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Note

Benzodiazepine Analogues

Part 18—^{13}C NMR Analysis of Schmidt Rearrangement Products from Flavonone Analogues

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ABSTRACT: ^{13}C NMR spectra of 1,4- and 1,5-benzoheterazepinones and their tetrazolo derivatives, prepared by the Schmidt rearrangement of flavanone analogues, are reported. The effects of the C-ring heteroatoms on the ^{13}C NMR chemical shifts of the ring-expanded products were found to be of diagnostic value in distinguishing the isomeric products from one another and from the corresponding precursors. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: ^{13}C NMR; flavanone analogues; Schmidt rearrangement; benzoheterazepinones; tetrazolobenzoheterazepinones

INTRODUCTION

Continued interest is structurally modified benzodiazepine analogues lies in the potential changes in pharmacological activity caused by such modifications, particularly in relation to the central nervous system.[1] Our interest in this field has been focused on the chemistry of analogues which differ in structure from the medicinally useful systems in (i) the position of the phenyl substituent, (ii) the nature and arrangement of the C-ring heteroatoms and, in some cases, (iii) the presence of a tetrazole moiety. These benzodiazepine analogues have been accessed through the Schmidt rearrangement of flavanone analogues[2] (Scheme 1) and some of them have been found to exhibit receptor binding properties.[3] When flavanoid analogues **1** (X = O, NH, S) were treated with azidotrimethylsilane (TMSA) in trifluoroacetic acid (TFA), various isomeric products were isolated depending on the nature of the

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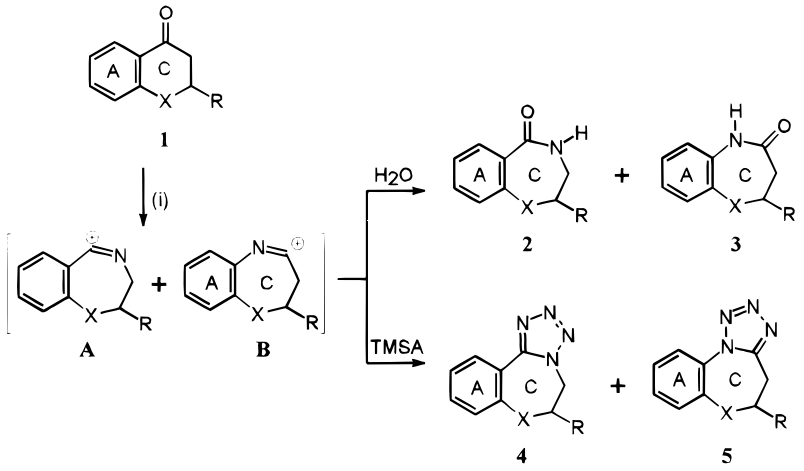


1-5	R	X
a	Ph	O
b	Ph	NH
c	Ph	S
d	H	S

Reagents: (i) TMSA / TFA

Scheme 1

CCC 0749-1581/98/010069–04 $17.50

heteroatom X. The reaction products can be divided into four categories: 1,4-benzoheterazepinones (**2**), 1,5-benzoheterazepinones (**3**), tetrazolo[1,5-*d*][1,4]benzoheterazepines (**4**) and the tetrazolo[5,1-*d*][1,5]benzoheterazepines (**5**).

The structure elucidation of these isomeric products required the application of spectroscopic techniques to establish the site of nitrogen insertion.[2] We have previously reported mass spectrometric studies of the oxa[2a,b] and aza[2c] derivatives and the conformational analysis of the benzoheterazepinones[4a] and the tetrazolo-1,4-benzoheterazepines[4b] using ^{1}H NMR spectroscopic, x-ray crystallographic and molecular modelling techniques. In this paper, we discuss comparative ^{13}C NMR chemical shift data as additional confirmatory evidence for the assigned structures of the isomeric benzodiazepine analogues shown in Scheme 1.

EXPERIMENTAL

The title compounds were prepared by the TMSA-mediated Schmidt rearrangement of flavanone analogues as described previously.[2] The 100 MHz ^{13}C NMR spectra were obtained for $CDCl_3$ solutions using a Bruker AMX 400 spectrometer. The following experimental parameters were employed: mode, Fourier transform, lock, internal deuterium in $CDCl_3$; temperature, 303 K; concentration, *ca.* 100 mg ml^{-1}; tube size, 5 mm; chemical shift values are given in ppm with reference to $CDCl_3$ (δ_C 77.00 ppm).

