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Note

^{1}H and ^{13}C NMR Spectra and Structure of a Dimerization Product of Bimakalin

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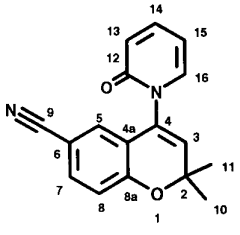
ABSTRACT: NMR spectra of bimakalin and its photodimer were analysed with 1D and 2D techniques. ^{1}H and ^{13}C data were assigned and are reported. The structure of the dimer and the stereochemistry of the cyclobutane ring were determined. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; bimakalin; photodimer; cyclobutane

INTRODUCTION

Bimakalin [4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (**1**)] is a pharmacologically interesting compound belonging to the class of potassium channel activators. It shared the fate of many potential pharmaceuticals when it ultimately failed in clinical tests to meet expectations as a vasodilatory agent.



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Bimakalin was synthesized by Bergmann and Gericke,[1] who also reported ^{1}H NMR data without assignments. An impurity is found in bimakalin, which forms under the influence of light even in the solid state. The reaction product could be isolated and shown by mass spectrometry to be a dimer of bimakalin.

The assignment of the ^{1}H and ^{13}C NMR spectra of bimakalin and its dimer and the elucidation of the structure of the dimerization product are described in this paper.

RESULTS AND DISCUSSION

The relevant part of the ^{1}H spectrum of bimakalin in DMSO-d_6 with numberings according to **1** is shown in Fig. 1.

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The proton resonances could be assigned in a straightforward manner from the chemical shift values and coupling constants. The NMR data for bimakalin are given in Table 1.

Table 2 contains the ^{13}C NMR data for bimakalin in $CDCl_3$ solution obtained from WALTZ-decoupled and fully coupled spectra. The assignments are based on C,H correlations over one and more bonds observed in two-dimensional HMQC[2,3] and HMBC[4] spectra.

The spectrum of the dimer **2**, the relevant part of which is shown in Fig. 2, is far more complicated than expected. In addition to the aromatic protons (δ 5.5–7.8) and the methyl signals (δ 1.4–1.5), it exhibits a series of resonances from aliphatic protons between δ 3.3 and 5.2. Closer inspection of the expanded room temperature spectrum in Fig. 2(A) reveals two sets of signals with an approximate intensity ratio of 2:1. These signals collapse at higher temperature [Fig. 2(B)] and are therefore due to a conformational equilibrium. The corresponding pairs of collapsing signals are indicated in Fig. 2(A). Additional weaker signals in the high temperature spectrum can be attributed to starting material.

Table 1. ^{1}H NMR data for bimakalin in DMSO-d_6

Chemical shifts relative to internal TMS		Coupling constants	
Proton	$\delta(^{1}H)$ (ppm)	Protons	J (Hz)
H-3	6.132	H-5, H-7	2.2
H-5	6.924	H-7, H-8	8.5
H-7	7.654	H-13, H-14	9.1
H-8	7.027	H-13, H-15	~1
H-10	1.544	H-13, H-16	~1
H-11	1.505	H-14, H-15	6.6
H-13	6.488	H-14, H-16	2.3
H-14	7.579	H-15, H-16	6.8
H-15	6.364		
H-16	7.558		

