

HETERODIENE SYNTHESSES—XII¹

THE CONFORMATIONAL ANALYSIS OF *CIS* AND *TRANS* 2-ALKOXY-4-PHENYL-2,3-DIHYDROPYRAN[2,3-*c*] PYRAZOLES: STERIC INTERACTIONS AND THE ANOMERIC EFFECT

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Abstract—The conformational equilibria of a homogeneous series of *cis* and *trans* 2-alkoxy-4-phenyl-2,3-dihydropyran[2,3-*c*] pyrazoles have been investigated by a graphical method, and the preferences are rationalized in terms of steric interactions between the 4 and 5-substituents and of the anomeric effect.

The anomeric interaction depends upon the nature of the alkoxy group and the conformational free-energy differences correlate with the steric parameters E_s .

In a previous paper² we investigated, with the aid of a graphical method,³ the conformational preferences of several 2,3-dihydropyran-isoxazoles, -indoles and -pyrazoles obtained from arylidene-oxindoles-isoxazolones and -pyrazolones in accordance with a 1,4-cycloaddition with vinyl ethers.⁴⁻⁶

The dihydropyran fragment exists in the rapidly inverting half-chair forms and the conformational equilibrium seems to be governed mainly by two factors:

(a) the anomeric effect which forces the alkoxy group into the axial position (Scheme 1-i)

(b) the conformational free enthalpy of the 4-aryl group which prefers the *pseudo*-equatorial position which is less destabilized by 1,3-interactions (Scheme 1-ii).

This latter preference seems to be counterbalanced by a steric interaction between the aryl group and the phenyl substituent on the adjacent ring. When its steric requirement is lowered a stronger preference for the C_4 -aryl equatorial conformer is expected, as suggested by indole derivatives.

In order to develop the study of the anomeric

effect in these derivatives and to investigate the role played by the substituent on the adjacent ring in the conformational preferences, we have prepared a suitable series of 2,3-dihydropyran[2,3-*c*] pyrazoles (Scheme 2) and we wish to present the results of their conformational analysis in this paper.

The dihydropyran protons absorb in the NMR spectrum as a strongly coupled ABMX system and a quantitative evaluation of the position in the conformational equilibrium requires a second order analysis. This was performed using the LAOCOON 3 computer program⁷ and the spectral parameters are reported in Table 1. All the alkoxy parameters are also included inasmuch as the methylene protons of ethoxy groups and methyls of *iso*-propoxy groups are diastereotopic due to the proximity of the chiral center at C_2 .

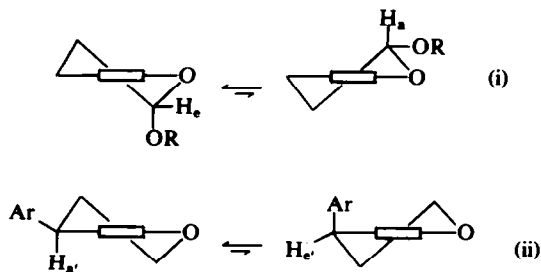
In the *CIS* series (5, 7 and 9) J_{34} and J_{23} are *trans* couplings whereas in the *TRANS* series (6, 8 and 10) the *trans* couplings are J_{34} and $J_{23'}$. Therefore, assuming that neither J_{aa} nor J_{ee} varies in the series, three equations can be written:

$$J_{34} = x(J_{3a4a} - J_{3e4e}) + J_{3e4e} \quad (\text{eqn 1})$$

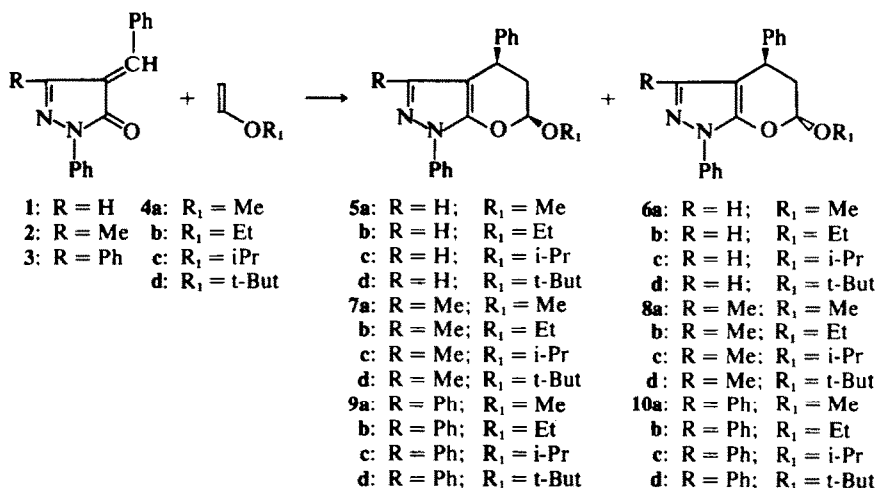
$$J_{23} = x(J_{2a3a} - J_{2e3e}) + J_{2e3e} \quad (\text{eqn 2—only for cis series})$$

