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Reactions between Azolium Salts and Nucleophilic Reagents

IX. Further Investigations of the *cine*-Substitution of Pyrazolium Salts

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A number of halogeno-pyrazoles and pyrazolium salts *1* have been prepared and base-catalyzed deuterium exchange and substitution of *1* have been studied. 1-Methyl-2-phenyl-4-halogeno pyrazolium tosylates *1f* when treated with sodium hydroxide afford only one of the possible *cine* substitution products, namely 1-phenyl-2-methyl-pyrazol-4-in-3-one *5f*. Analysis of the relative deuterium exchange rates of the 3- and 5-protons of 1-methyl-2-phenyl-pyrazolium tosylates leads to an exclusion of the intramolecular halogenation-substitution mechanism. Other experimental evidence indicates that *1f* reacts *via* an anomalous addition-elimination mechanism; the addition step being rate limiting. The product distribution being controlled by competition between pyrazolone formation from and ring cleavage of the initial addition compound. 1-Methyl-2-benzyl-4-halogeno pyrazolium tosylates *1d* when treated with base afford both of the possible *cine*-substitution products *5d* and *9d* indicating that the product distribution is influenced to a minor extent by competing ring-cleavage processes when the *N*-substituents are non-vinylic.

Recently it was found that 1,2-dimethyl-4-bromo-pyrazolium tosylate *1b*, when treated with sodium hydroxide or methoxide reacted with *cine*-substitution to give 1,2-dimethyl-pyrazol-4-in-3-one *5b*.[1] Although several mechanisms could be imagined for this reaction experiments showed that only two of these mechanisms were likely. One of these was an anomalous addition-elimination reaction (Fig. 2) (to be explained below). The other involved an intramolecular 1,2-migration of a bromonium ion from the 4-position to the 3-position followed by nucleophilic displacement with hydroxide or methoxide ions (Fig. 1) (to be explained below). Both possibilities are of considerable theoretical interest. Anomalous addition-elimination reactions are rare, especially in 5-membered rings;[2,3] intramolecular halogen migration-substitution mechanisms have been considered in aromatic systems,[4,5] but so far they have never been proved. In order to find evidence for a single mechanism the reaction between 4-halogeno substituted pyrazolium salts with two different *N*-substituents and sodium hydroxide or sodium methoxide has now been investigated.

Table 1. Preparation, melting points, and analytical data of 1,2-disubstituted pyrazolium tosylates.

Compound [a]	Starting material	Method of preparation	Yield of crude product [c] %	Melting point of crude product °C	Melting point after the second crystallisation °C	Analytical data Found: Calculated: C %	H %	N %	S %		%
1,2-Dimethyl-3-chloro-pyrazolium tosylate *1b* (X = Cl)	1-Methyl-5-chloro-pyrazole [b]	B	79	106–126	121–126	47.42 47.59	5.03 4.99	9.17 9.25	10.46; 10.59	Cl	11.61 11.71
1-Methyl-2-benzyl-pyrazolium tosylate *1c*	1-Benzyl-pyrazole [20]	B	100	oil	oil	62.64 62.77	5.83 5.85	8.27 8.13	9.45 9.31		
1-Methyl-2-benzyl-3-chloro-pyrazolium tosylate *8d* (X = Cl)	1-Benzyl-5-chloro-pyrazole [b]	B	71	oil	oil	56.87 57.06	5.16 5.05	7.30 7.39	8.43; 8.46	Cl	9.20 9.36
1-Methyl-2-benzyl-4-chloro-pyrazolium tosylate *1d* (X = Cl)	1-Benzyl-4-chloro-pyrazole [b]	B	100	oil	oil	53.45 57.06	4.99 5.05	7.42 7.39	8.38; 8.46	Cl	9.42 9.36
1-Methyl-2-benzyl-4-bromo-pyrazolium tosylate *1d*	1-Benzyl-4-bromo-pyrazole [20]	B	100	oil	oil	50.94 51.07	4.54 4.53	6.76 6.62	7.76; 7.58	Br	18.78 18.88
1-Methyl-2-benzyl-4-iodo-pyrazolium tosylate *1d* (X = I)	1-Benzyl-4-iodo-pyrazole [b]	B	88	63–66	119–126	46.16 45.97	4.07 4.07	5.89 5.96	6.99; 6.82	I	27.16 26.98
1-Methyl-2-benzyl-5-chloro-pyrazolium tosylate *4d* (X = Cl)	1-Methyl-5-chloro-pyrazole [b]	F	33	oil	oil	55.01 57.06	4.95 5.05	8.12 7.39	6.27; 8.46	Cl	13.80 9.36
	1-Benzyl-3-chloro-pyrazole [b]	B	40								

