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SYNTHESIS AND CONFORMATIONAL ANALYSIS OF SOME SPIROPYRAZOLINE ISOMERS

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Abstract: A series of spiropyrazolines has been synthesized by 1,3-dipolar cycloaddition of *E*- and *Z*-3-arylidene-chromanones, -1-thiochromanones, -flavanones, -1-thioflavanones as well as 2-benzylidene-1-indanone, -1-benzosuberone with diazomethane. It has been found that this cycloaddition is regio- and stereoselective affording *trans*- and *cis*-spiro-1-pyrazolines. Spiro-1-pyrazolines were converted into spiro-2-pyrazolines on acid-catalysed isomerization. Conformation and relative configuration of compounds prepared has been elucidated by various one- and two-dimensional n.m.r. methods

Previously we reported on the synthesis and stereochemistry of different spiro-1-pyrazolines obtained by the 1,3-dipolar cycloaddition of diazomethane to 2-arylidene-1-tetralones, 3-arylidene-chromanones, -1-thiochromanones and -flavanones.[1,2] It was shown that the reaction is regio- and stereoselective, *E*-arylidenes afford in one step *trans*-spiro-1-pyrazolines with respect to the position of the carbonyl and aryl groups. It was found that in case of *E*-3-benzylidene-flavanone despite of a further center of chirality at C-2' only one spiropyrazoline was obtained due to the predominance of a conformation with an axial phenyl group at C-2, and

the attack of the diazomethane proceeds from the sterically preferred side, i.e. opposite to the C-2 phenyl group.

Analogous reaction of chalcones to diazomethane yields 3-benzoyl-4-phenyl-1-pyrazolines, which immediately rearrange to the conjugated 2-pyrazolines.[3-5] In the case of 3-benzylidene-flavanone and 2-(4-chlorobenzylidene)-1-tetralone the cycloaddition of diazomethane to the *Z*-benzylidene isomers was also investigated.[1,2] These reactions resulted in the corresponding *cis*-spiro-1-pyrazolines, giving further support for the one-step mechanism of the ring closure. It was found that *cis* and also the *trans* spiro-1-pyrazolines obtained from 2-arylidene-1-tetralones rearrange into spiro-2-pyrazolines on proton catalysis.

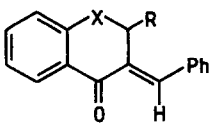
In this paper a detailed investigation of the cycloaddition of diazomethane to *Z*- and *E*-arylidene derivatives , the tautomerism and stereochemistry of the products elucidated by different n.m r. methods will be discussed.

Results and discussion

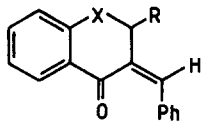
Spiro-1-pyrazolines under studies (Scheme 1) have been synthesized by the reaction of the *Z*- and *E*-isomers of exocyclic α,β-unsaturated ketones **1-4**, **13** and **14** with diazomethane in a mixture of ether and acetone as described in our previous papers.[1,2] Substances *cis*-**5**, *cis*-**6**, *cis*-**7**, *trans*-**15**, and *trans*-**16** are new compounds in this series. To investigate the spiro-1-pyrazoline -> spiro-2-pyrazoline tautomeric rearrangement the known trans-**5**, *trans*-**7** and *trans*-**8** compounds have also been utilized. Their published n.m.r. data,[1] together with those of *cis*-**8**, have been supplemented with the results of new measurements.

^1H and ^{13}C n.m.r. spectra of spiro-1-pyrazolines

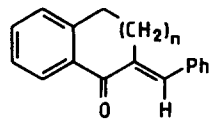
Since the spiro-1-pyrazoline -> spiro-2-pyrazoline rearrangement is an acid-catalysed process occassionally taking place during some hours, n.m.r. spectra of compounds **5-8**, **15**, and **16** were measured in acid-free deuteriochloroform. ^1H n m.r. assignments are summarized in Table 1. Over the utilization of the data of analogous compounds[1,2] assignments of the proton spectra have generally been corroborated experimentally as well. To the assignment of the aromatic protons decoupling of the signals of 5'-H and 7'-H was usually successful. However, n.O.e. difference spectroscopy used for the determination of the stereostructure proved to be beneficial to the assignments.



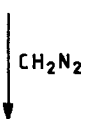
X:S, R:H *E*-**1**
X:S, R:Ph *E*-**2**
X:O, R:H *E*-**3**
X:O, R:Ph *E*-**4**

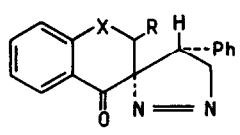


X·S, R:H *Z*-**1**
X:S, R:Ph *Z*-**2**
X:O, R:H *Z*-**3**
X:O, R Ph *Z*-**4**

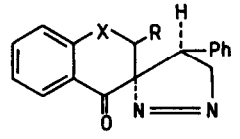


n:0 **13**
n:2 **14**

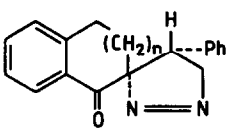




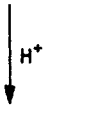
X:S, R:H *trans*-**5**
X·S, R:Ph *trans*-**6**
X:O, R:H *trans*-**7**
X·O, R:Ph *trans*-**8**

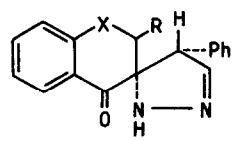


X:S, R:H *cis*-**5**
X:S, R:Ph *cis*-**6**
X:O, R:H *cis*-**7**
X O, R:Ph *cis*-**8**

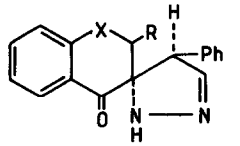


n:0 *trans*-**15**
n:2 *trans*-**16**

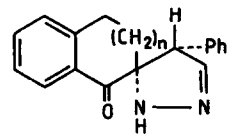




X:S, R:H *trans*-**9**
X:S, R:Ph *trans*-**10**
X O, R:H *trans*-**11**
X:O, R:Ph *trans*-**12**



X:S, R:H *cis*-**9**
X:S, R:Ph *cis*-**10**
X·O, R:H *cis*-**11**
X:O, R:Ph *cis*-**12**



n:0 *trans*-**17**
n:2 *trans*-**18**

Scheme 1.

