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Carbon-13 n.m.r. Studies of some Saturated 1,2-Oxazepine Derivatives

Kenner C. Rice
Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014, U.S.A.

Roderick E. Wasylishen*
Department of Chemistry, University of Winnipeg, Winnipeg, Manitoba, Canada R3B 2E9

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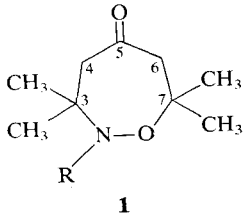
Abstract—The influence of incorporating an >N—H group, an oxygen atom and the >N—O< fragment in a saturated 7-membered ring system on carbon-13 n.m.r. chemical shifts is examined, and also, the influence of the dioxolane ring moiety on the ^{13}C chemical shifts in these ring systems. Substituent effects are generally additive except in cases where the ring is heavily substituted with methyl groups. A large upfield steric shift (γ effect) of 7–8 ppm is observed in two of the derivatives. An example of long range non-equivalence is also observed. Assignments of the ^{13}C n.m.r. spectra have been made by comparison with model compounds, and from proton coupled ^{13}C n.m.r. spectra. The synthesis of several new compounds is described.

INTRODUCTION

CONSIDERABLE attention has been directed at attempting to understand the origin of substituent effects on ^{13}C shielding constants.[1–6] Although some progress has been made,[2,3] ^{13}C chemical shifts are still generally 'accounted' for by a number of empirical parameters which have been derived from the study of appropriate model compounds. The largest substituent effects are usually the short range α and β shielding effects which generally appear to be relatively constant for any given substituent. In addition, organic substituents are also capable of exerting long range shielding effects (γ and δ) which appear to arise primarily from nonbonded interactions[1–6] between the substituent and the carbon under consideration. Since the latter interactions are very dependent on the three-dimensional structure of a molecule, appropriate empirical γ and δ parameters make ^{13}C n.m.r. spectroscopy an important technique in conformational studies.



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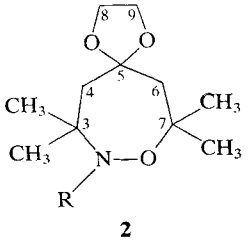
(**a**) R = H
(**b**) R = CH_3
(**c**) R = COC_6H_5



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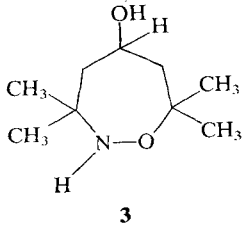
(**a**) R = H
(**b**) R = CH_3



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As part of our continuing interest in 7-membered ring heterocyclic compounds we report the results of a ^{13}C n.m.r. study on some saturated 1,2-oxazepine derivatives (**1–3**). In an earlier ^1H n.m.r. study we reported barriers for conformational inversion in **1** and **2a** which exceeded 18 kcal mol^{-1}.[7] Here we have obtained empirical α, β, γ and δ shielding increments for several of the substituents in these saturated 7-membered ring systems by examining a number of model compounds. Additivity of these substituent parameters is tested for several compounds including **1–3**.

EXPERIMENTAL

Materials

Boiling points and melting points (Hot Stage) are uncorrected. The i.r. spectra were determined using a Perkin-Elmer model 257 instrument. Microanalyses were performed by the Section on Microanalytical Services and Instrumentation, Laboratory of Chemistry, National Institutes of Health. Mass spectra were obtained using a Hitachi-Perkin Elmer RMU-6E instrument and showed the expected molecular ions $[M]^+$. Compounds **1a–1c**,[8a] **2a**,[7] **8**,[8b] **9**[8c] and **12**[7] were prepared as described previously. Cycloheptane (**4**), cycloheptanone (**5**) and oxepane (**7**) were purchased from Aldrich Chemical Co., Inc., Milwaukee, Wisconsin 53223. The remaining compounds (**2b**, **3**, **6**, **10**, and **11**) were prepared as described below.