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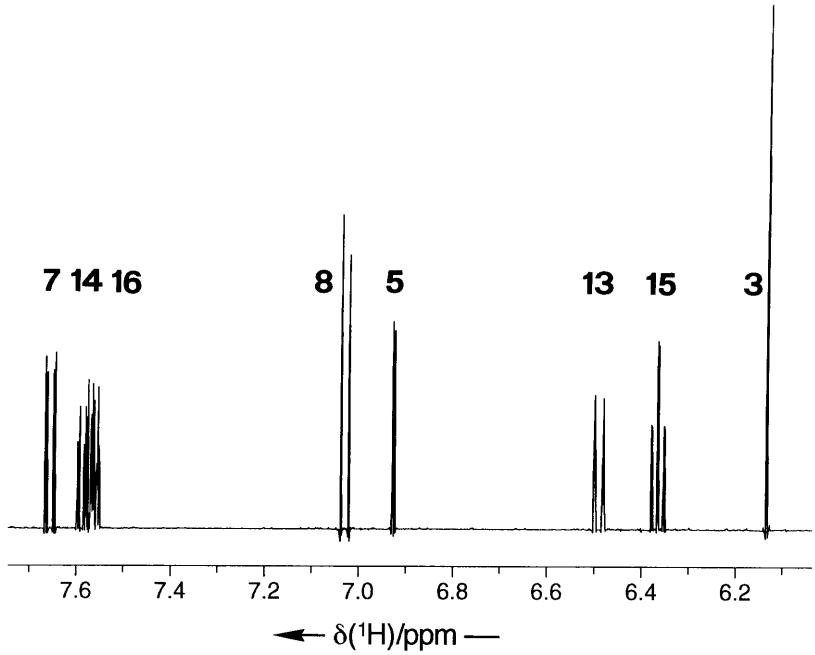
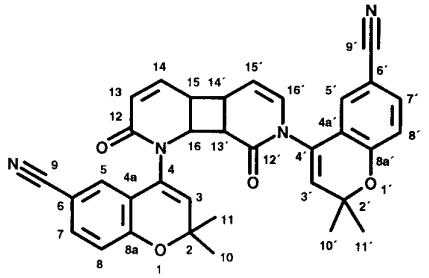


Figure 1. Relevant part of the 500 MHz ^{1}H NMR spectrum of bimakalin in DMSO-d_6. The numbering corresponds to **1**.



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Proton chemical shifts and coupling constants derived from the spectrum of the dimer in DMSO-d_6 at 120 °C are given in Table 3.

Table 4 contains the ^{13}C NMR data for the major component of the dimer from a solution in $CDCl_3$. The complete assignment required the analysis of 2D spectra (COSY[5] and C,H correlated HMQC and HMBC). The numbering used is given in **2** and corresponds to that of bimakalin.

Inspection of the proton NMR data in Tables 1 and 3 reveals that all signals originating from the chromene ring system are doubled in the dimer as compared with bimakalin. This means that the dimerization must involve the pyridone ring and that the reaction product must be asymmetric. Dimerizations of α-pyridones are well known[6–8] and can occur with the participation of three fragment structures as shown in Scheme 1.

Table 2. ^{13}C NMR data for bimakalin in $CDCl_3$

Chemical shifts relative to $CDCl_3$ ($\delta = 77.70$)		C,H coupling constants					
Carbon	$\delta(^{13}C)$ (ppm)	Nuclei	^1J (Hz)	Nuclei	$<^1J$ (Hz)	Nuclei	$<^1J$ (Hz)
C-2	79.14	C-3, H-3	164.6	C-2, H-10	3.8	C-10, H-3	1.6
C-3	130.39	C-5, H-5	164.5	C-2, H-11	3.8	C-10, H-11	4.1
C-4	134.34	C-7, H-7	165.7	C-3, H-10	3.8	C-11, H-3	1.6
C-4a	119.56	C-8, H-8	164.9	C-3, H-11	3.8	C-11, H-10	4.1
C-5	127.55	C-10, H-10	128.1	C-4a, H-3	5.7	C-12, H-13	2.4
C-6	104.96	C-11, H-11	128.1	C-4a, H-8	5.7	C-12, H-14	10.5[a]
C-7	134.92	C-13, H-13	168.7	C-5, H-7	7.1	C-12, H-16	5.4[a]
C-8	118.50	C-14, H-14	161.6	C-6, H-8	9.4	C-13, H-15	7.2
C-8a	157.45	C-15, H-15	170.7	C-7, H-5	7.3	C-14, H-16	8.9
C-9	119.41	C-16, H-16	180.9	C-8a, H-5	8.2[a]	C-15, H-13	8.9
C-10	28.73			C-8a, H-7	9.9[a]	C-15, H-16	3.1
C-11	28.89			C-8a, H-8	3.5	C-16, H-14	5.3[a]
C-12	162.26			C-9, H-5	5.2	C-16, H-15	8.2[a]
C-13	122.55			C-9, H-7	5.2		
C-14	141.18						
C-15	107.06						
C-16	138.14						

[a] Assignment uncertain. Possibly pairwise exchangeable.