Table 1. ^1H chemical shifts [p.p.m.] and characteristic coupling constants [Hz] of compounds **5-8** and **15-16**

	5 *cis*	**5** *trans*	**6** *cis*	**6** *trans*	**7** *cis*	**7** *trans*	**8** *cis*	**8** *trans*	**15** *trans*	**16**[d] *trans*
H-4	3.84	3.77	4.03	4.07	3.60	3.81	3.54	3.90	3.61	3.90
H_c-5	4.88	4.85	4.67	4.98	4.86	4.94	4.60	4.98	5.19	4.73
H_t-5	5.11	5.13	4.04	5.26	5.19	5.18	4.17	5.19	5.10	4.90
H_{ax}-2'	4.33	3.00	5.76		5.25	4.10	6.45		2.82[a]	1.85
H_{eq}-2'	2.66	3.73		4.39	4.29	4.50		5.57br	3.47[b]	1.65
H-5'	7.51	8.11	7.47	8 11	7.42	7.93	7.44	7 91	7.78	7.42
H-6'	6.90	7.21	6.93	7.14	6.80	7.07	6.85	6.99	7.40	c
H-7'	7.21	7.43	7.28	7.38	7.34	7.54	7.39	7.46	7.61	7.40
H-8'	7.07	7.28	7.07	7.17	6.85	7.02	6.99	6.94	7.39	7.20
H-2",6"	6.84	6.98	6.83	6.62	6.87	6.92	6.83	6.42	6.84	6.95
H-3",5"	6.90	7.25	6.90	6.98	6.97	7.25	6.96	6.93	7 25	c
H-4"	6.95	7.30	6.95	7 07	6 97	7.30	6.96	7 03	7.25	c
$H\text{-}2^+,6^+$			7.49	6.43br			7.55	6.88		
$H\text{-}3^+,5^+$			7.32	6 98			7.41	7.03		
$H\text{-}4^+$			7.37	7.07			7.37	7.15		
$^2J(5\text{-}CH_2)$	18.6	17.6	18 6	18.2	18.3	18.4	18.3	18.0	17.8	17.8
$^2J(2'\text{-}CH_2)$	13.5	13.7			11.6	12.6			17.6	14.9
$^3J(H\text{-}4,H\text{-}5_t)$	5.6	2.2	9.5	1.2	9.1	2 9	9.3	1 3	2.9	3.9
$^3J(H\text{-}4,H\text{-}5_c)$	9.3	8.3	4 6	7.8	7.8	8.4	6 8	7.8	8.6	8 3

br broad; [a] β; [b] α; c 7 25 -7.35;
[d] 1'-H_{ax} 3.41, 1'-H_{eq} 2.95, 1a'-H_{ax} 1.55, 1a'-H_{eq} 2.04;

The symbols H_{ax} and H_{eq} refer to the position of the protons in the predominating conformer.

In the course of such experiments difference spectra obtained on the irradiation of signals 2",6"-H, appearing at higher field as separated signals (Table 2), are decisive since beside protons of diagnostic value for the stereostructure, signals of 3",5"-H are determined as well. Another problem is the assignment of the 2'-H_2 methylene protons in compounds without a 2'-phenyl group. It is easy in the case of the tetralone derivatives since the 2'-H_2 protons are coupled with the 1'-H_2 ones while these protons are coupled only with each other in other substances investigated. The $\delta H_{ax} < \delta H_{eq}$ general rule is valid for our *trans* compounds

Table 2. Results of homonuclear n.O.e. experiments on selected compounds

Compound	Signal irradiated	n.O.e. enhancements (%)
cis **5**	4-H	5-H_{trans} (4.0); 2'-H_{eq} (3.3); 2",6"-H (5.7)
	2'-H_{eq}	4-H (4.3); 2'-H_{ax} (26.7)
	2'-H_{ax}	2'-H_{eq} (27)
	2",6"-H	4-H (6.8); 5-H_{cis} (5.5); 3",5"-H (> 8.2)
cis **6**	5-H_{cis}	5-H_{trans} (24.1); 2",6"-H (6.7)
	2'-H_{ax}	2^+,6^+-H (6.6)
trans **6**	4-H	5-H_{cis} (5.6); 2",6"-H (3.1); 2^+,6^+-H (8.8)
	2'-H_{eq}	2",6"-H (9.1); 2^+,6^+-H (3.8)
cis **7**	4-H	5-H_{trans} (3.5); 2'-H_{eq} (2.6); 2",6"-H (4.7)
	5-H_{cis}	5-H_{trans} (>6.9); 2",6"-H (4.7)
	2'-H_{eq}	4-H (3.3), 2'-H_{ax} (18.8)
trans **7**	2'-H_{ax}	2'-H_{eq} (24.5); 2",6"-H (1.5)
	2'-H_{eq}	2'-H_{ax} (23.6); 2",6"-H (1.9)
	2",6"-H	4-H (6.2); 5-H_{trans} (4.4); 2'-H_{eq} (2.0); 2'-H_{ax} (1.6); 3",5"-H (8.0)
cis **8**	4-H	5-H_{cis} (5.1); 2",6"-H (6.2); 2^+,6^+-H (4.6)
	5-H_{cis}	5-H_{trans} (11.8)
	5-H_{trans}	4-H (4.9), 5-H_{cis} (14.9)
	2'-H_{ax}	2^+,6^+-H (9.0)
	2^+,6^+-H	4-H (3.6); 2'-H_{ax} (5.6); 3^+,5^+-H (>5.5)
trans **8**	2'-H_{eq}	2",6"-H (2.8); 2^+,6^+-H (5.5)
	2",6"-H	4-H (5.0); 5-H_{trans} (1.8), 2'-H_{eq} (2.4); 3",5"-H (>4)
	2^+,6^+-H	4-H (1.5); 2'-H_{eq} (5.2); 2",6"-H (3.0)
cis **9**	4-H	5-H (3.0); 2'-H_{eq} (4.3); 2",6"-H (7.0)
	2'-H_{ax}	2'-H_{eq} (23.6)
	2'-H_{eq}	4-H (4.8), 2'-H_{ax} (26)
	2",6"-H	4-H (8)
trans **15**	2",6"-H	4-H (5.9); 5-H_{trans} (2.5), 2'-Hα (1.3); 1'-Hβ (1 3); 3",5"-H (11.5)
trans **16**	2",6"-H	4-H (3 8); 5-H_{trans} (2.6); 2'-H_{ax} (1.3); 2'-H_{eq} (1.8), 3",5"-H (5.4)
trans **18**	4-H	5-H (1.9); 2",6"-H (6.5)
	1'-H_2	1a'-H_2 + 2'-H_2 (6.1); 8'-H (4.2)
	2",6"-H	4-H (6 4); 1a'-H_2 + 2'-H_2 (2.6); 3",5"-H (7.9)

