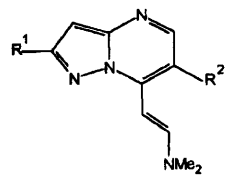
Chemistry of substituted pyrazolo[1,5-*a*]pyrimidines. Part 5.[1] 7-Oxo-6-[pyrazol-3′(5′)-yl]-4,7-dihydropyrazolo[1,5-*a*]pyrimidines from 6-ethoxycarbonyl-7-(2-dimethylaminovinyl)pyrazolo[1,5-*a*]-pyrimidines: elucidation of the reaction mechanism through NMR spectroscopy and X-ray diffraction analysis

Stefano Chimichi,*[a] Fabrizio Bruni,[b] Barbara Cosimelli,[a] Silvia Selleri[b] and Giovanni Valle[c]

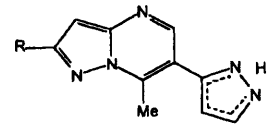
[a] *Dipartimento di Chimica Organica e Centro CNR sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, Via Gino Capponi 9, I-50121 Firenze, Italy*
[b] *Dipartimento di Scienze Farmaceutiche, Via Gino Capponi 9, I-50121 Firenze, Italy*
[c] *Centro di Studio sui Biopolimeri del CNR, Dipartimento di Chimica Organica, Via Marzolo 1, I-35100 Padova, Italy*

The reaction of 6-ethoxycarbonyl-7-(2-dimethylaminovinyl)pyrazolo[1,5-*a*]pyrimidines 1a,b with hydrazine hydrate in acetic acid solution gave rise to 7-oxo-6-[pyrazol-3′(5′)-yl]-4,7-dihydropyrazolo[1,5-*a*]pyrimidines 3a,b, a result very similar to the intramolecular cyclization previously reported for the corresponding 6-acetyl derivatives 1c,d. Treatment of compounds 3a,b with dimethyl sulfate gave rise to a mixture of the *N*-methyl derivatives 4a,b and 5a,b whose structures have been unambiguously established on the basis of NMR spectroscopy and confirmed by the X-ray structure of compound 4a. The same reaction carried out with methylhydrazine led to a mixture of 6-(1′-methylpyrazol-3′-yl)-7-oxo- 6a,b and 6-(1′-methylpyrazol-5′-yl)-7-oxo-4,7-dihydropyrazolo-[1,5-*a*]pyrimidine 7a,b in which the former were predominant. When the reaction was carried out in ethanol, a different regioselectivity was observed leading to the isolation of the open-chain intermediate compounds 11–13 which in turn give rise, predominantly, to the pyrazolopyrimidine derivative 7a. A reaction pathway based on the X-ray structure of compound 11 is proposed.

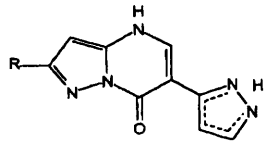
Recently we reported that reaction of 6-acetyl-7-(2-dimethylaminovinyl)pyrazolo[1,5-*a*]pyrimidines **1c,d** with hydrazine hydrate in acetic acid solution gives rise to 7-methyl-6-(pyrazol-3′-yl)pyrazolo[1,5-*a*]pyrimidines **2a,b** and not to the previously claimed pyrazolopyrimidodiazepine ring system.[1] We wish now to generalise this intramolecular cyclization which also led to 6-pyrazolyl derivatives starting from 6-ethoxycarbonyl-7-(2-dimethylaminovinyl)pyrazolo[1,5-*a*]pyrimidines **1a,b**. When the same reaction is carried out with methylhydrazine in ethanol under acid catalysis, a different regioselective attack affording compounds **6a** and **7a** in the ratio 5:95 is observed. Moreover, it was possible to isolate the open chain intermediate compounds **11–13** which have been characterised. NMR spectroscopy and X-ray analyses of compounds **4a** and **11** unambiguously confirmed the attributed structures and prompted us to suggest a reaction pathway.



1a R^1 = H, R^2 = CO_2Et
1b R^1 = Me, R^2 = CO_2Et
1c R^1 = H, R^2 = COMe
1d R^1 = Me, R^2 = COMe



