Chemistry of Substituted Pyrazolo[1,5-*a*]pyrimidines. Part 4.[1] A Structural Correction of a Series of Pyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepines on the Basis of NMR Spectroscopy and X-Ray Diffraction Analysis

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The reaction of a series of 6-acetyl-7-(2-dimethylaminovinyl)pyrazolo[1,5-*a*]pyrimidines **3** with hydrazine hydrate has been re-investigated and the nature of the reaction product unambiguously established on the basis of both NMR spectroscopy and X-ray diffraction. 7-Methyl-6-(pyrazol-3'-yl)pyrazolo[1,5-*a*]pyrimidines **1** and not, as formerly claimed, 6-methylpyrazolo[5',1':2,3]pyrimido-[5,4-*d*][1,2]diazepines **2** are shown to be the final products in the reaction of compounds **3** with hydrazine hydrate. The structures of compounds **1** have been rationalised on the basis of some diagnostic coupling constants' values and confirmed by the X-ray structure of 2,7-dimethyl-6-(pyrazol-3'-yl)pyrazolo[1,5-*a*]pyrimidine **1b**. The literature assignments for the quaternary carbon resonances have been revised and the signals unambiguously attributed by means of 2D experiments.

Two years ago some of us reported that reaction of a series of 6-acetyl-7-(2-dimethylaminovinyl)pyrazolo[1,5-*a*]pyrimidines with hydrazine hydrate in acetic acid solution gives rise to 6-methylpyrazolo[5',1':2,3]pyrimido[5,4-*d*][1,2]diazepines **2** through an intramolecular cyclisation.[2]

In order to study the benzodiazepine receptor affinity of this new heterocyclic system and to gain more insight into this reaction, in view of its general applicability to other 6-substituted-7-dimethylaminovinyl derivatives, we decided to carry out a complete ^{13}C NMR study on some of these compounds. We report here new NMR data and considerations that suggested how the structures of the previously reported products had to be amended to **1** and not, as formerly claimed, the 1,2-diazepines **2**. An X-ray analysis confirmed unequivocally that the correct structure was represented by **1**.

Results

The pyrazolopyrimidodiazepines **2** were described as the products of the intramolecular cyclisation of the enamines **3** with hydrazine hydrate.[2] However, the evidence for assigning the structures **2**, rather than the isomeric **1**, to the reaction products appeared to rely mainly on the interpretation of NMR spectral data. We repeated the reaction of dimethylaminovinyl derivatives **3a** and **b** with hydrazine hydrate in glacial acetic acid always obtaining the same products showing analytical (mps, NMR and IR) data in full agreement with those previously reported. Although no intermediates have been isolated, it seems possible that such reaction, in contrast to that for the enamines **4a** and **b**,[3] might proceed *via* two alternative pathways (see Scheme 1): while route (*a*) gives rise to the 1,2-diazepine ring, route (*b*) rationalises the formation of the isomeric compounds **1** through a nucleophilic attack of the NH_2 group on the electron poor C-7.

In order to resolve this point we re-examined the reported gated decoupled spectrum of compound **1a**. The DEPT spectrum showed five signals for the five tertiary carbon atoms among which that of C-5 was easily recognized as the simple doublet at δ 149.64 in the coupled spectrum. The resonances of