$$J_{23'} = x(J_{2e3'e} - J_{2a3'a}) + J_{2a3'a} \quad (\text{eqn 3—only for trans series})$$

where x is the mole fraction of conformer with the phenyl group at C_4 in the *pseudo*-equatorial position. Therefore, J_{trans} values can be reported in a graph in accordance with the previously adopted technique.²



SCHEME 1



SCHEME 2

One of the limiting factor of the method, in spite of its usefulness,⁸ depends upon the use of a heterogeneous set of derivatives where effects arising from different electronegativities of the groups are quite significant. Therefore, we have synthesized a homogeneous series of derivatives where identical substituent at C₄ and analogous substituents at C₂ ensure that the electronegativity of the C₂-C₃-C₄ fragment does not vary significantly.

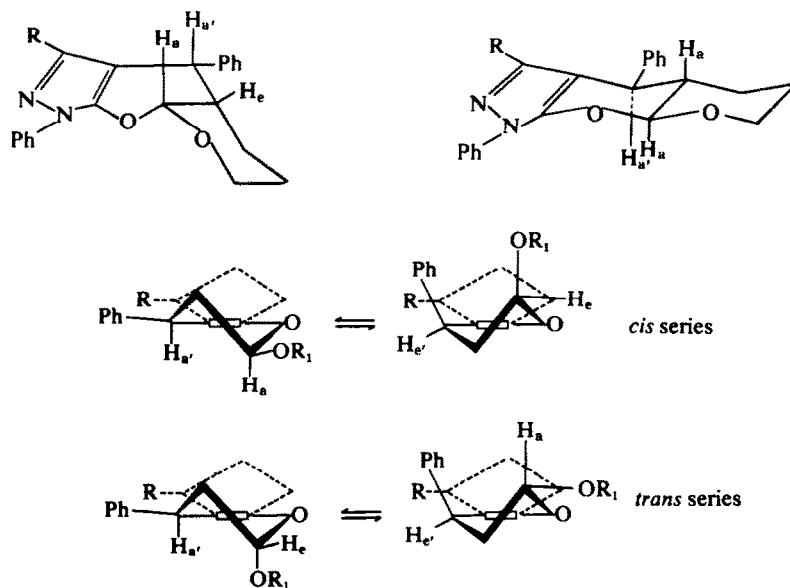
The second limit is the choice of the axes caused by the uncertainty of the spectral parameters of the rigid structures. To avoid this we have used the value we found during the equilibration of tetra-

hydropyran[2',3':2,3]-dihydropyran[6,5-c] pyrazoles¹ for the interaction between the *pseudo*-equatorial phenyl group at C₄ and the phenyl group or the hydrogen atom at C₅. As this regards rigid molecules with both C₂ and C₄ substituents in the equatorial position (Scheme 3), we have adopted

$$\Delta G_{C_{4eqPh}/C_{5H}}^{\circ} - \Delta G_{C_{4eqPh}/C_{5Ph}}^{\circ} = 0.65 \text{ Kcal}$$

in the *cis* series where the anomeric effect does not offer further stabilization to the C₄ *pseudo*-equatorial phenyl conformation.