2a R = H
2b R = Me

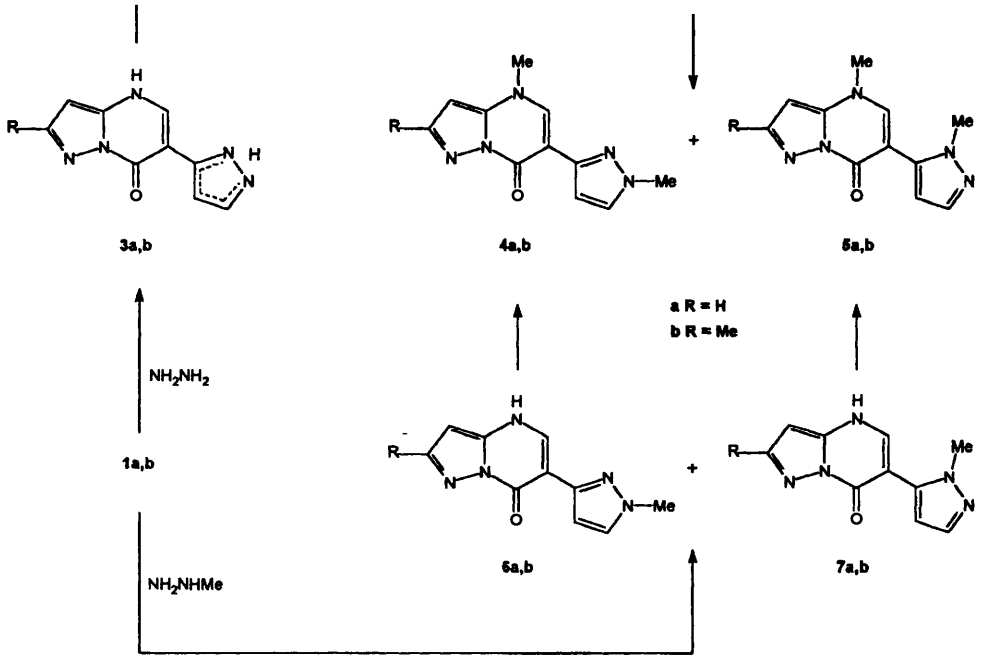


3a R = H
3b R = Me

Results

When the dimethylaminovinyl derivatives **1a,b** were allowed to react with hydrazine hydrate in glacial acetic acid we obtained compounds **3a,b** and no intermediates were isolated in acidic ethanolic solution at low temperatures. The 7-oxo-6-[pyrazol-3′(5′)-yl]-4,7-dihydropyrazolo[1,5-*a*]pyrimidine structures of such compounds have been ascertained as follows. Owing to proton exchange in [$^2H_6$]dimethyl sulfoxide solution, ^1H NMR spectra of **3a,b** were not well resolved and not all the carbon resonances could be observed in the proton decoupled ^{13}C NMR spectra. To overcome this problem, compounds **3a,b** were treated with dimethyl sulfate thus obtaining a mixture of the blocked *N*-methyl derivatives **4a,b** and **5a,b** (see Scheme 1).

Flash-chromatography ($CHCl_3$–MeOH, 20:3) allowed the compounds to be separated and carefully examined by NMR spectroscopy. NMR analysis of the 6-pyrazolylpyrazolopyrimidine structure[1] and the distinction between the isomeric compounds **4a,b** and **5a,b** rely mainly on their gated decoupled carbon spectra (Table 1). The DEPT spectrum of the fastest running product originating from **3a**, showed five signals for the five tertiary carbon atoms among which that of C-5 was easily recognized as the doublet of quartets at δ 138.43 in the coupled spectrum. The resonances of C-2 and C-3 were identified as the doublet of doublets and the doublet of doublet of doublets at δ 143.27 and 88.69, respectively, on the basis of both chemical



Scheme 1

shift considerations and multiplicity. These assignments were then confirmed by the coupled spectrum of the corresponding product obtained from compound **1b**: the signal at δ 88.63 appears now as a doublet of quartet of doublets and must be attributed to C-3. The carbon atoms at position 4′ and 5′ (or 3′) of the 6-pyrazolyl moiety appear as a doublet of doublets at δ 106.40 and as a doublet of doublet of quartets at δ 131.03, respectively, thus proving that the structure of pyrazol-3′-yl **4a** should be attributed to this compound. On the other hand, the corresponding low frequency signal (C-3′) of the slowest running product appears as a doublet of doublets, thus confirming the previous attribution and allowing distinction between the isomers.

Except for the CO and the C-6 signals which appear at δ 155.02 and 103.86, respectively, the resonances of the quaternary carbon atoms C-3a and C-3′ 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 144.67. The latter shows a fine structure of a doublet of pseudo-triplets and must be attributed to the C-3′ of **4a**.

As regards the methyl groups, in accordance with the proposed structures they appear both as quartets of doublets in **4a** and as a quartet of doublets and a simple quartet in **5a**. 2D NMR experiments (COSY, HETCOR and COLOC) were then performed and proved to be extremely useful. Thus, COLOC spectra of compound **4a** led us to distinguish between N-4-Me and N-1′-Me. The resonance at δ 40.20, which is coupled to 5-H, belongs to N-4-Me, whereas the signal at δ 38.87, coupled to 5′-H, must be attributed to the N-1′-Me. Whereas the resonance at δ 40.39 in the COLOC spectrum of **5a** is still coupled to the signal of 5-H, no long-range couplings appear for the signal at δ 37.75 attributed to N-1′-Me.

All the previous considerations hold for compounds **4b** and **5b**, too. Subsequent H,H-COSY spectra not only confirmed the distinction between the pairs of protons 2-H, 3-H and 5′-H, 4′-H in **4a**, but more interestingly allowed us to attribute the *N*-Me signals in all the examined compounds.

Looking at the ^{1}H NMR spectra of compounds **4a,b** and **5a,b** (Table 2), a significantly low frequency shift of the 5-H resonance can be observed. This shielding could be justified on the basis of a steric compression effect derived from a preferred conformation of the 6-pyrazol-5′-yl ring due to the presence of

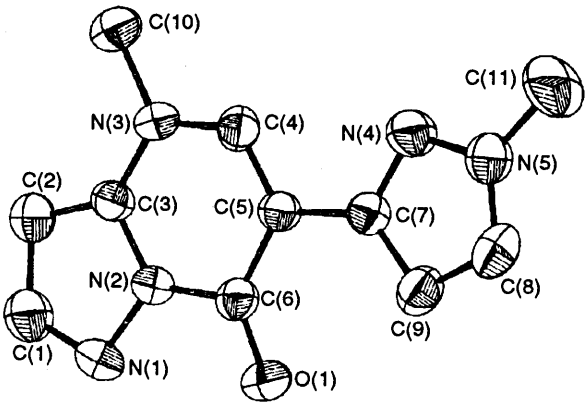


Fig. 1 X-Ray structure (ORTEP drawing) and numbering scheme of atoms for compound **4a**

the CO group at position 7. This hypothesis was confirmed by NOEDIF experiments: thus, irradiation of the 5-H resonance in **5a** gives a strong NOE effect on the N-1′-Me signal and a smaller one on the N-4-Me resonance. The corresponding experiment with **4a** does not show any significant NOE effect.