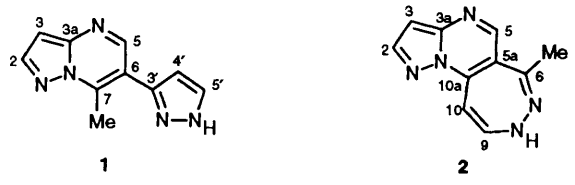
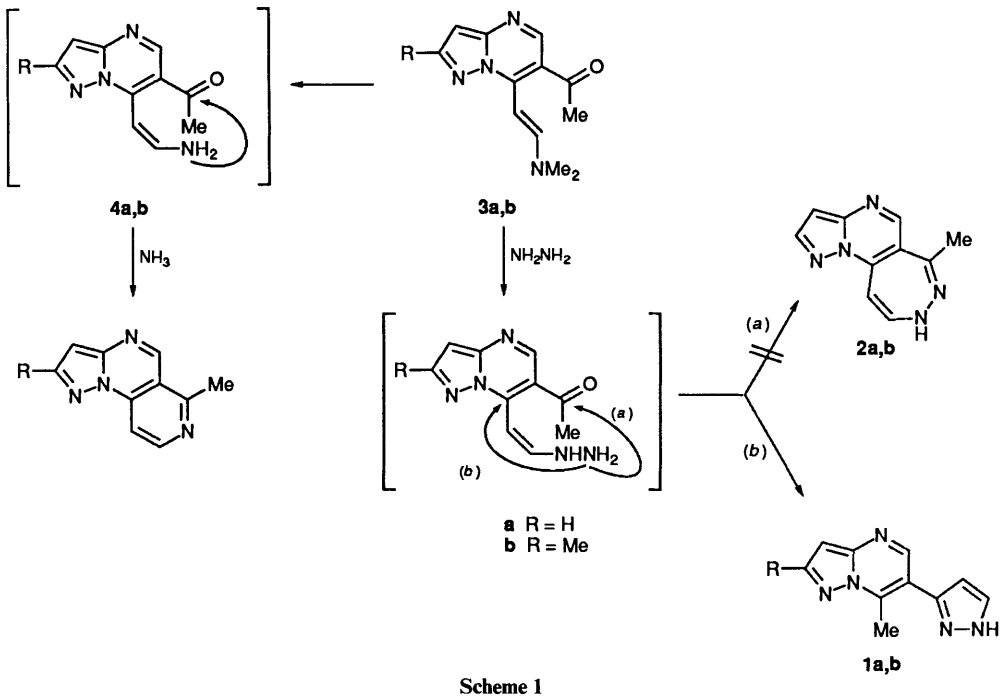


Fig. 1

C-2 and C-3 were identified as the doublets of doublets at δ 144.39 and 96.53, respectively, on the basis of chemical shift considerations. The carbon atoms at position 5' and 4' (C-9 and C-10 in **2a**, respectively) appear as a doublet of pseudo triplets and as a doublet of doublet of doublets, respectively, thus showing the expected multiplicity which, however, would be the same in both structures **1** and **2**. The latter signals were then simplified in two doublets of doublets after D_2O treatment of the sample.

Except the C-6 signal which appears at δ 114.10 (Table 1), the resonances of the quaternary carbon atoms C-3a, C-7 and C-3' of compound **1a** cannot be assigned on the basis of chemical shift considerations. The fine splitting pattern caused by long-range couplings allowed us to attribute the resonance at δ 147.04. The latter shows a fine structure of a doublet of pseudo triplets (intensities 1:2:2:2:1) and not that of a pseudo quintet as previously reported;[2] looking at the coupling constant values (Table 1), the diagnostic 13.9 Hz coupling (^3J through the nitrogen atom) must be attributed to the C-3a–5-H pattern according to literature data.[4–6] Because this attribution is in contrast with the previously reported one,[2] we examined the coupled spectra of **1b** (Table 2) with the aim that removal of one coupling could confirm the new assignment. As expected for the 2-substituted compounds (see also compound **1c**[2]), the signal of C-3a appears now as a doublet of doublets with J values in full agreement with those previously reported for similar compounds.[4] However, all the multiplicity considerations for the quaternary carbon atoms hold too for both structures **1** and **2**.

In order to achieve the required complete and unambiguous

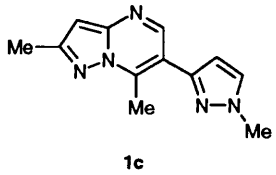


Scheme 1

Table 1 Carbon-13 chemical shifts (δ) and ^nJ(C, H) coupling constants (Hz) of compound **1a**[a]