RESULTS AND DISCUSSION

The ^{13}C NMR chemical shift data for the homocyclic A and C rings (for atom numbering, see Scheme 2) are given in Tables 1–3. The ^{13}C resonances were assigned on the basis of chemical shift theory,[5] signal intensities, substituent effects and, in some cases, DEPT and HETCOR data. The oxa (X = O, R = Ph)[2a,b] and aza (X = NH, R = Ph)[2c] derivatives **1**, on treatment with TMSA, have been found to afford the lactam **2** and tetrazolo **4** derivatives regioselectively, resulting from initial alkyl migration. On the other hand, the thia derivatives **1** (X = S; R = Ph, H) afford products resulting from both alkyl (C-3) and aryl (C-4a) migration.[2d] We have reported a mechanistic study of the TMSA-mediated Schmidt rearrangement of A- and B-ring substituted flavanones in TFA using ^{1}H NMR spectroscopy, which was undertaken to elucidate the observed regioselectivity of nitrogen insertion.[6] Within each series shown in Scheme 1, both substituted and unsubstituted derivatives show a similar trend in the chemical shift of the diagnostic C-ring carbons.[7] The B-ring ^{13}C resonances of the ring-expanded products and their corresponding precursors are comparable, so

Table 1. ^{13}C NMR chemical shift values (ppm) for the flavanone analogues 1

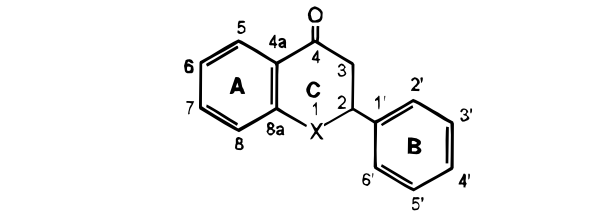
No.	X	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	C-1′	C-2′,6′	C-3′,5′	C-4′
1a	O	79.4	44.5	191.6	120.8	126.9	121.4	136.0	118.0	161.4	138.6	126.0	128.7	128.6
1b	NH	58.5	46.6	193.2	119.1	127.6	118.4	135.4	115.9	151.5	141.0	126.6	129.0	128.5
1c	S	47.7	45.5	194.3	130.4	129.2	127.2	133.6	125.2	142.1	138.4	127.4	129.0	128.4

Table 2. ^{13}C NMR chemical shift values (ppm) for the 1,4-benzoheterazepinones 2 and their 1,5-benzoheterazepinone analogues 3

No.	X	R	C-2	C-3	C=O	C-5a	C-6	C-7	C-8	C-9	C-9a
2a	O	Ph	85.9	46.3	171.1	125.8	130.9	123.6	133.3	122.4	154.6
2b	NH	Ph	64.8	46.8	172.1	120.5	132.2	119.4	132.9	119.2	145.2
2c	S	Ph	56.2	47.5	172.5	141.2	129.9	131.7	134.3	128.0	130.2
2d	S	H	34.4	33.6	173.9	126.9	129.8	126.4	135.4	123.8	141.5
3a	O	Ph	82.9	42.2	171.8	140.1	125.8	123.3	124.4	122.0	148.2
3c	S	Ph	53.2	41.5	172.1	143.4	125.7	130.2	123.2	135.9	126.7

Table 3. ^{13}C NMR chemical shift values (ppm) for tetrazolo[1,5-d][1,4]- (4) and tetrazolo[5,1-d][1,5]benzoheterazepine derivatives (5)

No.	X	R	C-2	C-3	C=N	C-5a	C-6	C-7	C-8	C-9	C-9a
4a	O	Ph	79.0	56.2	156.8	113.0	130.4	124.0	133.2	121.5	151.9
4b	NH	Ph	57.7	56.5	153.2	107.7	132.5	120.1	131.1	118.8	145.8
4c	S	Ph	54.7	53.5	154.2	128.0	134.2	131.2	132.1	128.8	138.6
4d	S	H	33.1	50.8	154.0	125.6	132.0	131.5	132.8	128.4	135.4
5d	S	H	23.5	35.3	153.7	137.3	120.2	130.2	125.5	125.0	127.3



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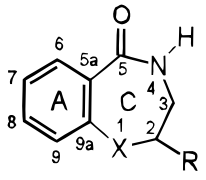

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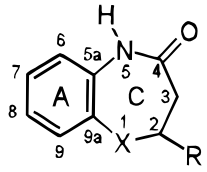

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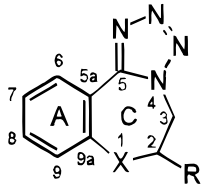

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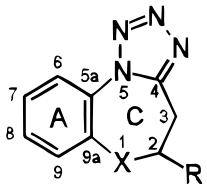

5

R = H, Ph

Scheme 2. Numbering of atoms for 1–5.

the B-ring signals of the ring-expanded systems have not been included in Tables 2 and 3.