Table 3. ^{13}C Chemical shifts [p.p.m.] of spiro-1-pyrazolines **5-8, 15** and **16**

	5 *cis*	**5** *trans*	**6** *cis*	**6** *trans*	**7** *cis*	**7** *trans*	**8** *cis*	**8** *trans*	**15** *trans*	**16** *trans*
C-3	97.1	97.9	102.5	103 2	96.9	97 8	101.2	102.5	105.1	105.2
C-4	44.0	44.3	39 7	48 4	46.7	42.2	40.8	42.0	44.2	44.8
C-5	84 6	85.1	85.8	89.7	83.4	85 4	84 0	88.3	86.7	83.5
C-2'	34.1	30.9	50 3	43 3	72 0	69.4	80.9	81 9	33.7	30.7[b]
C-4'	189.4	187 6	190.8	187.2	186.9	185.8	188.1	185.6	199.8	202.5
C-4a'	129.9	129.1	129 1	129.3	120.4	119.3	120.0	119.9	134.7	138.4
C-5'	129.3	130.5	129.6	129.5	127.2	127.7	127 1	127 0	124.9	126.4
C-6'	124.8	125.1	125.1	124 7	121.7	121 7	122.0	121.3	128 0	127 2
C-7'	133.1	133 9	133.3	134.4	136.2	136.8	136.1	137.2	135.9	132.0
C-8'	126 2	127.6[a]	126 0	127.2	117 2	118.0	117.3	118 6	126.6	129.3
C-8a'	139.7	142.1	139.7	140 9	160.6	161.5	160.4	159.7	153.4	141.2
C-1"	136.5	138.0	137.3	138.4	134.9	136 7	135.5	137.6	140.4	138 7
C-2",6"	128.2	128.6	128.6	126.6	128 1	127 8	128.4	127.9	127.5	128.2
C-3",5"	127.8	128 4	127 8	128.3	128 1	128.8	128.0	128.0	129.0	128.6
C-4"	127.0	127.2[a]	127 0	127 6	127.4	147.8	127.3	128.6	127 4	128 4
$C\text{-}1^+$			132.9	139.4			133.7	135 0		
$C\text{-}2^+,6^+$			128.6	126 6			127 0	127.9		
$C\text{-}3^+,5^+$			129.3	128.2			128.3	126.9		
$C\text{-}4^+$			129 1	127 0			128 8	128 4		

[a] Tentative assignment, [b] C-1' 33 1, C-1a' 23 6

but it became opposite in the case of the *cis*-derivatives and the 2'-H_{eq} signal appeared at higher field. Formerly we found[2,6] that protons at position 2' show different couplings with carbon C-8a' depending on their axial or equatorial orientation and this observation can be utilized for the structure elucidation This coupling constant can be measured by semiselective 2D-INEPT experiment[7] (Table 5) results of which will be discussed later. ^{13}C chemical shifts data are summarized in Table 3. In critical cases, e.g. *cis*-**8** the assignment has been corroborated by carbon-proton two-dimensional correlation and by COLOC[8] spectra (e.g. C-4" and $C\text{-}4^+$ signals) and one-dimensional semiselective INEPT[9] experiments have been utilized for the assignments (Table 4) This latter helped to

Table 4. ^{1}H-^{13}C Long-range correlations for compounds **5-8**, **15**, **16** and **18** observed by semiselective 1D and/or 2D INEPT as well as the COLOC experiment