δ	Assignment	Multiplicity[b]	^nJ/Hz
149.64	C-5	d	$^1J_{(5,5)}$ 183.8
147.04	C-3a	ddd[c]	$^3J_{(3a,5)}$ 13.9, $^2J_{(3a,3)}$ 7.1, $^3J_{(3a,2)}$ 7.1
145.12	C-3′ (C-10a)[d]	m	—
144.39	C-2	dd	$^1J_{(2,2)}$ 185.5, $^2J_{(2,3)}$ 5.4
142.95	C-7 (C-6)[d]	dq[e]	$^3J_{(7,5)}$ 6.6, $^2J_{(7,Me)}$ 6.6
129.74	C-5′ (C-9)[d]	ddd[c]	$^1J_{(5',5')}$ 187.6, $^2J_{(5',4')}$ 8.5, $^2J_{(5',NH)}$ 8.5
114.10	C-6 (C-5a)[d]	m	—
105.11	C-4′ (C-10)[d]	ddd	$^1J_{(4',4')}$ 176.5, $^2J_{(4',5')}$ 9.0, $^3J_{(4',NH)}$ 5.0
96.53	C-3	dd	$^1J_{(3,3)}$ 180.5, $^2J_{(3,2)}$ 9.8
14.72	7-Me (6-Me)[d]	q	^1J 130.9

[a] This work, for literature data see ref. 2. [b] Multiplicity: d = doublet, q = quartet, m = multiplet. [c] Appears as a doublet of triplets. [d] Corresponding carbon atom in **2a**. [e] Appears as a quintet.



1c

Fig. 2

assignment of carbon resonances, 2D NMR experiments (HETCOR, COSY and COLOC) were performed and proved to be extremely useful. Thus, for example, COLOC spectra of compound **1a** led us not only to confirm the above discussed C-3a assignment but also to distinguish between the multiplets attributable to C-3′ and C-7. Thus, the resonance at δ 147.04, which is connected to 5-H, 3-H and 2-H, belongs to C-3a, whereas the signal at δ 145.12, previously tentatively attributed to C-3a,[2] shows long-range connectivity to both 5-H and 5′-H and not to 7-Me and must be assigned to C-3′. On the other hand, the signal at δ 142.95 is attributed to C-7 and not to C-3′ (C-10a in **2**) as reported in the literature,[2] following its connectivity to 7-Me. A subsequent HETCOR spectrum, together with the H,H-COSY experiment, also allowed the distinction between the pairs of protons 2-H, 3-H and 5′-H, 4′-H. The latter assignment was then fully confirmed by the spectra of the 2-methyl derivative **1b**.

In spite of all these considerations, a distinction between the isomeric structures **1** and **2** cannot yet be achieved. Looking more carefully at the $^1J_{CH}$ (Tables 1 and 2) we noted that the values observed for $^1J_{5',5'}$ and $^1J_{4',4'}$ were very similar to those of $^1J_{2,2}$ and $^1J_{3,3}$, respectively (187 and 177 *vs.* 185 and 179 Hz). This seemed quite unusual, it being well known that on going from a five-membered ring to a larger one, the one-bond coupling constant value should become smaller.[7] Following this idea, we thought that the vicinal coupling between protons could assume a diagnostic meaning.

The ^{1}H NMR spectra of the examined compounds showed[2] a $^3J_{4',5'}$ value ranging from 2.0 to 2.6 Hz. This coupling not only appears to be analogous to that observed between 2-H and 3-H but is certainly too small to be attributed to a 1,2-benzodiazepine ring. As confirmed by numerous examples in the literature, the $^3J_{H,H}$ is in such systems much larger than the one observed here, being always comprised between 7 and 10 Hz.[8–10]

In order to definitively rule out the 1,2-benzodiazepine structure **2**, we performed an X-ray analysis on compound **1b** (see the ORTEP diagram of Fig. 3) that confirmed unequivocally the correct structure of 6-substituted pyra-

