IDENTIFICATION OF SUBSTITUTED FURYLTETRAZOLYL ACETATES BY MEANS OF ^{13}C NMR SPECTROMETRY

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^{13}C NMR data of a series of 5-[5-(substituted phenyl)-2-furyl]-1- and -2-tetrazolyl acetates are presented. Examination of diagnostic resonances emphasizing particularly those arising from the tetrazole ring system enabled both isomers to be easily distinguished. The chemical shift increment for 5-(2-furyl)-1- and -2-tetrazolyl acetate unit has been deduced.

Preparation of new semisynthetic cephalosporine antibiotics is directed, *inter alia*, by an appropriate selection of suitable heterocyclic acids[1]. 5-Substituted 1- and 2-tetrazolyl acetates *Ia–Im* and *IIa–IIj* synthesized for this purpose were distinguished by ^{1}H NMR spectra of the individual pairs of position isomers[2,3]. Structure assignment of some compounds was verified by an independent synthesis. Nevertheless, this problem can well be solved directly and reliably by ^{13}C NMR spectra. This method involves two criteria enabling to interprete the ^{13}C NMR spectra of compounds under investigation[4–7]: the $C_{(5)}$ resonance of $N_{(1)}$-substituted derivatives is markedly upfield shifted when compared with that of $N_{(2)}$ (*c*. 10 ppm), and shielding of the α-carbon of N-alkyl group of azoles increases in the series $=N—N(R)—N= \; < \; =N—N(R)—C= \; < \; =C—N(R)—C=$; consequently, $\delta_{CH_2}(I) < \delta_{CH_2}(II)$.

The tetrazole ring carbon atoms followed, indeed, the above-mentioned characteristics: $C_{(5)}(I) = 146{\cdot}5 - 147{\cdot}0$, and $C_{(5)}(II) = 157{\cdot}1 - 157{\cdot}7$ ppm. Moreover, these signals are of the lowest intensity (similarly as observed with other disubstituted tetrazoles[8]) and can easily be differentiated from other low-field absorptions. In line, the δ_{CH_2} for 1-tetrazolyl acetates resonates at 49·3 – 50·0 ppm, whilst that for 2-tetrazolyl acetates lies within 53·4 – 53·6 ppm.

A common feature of both series is that the chemical shift values of carbonyl carbons do not depend on the site of substitution at the tetrazole ring. These are close to 166 ppm, as can be expected for esters. Distinction of quaternary furan carbons was presumed from greater chemical shift differences between $C_{(2')}$ and $C_{(5')}$ for the given pair of isomers. This difference has been found for most of the pairs as being approximately double ($\Delta C_{(2')} \approx -3{\cdot}0$ and $\Delta C_{(5')} = 1{\cdot}2$ to $1{\cdot}5$ ppm),

Table I. Derivatives *Ii* and *IIi* only have the absolute value for $\Delta C_{(2')}$ and $\Delta C_{(5')}$ almost equal (3 and 4 ppm, respectively). The distinguishable triplet of $C_{(2')}$ in proton-coupled spectra offers another possibility to identify the isomers, since the $C_{(5')}$ of furan carbon is seen as a complex signal due to another long-range coupling with *ortho*-phenyl protons. Moreover, the reported chemical shift value for the quaternary furan carbon (154·0 ppm) of 2-phenylfuran[9] proved compatible.

Carbon atoms of the fundamental compound *Ia* were independently assigned by analysis of the proton-coupled spectrum, and the furan one-, two- and three-bond carbon-proton coupling constants found were confronted with the published data[10,11]. Following values were obtained:

$$^1J_{C(3'),H(3')} = 179{\cdot}7\,, \quad ^2J_{C(3'),H(4')} = 4{\cdot}9\,, \quad ^3J_{C(3'),H(5')} = 4{\cdot}9\,,$$

$$^1J_{C(4'),H(4')} = 180{\cdot}0\,, \quad ^2J_{C(4'),H(3')} = 2{\cdot}9\,, \quad ^3J_{C(4'),H(5')} = 12{\cdot}7\,,$$

$$^1J_{C(5'),H(5')} = 208{\cdot}3\,, \quad ^2J_{C(5'),H(4')} = 10{\cdot}8\,, \quad ^3J_{C(5'),H(3')} = 7{\cdot}8$$

Hz. As evident, the $C_{(3')}$ resonates at a lower field than $C_{(4')}$, (Table I). This feature can also be applied for other tetrazol derivatives under investigation, since effect of the aryl group present would not be imposed in a reverse direction. The recall to 2-phenylfuran[9] demonstrates the indicated tendency: C_β at the phenyl side resonates at 105·0, whereas $C_{\beta'}$ does at 111·6 ppm. Even here the afore-mentioned fact on different chemical shift differences holds (greater $\Delta C_{(3')}$ than $\Delta C_{(4')}$).