cis **5**	4-H	C-3, C-5, C-2', C-1", C-2",6"
	2'-H_{eq}	C-3, C-4, C-4', C-8a'
	7'-H	C-5', C-8a'
	8'-H	C-4a', C-6'
cis **6**	2'-H_{ax}	C-1^{+}, C-2^{+},6^{+}
trans **6**	4-H	C-3, C-2', C-4', C-1"
	2'-H_{ax}	C-3, C-4, C-4', C-8a', C-1^{+}, C-2^{+},6^{+}
	5'-H	C-4', C-7',C-8a'
	7'-H	C-5', C-8a'
	2",6"-H	C-4', C-4",
cis **7**[a]	4-H	C-3, C-5, C-2', C-4', C-1", C-2",6"
	2'-H_{eq}	C-3, C-4, C-4', C-8a'
	2'-H_{ax}	C-3, C-4, C-4', C-8a, C-1"
trans **7**[a]	4-H	C-3, C-4', C-1", C-2",6"
	2'-H_{eq}	C-3, C-4, C-4', C-8a'
	2'-H_{ax}	C-3, C-4, C-4', C-8a'
cis **8**	2'-H_{ax}	C-3, C-1^{+}, C-2^{+},6^{+}
	4-H	C-3, C-5, C-2', C-4'
	5'-H[b]	C-7', C-8a'
	6'-H[b]	C-4a', C-8'
	2^{+},6^{+}-H[b]	C-2', C-4^{+}
	3^{+},5^{+}-H[b]	C-1^{+}
trans **8**	4-H	C-3, C-4', C-1", C-2",6"
	7'-H	C-5', C-8a'
	2",6"-H	C-4, C-3",5"
	2^{+},6^{+}-H	C-2'
	2'-H_{eq}[a]	C-3, C-4', C-8a', C-1^{+}, C-2^{+},6^{+}
trans **15**	4-H	C-3, C-4', C-1", C-2",6"
	2'-Hα	C-3, C-4', C-4a', C-8', C-8a'
	7'-H	C-5', C-8a'
trans **16**	4-H	C-4', C-1", C-2",6"
	1'-H_{eq}	C-2', C-4a', C-8', C-8a'
trans **18**	4-H	C-3, C-5, C-4', C-2",6"
	1'-H_2	C-1a', C-2', C-4a', C-8', C-8a'
	8'-H	C-1', C-4a', C-6'

[a] by semiselective 2D INEPT (F2 projection); [b] by COLOC

differentiate the C-1" and C-1$^+$ singlet signals on the basis of polarization transfer originating from 4-H and 2'-H protons.

Table 5. Long-range J(C,H) coupling constants [Hz] for compounds **5-9** and **11**

	5 *cis*	**6** *trans*	**7** *cis*	**7** *trans*	**8** *cis*	**8**[a] *trans*	**9** *cis*	**11** *cis*
^2J(H-2'$_{ax}$,C-3)	2.8		1.9	<1	2.2		2.0	
^3J(H-2'$_{ax}$,C-4)	7.4		7.0	<1			7.4	
^3J(H-2'$_{ax}$,C-4')	1.8		2.0	2.1			1.6	
^3J(H-2'$_{ax}$,C-8a')	<1		<1	1 7			<1	
^2J(H-2'$_{eq}$,C-3)	5.2	6.6	3.6	2.0		5.0	5.8	4.3
^3J(H-2'$_{eq}$,C-4)	2.6	<1	3.4	<1		<1		
^3J(H-2'$_{eq}$,C-4')	7.6	7.3	6.6	2.8		6.2	6.8	6.2
^3J(H-2'$_{eq}$,C-8a')	8.2	6.6	8 3	2.9		6.3	8.5	8.4
^3J(H-2',C-2$^+$,6$^+$)		5.2[b]			3.4[c]		4.5[b]	
^2J(H-2',C-1$^+$)					4.0[c]	4.4[b]		
^2J(H-4,C-3)			4.0	1		<1	2.6	3.1
^2J(H-4,C-1")			5.3	2.5		4.5	6.9	6.9
^3J(H-4,C-4')			4.0	2.4		3 6	3.0	3.9
^3J(H-4,C-2",6")			5 3	2.8		5.7	5.3	5.6
^3J(H-4,C-5)			3.3				5.7	6.2
^3J(H-4,C-2')			5.9				8 8	

[a] at 50°C; [b] refers to coupling with 2'-H_{ax}; [c] refers to coupling with 2'-H_{eq}

Configuration and conformation

The 1,3-dipolar cycloaddition provided stereohomogeneous product in each case. In compounds **5**, **7**, **15** and **16** there are two, while in substances **6** and **8** three centres of chirality and, therefore, in these latter cases formation of four diastereomers can be taken into consideration. Although our studies have been performed with racemates, for sake of a better understanding one enantiomer is depicted in each case. N-2 is α positioned in each formula, *viz.* the C-3 configuration is constant which is S in the case of sulfur-containing and R in other compounds. The dipolar cycloaddition, *viz.* the concerted nature of the ring closure, is proved