X-Ray analysis of compound **4a** (see the ORTEP diagram of Fig. 1) confirmed unequivocally the correct structure of 4-methyl-6-(1′-methylpyrazol-3′-yl)-7-oxo-4,7-dihydropyrazolo-[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.

The same reaction carried out in acetic acid employing methylhydrazine as the nucleophile led in high yields to a mixture of compounds **6a,b** and **7a,b** in which the former are predominant (see Experimental); also in this case no intermediates can be isolated. The ^{1}H NMR data of compounds **6a,b** and **7a,b** (Table 2) agree well with the proposed structures; moreover, treatment of these compounds with iodomethane give rise to the same materials previously obtained by methylation of **3a,b**.

As the final part of this work, we tried to find some support for the previously suggested reaction mechanism.[1] The final product is envisioned to arise *via* initial substitution by the nucleophile of the *N*-dimethyl group of compounds **1** followed by a regiospecific attack of the newly formed NHR (R = H or Me) group on the electron deficient C-7. Subsequent opening of

Table 1 ^{13}C NMR data for compounds **4a,b** and **5a,b** (75 MHz, $CDCl_3$)

Compound	δ	Assignment	Multiplicity[a]	^nJ/Hz
4a	155.02	CO	d	$^3J_{CO,5}$ 8.4
	144.67	C-3′	dt	$^2J_{3',4'}$ 8.7, $^3J_{3',5}$ 3.9, $^3J_{3',5'}$ 3.9
	143.27	C-2	dd	$^1J_{2,2}$ 187.4, $^3J_{2,3}$ 4.3
	142.41	C-3a	m	
	138.43	C-5	dq	$^1J_{5,5}$ 179.6, $^3J_{5,N\text{-}4\text{-}Me}$ 3.6
	131.03	C-5′	ddq	$^1J_{5',5'}$ 185.7, $^2J_{5',4'}$ 9.4, $^3J_{5',N\text{-}1'\text{-}Me}$ 2.6
	106.40	C-4′	dd	$^1J_{4',4'}$ 181.9, $^2J_{4',5'}$ 8.6
	103.86	C-6	d	$^2J_{6,5}$ 1.2
	88.69	C-3	ddd	$^1J_{3,3}$ 180.4, $^2J_{3,2}$ 11.4, $^4J_{3,5}$ 1.4
	40.20	N-4-Me	qd	^1J 141.3, $^3J_{N\text{-}4\text{-}Me,5}$ 4.0
	38.87	N-1′-Me	qd	^1J 139.7, $^3J_{N\text{-}1'\text{-}Me,5'}$ 1.0
4b	154.76	CO	d	$^3J_{CO,5}$ 8.4
	153.33	C-2	qd	$^2J_{2,2\text{-}Me}$ 6.7, $^2J_{2,3}$ 3.8
	144.86	C-3′	dt	$^2J_{3',4'}$ 8.8, $^3J_{3',5}$ 3.9, $^3J_{3',5'}$ 3.9
	142.85	C-3a	m	
	137.87	C-5	dq	$^1J_{5,5}$ 179.6, $^3J_{5,N\text{-}4\text{-}Me}$ 3.6
	130.95	C-5′	ddq	$^1J_{5',5'}$ 185.6, $^2J_{5',4'}$ 9.5, $^3J_{5',N\text{-}1'\text{-}Me}$ 2.6
	106.41	C-4′	dd	$^1J_{4',4'}$ 181.9, $^2J_{4',5'}$ 8.6
	103.75	C-6	d	$^2J_{6,5}$ 1.2
	88.63	C-3	dqd	$^1J_{3,3}$ 178.4, $^2J_{3,2\text{-}Me}$ 3.5, $^4J_{3,5}$ 1.3
	40.03	N-4-Me	qd	^1J 141.3, $^3J_{N\text{-}4\text{-}Me,5}$ 4.0
	38.82	N-1′-Me	qd	^1J 139.7, $^3J_{N\text{-}1'\text{-}Me,5'}$ 1.0
	14.44	2-Me	q	^1J 128.0
5a	154.63	CO	d	$^3J_{CO,5}$ 8.3
	143.79	C-2	dd	$^1J_{2,2}$ 188.4, $^3J_{2,3}$ 4.3
	142.67	C-3a	m	
	142.31	C-5	dq	$^1J_{5,5}$ 179.5, $^3J_{5,N\text{-}4\text{-}Me}$ 3.6
	138.26	C-3′	dd	$^1J_{3',3'}$ 185.5, $^2J_{3',4'}$ 5.4
	135.15	C-5′	m	
	107.65	C-4′	dd	$^1J_{4',4'}$ 176.1, $^2J_{4',3'}$ 10.5
	100.81	C-6	d	$^2J_{6,5}$ 1.8
	89.70	C-3	ddd	$^1J_{3,3}$ 181.0, $^2J_{3,2}$ 11.2, $^4J_{3,5}$ 1.5
	40.39	N-4-Me	qd	^1J 141.8, $^3J_{N\text{-}4\text{-}Me,5}$ 3.9
	37.75	N-1′-Me	q	^1J 140.1
5b	154.29	CO	d	$^3J_{CO,5}$ 8.2
	153.98	C-2	qd	$^2J_{2,2\text{-}Me}$ 6.7, $^2J_{2,3}$ 3.9
	143.10	C-3a	m	
	141.72	C-5	dq	$^1J_{5,5}$ 179.2, $^3J_{5,N\text{-}4\text{-}Me}$ 3.8
	138.13	C-3′	dd	$^1J_{3',3'}$ 185.3, $^2J_{3',4'}$ 5.4
	135.38	C-5′	m	
	107.46	C-4′	dd	$^1J_{4',4'}$ 176.0, $^2J_{4',3'}$ 10.5
	100.77	C-6	d	$^2J_{6,5}$ 1.6
	89.55	C-3	dqd	$^1J_{3,3}$ 179.0, $^2J_{3,2\text{-}Me}$ 3.5, $^4J_{3,5}$ 1.3
	40.18	N-4-Me	qd	^1J 141.7, $^3J_{N\text{-}4\text{-}Me,5}$ 3.9
	37.73	N-1′-Me	q	^1J 140.1
	14.41	2-Me	q	^1J 128.4