1-Methyl-2-phenyl-pyrazolium tosylate *1e*	1-Phenyl-pyrazole [25]	A	100	106–108	107–109	61.70 61.80	5.61 5.49	8.57 8.48	9.54 9.71		
1,3-Dimethyl-2-phenyl-pyrazolium tosylate *10f*	1-Phenyl-5-methyl-pyrazole [22]	A	100	oil	oil	61.27 62.77	6.14 5.85	8.29 8.13	9.57 9.31		
1,5-Dimethyl-2-phenyl-pyrazolium tosylate *12f*	1-Phenyl-3-methyl-pyrazole [23]	A	100	oil	oil	62.92 62.77	5.98 5.85	8.00 8.13	9.12 9.31		
1-Methyl-2-phenyl-3-chloro-pyrazolium tosylate *8f* (X=Cl)	1-Phenyl-5-chloro-pyrazole [18]	A	100	oil	oil	55.86 55.96	4.84 4.69	7.82 7.68	8.58; 8.79	Cl	9.61 9.71
1-Methyl-2-phenyl-3-bromo-pyrazolium tosylate *8f*	1-Phenyl-5-bromo-pyrazole [b]	E	100	oil	oil	48.78 49.88	4.12 4.19	6.58 6.85	7.55; 7.84	Br	19.25 19.52
1-Methyl-2-phenyl-4-chloro-pyrazolium tosylate *1f* (X=Cl)	1-Phenyl-4-chloro-pyrazole [26]	A	97	152	152	55.88 55.96	4.64 4.69	7.53 7.68	8.55; 8.79	Cl	9.54 9.71
1-Methyl-2-phenyl-4-bromo-pyrazolium tosylate *1f*	1-Phenyl-4-bromo-pyrazole [27]	A	97	171	179–180	49.74 49.88	4.31 4.19	6.75 6.85	7.67; 7.84	Br	19.42 19.52
1-Methyl-2-phenyl-4-iodo-pyrazolium tosylate *1f* (X=I)	1-Phenyl-4-iodo-pyrazole [b]	C	91	156	156	44.60 44.74	3.91 3.76	5.95 6.14	7.19; 7.03	I	27.70 27.83
1,3-Dimethyl-2-phenyl-4-bromo pyrazolium tosylate *11f*	1-Phenyl-4-bromo-5-methyl pyrazole [b]	D	100			50.87 51.07	4.68 4.53	6.42 6.62	7.61; 7.58	Br	18.75 18.88
1,5-Dimethyl-2-phenyl-4-bromo pyrazolium tosylate *13f*	1-Phenyl-3-methyl-4-bromo-pyrazole [b]	D	98	164–168	164–168	50.87 51.07	4.62 4.53	6.49 6.62	7.67; 7.58	Br	18.89 18.88
1-Methyl-2-phenyl-5-chloro-pyrazolium tosylate *4f* (X=Cl)	1-Phenyl-3-chloro-pyrazole [b]	D	75	87–104	108–110	55.87 55.96	4.74 4.69	7.78 7.68	8.91; 8.79	Cl	9.53 9.71
1-Methyl-2-phenyl-5-bromo-pyrazolium tosylate *4f*	1-Phenyl-3-bromo-pyrazole [b]	E	74	oil	oil	49.63 49.88	4.14 4.19	6.92 6.85	7.68; 7.84	Br	19.70 19.52

[a] All pure pyrazolium tosylates were colourless. [b] Preparation of the starting material is described above. [c] In all cases the crude product contained only traces of impurities and could be used directly for synthetic purposes. The loss by the different purification procedures is only a few per cent except in the case of method E which results in an appreciable loss.

Table 2. NMR-spectra of 1,2-disubstituted pyrazolium salts in deuterium oxide with DSS as an internal standard.