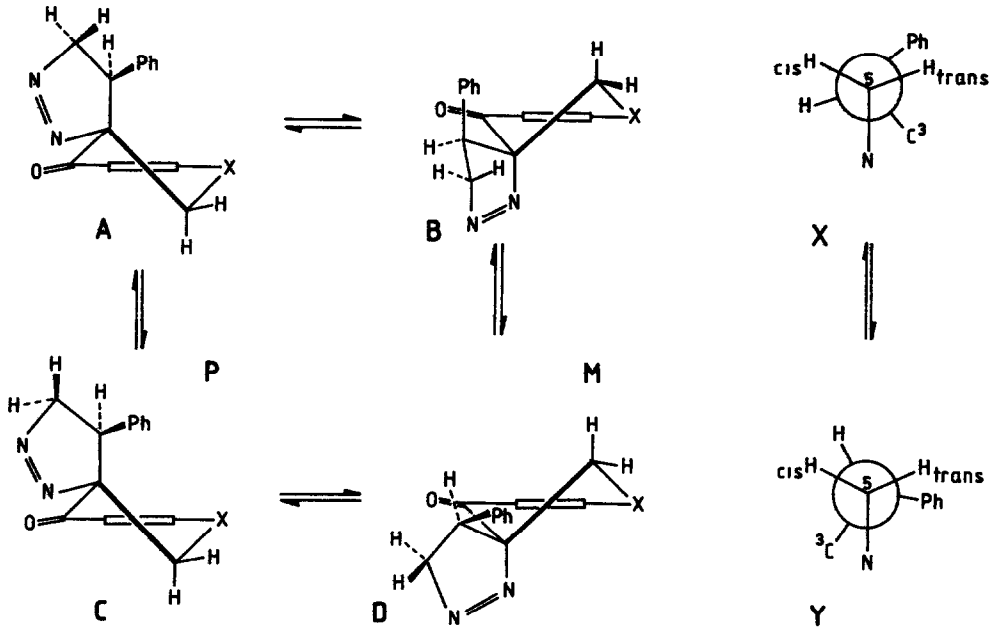


Figure 1. Conformational equilibrium of *trans* spiro-1-pyrazolines

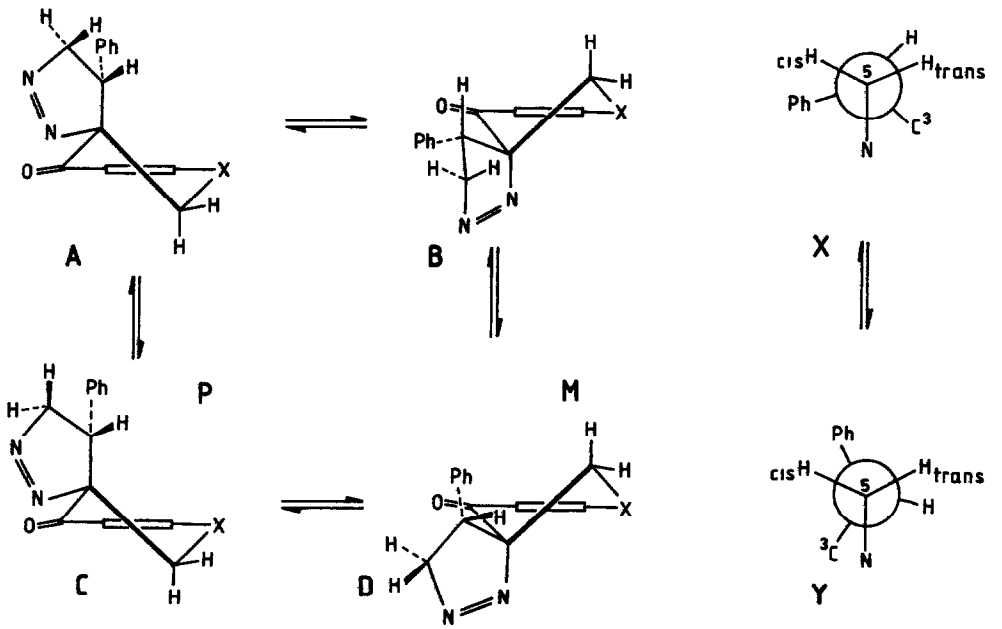


Figure 2. Conformational equilibrium of *cis* spiro-1-pyrazolines

by the structure of the products since the 4-phenyl moiety in spiro-1-pyrazolines obtained from starting materials of *E*-configuration is *trans* and *cis* if prepared from *Z*-arylidenes relating to the carbonyl group.[6] This *cis/trans* convention is used for the differentiation of the 5-H_2 methylene protons as well.

For the determination of the stereostructure it should be taken into consideration that both the carbonyl-bearing and the five-membered rings are flexible and the simultaneous conformational motion of the two rings should be controlled

Inspection of molecular models reveals that the pyrazoline ring may adopt two envelope conformations (*X* and *Y*) where C-4 is out of the plane formed by the other four atoms (Figure 1 and 2) This conformational equilibrium can be investigated with the help of the coupling between the 4-H and 5-H_2 protons. However, owing to the different chirality of the C-4, the identical type of conformations is characterized by different vicinal coupling constants in the *cis* and *trans* substances. Coupling constants measured and calculated from the spectra show that in the *cis* compounds 4-H is coupled with a *gauche* and an *anti* while in the *trans* derivatives with two *gauche* protons indicating the predominance of the *Y* type conformers in each case.

Owing to the lack of vicinal protons, determination of the dominant conformer of six-membered heterocycles containing oxygen and sulfur heteroatom and carbonyl moiety is more difficult than in the case of the tetralone derivatives.[2] The six-membered rings adopt halfchair, approaching sofa, conformers of opposite helicity (P and M) where N-2 is equatorial (*A*, *C*) or axial (*B*, *D*). In our previous paper[1] the dominance of conformer *D* of the *trans*-compounds was deduced from homonuclear n.O.e. data. In the case of the newly synthesized *cis*-derivatives beside the n.O.e. data (Table 2) $J(^{13}C,^{1}H)$ long-range couplings have been utilized (Table 5) as well. It has already been mentioned that the 2'-H_{ax} and 2'-H_{eq} signals have unequivocally been determined by means of their coupling with the C-8a' atoms.[10] Couplings of the 2'-H atoms served as further important proof for the conformational analysis. In compounds *cis*-**5** and *cis*-**7** it is unambiguously proved that 2'-H_{ax} and C-4 are antiperiplanar since their coupling constants are 7.4 and 7.0 Hz while the couplings of the 2'-H_{eq} are smaller, *viz.* 2.6 and 3.4 Hz. This indicates that N-2 is equatorial in the dominant conformer since an axial arrangement would result in an opposite trend All these observations, taking the conformation of the pyrazoline ring into consideration as well, prove the dominance of conformer *C* in the *cis*-compounds.

In the case of compounds with 2'-phenyl group (**6** and **8**) formation of further isomers should be taken into consideration. Our observations proved that from both the *Z*- and *E*-isomers of the 3-benzylideneflavanone and -1-thioflavanone only one product was formed which can be a consequence of the dominant conformer of the starting materials.[10] In our previous paper relative configuration of the *trans*-**8** spiro-1-pyrazoline proved to be analogous to those of the appropriate chromanone derivative *trans*-**7** (type *D*) where the 2'-phenyl group is axial.[1] The above-discussed stereochemical findings have been confirmed by n.O.e. data obtained by the irradiation of novel signals (Table 2). Spatial proximity of the 2',6'-H *ortho*-protons of the 2'-phenyl group and 4-H, which is possible only in conformer *D*, was corroborated by n.O e. measurement. An independent proof of this effect was the selective two-dimensional INEPT experiment on the 2'-H proton as well. In this compound the coupling constant between the 2'-H proton and the C-8a' carbon is 6.8 Hz indicating that this proton is equatorial, therefore, the 2'-phenyl group should adopt an axial arrangement. Similar coupling constant value was measured in compound *trans*-**6** referring to the structural similarity of the two compounds.