[a] Multiplicity: d = doublet, t = triplet, q = quartet, m = multiplet.

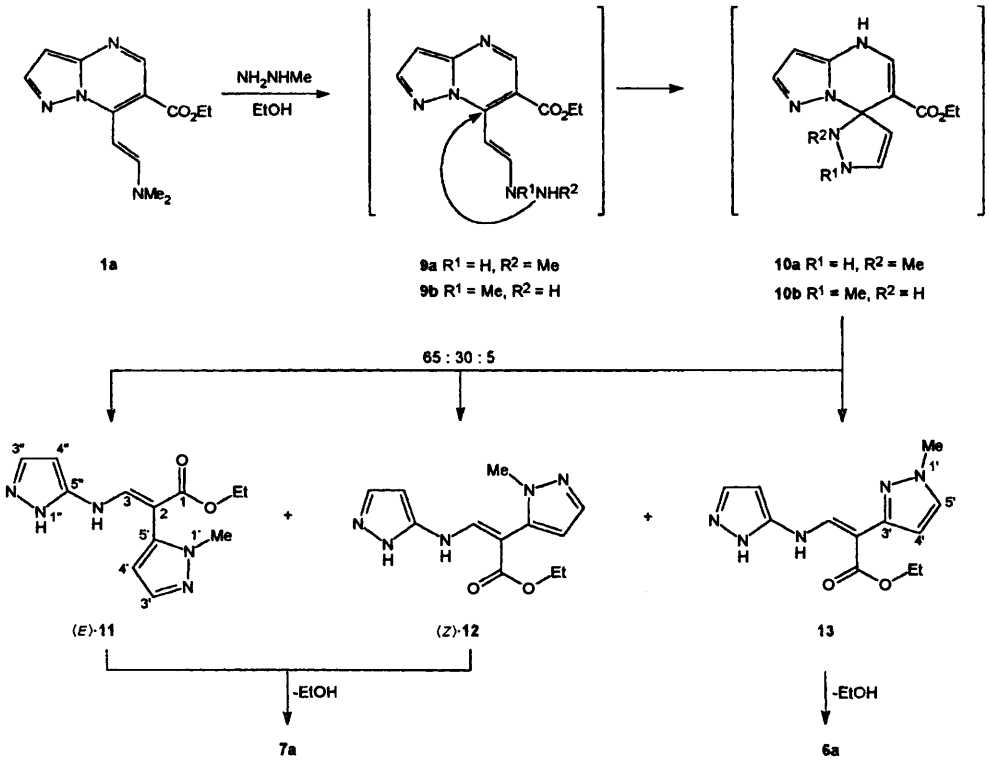
Table 2 ^1H NMR data for compounds **4a,b–7a,b** (300 MHz, $CDCl_3$)

Compound	2-H	2-Me	3-H	5-H	3′-H	5′-H	4′-H	N-4-Me	N-1′-Me	N-H
4a	7.87 d, *J* 2.0		6.02 d, *J* 2.0	8.12 s		7.35 d, *J* 2.3	7.08 d, *J* 2.3	3.72 s	3.88 s	
4b		2.39 s	5.81 s	8.02 s		7.33 d, *J* 2.3	7.06 d, *J* 2.3	3.65 s	3.86 s	
5a	7.91 d, *J* 2.0		6.12 d, *J* 2.0	7.51 s	7.42 d, *J* 1.8		6.17 d, *J* 1.8	3.75 s	3.80 s	
5b		2.41 s	5.91 s	7.40 s	7.38 d, *J* 1.8		6.14 d, *J* 1.8	3.67 s	3.78 s	
6a[a]	7.91 d, *J* 1.9		6.23 d, *J* 1.9	8.42 s		7.71 d, *J* 2.1	6.87 d, *J* 2.1		3.88 s	12.80 br s exch.
6b[a]		2.32 s	6.05 s	8.33 s		7.70 d, *J* 2.1	6.84 d, *J* 2.1		3.87 s	12.50 br s exch.
7a[a]	7.97 d, *J* 2.0		6.28 d, *J* 2.0	8.09 s	7.46 d, *J* 1.8		6.33 d, *J* 1.8		3.74 s	12.86 br s exch.
7b[a]		2.34 s	6.08 s	8.01 s	7.44 d, *J* 1.8		6.30 d, *J* 1.8		3.72 s	12.55 br s exch.

[a] In $^2[H]_6$DMSO.

the spiro compound and elimination of ethanol under acid conditions gives rise to the final products (see Scheme 2). Thus, reaction of **1a** with methylhydrazine in ethanol containing acetic acid gives compounds **6a** and **7a** in the ratio 5:95, respectively, a result opposite to that observed for the same reaction carried out in acetic acid alone.

