-increments (~ 0 for CHO and ~ 7 ppm for the vinyl group) and very similar γ-increments (~ —2 ppm). Consequently δ_{11} values in these compounds must differ significantly from each other and δ_9 values must be similar. Such an effect is observed in fact (see Table 1) and allows the assignment of δ_9 and δ_{11} in compounds **3** and **5 a**, and—as a consequence of the calculations described above—also for all other compounds from the series.

Similar δ_9 values can be rationalized by the similar γ-increments of all of the substituents attached to the atom 12 and similar β-increments of the  and  groups. Different β-increments of the carbon 12 substituents are, however, responsible for the differences between the δ_{11} values.

An apparent case is the spectrum of enone **1**. This compound is a cyclopentene derivative in which the 7-carbonyl group is conjugated with the double bond. Such conjugation significantly affects the chemical shifts of the carbons 6 and 7, and also, but much weaker, that of the carbon 5. The chemical shifts of atoms 1–4 are practically the same as for saturated compounds.

The only problem in the interpretation of the spectrum of compound **1**

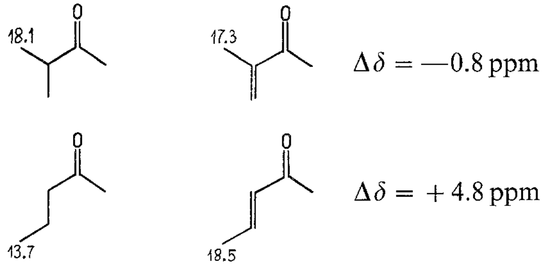
Scheme 2



is the distinction between carbons 9 and 11. A useful method for solving this problem is an analysis of the distribution of the partial charges in the conjugated system[9] shown in Scheme 2.

The partial positive charge on carbon 12 effects the decrease of the electron density on the atom 11 and consequently the increase of its chemical shift value. On the other hand the electron density on carbon 9 and consequently its chemical shift does not change significantly. A strong support for the above statement are literature data[7] shown in Scheme 3.

Scheme 3



The ^{13}C NMR spectrum of enone **1** was published first by *Newton* et al.[5] in 1980, but the interpretation differs significantly (in the case of five carbon atoms) from that described by us. Due to the arguments presented above, *Newton*'s interpretation is incorrect.

The last two positions in Table 1 represented the spectra of two mixtures, each of them containing two diastereoisomers of 7-hydroxy-9,11-dideoxy-*PGF*$_1$ methyl esters (**11**). The interpretation shown in the table is only tentative because of difficulties with separation of the mixtures and lack of appropriate model compounds.

References

[1] *Cooper G. F., Fried J.*, Proc. Natl. Acad. Sci. USA **70**, 1579 (1973).

[2] *Lukacs G., Piriou F., Gero S. D., Van Dorp D. A., Hagaman E., Wenkert E.*, Tetrahedron Lett. **1973**, 515.

[3] *Rackham D. M., Cowdrey S. E., Gutteridge N. J. A., Osborne D. J.*, Org. Magn. Reson. **9**, 160 (1977).

[4] *Mizsak S., Slomp G.*, Prostaglandins **10**, 807 (1975).

[5] *Newton R. F., Reynolds D. P., Greenwood J., Scheinmann F.*, J. Chem. Soc. Perkin Trans. I **1980**, 2346.

[6] *Danikiewicz W., Jaworski T., Kwiatkowski S.,* Monatsh. Chem. **117**, 1177 (1986).

[7] *Bremser W., Ernst L., Franke B., Gerhards R., Hardt A.,* Carbon-13 NMR Spectral Data. Weinheim: Verlag Chemie. 1979.

[8] *Wehrli F. W., Wirthlin T.,* Interpretation of Carbon-13 NMR Spectra, p. 37. London: Heyden and Son Ltd. 1976.

[9] *Levy G. C., Lichter R. L., Nelson G. L.,* Carbon-13 Nuclear Magnetic Resonance Spectroscopy, p. 66. New York: John Wiley and Sons. 1980.