Flavanone analogues

In order to distinguish between the isomeric products and to establish the mode of nitrogen insertion (1,4- or 1,5-), it was necessary to establish the ^{13}C NMR chemical shifts for the flavanoid precursors **1** (R = Ph). To our knowledge, only the flavanones **1** (X = O, R = Ar) have previously been subjected to a detailed ^{13}C NMR study[8] and, consequently, we have included ^{13}C NMR spectral data for the parent aza (X = NH) and thia (X = S) analogues. The ^{13}C NMR spectra of the flavanone analogues exhibit signals in the aromatic, carbonyl and aliphatic regions (Table 1). The carbonyl carbon (C-4) in these systems resonates in the narrow range, δ_C 191.6–194.3 ppm, and is relatively insensitive to the nature of the heteroatom X. The difference in electronegativities of the heteroatoms X (O > N > S) is clearly demonstrated, however, by the chemical shifts of the adjacent carbons (C-2 and C-8a) in these analogues. The observed trend in the shielding of the A-ring C-*ortho* (C-8) and C-*para* (C-6) nuclei presumably reflects the difference in π-electron delocalization by the heteratom X (N > O > S). The ^{13}C resonances of the B-ring nuclei have been included in Table 1 to illustrate their insensitivity towards variation of the heteroatom (X), the signal assignments for the aromatic carbons of the flavanone analogues having been made by comparison with the literature data for the oxa derivative **1a**.[8]

1,4-Benzoheterazepinones (2) and the isomeric 1,5-benzoheterazepinones (3)

The carbonyl carbons of the lactam derivatives **2** and **3** resonate in the region δ_C 171.0–174.0 ppm, confirming the lactam functionality and thus distinguishing these compounds from their corresponding precursors. The known 1,5-benzoxazepinone derivative **3a**, included in Table 3, was isolated as a minor product using the hydrazoic acid-mediated Schmidt rearrangement of flavanone **1a**.[9] Isolation of the isomeric thia products **2** and **3** from both alkyl and aryl migration reflects the non-regioselectivity of nitrogen insertion into the C-ring of thioflavanone precursors **1** (X = S).[2d] Thiochromanone **1d** (R = H, X = S), however, afforded the 1,4-isomer **2d** as the sole lactam derivative.[2d] The relative downfield shift of the 3-methylene signal in the spectra of compounds **2** reflects the deshielding effect of the adjacent amide nitrogen and confirms nitrogen insertion via alkyl migration. On the other hand, the formation of lactams **3** via aryl migration is confirmed by the significant downfield shift of the C-5a signal due to deshielding by the amide nitrogen, the observed chemical shift values being consistent with the published data[10] for benzothiazepinine derivatives of type **3** (X = S, R = Ar) in DMSO-d_6. The heteroatoms X display effects similar to those described for the precursors **1** (Table 1) on the adjacent carbon atoms (C-2 and C-9a) and the A-ring carbons *ortho* and *para* to X (i.e. C-9 and C-7, respectively). Available published data on the ^{13}C NMR chemical shift data for the 1,4-benzodiazepine analogues related to systems **2** focus mainly on the 1,4-benzodiazepine-2,5-diones.[11] Other ^{13}C NMR studies of 1,5-benzodiazepinones[12,13] focus on compounds closely related to **3** (X = NR), but not bearing a phenyl substituent, and on 1,5-benzodiazepinone-2,4-diones.[14]

Tetrazolo[1,5-*d*][1,4]- (4) and tetrazolo[5,1-*d*][1,5]benzoheterazepine derivatives (5)

The spectra of the tetrazolo derivatives **4** and **5** are characterized by the absence of a ^{13}C=O signal and the appearance of the ^{13}C=N resonance[5] in the region, δ_C 150.0–157.0 ppm. Nitrogen insertion via alkyl migration in compounds **4** is confirmed by the significant downfield shift of the resonance corresponding to the methylene carbon (C-3). On the other hand, the high-field shift of the 3-methylene signal to δ_C 23.5 ppm and the significant downfield shift of the C-5a signal to δ_C 137.3 ppm distinguish **5d** from the isomeric 1,4-tetrazolo derivative **4d**.

CONCLUSION

Compound **2a**, prepared by the hydrazoic acid-mediated Schmidt rearrangement of **1a**,[9] was, at one stage, erroneously identified as a 1,5-benzoxazepinone,[15] and it is apparent that unambigous structural analysis of the ring-expanded Schmidt rearrangement products requires a combination of spectroscopic techniques. This study demonstrates the application of ^{13}C NMR spectroscopy in distinguishing between isomeric products, explores the effects of heteroatoms (O, N, S) on the chemical shift values and extends the existing data on benzodiazepine analogues.

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