Evidence for this pathway came from the isolation of the intermediate compounds **11–13**. Thus, if the reaction is stopped when all the starting material disappeared (TLC) and the solvent evaporated, we obtain a solid mainly consisting of two compounds with traces of a third one. Flash-chromatography ($CHCl_3$–MeOH, 20:3) on this solid allowed the isolation of three isomeric compounds of molecular formula $C_{12}H_{15}N_5O_2$ in the ratio 65:30:5. The ^1H NMR spectra of all these solids (Table 4) are very similar; in particular they show the presence of an ethoxycarbonyl group and of two NH signals (Table 4). In all the compounds the lowest frequency NH resonance appears as a large doublet (*J* 13 Hz) connected to a signal which in turn became a singlet after treatment of the sample with deuterium oxide or by a double resonance experiment. The latter signal is easily attributed to 3-H by an HETCOR experiment; on this basis and considering that the most abundant compounds in the



Scheme 2

Table 3 Selected bond distances (Å) and angles (°) for the crystal structure of **4a**[a]

O(1)–C(6)	1.226(4)	N(5)–N(4)–C(7)	105.2(3)
N(1)–C(1)	1.321(6)	N(4)–N(5)–C(8)	112.4(3)
N(2)–C(6)	1.404(4)	N(1)–N(2)–C(3)	111.1(3)
N(3)–C(4)	1.352(5)	N(2)–N(1)–C(1)	103.3(3)
N(4)–N(5)	1.349(5)	C(3)–N(3)–C(4)	118.4(3)
N(5)–C(8)	1.334(6)	N(5)–C(8)–C(9)	107.1(4)
C(1)–C(2)	1.392(6)	C(7)–C(9)–C(8)	104.7(3)
C(4)–C(5)	1.345(5)	N(4)–C(7)–C(9)	110.6(3)
C(5)–C(7)	1.466(5)	N(3)–C(3)–C(2)	113.6(3)
C(8)–C(9)	1.380(6)	N(3)–C(4)–C(5)	124.7(3)
N(1)–N(2)	1.379(4)	C(1)–C(2)–C(3)	103.7(3)
N(2)–C(3)	1.360(4)	N(1)–C(1)–C(2)	114.1(4)
N(3)–C(3)	1.363(4)	C(3)–N(2)–C(6)	126.2(3)
N(3)–C(10)	1.473(5)	C(5)–C(7)–C(9)	129.9(3)
N(4)–C(7)	1.335(4)	C(6)–C(5)–C(7)	119.3(3)
N(5)–C(11)	1.454(6)	C(4)–C(5)–C(6)	119.9(3)
C(2)–C(3)	1.369(5)	O(1)–C(6)–N(2)	120.0(3)
C(5)–C(6)	1.450(5)	N(4)-N(5)–C(11)	119.1(3)
C(7)–C(9)	1.410(5)	C(4)–N(3)–C(10)	122.2(3)
		N(2)–C(3)–N(3)	118.5(3)
		O(1)–C(6)–C(5)	127.7(3)

[a] For the numbering scheme of atoms, see Fig. 1.

same experimental conditions give the same final product **7a**, we attributed the structure of 2-(1′-methylpyrazol-5′-yl)-3-(pyrazol-5″-yl)aminopropenoate to both these compounds that must be diastereoisomers.

Finally, we turned our attention towards devising a reliable method for the assignment of the configuration of the trisubstituted alkenic linkage in the two most abundant products. Initial stereochemical assignment was based on chemical shift considerations on 3-H; this proton resonates at δ 8.50 and 7.61, respectively, thus reflecting a different spatial arrangement in the examined compounds. Considering the anisotropy effects of the C=O group, the *E* configuration was initially attributed to the compound showing the most deshielded 3-H, namely compound **11**. Support for this configurational assignment came from the fine splitting pattern

Table 4 ^{1}H NMR data for compounds **11** and **12** (600 MHz, [$^2H_6$]DMSO)[a]

	δ, multiplicity,[b] *J*/Hz	
Assignment	**11**	**12**
N-1″-H	12.35 br, exch.	12.41 br, exch.
N-H	9.04 d, exch., *J* 13.6	10.30 d, exch., *J* 13.1
3-H	8.50 d, *J* 13.6	7.61 d, *J* 13.1
3″-H	7.66 dd,[c] *J* 2.0, 2.0	7.62 dd,[c] *J* 2.1, 2.1
3′-H	7.54 d, *J* 1.8	7.33 d, *J* 1.8
4′-H	6.24 d, *J* 1.8	6.11 d, *J* 1.8
4″-H	5.94 dd,[c] *J* 2.0, 2.0	6.23 dd,[c] *J* 2.1, 2.1
OCH_2CH_3	4.19 q, *J* 7.0	4.16 q, *J* 7.1
N-1′-Me	3.69 s	3.62 s
OCH_2CH_3	1.27 t, *J* 7.0	1.18 t, *J* 7.1

[a] For the numbering scheme, see Scheme 2. [b] Multiplicity: s = singlet, d = doublet, t = triplet, q = quartet. [c] Appear as a pseudo-triplet.

observed in the coupled ^{13}C NMR spectra of compounds **11** and **12**. In particular, the C=O carbon atom resonating at δ 166.73 and 167.63, respectively, appears in both compounds as a doublet of triplets but in compound **11** it has a $^3J_{C1,H3}$ value smaller with respect to that observed for compound **12** (7.6 Hz *vs.* 10.6 Hz). It is well known that vicinal ^{13}C–^{1}H coupling constants can be useful for stereochemical assignments particularly when both isomers are available for comparison.[2] On these grounds the relationship $^3J_{cis} < {}^3J_{trans}$ appears to be generally valid, thus confirming the *E*,*Z* attribution to compounds **11** and **12**, respectively.