At the same time, however, in the *cis*-**8** the ^{3}J(2'-H,C-8a') coupling constant value is less than 1 Hz, and on the C-8a' signal no polarization transfer was detected either in one- or two-dimensional semiselective INEPT experiments On all these bases the 2-phenyl group should be equatorial in the *cis*-compounds which was corroborated by n.O.e. measurements as well. N.O.e. data were utilized to determine whether N-2 atom is equatorial or axial on the six-membered ring. In the former case 2'-H and 4-H and 2'-H and 2",6"-H, respectively, protons are far from each other while in spatial proximity in the latter one. N.O e indicating such a spatial proximity was not detected, *viz*. N-2 is equatorial similarly to those observed for compounds *cis*-**5** and *cis*-**7** (P helicity) As a result of the similar conformation of the six-membered ring in compounds *cis*-**5** and *cis*-**8** δ5'-H is between 7.42 and 7.51 ppm as a consequence of the fact that 5'-H is above the plane of the 4-phenyl group. No spatial proximity is possible between the 5'-H and the 4-phenyl group in the *trans*-**5** and *trans*-**8** and, therefore, chemical shift of the 5'-H is considerably higher (7.91 - 8.11 ppm). In compounds *cis*-**5** - *cis*-**8** an upfield effect originating also from the 4-phenyl group is detected on the 6'-H, 7'-H, and 8'-H signals but, owing to longer intramolecular distances, the extent of which is smaller.

In the case of *cis*-**5** and *cis*-**7** the $\delta 2'\text{-}H_{ax} > \delta 2'\text{-}H_{eq}$ anomalous sequence can be explained taking into account that the relative arrangement of

these methylene protons is opposite to the anisotropic N=N double bond if compared with the appropriate *trans*-compounds.

Relative configuration determined for *cis*-**6** and *cis*-**8** is in accordance with the one-step mechanism of the ring closure reaction since the attack of diazomethane takes place at the sterically preferred side opposite to the 2-phenyl group. Because of the unfavourable steric interaction of the 2'-phenyl and 4-phenyl groups in the primary product the above-discussed conformation *C* is formed by the inversion of the six-membered ring.

In the *cis*-**7** J(4-H,C-2",6") = 5.3 Hz coupling constant value provides further information concerning the conformation of the phenyl group at C-4 atom. The measured values are in agreement with the data of *trans*- and *cis*-(±)-3,4,4',5'-tetrahydro-4'-(4-chlorophenyl)-spiro[naphthalene-2(1H)-3'-[3H]-pyrazol]-1-ones[2] proving that in the dominant rotamer the H-C(4) bond and the 4-phenyl group are nearly coplanar. In the *trans*-**7** isomer J(4-H,C-2",6") coupling constant decreased to 2.8 Hz indicating an increase of the population of rotamer where 4-H is perpendicular to the plane of the 4-phenyl group. It is worth mentioning that in the *trans*-**8**, owing to the presence of a phenyl group at C-2', the J(4-H,C-2",6") coupling constant value increases (5.7 Hz) and the J(2'-H,C-2^+,6^+) coupling constant is relatively high (4.5 Hz) indicating such an arrangement where the two phenyl groups are nearly coplanar. In the *trans*-**6** a coplanar arrangement of 2'-H_{eq} and C-2' phenyl group is favoured as well.

Structure of the homologous *trans*-**15** and *trans*-**16** was unequivocally proved by n.O.e. data obtained on the irradiation of the 2",6"-H protons. On the basis of the J(4-H,5-H) couplings conformation of the pyrazoline ring is similar to those described earlier. In the *trans*-**15** ring bearing a carbonyl group is nearly planar and, therefore, designations axial and equatorial are without sence in this case However, in the *trans*-**16** on the basis of the coupling of the *trans*-protons of the seven-membered ring (^{3}J(1'-H_{ax},1a-H) = ^{3}J(1a'-H_{ax},2'-H_{ax}) = 9.5 Hz) a dominant chair conformer should be taken into consideration where no coplanar arrangement between the C=O group and the condensed aromatic ring can be considered. This is corroborated by a considerable descrease in the chemical shift of the 5'-H proton (δ5'-H=7.42 ppm) and a paramagnetic shift of the signal of the C-4' carbonyl carbon atom (δC-4'=202.5). As in all other *trans*-compounds the N-2 atom is axial in this case as well where the 2",6"-H protons are in spatial proximity only with the 2'-H_2 protons of the seven-membered ring as deduced from the n.O.e. data (Table 2).

Tautomerism

It is known that 3-benzoyl-4-phenyl-1-pyrazolines obtained by the cycloaddition of chalcones with diazomethane are spontaneously isomerized into 2-pyrazolines.[5] No such rearrangement was observed for the previously investigated *trans*-spiro-1-pyrazolines.[1] However, in the case of *cis*-**5** and *cis*-**7** signals of 2-pyrazoline isomers appeared during one day in $CDCl_3$ solution. Tautomerism was accelerated by the addition of a trace of trifluoroacetic acid to the $CDCl_3$ solution. Such conversion proved to be considerably faster in the case of *cis*-isomers than for *trans*-ones since rearrangement of the *trans*-spiro-1-pyrazolines into spiro-2-pyrazolines was not complete even during one month at room temperature. In the case of *trans*-**5** and *trans*-**7** *trans*-*cis* isomerization and formation of spiro-cyclopropane and β-methylarylidene derivatives[10] on nitrogen loss have also been observed. Nitrogen loss of *cis*- and *trans*-spiro-1-pyrazolines comprising flavanone or 1-thioflavanone moiety is considerably