2,3,3,7,7-Pentamethyl-1,2-oxazepine-5-one ethylene ketal (**2b**). A solution of 2,3,3,7,7-pentamethyl-1,2-oxazepine-5-one (**1b**)[8] (3·73 g, 20·13 mmol) and *p*-toluenesulfonic acid·H_2O (1·70 g, 8·93 mmol) in 2-ethyl-2-methyl-1,3-dioxolane (50 ml) was refluxed while the 2-butanone formed in the transketalization was removed by slow distillation through a spinning band column. After 9 h the reaction was complete as indicated by t.l.c. (silica gel 60 F 254; hexane + Et_2O, 2·5:1; 2,4-dinitrophenylhydrazine spray). The dark solution was cooled, poured into excess 5% $NaHCO_3$ and the mixture extracted with Et_2O (3 × 50 ml). The Et_2O extract was washed with 5% $NaHCO_3$, brine, and then dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed over silica gel 60 (hexane + Et_2O, 3:1). The fractions containing the ketal were combined, concentrated and distilled to give 2·54 g (55%) of **2b**, b.p. 66–68 °C at 0·2 mm; $[M]^+ = 229$; i.r. (film) 2965, 1362 and 1090 cm^{-1}; n.m.r. (220 MHz, $^+CDCl_3$) δ 1·04 (s, 3H), 1·08 (s, 3H), 1·20 (s, 3H), 1·23 (s, 3H), 1·63 (d, 1H, J = 14 Hz), 1·75 (d, 1H, J = 14 Hz), 1·95 (d, 1H, J = 14 Hz), 2·35 (d, 1H, J = 14 Hz,) 2·49 (s, 3H) and 3·77–4·05 (m,4H). (Found: C, 62·56; H, 10·23; N, 5·86. $C_{12}H_{23}NO_3$ requires C, 62·85; H, 10·11, N, 6·11%.)

* Author to whom correspondence should be addressed.

TABLE 1. ^{13}C N.M.R. CHEMICAL SHIFTS OF SOME 7-MEMBERED RING COMPOUNDS (PPM FROM TMS)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
Cycloheptane (**4**)	28·4[5]	28·4[5]	28·4[5]	28·4[5]	28·4[5]	28·4[5]	28·4[5]	—	—
Cycloheptanone (**5**)	214·9	43·9	24·5	30·6	30·6	24·5	43·9	—	—
Cycloheptanone ethylene ketal (**6**)	113·1	38·5	22·5	29·3	29·3	22·5	38·5	64·0	64·0
Oxepane (**7**)	—	70·1	31·0	27·0	27·0	31·0	70·1	—	—
Hexahydro-1*H*-azepine (**8**)	—	49·3	31·5	27·2	27·2	31·5	49·3	—	—
4-Oxepanone (**9**)	—	66·4	46·6	211·9	43·1	26·7	73·6	—	—
4-Oxepanone ethylene ketal (**10**)	—	64·2	41·5	111·1	35·7	23·8	70·1	64·2	64·2
Hexahydro-4*H*-azepine-4-oneethylene ketal (**11**)	—	43·6	42·1	112·0	36·9	24·8	49·6	64·1	64·1
Hexahydro-1,2-oxazepine-5-one ethylene ketal (**12**)	—	—	47·9	38·8	110·9	38·0	67·4	64·5	64·5

5-Hydroxy-3,3,7,7-tetramethyl-1,2-oxazepine (**3**). To a solution of 3,3,7,7-tetramethyl-1,2-oxazepine-5- one(**1a**)[8a] (1·71 g, 10·0 mmol) in isopropanol (20 ml) was added H_2O (5 ml) and $NaBH_4$ (500 mg, 13·21 mmol). After stirring for 15 h, the solvent was evaporated, H_2O (20 ml) added and the mixture extracted with Et_2O (3 × 25 ml). The Et_2O extract was dried ($MgSO_4$) and evaporated. Hexane (2 × 50 ml) was then added and evaporated from the residue. The resulting solid was recrystallized from hexane (cooling to −75°C) to give 1·57 g (91%) of **3**, m.p. 69·5–71 °C; $[M]^+$ = 173; i.r. ($CHCl_3$), 2960, 2928, 1381 and 1367 cm^{-1}; n.m.r. (220 MHz, $CDCl_3$) δ 0·98 (s, 3H), 1·15 (s, 3H), 1·25 (2s, 3H each) 1·46–1·62 (m, 1H), 1·66–1·86 (m, 2H), 2·11–2·15 (m, 1H), 2·27 (broad s, 1H, exchanges with D_2O), 3·98–4·12 (m, 1H) and 4·47 (broad s, 1H, exchanges with D_2O). (Found: C, 62·31; H, 11·27; N, 7·95. $C_9H_{19}NO_2$ requires C, 62·39; H, 11·05; N, 8·09%.)

