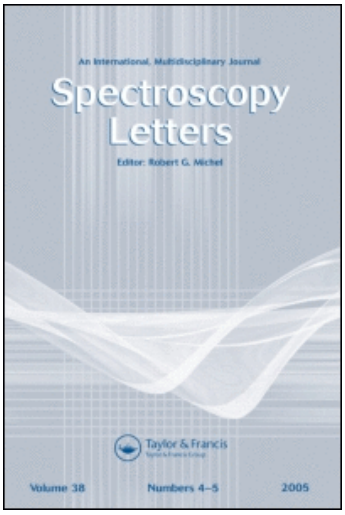

Spectroscopy Letters

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

Carbon-13 Nuclear Magnetic Resonance of Some New β-Blockers. - Part I

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To cite this Article Aboul-enein, Hassan Y. , Hassan, Mahmoud M. A. and Jado, Ahmad I.(1983) 'Carbon-13 Nuclear Magnetic Resonance of Some New β-Blockers. - Part I', Spectroscopy Letters, 16: 3, 151 — 158
To link to this Article: DOI: 10.1080/00387018308062331
URL: http://dx.doi.org/10.1080/00387018308062331

SPECTROSCOPY LETTERS, 16(3), 151-158 (1983)

Carbon-13 Nuclear Magnetic Resonance of Some New β-Blockers - Part I*.

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Abstract:

The assignment of the Carbon - 13NMR resonances of Penbutolol, Timolol, Pindolol and Nadolol, new and non-cardioselective β-adrenergic blockers, in deuterated chloroform or deuterated dimethylsulfoxide has been made. The assignments were made using model compounds, chemical shift arguments, peak intensities and signal multiplicities observed in the single-frequency off-resonance decoupled (SFORD) spectra. From the ^{13}C-NMR chemical shifts it can be concluded that the aromatic ring systems in these compounds have negligible effects on the 2-propanol side-chain which is essential for the biological activity of β-adrenergic blockers.

Introduction:

Several new β-adrenergic blockers which are mainly used for the treatment of essential hypertension and angina pectoris among other conditions (1), have been marketed recently. In conjunction with work on the determination and development of new analytical procedures for some newly introduced β-blockers (2, 3, 4, 5), we undertook a ^{13}C-NMR study of some of these compounds.

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* Presented at 183rd ACS National Meeting, Las Vegas, Nevada, March 28- April 2, 1982. Abstract MEDI 016.

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 0038-7010/83/1603-0151$3.50/0

The β-adrenergic blockers studied are:

Penbutolol (I) : 1-(tert-butylamino)-3-(o-cyclo pentylphenoxy)-2-propanol

Timolol (II):(S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)1, 2, 5-thiadiazol-3yl] oxy] -2-propanol

Pindolol (III): 1-(indol-4-yloxy)-3-(isopropylamino)-2-propanol

Nadolol (IV): 1-(tert-butylamino)-3- [(5,6,7,8-tetrahydro-cis-6-, 7-dihydroxy-1-naphthlyl)oxy]-2-propanol.

The aim of this work is to study ^{13}C-chemical shifts for the aforementioned new β-blockers and to investigate the effect of the different aromatic rings on the carobon chemical shifts of the aliphatic 2-propanol side chain which is essential for the biological activity.

The chemical shift data presented in this report could be applied to assign carbon chemical shifts of similar compounds and hence their structural elucidation.

Results and Discussion:

The ^{13}C-NMR chemical shifts of penbutolol, timolol, pindolol and nadolol are presented in tables 1-4 respectively.

The carbon resonances have been assigned in accordance with:

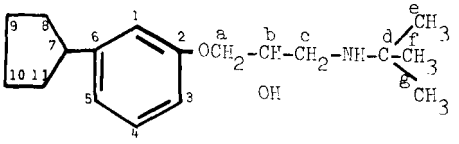
A) Chemical shift considerations (6), particularly about substituent effects in the benzene series (7).

B) Signal multiplicites determined from off-resonance decoupling.

C) Peak intensities.

D) Comparison of chemical shifts for model compounds structurally related to the β-blockers under study and correlation of unsubstituted and some substituted benzene, indole and tetrahydro-

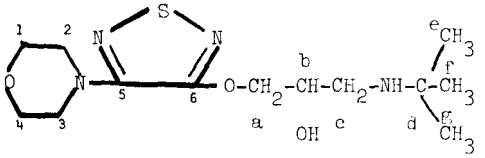
^{13}C-NMR of Penbutolol ($CDCl_3$) - Table 1.



Carbon No.	Chemical Shift (ppm)	Carbon No.	Chemical Shift (ppm)
C-1	126.54 (d)	C-a	70.81 (t)
C-2	156.30 (s)	C-b	68.96 (d)
C-3	126.25 (d)	C-c	44.94 (t)
C-4	120.71 (d)	C-d	50.19 (s)
C-5	111.56 (d)	C-e	
C-6	134.52 (s)	C-f	29.08 (q)
C-7	39.29 (d)	C-g	
C-8			
C-9			
C-10	29.67 (t)		
C-11			

s = singlet, d = doublet, t = triplet, q = quartet

^{13}C-NMR of Timolol in $CDCl_3$ - Table 2



Carbon No.	Chemical Shift (ppm)	Carbon No.	Chemical Shift (ppm)
C-1	66.47 (t)	C-a	72.90 (t)
C-2	47.95 (t)	C-b	68.32 (d)
C-3	47.95 (t)	C-c	48.53 (t)
C-4	66.47 (t)	C-d	50.39 (s)
C-5	149.89 (s)	C-e	
C-6	153.79 (s)	C-f	29.04 (q)
		C-g	

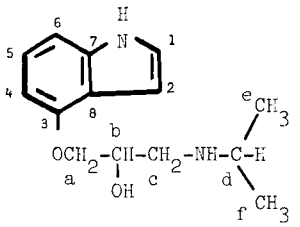
s = singlet, d = doublet, t = triplet, q = quartet

naphthalene rings to penbutolol, pindolol, and nadolol respectively(8).