To verify rigorously the *E* geometry of the most abundant compound **11** and, in turn, to confirm the validity of the above empirical NMR correlation, we completed an X-ray analysis of this compound. Some selected bond lengths and bond angles are reported in Table 5 and crystallographic details are given in the Experimental section. The ORTEP plot, shown in Fig. 2, not only confirms both the structure and the alkenic configuration of the intermediate compound **11**, but also strengthens the validity of the NMR assignments.

Table 5 Selected bond distances (Å) and angles (°) for the crystal structure of **11**[a]

O(1)–C(10)	1.21(1)	N(1)–N(2)–C(3)	104.2(7)
N(1)–C(1)	1.32(1)	N(2)–N(1)–C(1)	112.4(8)
N(1)–N(2)	1.363(8)	N(1)–C(1)–C(2)	106.6(8)
N(2)–C(3)	1.286(8)	C(1)–C(2)–C(3)	103.7(8)
N(3)–C(3)	1.417(9)	N(2)–C(3)–C(2)	113.1(8)
N(3)–C(4)	1.311(9)	N(3)–C(3)–C(2)	129.6(8)
C(1)–C(2)	1.384(9)	N(2)–C(3)–N(3)	117.3(7)
C(2)–C(3)	1.39(1)	C(3)–N(3)–C(4)	122.7(8)
C(4)–C(5)	1.342(9)	N(3)–C(4)–C(5)	128.1(9)
C(5)–C(6)	1.48(1)	C(4)–C(5)–C(10)	114.6(8)
C(6)–C(7)	1.38(1)	O(1)–C(10)–C(5)	124.3(9)
C(7)–C(8)	1.37(1)	O(2)–C(10)–C(5)	113.3(8)
N(4)–C(8)	1.31(1)	C(4)–C(5)–C(6)	120.7(8)
N(4)–N(5)	1.347(9)	C(5)–C(6)–C(7)	130.9(6)
N(5)–C(6)	1.360(8)	C(6)–C(7)–C(8)	105.3(6)
N(5)–C(9)	1.44(1)	N(4)–C(8)–C(7)	113.0(7)
C(5)–C(10)	1.45(1)	N(5)–N(4)–C(8)	104.4(7)
O(2)–C(10)	1.332(8)	N(4)–N(5)–C(6)	112.2(6)
C(11)–C(12)	1.49(1)	N(5)–C(6)–C(7)	105.1(6)
O(2)–C(11)	1.47(1)	C(6)–N(5)–C(9)	127.4(8)

[a] For the numbering scheme of atoms, see Fig. 2.

Experimental

Warning

Methylhydrazine is a potent colorectal carcinogen and must be handled with care.

All melting points were determined on a Gallenkamp MFB-595-010M melting point apparatus (accuracy ± 0.5 °C) and are uncorrected. ^{13}C and ^{1}H NMR spectra were measured on a Bruker AM-600 or a Varian VXR-300 instrument in the Fourier transform mode. Unless otherwise stated, all ^{13}C NMR spectra were recorded at 25 ± 0.5 °C for solutions in anhydrous deuteriochloroform. ^{13}C NMR 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 per point, *i.e.* 0.01 ppm), quadrature phase detection and pulse width 7 μs (*ca.* 30°). Chemical shifts (δ) are reported in ppm high frequency from tetramethylsilane as the secondary internal reference (central line of the solvent at δ 77.00) and coupling constants in Hz. The 2D NMR spectra were recorded using the standard Bruker or Varian software. Mass spectra were recorded with a Carlo Erba QMD 1000 instrument operating in the electron impact mode at 70 eV and a 200 °C source temperature. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck 230–400 mesh) were used for analytical TLC and for flash chromatography, respectively. Solvents were removed under reduced pressure.

Compounds **1a**[3] and **1b**[4] were synthesised according to the published procedures.

General procedure for the preparation of pyrazolylpyrazolopyrimidines 3a,b

Hydrazine monohydrate (2 mmol) was added in one batch to a stirred solution of the appropriate 6-ethoxycarbonyl-7-(2-dimethylaminovinyl)pyrazolo[1,5-*a*]pyrimidine **1a,b** (2 mmol) in glacial acetic acid (20 cm^3) containing sodium acetate (0.4 g) and the reaction mixture was refluxed for 2 h.

7-Oxo-6-[pyrazol-3′(5′)-yl]-4,7-dihydropyrazolo[1,5-*a*]pyrimidine **3a** was obtained as a white solid by filtration in 87% yield, mp > 300 °C (from propan-2-ol) (Found: C, 53.6; H, 3.6; N, 34.6. $C_9H_7N_5O$ requires C, 53.7; H, 3.5; N, 34.8%), δ_H(200 MHz; ^{2}[H_6]DMSO) 6.24 (1 H, d, *J* 1.8, 3-H), 6.83 (1 H, br s, 4′-H), 7.66 [1 H, br s, 3′(5′)-H], 7.92 (1 H, d, *J* 1.8, 2-H), 8.43 (1 H, s, 5-H), 12.71 (1 H, br s, exch., N-H) and 12.83 (1 H, br s, exch., N-H).