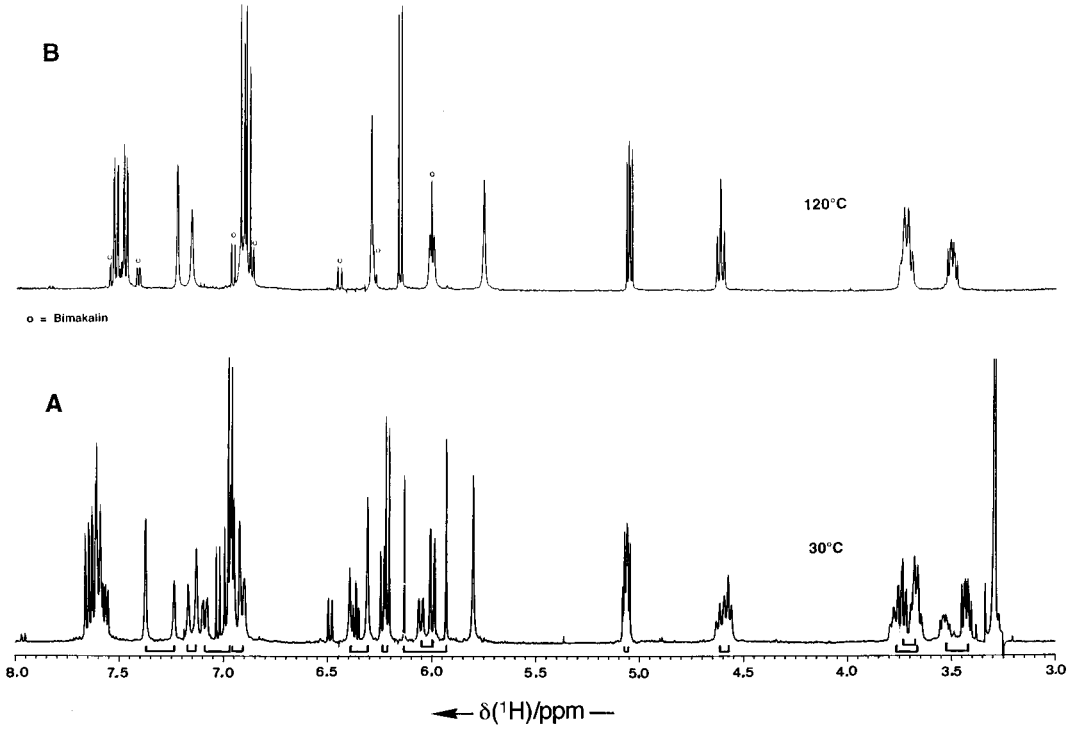
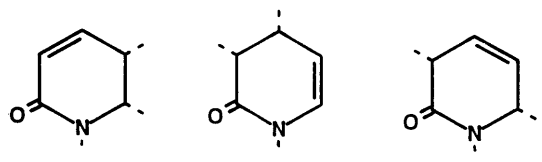
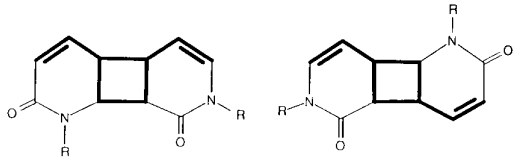


Figure 2. Part of the 500 MHz ^{1}H NMR spectrum of the dimer of bimakalin in DMSO-d_6 at (A) 30 and (B) at 120 °C.



Scheme 1.



Scheme 2.