The graph is shown in Fig 1 and the correlation



SCHEME 3

Table 1

Compd	Chemical shifts				Coupling constants				Aromatic protons (M)	—OR'	
	H ₂	H ₃	H _{3'}	H ₄	J ₂₃	J _{23'}	J ₃₄	J _{34'}		R	—OMe
5a	5:24	2:06	2:30	4:05	8:16	1:88	9:23	6:34	13:92	a	3:52(S)
7a	5:26	2:11	2:36	4:03	7:46	1:90	8:49	6:69	13:89	b	3:54(S)
9a	5:31	2:21	2:39	4:33	5:37	2:47	6:41	6:41	13:60	a	3:58(S)
6a	5:35	1:92	2:26	4:15	2:51	2:51	11:23	5:51	13:78	a	3:54(S)
8a	5:29	1:97	2:28	4:07	2:62	2:88	10:47	5:80	13:65	b	3:44(S)
10a	5:26	2:03	2:33	4:39	2:03	5:43	7:08	5:90	13:34	b	3:53(S)
5b	5:41	2:10	2:35	4:10	8:15	1:98	9:30	6:31	13:64	a	Me
7b	5:35	2:11	2:35	4:03	7:59	1:82	8:56	6:52	13:98	a	δH _A
9b ^c	5:35	2:12	2:36	4:30	5:2	2:7	6:5	6:5	14:0	b	δH _B
6b	5:50	1:92	2:25	4:17	2:61	2:65	11:17	5:62	13:99	a	—OCH ₃
8b	5:39	1:96	2:27	4:09	2:31	3:25	10:43	5:79	13:86	b	δMe
10b ^c	5:32	2:05	2:35	4:39	2:2	5:9	6:95	5:6	13:5	b	J _{AMe} ≡ J _{BMe}
5c	5:50	2:09	2:30	4:10	8:53	1:50	9:47	6:60	13:91	a	δOCH
7c	5:47	2:15	2:36	4:07	7:32	1:90	8:80	6:56	13:73	a	δMe ₁
9c	5:54	2:20	2:39	4:38	5:77	2:28	6:65	6:67	13:72	b	δMe ₂
6c	5:65	1:85	2:14	4:17	2:08	2:76	10:99	5:51	13:44	a	J _{HMe}
8c	5:51	1:96	2:24	4:12	2:30	3:14	10:20	5:61	13:63	b	—Ot,But
10c	5:41	1:99	2:30	4:40	1:97	5:86	6:55	5:96	13:70	b	1:27(S)
5d	5:64	2:08	2:18	4:10	8:77	1:70	9:75	6:27	13:85	a	1:27(S)
7d	5:61	2:12	2:25	4:06	7:83	2:17	9:02	6:54	13:58	b	1:27(S)
9d	5:38	2:08	2:22	4:29	6:02	2:05	6:96	6:56	13:83	a	1:12(S)
4d	5:74	1:90	2:11	4:19	2:30	2:89	10:61	5:20	13:17	a	1:24(S)
8d	5:68	1:92	2:14	4:10	2:15	3:79	9:59	5:59	13:35	b	1:22(S)
10d	5:59	1:99	2:31	4:40	1:86	6:21	5:97	6:00	13:44	b	1:24(S)

^aOverlapped by aromatic protons.

^bAromatic protons.

^cValues taken from ref. 18.

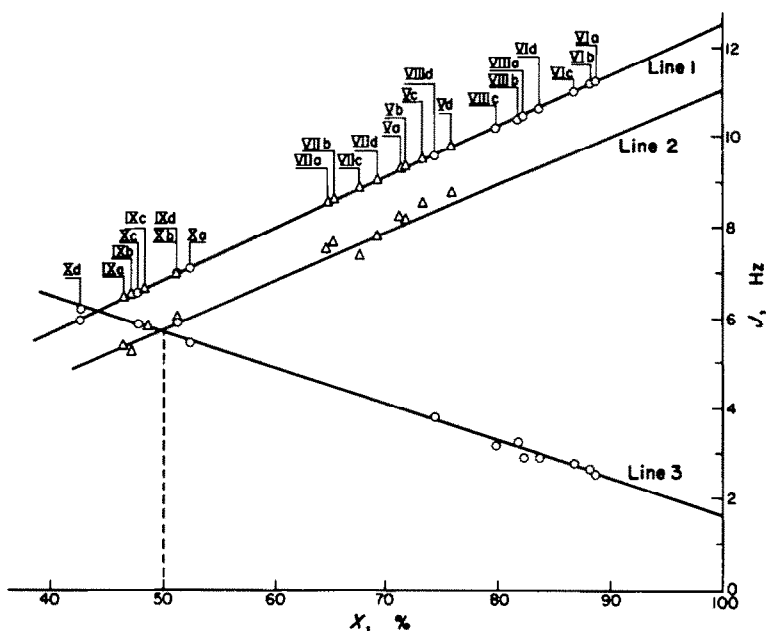


Fig 1.

of J_{23} and $J_{23'}$ points was carried out according to the approach of Jaffé⁹ and the results are reported in Table 2.