2-Methyl-7-oxo-6-[pyrazol-3′(5′)-yl]-4,7-dihydropyrazolo-[1,5-*a*]pyrimidine **3b** was obtained as a white solid by filtration in 80% yield, mp > 300 °C (from ethanol) (Found: C, 55.6; H, 4.1; N, 32.4. $C_{10}H_9N_5O$ requires C, 55.8; H, 4.2; N, 32.5%), δ_H(200 MHz; ^{2}[H_6]DMSO) 2.31 (3 H, s, 2-Me), 6.05 (1 H, s, 3-H), 6.81 (1 H, br s, 4′-H), 7.66 [1 H, br s, 3′(5′)-H], 8.35 (1 H, s, 5-H), 12.55 (1 H, br s, exch., N-H) and 12.80 (1 H, br s, exch., N-H).

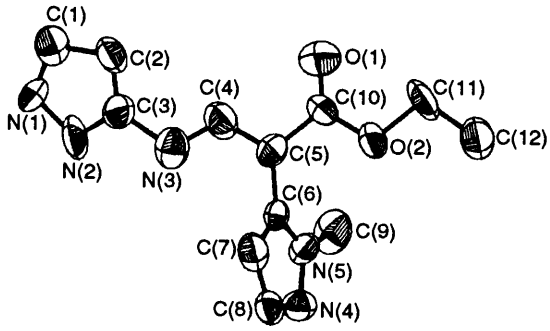


Fig. 2 X-Ray structure (ORTEP drawing) and numbering scheme of atoms for the intermediate **11**

Reaction of compound 1a with methylhydrazine

(*i*) Methylhydrazine (2 mmol) was added in one batch to a stirred solution of 6-ethoxycarbonyl-7-(2-dimethylaminovinyl)pyrazolo[1,5-*a*]pyrimidine **1a** (2 mmol) in glacial acetic acid (20 cm^3) containing sodium acetate (0.4 g) and the reaction mixture was refluxed for 2 h. After cooling, evaporation of the solvent gave a solid which was washed with water and dried to afford a mixture (0.37 g, 86%) of isomeric compounds **6a** and **7a** in the ratio 80:20, respectively. The mixture was separated *via* flash chromatography by eluting with $CHCl_3$–MeOH, 20:3.

The first material eluted was 6-(1′-methylpyrazol-3′-yl)-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine **6a**, mp > 300 °C (Found: C, 55.7; H, 4.2; N, 32.4. $C_{10}H_9N_5O$ requires C, 55.8; H, 4.2; N, 32.5%).

The second product eluted was 6-(1′-methylpyrazol-5′-yl)-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine **7a**, mp > 300 °C (Found: C, 55.9; H, 4.1; N, 32.3. $C_{10}H_9N_5O$ requires C, 55.8; H, 4.2; N, 32.5%).

(*ii*) Methylhydrazine (10 mmol) was added in one batch to a stirred solution of 6-ethoxycarbonyl-7-(2-dimethylaminovinyl)-pyrazolo[1,5-*a*]pyrimidine **1a** (10 mmol) in ethanol (30 cm^3) containing acetic acid (1 cm^3). The reaction mixture was then refluxed until the disappearance of the starting material (TLC, 4 h); evaporation of the solvent gave a solid (2.1 g, 80%) mainly consisting (^{1}H NMR spectrum) of a mixture of the isomeric compounds **11** and **12**, in the ratio 65:30, respectively, with traces (*ca.* 5%) of compound **13**. Flash chromatography with $CHCl_3$–MeOH, 20:3 as eluent afforded the analytical products.

The first material eluted was ethyl 2-(1′-methylpyrazol-3′-yl)-3-(pyrazol-5″-ylamino)propenoate **13**, δ_H(200 MHz; ^{2}[H_6]DMSO) 1.27 (3 H, t, *J* 7.0, $CO_2CH_2CH_3$), 3.91 (3 H, s, N-1′-Me), 4.17 (2 H, q, *J* 7.0, $CO_2CH_2CH_3$), 6.12 (1 H, dd, *J* 2.0, 2.0, 4″-H), 6.72 (1 H, d, *J* 2.3, 4′-H), 7.68 (1 H, dd, *J* 2.0, 2.0, 3″-H), 7.69 (1 H, d, *J* 2.3, 5′-H), 8.24 (1 H, d, *J* 13.0, 3-H), 10.81 (1 H, d, exch., *J* 13.0, N-H) and 12.37 (1 H, br s, exch., N-1″-H); *m/z* 261 (M^+).

The second product was ethyl (*Z*)-2-(1′-methylpyrazol-5′-yl)-3-(pyrazol-5″-ylamino)propenoate **12**, mp 200 °C (decomp.) (Found: C, 55.3; H, 5.7; N, 26.9. $C_{12}H_{15}N_5O_2$ requires C, 55.2; H, 5.8; N, 26.8%), δ_C(150 MHz; ^{2}[H_6]DMSO) 14.62 (OCH_2CH_3), 36.78 (N-1′-Me), 59.71 (OCH_2CH_3), 88.98 (C-2), 92.78 (C-4″), 107.17 (C-4′), 130.51 (C-3″), 137.53 (C-3′), 139.28 (C-5′), 146.71 (C-3), 149.51 (C-5″) and 167.63 (CO); *m/z* 261 (M^+).

The slowest eluted product was ethyl (*E*)-2-(1′-methylpyrazol-5′-yl)-3-(pyrazol-5″-ylamino)propenoate **11**, mp 212–213 °C

(from propan-2-ol) (Found: C, 55.3; H, 5.7; N, 26.9. $C_{12}H_{15}N_5O_2$ requires C, 55.2; H, 5.8; N, 26.8%), δ_C(150 MHz; ^{2}[H$_6$]DMSO) 14.77 (OCH_2CH_3), 36.60 (N-1′-Me), 59.46 (OCH_2CH_3), 91.59 (C-2), 93.54 (C-4″), 107.47 (C-4′), 130.09 (C-3″), 135.35 (C-5′), 137.95 (C-3′), 143.46 (C-3), 149.87 (C-5″) and 166.73 (CO); *m/z* 261 (M^+).