Table 3. ^{1}H NMR data for the bimakalin dimer

Chemical shifts of the dimer in DMSO-d_6 at 120 °C (relative to internal TMS)				Average[a] coupling constants	
Proton	δ(^{1}H) (ppm)	Proton	δ(^{1}H) (ppm)	Protons	J (Hz)
H-3	6.297	H-3′	5.755	H-5, H-7	2.1
H-5	7.161	H-5′	7.229	H-7, H-8	8.4
H-7	7.479	H-7′	7.525	H-13, H-14	10.1
H-8	6.915	H-8′	6.888	H-13, H-15	1.8
H-10	1.483	H-10′	1.478	H-14, H-15	2.8
H-11	1.469	H-11′	1.439	H-15, H-16	8.6
H-13	6.007	H-13′	3.71	H-5′, H-7′	2.1
H-14	6.97	H-14′	3.499	H-7′, H-8′	8.4
H-15	3.73	H-15′	5.054	H-13′, H-14′	9.4
H-16	4.616	H-16′	6.16	H-13′, H-15	2.4
				H-13′, H-16	8.6
				H-14′, H-15′	5.8
				H-14′, H-15	8.3
				H-15′, H-16′	7.9

[a] Overlap and line broadening did not allow the determination of all couplings from the solution in DMSO. Couplings are therefore averages over measurements in DMSO, $CDCl_3$ and C_6D_6.

Table 4. ^{13}C NMR data for the bimakalin dimer in $CDCl_3$

Chemical shifts relative to $CDCl_3$ (δ = 77.70)			
Carbon	$\delta(^{13}C)$ (ppm)	Carbon	$\delta(^{13}C)$ (ppm)
C-2	79.65	C-2′	79.42
C-3	132.62	C-3′	130.73
C-4	132.25	C-4′	132.80
C-4a	120.06	C-4a′	119.66
C-5	126.79	C-5′	127.37
C-6	104.71	C-6′	104.53
C-7	134.41	C-7′	134.79
C-8	118.70	C-8′	118.47
C-8a	158.43	C-8a′	158.18
C-9	119.82	C-9′	119.69
C-10	28.81	C-10′	28.67
C-11	29.27	C-11′	29.05
C-12	162.69	C-12′	166.12
C-13	126.48	C-13′	45.82
C-14	140.96	C-14′	34.43
C-15	44.33	C-15′	100.82
C-16	57.71	C-16′	132.25

Combination of these three partial structures in a 'head-to-head' or 'head-to-tail' manner (see Scheme 2 for the AB–AB′ pair) leads to 12 different products, if one ignores three-dimensional stereochemistry. Only six of these structures are asymmetric (AB, AB′, AC, AC′, BC and BC′) as required by the experimental data.

Figure 3 shows the relevant part of a COSY spectrum obtained from a solution of the dimer in C_6D_6. Ignoring signals from the minor conformer, the coupling pattern shown in the inset can be derived, i.e. the dimerization occurs with the formation of a cyclobutane ring. Of the two possible structures, only AB remains, since AB′ has a different coupling sequence as indicated in Scheme 2.

Although the sequence of atoms in the dihydropyridone moiety of the dimer is thus determined, nevertheless two different assignments of the chemical shifts are possible involving an exchange of the left and right halves of the molecule. A distinction between those alternatives could be made by calculating their ^{13}C chemical shifts.[9] The correct assignment in Table 4 gives an average deviation of 5.2 ppm between the calculated and observed shifts compared with 18.1 ppm and a maximum difference of 49.5 ppm for the other assignment.

Stereochemical information on organic compounds is usually derived from vicinal H,H coupling constants. Unfortunately, values for the cyclobutane system vary widely with overlapping ranges for *cis* (4.6–11.5 Hz) and *trans* (2.0–10.7 Hz) couplings.[10] No explicit Karplus-type relationship has yet been formulated for cyclobutanes, most likely because of the strong influence of