Even if the theoretical J_{23} and $J_{23'}$ values are not identical, at $x = 0.5$ line 2 and 3 have values significantly close, enough to support the assumption² that intercept of these lines must occur for $x = 0.5$.

From individual equilibrium constants, the conformational free energy ΔG° was determined and the values for each adduct are reported in Table 3.

Coupling constants were determined to ± 0.05 Hz,¹⁰ error in x occurs in the range $\pm 0.5\%$, therefore the error involved in ΔG° values varies from ± 0.1 to 0.035 Kcal in the range of the above reported equilibria.

Steric interactions

From conformational free energy values it seems clear that the phenyl group at C_5 destabilizes

the *pseudo-equatorial* position of the C_4 phenyl group and a decreased steric requirement of the group at C_5 shifts the equilibrium in its favour.

The energies change from the *cis* to the *trans* series and are larger for the latter. This seems reasonable as the anomeric effect favours the opposite conformations and 1,3-diaxial interactions are different in the series (Scheme 3).

The values of the interactions $C_4\text{Ph}/C_3\text{Ph}$ and $C_4\text{Ph}/C_3\text{Me}$, the $C_4\text{Ph}/C_3\text{H}$ interaction = 0, are reported in Tables 4 and 5 for the *cis* and *trans* series respectively. In the former series the $C_4\text{Ph}/C_3\text{Me}$ interaction does not vary significantly from the value previously found.¹

Anomeric effect

In addition to the above reported steric interactions, it is interesting to examine the variation of the conformational free energy when the alkoxy group is successively MeO- , EtO- , $i\text{-PrO-}$ and $t\text{-BuO-}$.

Table 2

line ^a	<i>n</i>	ρ	<i>i</i>		<i>c</i>
1	24	0.113	$J_{3a4a} = 12.50$	$J_{3e4e} = 1.15$	—
2	12	0.112	$J_{2a3a} = 11.01$	$J_{2e3e} = 0.16$	0.9913
3	12	-0.082	$J_{2a3'a} = 9.82$	$J_{2e3'e} = 1.63$	0.9955

^aSee Fig 1.

n = number of points.

ρ = slope as determined by method of least squares.

i = intercepts, all values in Hz.

c = correlation coefficient.

Table 3

Compd	J ₃₄	% Ph pseudo-equat	% Ph pseudo-axial	K ^a	ΔG ^{°b} (kcal/mol)
5a	9.23	71.5	28.5	2.5088	0.56
b	9.30	72	28	2.5714	0.58
c	9.47	73.5	26.5	2.7735	0.62
d	9.75	76	24	3.1667	0.71
7a	8.49	65	35	1.8571	0.38
b	8.56	65.5	34.5	1.8985	0.39
c	8.80	67.5	32.5	2.0769	0.44
d	9.02	69.5	30.5	2.2786	0.51
9a	6.41	46.5	53.5	0.8691	-0.09
b	6.50	47	53	0.8868	-0.08
c	6.65	48.5	51.5	0.9417	-0.04
d	6.96	51.5	48.5	1.0618	0.04
6a	11.23	89	11	8.0909	1.28
b	11.17	88.5	11.5	7.6956	1.26
c	10.99	87	13	6.6923	1.16
d	10.61	83.5	16.5	5.0606	0.99
8a	10.47	82.5	17.5	4.7142	0.95
b	10.43	82	18	4.5555	0.93
c	10.20	80	20	4.0000	0.84
d	9.59	74.5	25.5	2.9215	0.66
10a	7.08	52.5	47.5	1.1052	0.06
b	6.95	51.5	48.5	1.0618	0.04
c	6.55	48	52	0.9230	-0.05
d	5.97	42.5	57.5	0.7391	-0.19

^aK = [pseudo-equatorial]/[pseudo-axial].

^bCalculated at 35° on values of K: a positive value indicates the equilibrium favors the pseudo-equatorial conformation.