Table 2 ^{13}C NMR Data for compounds **1b** and **1c**

	Compound	δ	Assignment	Multiplicity[a]	^nJ/Hz
	1b	153.81	C-2	dq	$^2J_{(2,Me)}$ 6.7, $^2J_{(2,3)}$ 5.4
		149.23	C-5	d	$^1J_{(5,5)}$ 183.2
		147.76	C-3a	dd	$^3J_{(3a,5)}$ 13.9, $^2J_{(3a,3)}$ 7.6
		145.35	C-3′	m	—
		142.48	C-7	dq[b]	$^3J_{(7,5)}$ 6.2, $^2J_{(7,Me)}$ 6.2
		129.70	C-5′	ddd[c]	$^1J_{(5',5')}$ 187.2, $^2J_{(5',4')}$ 8.4, $^2J_{(5',NH)}$ 8.4
		113.43	C-6	dq	$^2J_{(6,5)}$ 8.2, $^3J_{(6,Me)}$ 4.1
		104.98	C-4′	ddd	$^1J_{(4',4')}$ 176.5, $^2J_{(4',5')}$ 9.0, $^3J_{(4',NH)}$ 4.6
		95.70	C-3	dq	$^1J_{(3,3)}$ 178.5, $^3J_{(3,Me)}$ 3.6
		14.74	7-Me	q	^1J 130.6
		14.46	2-Me	q	^1J 127.5
	1c	153.89	C-2	qd	$^2J_{(2,Me)}$ 6.6, $^2J_{(2,3)}$ 5.2
		149.04	C-5	d	$^1J_{(5,5)}$ 183.7
		147.72	C-3a	dd	$^3J_{(3a,5)}$ 14.0, $^2J_{(3a,3)}$ 7.9
		145.19	C-3′	m	—
		142.46	C-7	dq[b]	$^3J_{(7,5)}$ 6.5, $^2J_{(7,Me)}$ 6.5
		132.15	C-5′	ddq	$^1J_{(5',5')}$ 187.1, $^2J_{(5',4')}$ 8.6, $^3J_{(5',NMe)}$ 2.5
		113.10	C-6	dq	$^2J_{(6,5)}$ 8.2, $^3J_{(6,Me)}$ 4.1
		105.77	C-4′	dd	$^1J_{(4',4')}$ 177.0, $^2J_{(4',5')}$ 9.1
		95.75	C-3	dq	$^1J_{(3,3)}$ 178.8, $^3J_{(3,Me)}$ 3.4
		38.78	N-Me	qd	^1J 140.0
		14.75	7-Me	q	^1J 130.7
		14.47	2-Me	q	^1J 127.5

[a] Multiplicity: d = doublet, q = quartet, m = multiplet. [b] Appears as a quintet. [c] Appears as a doublet of triplets.

Table 3 Selected bond distances (Å) and angles (°) for the crystal structure of **1b**[a]

N(1)–N(2)	1.355(2)	N(2)–N(1)–C(3)	104.7(2)
N(1)–C(3)	1.323(2)	N(1)–N(2)–C(1)	112.4(2)
N(2)–C(1)	1.333(3)	N(4)–N(3)–C(6)	111.4(2)
N(3)–N(4)	1.356(2)	N(3)–N(4)–C(8)	104.2(2)
N(3)–C(6)	1.394(3)	C(5)–N(5)–C(6)	116.4(3)
N(3)–C(10)	1.366(2)	N(2)–C(1)–C(2)	106.9(2)
N(4)–C(8)	1.346(3)	C(1)–C(2)–C(3)	104.9(2)
N(5)–C(5)	1.298(3)	N(1)–C(3)–C(2)	111.1(2)
N(5)–C(6)	1.356(2)	N(5)–C(6)–C(7)	133.2(2)
C(1)–C(2)	1.370(3)	N(3)–C(6)–C(7)	106.1(2)
C(2)–C(3)	1.404(3)	C(6)–C(7)–C(8)	105.3(2)
C(3)–C(4)	1.476(3)	N(4)–C(8)–C(7)	113.1(2)
C(4)–C(5)	1.432(3)	C(6)–N(3)–C(10)	123.3(2)
C(4)–C(10)	1.380(3)	C(2)–C(3)–C(4)	126.0(2)
C(6)–C(7)	1.382(3)	C(3)–C(4)–C(10)	125.0(3)
C(7)–C(8)	1.378(3)	C(5)–C(4)–C(10)	117.7(3)
C(8)–C(9)	1.490(3)	N(5)–C(5)–C(4)	125.8(2)
C(10)–C(11)	1.488(3)	N(4)–C(8)–C(9)	119.5(2)
		N(3)–C(10)–C(11)	116.9(2)