The benzene carbons of decoupled spectra of *Ib* and *IIb* revealed three peaks well removed from the others. Both limit signals close to 129 and 124 ppm with approximately 3 : 2 intensities correspond to CH atoms, whereas the central line (128·8 ppm) was assigned the *ipso*-carbon atom. Since shift of the *meta*-carbon with respect to the position of the substituent is relatively not influenced by the nature of substitution[12], the low-field signal was ascribed to *meta*- and *para*-carbons. On the other hand, the right extreme signal had to belong to the *ortho*-carbons. As it likewise follows from these findings, the substitution effect of 5-(2-furyl)-1- and -2-tetrazolyl acetate unit upon the benzene ring is significant in the *ortho*-position only (an upfield shift about 4·4 ppm), other positions being influenced only sparingly (*ipso* 0·3, *meta*- and *para* 0·6 ppm downfield shift each). The aromatic carbon shifts for other derivatives were predicted from the additivity rule employing chemical shift values for phenyl ring of compounds *Ib* or *IIb* and the corresponding increments[13]. To this point it is noteworthy to mention that the calculated and observed chemical shifts were in a good agreement. Some differences were observed with *ortho*-substituted derivatives *If*, *IIf*, *Ih*, *IIh*, and *Ii*, *IIi* in positions 1″, 2″, and 6″ only; this could be, however, rationalized by a mutual influence of the neighbouring substituents. The anisotropy effect of furan ring is likely involved, too. This effect