Cycloheptanone ethylene ketal (**6**). This compound was prepared, using the method described below for **10**, from cycloheptanone (**5**) (22·4 g, 200 mmol), ethylene glycol (30·0 g, 480 mmol), *p*-toluenesulfonic acid ·H_2O (200 mg) and benzene (100 ml). Distillation of the crude material gave 27·2 g (87%) of **6**, b.p. 77–78 °C at 10 mm, $[M]^+$ = 156. (Lit.[8d] b.p. 51 °C at 1·3 mm.)

4-Oxepanone ethylene ketal (**10**). 4-Oxepanone (**9**)[8c] (4·57 g, 40 mmol), ethylene glycol (10 g, 161 mmol), *p*-toluenesulfonic acid ·H_2O (20 mg) and benzene (50 ml) were refluxed using a Dean-Stark apparatus for separation of H_2O produced in the reaction. When production of H_2O had ceased (2·5 h) the mixture was cooled, shaken with 5% $NaHCO_3$ (50 ml) and the benzene removed. The aqueous layer was saturated with NaCl and extracted with Et_2O (50 ml). The combined extracts were dried ($CaCl_2$), concentrated and distilled to give 5·53 g (87%) of **10** as a colorless oil, b.p. 99–101 °C at 10 mm; $[M]^+$ = 158; i.r. (film) 1137 cm^{-1}; n.m.r. (220 MHz, $CDCl_3$) δ 1·72–1·85 (m, 2H), 1·85–2·00 (m, 4H), 3·59–3·70 (m, 2H), 3·71–3·82 (3 lines, 2H) and 3·93 (s, 4H). (Found: C, 59·65; H, 8·92. $C_8H_{14}O_3$ requires: C, 60·74, H, 8·92%.)

Hexahydro-4H-azepine-4-one ethylene ketal (**11**). A mixture of 1-benzylhexahydro-4*H*-azepine-4-one hydrochloride[8e] (23·0 g, 95·9 mmol), ethylene glycol (100 ml) and toluene (100 ml) was refluxed using a Dean-Stark apparatus until 20 ml of ethylene glycol-water had been collected (~2 h). The solution was cooled, neutralized with NH_3 gas and washed with H_2O (200 ml). The toluene layer was separated and the aqueous layer extracted with Et_2O (2 × 150 ml). The toluene and Et_2O extracts were combined, washed with H_2O (50 ml), dried (Na_2SO_4) and concentrated. The residue was distilled to give 22·8 g (96%) of *1-benzylhexahydro-4H-azepine-4-one ethylene ketal*, b.p. 118–120 °C at 0·05 mm (Lit. [8f] b.p. 120–121 °C at 0·13 mm), $[M]^+$ = 247, i.r. (film) 2939, 1494 and 1116 cm^{-1}; n.m.r. (220 MHz, $CDCl_3$) δ 1·59–1·75 (m, 2H), 1·82–1·98 (m, 4H), 2·50–2·68 (m, 4H), 3·56 (s, 2H), 3.79 (s, 4H) and 7·11–7·36 (m, 5H). (Found: C, 73·08; H, 8·45; N, 5·48. $C_{15}H_{21}NO_2$ requires: C, 72·84; H, 8·56; N, 5·66.) A solution of the *N*-benzyl ethylene ketal (21·2 g, 85·7 mmol) from above, in EtAc (200 ml) containing 5% Pd on C (6·0 g) was shaken with H_2 at an initial pressure of 46 psi. After 15 h the calculated amount of H_2 had been absorbed. The solution was filtered through Celite, concentrated and distilled to give 12·2 g (90·5%) of **11**; b.p. 55–56 °C at 0·04 mm (Lit.[8f] b.p. 58–60 °C at 0·05 mm); $[M]^+$ = 157; i.r. (film) 2930, 1158 and 1110 cm^{-1}; n.m.r. (220 MHz, $CDCl_3$) δ 1·60–1·74 (m, 2H), 1·64 (s, 1H, exchanges with D_2O), 1·85–1·97 (m, 4H), 2·77–2·95 (m, 4H) and 3·91 (s, 4H).