Table 4
cis Series

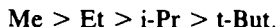
Compd and interactions	a	b	c	d	Medium values (kcal/mol)
5	0.56	0.58	0.62	0.71	
7	0.38	0.39	0.44	0.51	
9	-0.09	-0.07	-0.04	0.04	
C ₄ Ph/C ₅ Me (5-7)	0.18	0.19	0.18	0.20	0.19
C ₄ Ph/C ₅ Ph (5-9)	0.65	0.65	0.66	0.67	0.66

Table 5
trans Series

Compd and interactions	a	b	c	d	Medium values (kcal/mol)
6	1.28	1.26	1.16	0.99	
8	0.95	0.93	0.84	0.66	
10	0.06	0.04	-0.05	-0.19	
C ₄ Ph/C ₅ Me (6-8)	0.33	0.33	0.32	0.33	0.33
C ₄ Ph/C ₅ Ph (6-10)	1.22	1.22	1.21	1.18	1.21

ButO- as this represents the change of the anomeric effect depending on the nature of the alkoxy group.

It is well known that the magnitude of the anomeric effect decreases in the order



This has been rationalized either due to increased dipolar interaction when the substituent increases its polarity¹¹ or in terms of steric effects which destabilize the axial conformation.¹² Therefore, if the anomeric effect consists in the destabilization of polar bonds *gauche* to lone pairs¹³ (Fig 2)



Fig 2.

we can consider the above reported variation (Me/t-But) as due either to variation of the polarity of the C-X bond whose increase (Me) will destabilize the (a) rotamer, or due to variation of the steric interactions whose increase (t-But) will destabilize the (b) rotamer. A linear correlation of the conformational free energy with Taft parameters σ^* will be consistent with the first assumption, whereas a correlation with E_s steric parameters will be required if the second model is correct.

In previous papers on the subject, Pierson and Rundquist¹¹ gave a correlation of ΔG° of 2-alkoxytetrahydropyrans (NMR hydrogen shift) with σ^* but values found from Havinga *et al.*¹⁴ by dipole moments of the same compounds do not correlate and Eliel¹² found values from equilibration of 2-alkoxy-6-methyltetrahydropyrans, which for MeO, EtO, i-PrO and t-ButO nicely correlate with steric parameters E_s .

Our results are shown in Fig 3 and if we consider that the series are homogeneous and the variation in equilibria small, uncertainty of the method should be negligible.

We found good linear correlations in all six series (5-10) between ΔG° values and E_s parameters with opposite slope of the lines in the *cis* and in the *trans* series, as expected. The statistical treatment is reported in Table 6.

The small difference in the slopes could be interpreted in terms of variation in the magnitude of the effect when increased interactions (R = H, Me, Ph) are involved, but the variation could fall within the limits of error.

From the above reported considerations the model for the change in the anomeric effect in the alkyl series can be the diminished population of

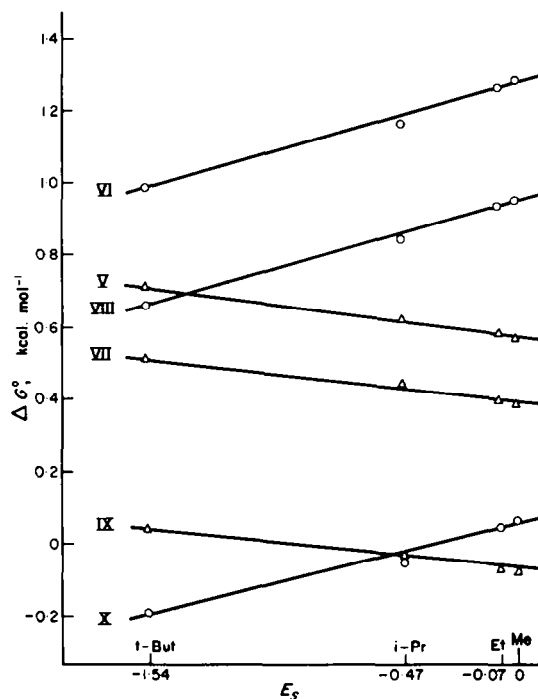


Fig 3. The relationship between steric parameters E_s and conformational free-energy difference of 2-alkoxy-4-phenyl-2,3-dihydropyran [2,3-c] pyrazoles.