[a] For the numbering scheme of atoms, see Fig. 3.

zolo[1,5-*a*]pyrimidine. Some selected bond lengths and bond angles are reported in Table 3, and crystallographic details are given in the Experimental section. Tables of atomic co-ordinates, anisotropic thermal parameters and hydrogen positions have been deposited at Cambridge Crystallographic Data Centre (CCDC).*

Experimental

Carbon-13 and proton NMR spectra were measured on a Varian VXR-300 or a Varian Gemini-200 instrument in the Fourier transform mode. All carbon spectra were recorded at 25 ± 0.5 °C for 0.5 mol dm^{-3} solutions in anhydrous [$^2H_6$]dimethyl sulfoxide. Proton coupled spectra were obtained in the 'gated decoupling' mode. Typical conditions were spectral width 16 500 Hz, 64 K data points (digital resolution of 0.5 Hz/point, *i.e.* 0.01 ppm), quadrature phase detection and pulse width 7 μs (≈30°). Chemical shifts (δ) are reported in ppm high frequency from tetramethylsilane as secondary internal reference (central line of the solvent multiplet at δ 39.5) and coupling constants in Hz. The 2D NMR spectra were recorded using the standard Varian software. COSY spectrum was obtained with spectral width of 2280.0 Hz in both dimensions, acquisition times of 0.225 s, 256 increments with 32 transients per increment, a delay of 1 s between transients and data processed as 1024 × 1024 matrices. For the HETCOR and COLOC experiments, the ^1H spectral width was 2100 Hz and the ^{13}C spectral width 9640 Hz. The HETCOR experiments were set up for ^1J = 180 Hz, and 128 transients were accumulated into 2048 real points for each of the 256 increments in T_1. The COLOC experiments were set up for $^nJ_{C,H}$ = 6 or 14 Hz, and 128 transients were accumulated into 2048 real points for each of the 128 increments in T_1.

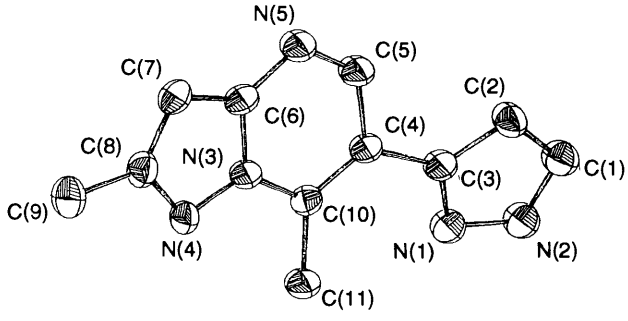


Fig. 3 X-Ray structure (ORTEP drawing) and numbering scheme of atoms for compound **1b**

Compounds **1a–c** were synthesised according to the published procedure.[2]

X-Ray Crystallography.—X-Ray diffraction data were measured on a Philips PW1100 diffractometer θ–2θ scan mode

* For details of the deposition scheme, see 'Instructions for Authors (1994),' *J. Chem. Soc., Perkin Trans. 2*, issue 1, 1994.

to $2\theta = 56°$, with Mo-Kα radiation ($\lambda = 0.710\,70$ Å). The structure was phased by SHELX 76 programs and the final refinement was carried out by full-matrix least squares procedures using 1766 reflections with $F > 3\sigma(F)$ and converged at $R = 0.054$ and $R_w = 0.068$ with $W = 1/[\sigma^2(F) + 0.01F^2]$. The non-H atoms thermal parameters were anisotropic, H atoms were located on a DF map and isotropically refined.

Crystal data. **1b**, $C_{11}H_{11}N_5$, $M = 213.24$, monoclinic, space group $P2_1/n$, $a = 7.285(1)$, $b = 17.185(2)$, $c = 8.561(1)$ Å, $\beta = 107.7(2)°$, $Z = 4$, $D_c = 1.390\,g\,cm^{-3}$, $F(000) = 448$, $T = 313$ K.

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