N.m.r. spectra

Proton-decoupled ^{13}C n.m.r. spectra were obtained on a Varian CFT-20 spectrometer (10 mm probe). All spectra were obtained for approximately 1 M solutions in chloroform-*d* at 35 ± 2 °C. TMS was used as an internal reference. Acquisition times were generally greater than 0·5 s; hence the chemical shift values are precise to approximately ± 0·1 ppm. Sensitivity enhancement factors of −0·3 were used in most cases to improve the signal-to-noise ratio. Proton n.m.r. spectra were determined using a Varian HR-220 spectrometer for approximately 5% (w/w) solutions using TMS as the internal standard. The multiplicity, integrated peak areas and coupling constants are indicated in parenthesis.

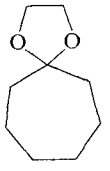
RESULTS AND DISCUSSION

Model compounds

Before discussing the ^{13}C n.m.r. chemical shifts observed in **1–3** we will present data for a number of model compounds containing a saturated 7-membered ring (see Table 1).

The ^{13}C chemical shift for cycloheptane in chloroform-*d* is in good agreement with the value reported in carbon disulfide by Christl and Roberts.[9] The values for cycloheptanone are also in fair agreement with the values obtained[9] for a dioxane solution. Our values for cycloheptanone agree well with those given by Grover *et al.*;[6b] however, there is some problem concerning the assignment of C-3=C-6 and C-4=C-5. Our results tend to support the assignment made by Christl and Roberts.[9]

The chemical shift values for cycloheptanone ethylene ketal (**6**) indicate α, β, γ and δ



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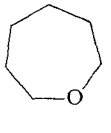
substituent effects of 84·7, 10·1, −5·9 and 0·9 ppm, respectively, where a positive value indicates a downfield shift relative to cycloheptane. For cyclohexanone ethylene ketal we observe α, β, γ and δ substituent effects of 81·2, 7·4, −3·8 and −2·6 ppm, respectively. The chemical shifts of the two carbons of the ethylene ketal ring of cycloheptanone ethylene ketal and cyclohexanone ethylene ketal are 64·0 and 64·2 ppm, respectively. In cycloheptanol, the α, β, γ and δ substituent effects are 44·2, 9·5, −4·9 and 0·4 ppm, respectively.[9]

In both oxepane (**7**) and hexahydro-1*H*-azepine (**8**)



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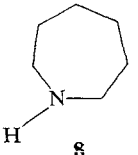

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TABLE 2. ^{13}C CHEMICAL SHIFTS IN COMPOUNDS 1–3 (PPM FROM TMS)[a]

Compound	C-3	C-4	C-5	C-6	C-7	Methyl groups				Other
1a	55·7	56·7	207·5	53·4	76·2	27·0,	26·6,	25·8,	25·6	—
1b	60·3	57·8	207·5	54·2	76·3	26·8,	26·8,	26·8,	17·8	N—CH_3, 39·5
1c	62·8	55·3	206·6	52·1	81·5	26·1,	25·8,	25·2,	25·1	CO 173·4, C-1 136·9, C-*p* 129·9, C-*m* or C-*o* 128·6, or 127·4
2a	55·2	49·7	110·9	46·7	76·1	28·0,	27·6,	27·0,	26·0	C-8 or C-9 64·9, or 63·0
2b	59·2	50·6	110·9	46·5	76·6	28·1,	27·0,	26·1,	19·1	N—CH_3, 39·5 C-8 or C-9 64·2, or 63·3
3	55·1	52·7	66·6	50·1	75·9	27·7,	27·0,	26·7	25·2	—

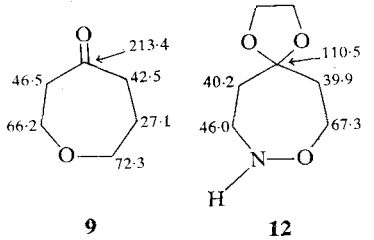
[a] It was not possible to distinguish between C-4 and C-6.