Furthermore, the ^{13}C-NMR chemical shifts for the 2-propanol side chain are shown in Table 5. It can generally be pointed out that the aromatic ring carbons have little effect on the carbon chemical shift of the methylene group $-C_aH_2-$ of the side chain as seen in nadolol.

Deshielding effect for the methylene group $-C_cH_2-$ in timolol and pindolol is also expected due to strong ring current of 1,2,5 - thiadiazole and indole ring system induced by the benzene ring as seen in penbutolol.

^{13}C-NMR of Pindolol in (DMSO-d_6) - Table 3



Carbon No.	Chemical Shift (ppm)	Carbon No.	Chemical Shift (ppm)
C-1	123.19 (d)	C-a	70.81 (t)
C-2	104.77 (d)	C-b	68.51 (d)
C-3	152.13 (s)	C-c	48.05 (t)
C-4	98.34 (d)	C-d	50.10 (d)
C-5	100.19 (d)	C-e	22.90 (q)
C-6	121.53 (d)	C-f	
C-7	137.32 (s)		
C-8	118.51		

s = singlet, d = doublet, t = triplet, q = quartet.

However, there is a close relationship between the chemical shifts of these β-blockers studied.

Experimental:

Authentic samples of β-blockers were kindly donated from the manufacturers as listed:

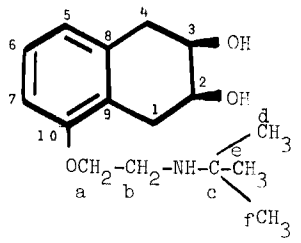
Pindolol, Sandoz Ltd., Basle, Switzerland.

Penbutolol, Hoechst, Frankfurt-Main, West Germany.

Timolol, Merck Sharpe & Dohme, Pahway, N.J., U.S.A.

Nadolol, Squibb & Sons Inc., New Brunswick, N.J., U.S.A.,

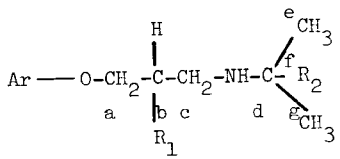
^{13}C-NMR of Nadolol in DMSO-d_6 - Table 4

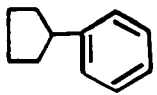
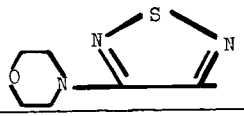
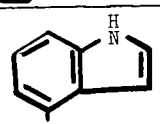
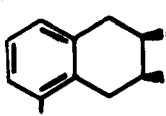


Carbon No.	Chemical Shift (ppm)		Carbon No.	Chemical Shift (ppm)	
C-1	34.40	(t)	C-a	67.98	(t)
C-2	69.04	(d)	C-b	45.32	(t)
C-3	69.04	(d)	C-c	49.43	(s)
C-4	70.57	(d)	C-d		
C-5	125.87	(d)	C-e	28.88	(q)
C-6	108.14	(d)	C-f		
C-7					
C-8	120.71	(d)			
C-9	135.50	(s)			
C-10	156.28	(s)			

s = singlet, d = doublet, t = triplet, q = quartet.

Side Chain Carbon Chemical Shifts - Table 5



Compound	Ar	Solvent	Carbon Chemical Shifts δ (ppm) A	B	C	D	E	F	G
Penbutolol R_1=OH, R_2=Me		$CDCl_3$	70.81 (t)	68.96 (d)	44.94 (t)	50.19 (s)	29.08 (q)	29.08 (q)	29.08 (q)
Timolol R_1=OH, R_2=Me		$CDCl_3$	72.90 (t)	68.32 (d)	48.53 (t)	50.39 (s)	29.04 (q)	29.04 (q)	29.04 (q)
Pindolol R_1=OH, R_2=H		$DMSO-d_6$	70.81 (t)	68.51 (d)	48.05 (t)	50.10 (d)	22.90 (q)	-	22.90 (q)
Nadolol R_1=H, R_2=Me		$DMSO-d_6$	67.98 (t)	45.32 (t)	-	49.43 (s)	28.88 (q)	28.88 (q)	28.88 (q)

s = singlet, d = doublet, t = triplet, q = quartet.

through Squibb Middle East, S.A.

^{13}C-NMR spectra were recorded on Jeol FX-100 and Varian FT-80 Fourier transform spectrometers operating at 25 MHz and 20 MHz respectively for carbon spectra. The compounds were studied as solutes in $CDCl_3$ or DMSO-d_6 as indicated using 10 mm sample tubes at 24 2 °C.

All chemical shifts were measured relative to the trimethylsilyl group of tetramethylsilane (TMS). In all cases, both proton noise decoupled and single frequency off-resonance spectra were obtained. Accumulation of transients made at a spectral width of 5000 Hz;

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Received: October 19, 1982
Accepted: November 30, 1982