Table 6. ^1H n.m.r. chemical shifts [p.p.m] and characteristic coupling constants [Hz] of spiro-2-pyrazolines **9**, **11**, **17** and **18**

	9 *cis*	**9** *trans*	**11** *cis*	**11**[a] *trans*	**17**[a] *trans*	**18**[b] *trans*
H-4	4.90	5.17	4 66	4.86	4.52	4.48
H_{cis}-5	6.67	6.93	6.75	6.95	6.88	6.81
H_{ax}-2'	3.60	2.88	4.29	4.13	2.90	2.82
H_{eq}-2'	3.01	2 76	4.41	3.85	2.82	2.82
H-5'	7.24	8.13	7.21	7.95	7.79	7.38
H-6'	6.79	7.21	6.71	7.09	7.36	
H-7'	7.15	7.38	7.32	7.48	7.52	7.38
H-8'	7.04	7.18	6.90	6 92	7.17	7.20
H-2",6"	6.84	7.33	6.80	7.37	7.03	7.11
H-3",5"	6.88	7.22	6.98	7.15	7.20	7.30
H-4"	6.94	7.32	6.95	7.04	7.30	7.30
NH	6 14	6.11	6 48	6.95		7.25
$^2J(2'\text{-}CH_2)$	13.4	13.7	11.5	11.5	17.8	
$^3J(H\text{-}4,H\text{-}5)$	1 5	1.1	1.0	1.0	1.2	1.6

[a] data taken from the mixture of 1- and 2-pyrazolines;
[b] 1'-H_2 and 1a'-H_2 signals appear in the range 1.65-1.80 p.p.m.

faster than the isomerization into spiro-2-pyrazolines and, therefore, tautomerized derivatives of these compounds have not been investigated. Substances *trans*-**15** and *trans*-**16** have also been isomerized into *trans*-**17** and *trans*-**18** on acid catalysis as described for the six-membered homologous compounds[2] but the conversion was 99% for *trans*-**16** and only 25% for *trans*-**15**.

The formation of 2-pyrazolines from 1-pyrazolines can be established by observing the NH protons and downfield shift of the 5-H signal. Moreover, C-5 is sp^2 hybridized exhibiting chemical shifts in the range of 145 2 - 147.3 ppm and a characteristic $^1J(C,H)$ value of *ca* 190 Hz.

Table 7. ^{13}C n.m.r. chemical shifts [p p.m] of spiro-2-pyrazolines **9**, **11**, **17** and **18**

	9 *cis*	**9** *trans*	**11** *cis*	**11**[b] *trans*	**17** *trans*	**18** *trans*
C-3	71 4	69.7	74.1	70.1	75.6	77.6
C-4	59.0	55.9	61 0	55 7	58.9	57.0
C-5	145.6	146 3	146.2	146 4	145.2	147.3
C-2'	37.2	32.4	71 3	70.1	36.7	32 6[c]
C-4'	192.8	190.0	192.0	189 9	204.7	208.1
C-4a'	129.9	129 4	121.8	120.4	134.2	137.8
C-5'	129.3	130 9	126 9	128.3	124.8	127.7
C-6'	129.4	125.3	121 4	122 1	127.9	126.9
C-7'	132 9	133 6	136.0	136.7	135 6	131.2
C-8'	126.2	126 7	117 1	117 9	126.3	129.6
C-8a'	140.0	140.4	160 8	160 9	151 4	139.1
C-1"	134.1	133 8	133.7	133.1	135.2	134 5
C-2",6"	128.7	128.8a	128 9	129.0	128 7	129.6
C-3",5"	127.8	129.2a	128.1	129 0	128.9	128 7
C-4"	127.5	128.0	127 7	128.4	127.9	128.5

[a] tentative assignment, [b] measured in mixture of isomers;
[c] C-1' 34.6, C-1a' 24.6

The six-membered ring can exist in two halfchair conformations while the 2-pyrazoline ring can adopt two envelope conformers where C-3 is out

of the plane formed by the other atoms of the five-membered ring. The value of ^3J(4-H,5-H)=1.0-1.6 Hz obtained indicates the preference of conformers where the dihedral angle between these protons is nearly 90°. In *cis*-**9** and *cis*-**11** J(2'-H_{eq},C-8a') coupling constants are 8.4 and 8.5 Hz proving that the equilibrium of the two halfchair conformers of the six-membered ring is shifted to one direction. In the case of the *cis*-**9** the n.O.e. experiment proved that the 4-H is in spatial proximity only with one of the two 2'-H_2 methylene protons (δ2'-H_{eq}=3.2 ppm) indicating that in the dominant conformer C-4 is axial. In this compound the ^3J(4-H,C-2",6") coupling constant is 5.3 Hz proving the predominance of rotamer where the 4-H bond and the 4-phenyl group are coplanar. As a consequence of this the condensed aromatic ring and the 4-phenyl group are mutually above the plane of each other resulting in a diamagnetic shift of these aromatic protons. This anisotropic effect is the most pronounced in the chemical shift of 5'-H (Table 6). ^{1}H n.m r. chemical shift and ^3J(C,H) coupling data of *cis*-**11** reveal that its conformation is similar to that of *cis*-**9**. As a result of the tautomeric rearrangement the conformation of compounds *trans*-**16** and *trans*-**18** with seven-membered ring changed. In the case of *trans*-**18** fast conversion of the conformers took place at room temperature resulting in the averaging of the signals of the methylene protons of the seven-membered ring.