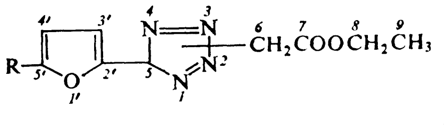
TABLE I

^{13}C NMR data of compounds *Ia*–*Im* and *IIa*–*IIj*

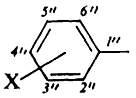
Compound	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(2')}$	$C_{(3')}$	$C_{(4')}$	$C_{(5')}$	$C_{(1'')}$	$C_{(2'')}$	$C_{(3'')}$	$C_{(4'')}$	$C_{(5'')}$	$C_{(6'')}$	Other	$\Delta C_{(2')}$[a]	$\Delta C_{(5')}$[a]
Ia	147·0	49·5	166·4	62·0	13·8	138·8	114·8	112·6	147·0	—	—	—	—	—	—		−3·1	1·5
IIa	157·7	53·5	166·1	62·1	13·8	141·9	111·9[b]	112·2[b]	145·5	—	—	—	—	—	—			
Ib	146·7	49·7	166·6	61·9	13·8	138·3	116·9	108·2	156·3	128·8	124·1	129·0	129·0	129·0	124·1	—	−3·1	1·2
IIb	157·7	53·5	166·1	62·2	13·9	141·4	114·2	108·1	155·1	128·5	124·0	129·1	129·1	129·1	124·0	—		
Ic	146·6	49·8	166·7	62·0	13·8	138·6	117·0	109·2	155·3	127·9	126·0	132·0	122·2	132·0	126·0	—	−3·0	1·4
IIc	157·5	53·5	166·0	62·1	13·9	141·6	114·2	108·8	153·9	128·5	125·9	132·0	121·5	132·0	125·9	—	—	—
Id	146·7	49·7	166·6	62·0	13·9	138·6	117·0	109·0	155·2	127·6	125·9	129·1	133·5	129·1	125·9	—	−3·0	1·3
IId	157·4	53·5	166·0	62·1	13·9	141·6	114·2	108·7	153·9	128·1	125·6	129·1	132·9	129·1	125·6	—	—	—
Ie	146·5	49·7	166·6	62·0	13·7	138·8	116·8	109·6	154·6	130·5	123·6	133·9	128·6	130·8	122·6	—	−3·1	1·2
IIe	157·5	53·6	166·0	62·2	13·9	141·9	114·2	109·4	153·4	131·2	123·5	133·9	128·1	131·0	122·5	—	—	—
If	146·6	49·7	166·5	62·0	13·7	138·6	116·6	113·1	152·6	127·0	129·8	130·4[b]	130·9[b]	128·4	127·7	—	−2·9	1·5
IIf	157·3	53·5	165·9	62·0	13·9	141·5	113·7	112·8	151·1	127·7	129·6	129·8[b]	130·8[b]	128·2	127·7	—	—	—
Ig	146·7	49·7	166·6	62·0	13·8	137·6	117·0	106·5	156·6	121·5	125·8	114·4	159·8	114·4	125·8	55·3	−3·0	1·3
IIg	157·7	53·4	166·0	62·0	13·9	140·6	114·1	106·3	155·3	122·1	125·6	114·5	159·5	114·5	125·6	55·2	—	—
Ih	146·8	49·7	166·7	62·0	13·8	137·4	116·9	112·1	153·1	117·2	155·7	112·1	130·2	120·6	125·6	55·6	−2·9	1·5
IIh	157·7	53·5	166·1	62·1	13·9	140·3	114·0	111·9	151·6	117·8	155·6	111·9	129·6	120·8	125·5	55·6	—	—
Ii	146·5	49·3	166·2	62·0	13·6	139·7	116·9	112·4	151·5	121·8	147·0	124·4	130·6	133·0	129·8	—	−3·1	4·4
IIi	157·1	53·5	165·9	62·0	13·8	142·8	113·9	111·9	147·1	122·2	150·1	124·2	130·1	132·8	129·5	—	—	—
Ij	146·7	49·7	166·5	62·0	13·8	138·2	116·9	108·1	156·5	128·7	124·6	138·3	129·7	128·9	121·3	21·0	−3·0	1·3
IIj	157·6	53·5	166·0	62·0	13·9	141·2	114·1	107·8	155·2	129·2	124·3	138·3	129·2	129·0	121·2	21·0	—	—
Ik	146·7	49·6	166·2	61·9	13·7	137·8	116·8	107·3	156·7	138·7	124·0	129·5	126·0	129·5	124·0	20·8	—	—
Il	146·7	50·0	166·8	62·3	14·0	140·2	117·4	112·3	154·3	134·5	125·1	124·6	147·1	124·6	125·1	—	—	—
Im	146·6	49·6	166·2	61·8	13·5	139·1	115·7	114·9	150·1	132·3	135·2	128·8	132·6	128·8	135·2	—	—	—

[a] $\Delta\delta = \delta_I - \delta_{II}$; [b] these values can be interchanged.

can come into consideration at a restriction of partial rotation around the $C_{(5')}$—$C_{(1'')}$ bond, especially when bulky substituents were located in position 2″. The correctness of the calculated assignments was verified with *meta*-derivatives. Especially the $C_{(5'')}$ signals in proton-coupled spectra displayed only the large $^1J_{CH}$ coupling due to a lack of three-bond CH coupling.



R is numbered in the following way:



Ia, *IIa*, R = H
Ib, *IIb*; R = C_6H_5
Ic, *IIc*; R = 4-Br—C_6H_4
Id, *IId*; R = 4-Cl—C_6H_4
Ie, *IIe*; R = 3-Cl—C_6H_4
If, *IIf*; R = 2-Cl—C_6H_4
Ig, *IIg*; R = 4-CH_3O—C_6H_4
Ih, *IIh*; R = 2-CH_3O—C_6H_4
Ii, *IIi*; R = 2-NO_2—C_6H_4
Ij, *IIj*; R = 3-CH_3—C_6H_4
Ik; R = 4-CH_3—C_6H_4
Il; R = 4-NO_2—C_6H_4
Im; R = 2,6-Cl_2—C_6H_3

To sum up, the dependence of the chemical shift of the tetrazol carbon on the substitution of the phenyl group even in the presence of sole phenyl in position 5′ of the furan ring is evidently negligible. This fact could allow to assume that transmission of the aryl group effect through π-electron framework of the furan ring to tetrazol is not taking place as a result of a lack of coplanarity between both heterocyclic systems.

EXPERIMENTAL

Synthesis of the investigated compounds was already reported[2,3]. The ^{13}C NMR spectra of 0·2 mol l^{-1} hexadeuteriodimethyl sulfoxide solutions were recorded with a JEOL FX 100 spectrometer operating at 25·04 MHz in 10 mm o.d. — tubes using 8 K data points. Spectral width 6 000 Hz, sample temperature 21°C. The chemical shift values were corrected with respect to tetramethylsilane by adding 39·6 ppm to the central line of the solvent.

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