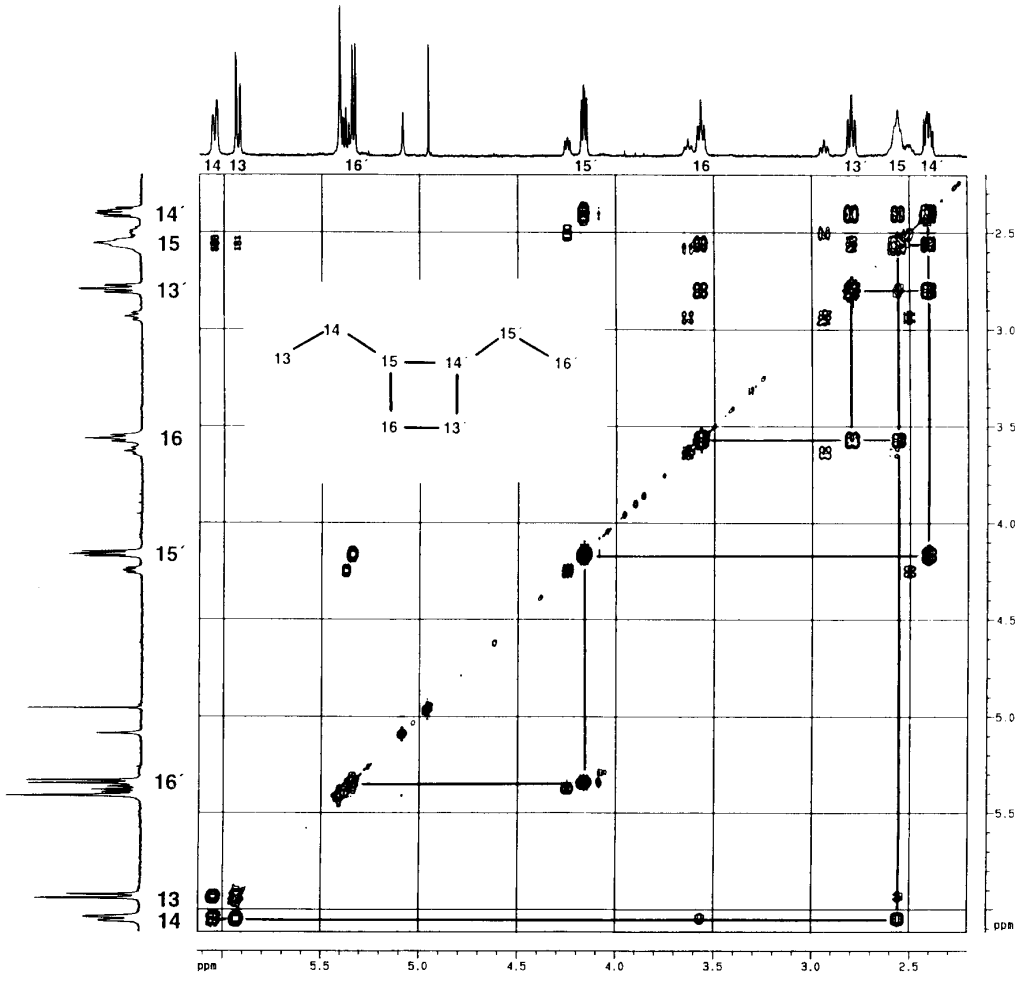


Figure 3. Part of the $^1H,^1H$ COSY spectrum of the dimer of bimakalin in C_6D_6.

factors such as ring strain and bond angles, which are difficult to assess. It is nevertheless possible to discuss the relative magnitude of vicinal couplings in cyclobutane rings in terms of dihedral angles reflecting configurational and conformational features.[11] There are four different configurations for a 1,2,3,4-tetrasubstituted cyclobutane [*ttt*, *ttc*, *tct* and *ccc* (*t* = *trans*, *c* = *cis*)]. For three of these (*ttt*, *ttc* and *ccc*) conformations are possible which, according to a Karplus-type angular dependence, would have four relatively large coupling constants as found experimentally for the dimer of bimakalin (8.3–9.4 Hz). Assuming that the two protons on a particular dihydropyridone ring are *cis* to each other, as found in other similar dimerization products,[12] then the configuration of the dimer can only be all-*cis*.

This could be confirmed by recording a 2D NOESY[13,14] spectrum of the dimer in C_6D_6 solution. Negative NOE effects between all cyclobutane protons including cross-ring effects from H-13′ to H-15 and from H-14′ to H-16 could be observed. The only exception was a missing signal between H-15 and H-14′, which was obscured by an interfering exchange peak.

EXPERIMENTAL

NMR spectra were recorded at 303 K [except for the spectrum in Fig. 2(A), which was measured at 393 K) on a Bruker AM 500 spectrometer with a dual probehead (^{1}H and ^{13}C) and equipped for inverse detection. Chemical shifts were referenced to internal TMS. Standard Bruker pulse programmes were used throughout. The 2D spectra were processed on a Bruker X32 data station. The spectroscopic details were as follows.