It is worth mentioning that in the *cis*-spiro-1-pyrazolines (**5** and **7**) and *cis*-spiro-2-pyrazolines (**9** and **11**) C-4 atom is axial in the favoured conformer of the six-membered ring. It is understandable by taking into consideration that in the other halfchair conformer with an equatorial C-4 atom between the C=O and 4-phenyl groups an unfavourable steric interaction would appear and to avoid this effect conformer type *P* predominates

EXPERIMENTAL

Starting α,β-unsaturated ketones *Z*-**2**, *E*-**2**, *E*-**13**, and *E*-**14** were prepared according to known procedures.[6,11,12] TLC was performed on KIESELGEL 60 F_{254} (Merck) layer using hexane:acetone (7·3 v/v) as eluant.

Z-3-Benzylidene-1-thiochromanone (*Z*-**1**).
E-3-Benzylidene-1-thiochromanone (*E*-**1**, 2.0 g) was dissolved in anhydrous benzene (500 ml) and irradiated at room temperature for 24 h with a mercury arc lamp. The solvent was evaporated under reduced pressure and the

residue was purified on a Kieselgel 60 (Merck) column using hexane:benzene (3:2 v/v) as eluant to afford 0.8 g (40.0 %) of crystalline product, m.p. 83-84 °C. Anal. Calcd. for $C_{16}H_{12}OS$ (252.26) C, 76.17; H, 4.79; Found C, 76.31; H, 4.83. ^1H n.m.r. ($CDCl_3$) 3.84 (s, 2H), 6.82 (s, 1H), 7.10-8.18 (m, 9 aromat. H).

Z-3-Benzylidene-chromanone (Z-3)

E-3-Benzylidene-chromanone (*E*-**3**, 2.0 g) was isomerized as described for *E*-**1** to afford 0.7 g (35.0 %) of crystalline material, m.p. 65-66 °C. Anal. Calcd. for $C_{16}H_{12}O_2$ (236.26) C, 81.35; H, 5.12; Found C, 81.18; H, 5.16. ^1H n.m.r. ($CDCl_3$) 4.98 (s, 2H), 6.83 (s, 1H), 6.94-8.10 (m, 9 aromat. H).

General procedure for the synthesis of spiro-1-pyrazolines

A mixture of the appropriate α,β-unsaturated ketone (5.0 mmol), diazomethane (25.0 mmol), anhydrous ether (50 ml) and anhydrous acetone (50 ml) was left to stand in refrigerator for 48 h, the solvent was evaporated under reduced pressure, and the residue crystallized from methanol to obtain compounds *cis*-**5**, *cis*-**6**, *cis*-**7**, *trans*-**6**, *trans*-**15** and *trans*-**16**.

cis-4',5'-Dihydro-4'-phenyl-spiro[2H-1-benzothiopyran-3(4H),3'-[3H]pyrazol]-4-one (cis-5). Yield 82.7 %, m.p. 122-123 °C, Anal. Calcd. for $C_{17}H_{14}N_2OS$ (294.28) C, 69.38; H, 4.79; N, 9 51; Found C, 69.22; H, 4.89; N, 9.44.

cis-4',5'-Dihydro-2,4'-diphenyl-spiro[2H-1-benzothiopyran-3(4H),3'-[3H]-pyrazol]-4-one (cis-6). Yield 62.5 %, m.p. 172-173 °C, Anal. Calcd. for $C_{23}H_{18}N_2OS$ (370.37) C, 74.58; H, 4.89; N, 7.56; Found C, 74.45; H, 4.92; N, 7.61.

cis-4',5'-Dihydro-4'-phenyl-spiro[2H-1-benzopyran-3(4H),3'-[3H]pyrazol]-4-one (cis-7). Yield 71.4 %, m.p. 135-136 °C, Anal. Calcd. for $C_{17}H_{14}N_2O_2$ (278.28) C, 73.37; H, 5.07; N, 10.06; Found C, 73.44; H, 4.98; N, 10.17.

trans-4',5'-Dihydro-2,4'-diphenyl-spiro[2H-1-benzothiopyran-3(4H),3'[3H]-pyrazol]-4-one (trans-6). Yield 70.6 %, m.p. 125-126 °C, Anal. Calcd. for $C_{23}H_{18}N_2OS$ (370.37) C, 74.58; H, 4.89; N, 7.56; Found C, 74.52; H, 4.94; N, 7 52.

*trans-4',5'-Dihydro-4'-phenyl-spiro[indene-2(1H),3'-[3H]pyrazol]-1-one (trans-**15**).* Yield 84.6 %, m.p. 87-88 °C, Anal. Calcd. for $C_{17}H_{14}N_2O$ (262.28) C, 77.84; H, 5.38; N, 10.67; Found C, 77.62; H, 5.29; N, 10.53.

*trans-4',5'-Dihydro-4'-phenyl-spiro[benzocycloheptane-2(1H),3'-[3H]pyrazol]-1-one (trans-**16**).* Yield 82.7 %, m.p. 75-76 °C, Anal. Calcd. for $C_{19}H_{18}N_2O$ (290.33) C, 78.59; H, 6.25, N, 9.64; Found C, 78.37; H, 6.17; N, 9.73.

The n.m.r. spectra were obtained on Bruker AM-400 and AC-250 spectrometers at room temperature in $CDCl_3$. Chemical shifts are given on the δ scale. In the 1D measurements 64K data points were used for FID. For homonuclear n.O.e. experiments a delay time of 7 s was applied. N.O.e. difference and 2D carbon-proton correlated experiments were run using the Bruker software package. In the 2D experiments 1K x 1K data matrices were transformed. In the case of the 2D semiselective INEPT measurements the data matrices were 1K x 64 data points, and the spectral width in the F1 (proton) dimension was 16 Hz. Selected traces were zero-filled to give a final digital resolution of 0.06 Hz. Shifted sine-bell multiplication in F2 (carbon) and Gaussian multiplication in F1 dimension was applied, before doing the Fourier tranformations.

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