Reaction of compound 1b with methylhydrazine

Operating as (*i*) for **1a**, a mixture (0.38 g, 83%) of isomeric compounds **6b** and **7b** in the ratio 70:30, respectively, was obtained. The mixture was separated *via* flash chromatography by eluting with $CHCl_3$–MeOH, 20:3.

The first solid eluted was 2-methyl-6-(1′-methylpyrazol-3′-yl)-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine **6b**, mp > 300 °C (from ethanol) (Found: C, 57.7; H, 4.6; N, 30.3. $C_{11}H_{11}N_5O$ requires C, 57.6; H, 4.8; N, 30.55%).

The second product eluted was 2-methyl-6-(1′-methylpyrazol-5′-yl)-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine **7b**, mp > 300 °C (Found: C, 57.7; H, 4.7; N, 30.4. $C_{11}H_{11}N_5O$ requires C, 57.6; H, 4.8; N, 30.55%).

General procedure for the methylation of pyrazolylpyrazolopyrimidines 6a,b and 7a,b

Iodomethane (1 mmol) was added to a stirred solution of the appropriate pyrazolylpyrazolopyrimidine (1 mmol) in dimethylformamide (20 cm^3) containing potassium carbonate (1 mmol) and the reaction mixture was maintained at 80 °C for 6 h.

4-Methyl-6-(1′-methylpyrazol-3′-yl)-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine **4a** was obtained by filtration as a pale yellow solid in 75% yield, mp 268–269 °C (from propan-2-ol) (Found: C, 57.5; H, 4.9; N, 30.4. $C_{11}H_{11}N_5O$ requires C, 57.6; H, 4.8; N, 30.55%).

2-Methyl-4-methyl-6-(1′-methylpyrazol-3′-yl)-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine **4b** was obtained by filtration as a pale yellow solid in 77% yield, mp 294–295 °C (from propan-2-ol) (Found: C, 59.4; H, 5.2; N, 28.7. $C_{12}H_{13}N_5O$ requires C, 59.25; H, 5.4; N, 28.8%).

4-Methyl-6-(1′-methylpyrazol-5′-yl)-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine **5a** was obtained by filtration in 75% yield, mp 225–226 °C (from propan-2-ol) (Found: C, 57.4; H, 4.8; N, 30.3. $C_{11}H_{11}N_5O$ requires C, 57.6; H, 4.8; N, 30.55%).

2-Methyl-4-methyl-6-(1′-methylpyrazol-5′-yl)-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine **5b** was obtained by filtration in 80% yield, mp 201–202 °C (from propan-2-ol) (Found: C, 59.3; H, 5.3; N, 28.7. $C_{12}H_{13}N_5O$ requires C, 59.25; H, 5.4; N, 28.8%).

Methylation of compounds 3a,b

Dimethyl sulfate (16 mmol) was added to a solution of the appropriate compound (2 mmol) in sodium hydroxide (10%) and the mixture was heated for 5 h. After cooling, an ivory solid containing predominantly (TLC and ^{1}H NMR spectrum) the dimethyl derivatives **4a,b** and **5a,b** was filtered off, washed with the minimum amount of water and dried. Flash chromatography ($CHCl_3$–MeOH, 20:3) gave materials identical to those previously described.

X-Ray crystallography

X-Ray diffraction data were measured on a Philips PW1100 diffractometer θ-2θ scan mode to $2\theta = 56°$, with Mo-Kα radiation (λ = 0.710 70 Å). For compound **4a**, the structure was phased by direct method programs and the final refinement was carried out by full-matrix blocked least squares procedures using 2622 reflections with $F > 4\sigma(F)$ and converged at R = 0.0452 and R_w = 0.0482 with $W = 1/[\sigma^2(F) + 0.01F^2]$. For compound **11**, the structure was solved by the SIR92 program [5] and refined by full-matrix blocked least squares procedures using 3112 reflections with $F > 5\sigma(F)$ and converged at R = 0.071 and R_w = 0.081 with $W = 1/[\sigma^2(F) + 0.006F^2]$.

The non-H atoms thermal parameters were anisotropic, H atoms were located on a DF map and isotropically refined.

Crystal data

4a, $C_{11}H_{11}N_5O$, M = 229.24, orthorhombic, space group *Pbca* (N61), a = 18.783(2), b = 14.510(2), c = 7.963(1) Å, Z = 8, D_c = 1.40 g cm^{-3}, $F(000)$ = 960, T = 313 K.

11, $C_{12}H_{15}N_5O_2$, M = 261.29, triclinic, space group $P\bar{1}$, a = 10.726(2), b = 9.137(2), c = 7.496(1) Å, α = 112.4(2)°, β = 90.8(2)°, γ = 105.7(2)°, Z = 2, D_c = 1.34 g cm^{-3}, μ = 0.90 cm^{-1}, $F(000)$ = 276, T = 313 K.

Supplementary data—Tables of fractional atomic coordinates, bond lengths and bond angles are available from the Cambridge Crystallographic Data Centre.†

† For details of the CCDC deposition scheme, see 'Instructions for Authors (1996)', *J. Chem. Soc., Perkin Trans. 2*, 1996, issue 1. Any request to the CCDC for this material should quote the full literature citation and the ref. no. 188/3.

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