Table 6

Compd	n	ρ	i	c
6	4	0.185	1.269	0.9937
8	4	0.186	0.941	0.9972
10	4	0.159	0.048	0.9904
5	4	-0.093	0.569	0.9940
7	4	-0.083	0.387	0.9869
9	4	-0.083	-0.086	0.9968

the sterically hindered axial rotamer; the increased 1,3-diaxial interactions can diminish the degree of freedom of the alkoxy group and therefore influence the entropy term.

These results show that the graphical method can be a useful tool, if used with care, to gain quantitative informations on the conformational equilibria of a homogeneous series of derivatives.

EXPERIMENTAL

All m.p.s are uncorrected. Microanalyses were performed by Dr. L. Dacrema Maggi. The statistical treatment of data was performed on Olivetti 101.

Materials. Methyl vinyl ether (Fluka), ethyl vinyl ether (Erba), i-propyl vinyl ether (BASF) and t-butyl vinyl ether (K & K Lab.) were used without further purification. 1-Phenyl-4-benzal-5-pyrazolone,¹⁵ 1-phenyl-3-methyl-4-benzal-5-pyrazolone¹⁶ and 1,3-diphenyl-4-

benzal-5-pyrazolone¹⁷ were prepared in accordance with the literature.

cis [2,4] (**5a**) and *trans* [2,4] (**6a**) 2-Methoxy-4,7-diphenyl-2,3-dihydropyran [2,3-*c*] pyrazoles. A mixture of 1-phenyl-4-benzal-5-pyrazolone (0.32 g) and methyl vinyl ether (3.0 ml) was heated into a Parr bomb at 80° for about 50 hr. The light amber soln was allowed to evaporate and a homogeneous portion (about 50 mg) of the oily residue was monitored by NMR. Inspection of

dryness, were chromatographed over silicagel Merck (eluant: cyclohexane (Cy)/AcOEt 9:1). **6a** (0.08 g) was eluted first (followed by a second crop of **5a**—0.05 g; tot. 0.28 g) and crystallization from a mixture of dIPE and light petroleum gave small white prisms, m.p. 125–6° (Found: C, 74.54; H, 6.07; N, 9.22. Calc for C₁₉H₁₈N₂O₂: C, 74.79; H, 5.92; N, 9.15%).

The following adducts were obtained by analogous method:

Table 7

Compd	React. time at 80° (*)	Type of separation	Yield	m.p. (solvent)	Physical state	Elemental analysis
5b	30 hr	Fract. Cryst. dIPE	73%	87–8° (dIPE)	large colourless needles	found: C, 74.82; H, 6.31; N, 8.90 calc: C, 74.97; H, 6.29; N, 8.74%
6b	30 hr	id. id. + Col. Chrom. Cy/AcOEt 9:1	27%	104–5° (Pet. Eth)	small white needles	found: C, 74.46; H, 6.39; N, 8.91 calc: C, 74.97; H, 6.29; N, 8.74%
5c	60 hr	Col. Chrom. Cy/AcOEt 9:1	60%	88–9° (Cyhex.)	small colourless needles	found: C, 75.57; H, 6.79; N, 8.53 calc: C, 75.42; H, 6.63; N, 8.38%
6c	60 hr	Col. Chrom. Cy/AcOEt 9:1	40%	115° (Cyhex.)	small white prisms	found: C, 75.69; H, 6.75; N, 8.16 calc: C, 75.42; H, 6.63; N, 8.38%
5d	7 days	Col. Chrom. Cy/AcOEt 9:1	42%	119–20° (dIPE)	colourless platelets	found: C, 75.75; H, 7.01; N, 8.14 calc: C, 75.83; H, 6.94; N, 8.04%
6d	7 days	Fract. Cryst. (Pet. Eth.)	58%	122–3° (Cyhex.)	colourless needles	found: C, 75.94; H, 7.03; N, 7.98 calc: C, 75.83; H, 6.94; N, 8.04%
7a	40 hr	Fract. Cryst. dIPE	69%	103–4° (dIPE)	large colourless crystals	found: C, 75.12; H, 6.30; N, 8.97 calc: C, 74.97; H, 6.29; N, 8.74%
8a	40 hr	Fract. Cryst. dIPE	31%	110–1° (Pet. Eth)	long colourless prisms	found: C, 75.23; H, 6.22; N, 8.60 calc: C, 74.97; H, 6.29; N, 8.74%
7b	46 hr	Fract. Cryst. dIPE	49%	110–1° (Pet. Eth)	small colourless prisms	found: C, 75.25; H, 6.58; N, 8.31 calc: C, 75.42; H, 6.63; N, 8.38%
8b	46 hr	Fract. Cryst. (dIPE/Pet. Eth.)	51%	97–8° (dIPE/PE)	colourless prisms	found: C, 75.67; H, 6.64; N, 8.31 calc: C, 75.42; H, 6.63; N, 8.38%
7c	60 hr	Col. Chrom. Cy/AcOEt 93:7	60%	81–2° (Cyhex.)	large colourless prisms	found: C, 75.67; H, 7.00; N, 8.01 calc: C, 75.83; H, 6.94; N, 8.04%
8c	60 hr	Col. Chrom. Cy/AcOEt 93:7	40%	82–3° (Cyhex.)	small white prisms	found: C, 75.83; H, 6.94; N, 8.04% calc: C, 75.83; H, 6.94; N, 8.04%
7d	7 days	Col. Chrom. Cy/AcOEt 95:5	65%	83–4° (Pet. Eth)	light cream coloured needles	found: C, 76.02; H, 7.27; N, 7.79 calc: C, 76.21; H, 7.23; N, 7.73%
8d	7 days	Col. Chrom. Cy/AcOEt 95:5	35%	114–5° (Pet. Eth)	large colourless prisms	found: C, 76.36; H, 7.27; N, 7.88 calc: C, 76.21; H, 7.23; N, 7.73%
9a	40 hr	Fract. Cryst. dIPE	55%	161–2° (dIPE)	colourless prisms	found: C, 77.97; H, 5.91; N, 7.23 calc: C, 78.51; H, 5.80; N, 7.33%
10a	40 hr	id. id. + Col. Chrom. Cy/AcOEt 9:1	45%	b.p. 230°/0.4 mm	viscous yellow oil	found: C, 78.83; H, 6.00; N, 7.29 calc: C, 78.51; H, 5.80; N, 7.33%
9b	48 hr	Col. Chrom. Cy/AcOEt 9:1 or Fract. Cryst. ⁵	46%	163–4°	small colourless crystals	lit. ⁵ m.p. identical
10b	48 hr	id. id. as 9b	54%	97–8°	small colourless crystals	lit. ⁵ m.p. identical
9c	48 hr	Fract. Cryst. dIPE	55%	141–2° (dIPE)	small white crystals	found: C, 79.30; H, 6.43; N, 7.13 calc: C, 79.00; H, 6.38; N, 6.83%
10c	48 hr	id. id. + Col. Chrom. Cy/AcOEt 9:1	45%	119–20° (Pet. Eth)	small white prisms	found: C, 78.89; H, 6.29; N, 6.91 calc: C, 79.00; H, 6.38; N, 6.83%
9d	5 days	Fract. Cryst. dIPE	75%	140–1° (Cyhex.)	small white prisms	found: C, 79.49; H, 6.66; N, 6.65 calc: C, 79.21; H, 6.65; N, 6.60%
10d	5 days	id. id. + Col. Chrom. Cy/AcOEt 9:1	25%	112–3° (Cyhex)	small white crystals	found: C, 79.22; H, 6.77; N, 6.86 calc: C, 79.21; H, 6.65; N, 6.60%

*The different reaction times, under these experimental conditions, are mainly due to the different solubilities of the starting pyrazolone in the different vinyl ethers. The different reaction rates will be discussed in a future paper.

the OMe group region proved that the mixture consisted of *cis* and *trans* isomers (**5a** and **6b**) in the ratio 80:20. A fractional crystallization from di-isopropyl ether (dIPE) allowed isolation of the major product (**5a**—0.23 g) as colourless prisms, m.p. 115–6° (Found: C, 74.74; H, 5.96; N, 9.14. Calc for C₁₉H₁₈N₂O₂: C, 74.79; H, 5.92; N, 9.15%). The mother liquors, after evaporation to

NMR spectra. All NMR experiments were performed using a Perkin Elmer R-12 A spectrometer (**9b** and **10b**)¹⁸ on Varian A-60. All compounds were examined as 5–10% solns in CDCl₃, chemical shifts are expressed in ppm (δ scale) from TMS as internal standard.

The program LAOCOON 3 was used on UNIVAC 1108 computer.

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