the influence of the heteroatom is to deshield the adjacent carbon nuclei by 41·7 and 20·9 ppm, respectively. The corresponding α substituent effects in tetrahydropyran and piperidine relative to cyclohexane are approximately 41·3 ppm[10] and 20·4 ppm.[11–13] In tetrahydropyran, the β and γ substituent effects are −0·1 and −3·2 ppm, respectively.[10] Assuming C-3 and C-6 are to low field of C-4 and C-5, the β and γ substituent effects in oxepane are 2·6 and −1·4 ppm, respectively. In piperidine, the β and γ substituent effects are 0·4 and −1·6 ppm, respectively.[11] If one assumes C-3 and C-6 are to low field of C-4 and C-5, the β and γ substituent effects in hexahydro-1*H*-azepine are 3·1 and −1·2 ppm, respectively.

It is of interest to compare the substituent effects in these saturated cyclic derivatives with those in acyclic aliphatic alcohols and amines. For secondary alcohols α, β, γ and δ substituent effects are approximately[1,4] 40·8, 7·7, −3·7 and 0·3 ppm, respectively compared with α, β and γ effects of 41·7, 2·6 and −1·4 ppm in oxepane. For secondary amines α, β, γ and δ substituent effects are approximately[14] 19·9, −0·4, −2·7 and −0·6 ppm, respectively, compared with α, β and γ effects of 20·9, 3·1 and −1·2 ppm in hexahydro-1*H*-azepine. Our tentative assignments for the β and γ substituent effects in oxepane and hexahydro-1*H*-azepine seem reasonable on the basis of these results. Our assignment also seems to be in line with the experimental observations of Eliel *et al.*[15] who have reported marked upfield ^{13}C chemical shifts for ^{13}C nuclei located γ and *anti*-periplanar to the heteroatoms N, O or F.

Finally, if the above assignment is correct for oxepane, we find $^1J(^{13}C\text{-}2, H) = 140 \pm 1$ Hz, $^1J(^{13}C\text{-}3, H) = 124{\cdot}5 \pm 1$ Hz and $^1J(^{13}C\text{-}4, H) = 127 \pm 1$ Hz assuming the ^{13}C n.m.r. spectrum is first-order. For cycloheptane $^1J(^{13}C, H)$ has been reported as 123 Hz.[1b]

The ^{13}C chemical shifts observed for the last four compounds listed in Table 1 (**9–12**) were assigned by assuming that substituent effects are additive in the cycloheptane ring system. For example, for **9** and **12** the following chemical shifts are predicted on the basis of additivity (shown below). For **9–12** the predicted and observed ^{13}C chemical shifts differed by 1·9 ppm or less,



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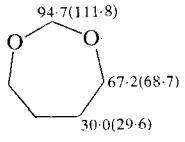
12

with an average deviation of 0·75 ppm. It is of interest to note that the deviations between the observed and calculated values on the basis of additivity for **12** are 1·9 ppm or less with an average deviation of 1·14 ppm. This relatively good agreement observed for a saturated 7-membered ring heterocyclic molecule containing two electronegative heteroatoms which are adjacent to one another is to be contrasted with results obtained for 1,3-dioxacycloheptane. Observed[16,17] and calculated ^{13}C chemical shift values (given in parentheses) are shown below. Agreement between observed and calculated chemical shifts are good except for C-2. Similar effects have been observed in 1,3-dioxanes.[18] In the case



of **12** the O and N atoms appear to perturb one another in an additive manner.

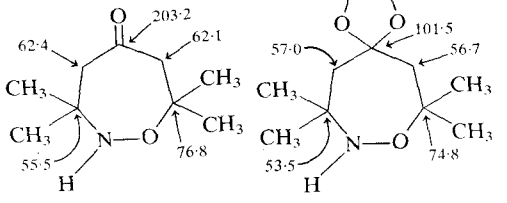
Compounds 1 and 2

Ring carbon resonances. The ^{13}C chemical shifts of **1–3** are given in Table 2. The assignment of the C-3, C-5 and C-7 resonances is straightforward in all cases since C-7 is 17–21 ppm to low field of C-3, while the chemical shifts of C-5 in **1**, **2** and **3** are approximately 207, 111 and 66·6 ppm, respectively.