^{1}H NMR spectra

Spectrometer frequency (SF) = 500.13 MHz, spectral width (SW) = 20 ppm, pulse width (PW) = 10.7 μs (90° flip angle), acquisition time (AQ) = 1.64 s, relaxation delay (RD) = 2.0 s, number of scans (NS) = 32, number of data points (DP) = 32K, digital resolution after Fourier transformation (DR) = 0.61 Hz per point.

^{13}C NMR spectra

The spectra were recorded with NOE enhancement. Waltz decoupling during acquisition was used for the decoupled spectra. FIDs were zero-filled to 64K. An exponential multiplication of 1 Hz was employed to improve the signal-to-noise ratio.

SF = 125.75 MHz, SW = 248 ppm, PW = 9.6 μs (65°), AQ = 0.52 s, RD = 1.0 s, NS = 15 000, DP = 32K, DR = 1.0 Hz per point.

2D COSY spectrum

A standard COSY spectrum with a 90°, 90° pulse sequence was recorded.[5] The F_1 domain was zero-filled to 1K. Both domains were multiplied with a sine function. Fourier transformation was performed in the magnitude mode.

SF = 500.13 MHz, SW = 8.77 ppm, PW = 10.7 μs (90°), AQ = 0.23 s, RD = 1.2 s, NS = 128, DP (in F_1) = 512, DP (in F_2) = 2K, DR = 4.3 Hz per point.

2D NOESY spectrum

The spectrum was recorded in the phase-sensitive TPPI mode[13,14] with a mixing time of 0.5 s. Zero-filling to 512 in F_1 and to 2K in F_2 was applied. Both domains were multiplied by a $\cos^2$ function.

SF = 500.13 MHz, SW = 8.5 ppm, PW = 11.1 μs (90°), AQ = 0.12 s, RD = 1.0 s, NS = 96, DP (F_1) = 256, DP (F_2) = 1K, DR(F_2) = 4.3 Hz per point.

2D HMQC spectra

C,H correlations via ^1J(CH) were observed in the phase-sensitive TPPI mode with inverse detection.[2,3] Decoupling during acquisition was achieved with a GARP sequence. The refocusing delay 1/[2J(CH)] was 3.45 ms, corresponding to ^1J(CH) of 145 Hz. Both domains were zero-filled and multiplied by a sine function.

SF (F_1) = 125.75 MHz, SW (F_1) = 198.8 ppm, PW (^{13}C) = 13.0 and 26.0 μs for 90° and 180° flip angles, respectively, DP (F_1) = 256, DR (F_1) = 48.8 Hz per point, SF (F_2) = 500.13 MHz, SW (F_2) = 9.26 ppm, PW (^{1}H) = 11.2 and 22.4 μs for 90° and 180° flip angles, respectively, AQ = 0.11 s, RD = 0.60 s, NS = 128, DP (F_2) = 1K, DR (F_2) = 4.5 Hz per point.

2D HMBC spectra

The spectra, which correlate ^{1}H with ^{13}C resonances via long-range couplings, were obtained in the inverse technique and processed in the magnitude mode.[4] The evolution period for the long-range couplings [0.5/$^n J$(CH)] was set at 60 ms, equivalent to $^n J$(CH) = 11 Hz. Directly bonded couplings were suppressed as far as possible by a low-pass J-filter with a delay of 3.45 ms corresponding to a J value of 145 Hz. Both domains were zero-filled and multiplied by sine functions.

SF (F_1) = 125.75 MHz, SW (F_1) = 198.8 ppm, PW (^{13}C) = 13.05 μs (90°), DP (F_1) = 512, DR (F_1) = 24.4 Hz per point, SF (F_2) = 500.13 MHz, SW (F_2) = 9.26 ppm, PW (^{1}H) = 11.2 and 22.4 μs for 90° and 180° flip angles, respectively, AQ = 0.22 s, RD = 1.0 s, NS = 80, DP (F_2) = 2K, DR (F_2) = 2.3 Hz per point.

Acknowledgements

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