On going from **1a** to **1b**, C-3 shifts downfield by 4·6 ppm, while C-7 shifts downfield by only 0·1 ppm. Similarly, on going from **2a** to **2b**, C-3 shifts downfield by 4·0 ppm, while C-7 shifts downfield by only 0·5 ppm. In both cases the β substituent effect of the N—CH_3 group is less than half that for a C—CH_3 group in methylcycloheptane. In sharp contrast to the N–CH_3 substituent effect, that of the N–C(=O)–φ group is much more pronounced. C-3 shifts downfield by 7·1 ppm, while C-7 also shifts downfield by 5·3 ppm. The large substituent effect observed here for C-7 may be due in part to increased s character of the N—C bond atom in the N—C(=O)–φ fragment.

On the basis of additivity one would expect C-4 and C-6 to have chemical shifts which differ by less than 0·3 ppm (see compound **12**); however, for all compounds **1** and **2** their chemical shifts differ by 3–4 ppm. At this time it is not possible to distinguish between C-4 and C-6; nevertheless it is of interest to compare the observed

values with those predicted using additivity parameters given by Christl and Roberts.[9] For 1,1-dimethylcycloheptane they find α, β, γ and δ substituent effects of 5·1, 14·4, −4·4 and 2·6 ppm, respectively. For methylcycloheptane, the methyl substituent effects are 6·7, 9·3, −1·3 and 0·7 ppm, respectively, for α, β, γ and δ. Using the above values one predicts ^{13}C chemical shifts for 1,1,4-trimethylheptane which are in good agreement with experiment (average deviation less than 0·6 ppm). Using the substituent parameters observed for 1,1-dimethylcycloheptane and those obtained from the compounds in Table 1, one predicts the following chemical shifts for **1a** and **1b**.



1a **2a**

In both **1a** and **2a** the agreement between predicted and observed chemical shifts for C-3 and C-7 is fair. However, the observed ^{13}C chemical shifts of C-4 and C-6 are about 5·5 and 8·7 ppm to high field of those predicted, while those for C-5 are 4·3 and 9·4 ppm to low field of those predicted on the basis of additivity. The reasons for these deviations are not clear.

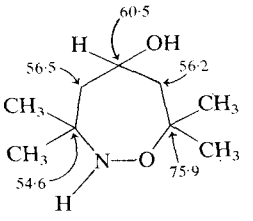
Methyl group carbon resonances. In 1,1-dimethylcycloheptane the methyl group carbons resonate at 31·1 ppm.[9] For compounds **1a**, **2a** and **3** all methyl carbons resonate between 25·2 and 28·0 ppm, a range of 2·8 ppm. For **1b** and **2b** one of the C—$\underline{C}H_3$ resonances is shifted upfield by at least 7·8 and 6·9 ppm, respectively. This large upfield shift must result from a nonbonded steric interaction (γ effect) between a methyl group attached to C-3 and the N—CH_3 group. It is interesting to note that in **1c** all C—CH_3 resonances are observed between 25·1 and 26·1 ppm, thus indicating a negligible γ effect due to the presence of the *N*-benzoyl substituent.

Other substituent carbon resonances. In both **2a** and **2b**, C-8 and C-9 of the dioxolane ring are nonequivalent as expected.[7] In the case of **12**, both C-8 and C-9 are equivalent as expected.[7]

The ^{13}C chemical shifts of the *N*-benzoyl moiety in **1c** are in fair agreement with those observed for acetophenone.[1]

Compound 3

Using the results of Christl and Roberts[9] and the results discussed above for the model compounds studied in this work, the ^{13}C chemical shifts shown in formula **3** were calculated on the basis of additivity. Observed values for **3** are given in Table 2. Observed and calculated values for C-3 and C-7 are in fair agreement. Although C-4 and C-6 are predicted to have very similar chemical shifts, the observed values differ by 2·6 ppm. Furthermore the observed values are approximately 3·8 and



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6·1 ppm to high field of those calculated. In contrast C-5 is observed 6·1 ppm downfield from the value calculated on the basis of additivity. Similar unexplained deviations were observed in compounds **1a** and **2a**.

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