Pyrazolium tosylate	H-3 ppm	H-4 ppm	H-5 ppm	N_1-CH_3 N_2-CH_2 ppm	C-CH_3 ppm	J_{H3H4}[b] Hz	J_{H4H5} Hz	J_{H3H5} Hz	J_{CH_3H5} Hz	J_{CH_3H4} Hz
1,2-Dimethyl-3-chloro- *1b* (X=Cl)		6.80	8.14	4.07 3.98[c]			3.2		0.6	
1-Methyl-2-benzyl- *1c*	8.18	6.81		3.98 5.65		3.1	3.1			
1-Methyl-2-benzyl-3-chloro- *8d* (X=Cl)		7.00	8.29	4.02 5.78			3.1		0.6	
1-Methyl-2-benzyl-4-chloro- *1d* (X=Cl)	8.24[d]		8.32[d]	4.03 5.62				1.2	0.6	
1-Methyl-2-benzyl-4-bromo- *1d*	8.27[d]		8.34[d]	4.05 5.64				1.2	0.6	
1-Methyl-2-benzyl-4-iodo- *1d*	8.25[d]		8.32[d]	4.05 5.65				0.9	0.6	
1-Methyl-2-benzyl-5-chloro- *4d* (X=Cl)	8.25	6.93		3.96 5.69		3.1				
1-Methyl-2-phenyl- *1e*	8.36[a]	6.96	8.41[a]	3.92		3.0	3.0	1.1	0.6	
1,3-Dimethyl-2-phenyl- *10e*		6.78	8.27	3.78	2.27		3.0		0.5	0.8

1,5-Dimethyl-2-phenyl- *12e*	8.24	6.82	8.24	3.75	2.57		3.1		0.2	0.4
1-Methyl-2-phenyl-3-chloro- *8f* (X=Cl)		7.12	8.49	3.89			3.2		0.6	
1-Methyl-2-phenyl-3-bromo- *8f*		7.15	8.42	3.88			3.1		0.5	
1-Methyl-2-phenyl-4-chloro- *1f* (X=Cl)	8.51[a]		8.55	3.91				1.1	0.6	
1-Methyl-2-phenyl-4-bromo- *1f*	8.50[a]		8.56[a]	3.91				1.1	0.6	
1-Methyl-2-phenyl-4-iodo- *1f* (X=I)	8.39[a]		8.47[a]	3.92				1.1	0.6	
1,3-Dimethyl-2-phenyl-4-bromo- *11f*			8.47	3.80	2.37				0.6	
1,5-Dimethyl-2-phenyl-4-bromo- *13f*	8.42			3.80	2.55					
1-Methyl-2-phenyl-5-chloro- *4f* (X=Cl)		7.14	8.45	3.87			3.2			
1-Methyl-2-phenyl-5-bromo- *4f*	8.37	7.17		3.88		3.2				

[a] The assignment of the H-3 and H-5 signals was based on the fact that H-3 of *12f* and *13f* resonates at a higher field than H-5 of *10f* and *11f*, respectively (see also Ref. 14). Furthermore H-5 couples with the N-CH_3 group whereas H-3 does not. [b] All coupling constants were obtained by first order analysis. [c] N_2-CH_3. [d] The assignment of the H-3 and H-5 signals was based on the fact that H-3 of *4d* (X=Cl) absorbs at a higher field than H-5 of *8d* (X=Cl). Furthermore, the coupling between H-5 and the N-CH_3 group is larger than the coupling between H-5 and the N-CH_2 group.

RESULTS

The pyrazolium salts were prepared from 1-substituted pyrazoles and methyl tosylate (see Experimental) and they were identified through their NMR-spectra (Table 2).

The heteroaromatic protons of pyrazolium salts are acidic and the rate of the base-catalyzed exchange of these protons with deuterium was measured (see Table 3).

When 1-methyl-2-benzyl-4-bromo-pyrazolium tosylate *1d* was treated with sodium hydroxide both possible isomers, namely 1-benzyl-2-methyl-

Table 3. Deuterium exchange rates of 1-methyl-2-phenyl-pyrazolium tosylates.*

Pyrazolium tosylate	Proton	pD	$T_{1/2}$[a] min	Relative rate[b]
1-Methyl-2-benzyl-	H-3[h]	12.63[e]	6.5	0.81
1c	H-5[h]	12.63[e]	7.3	0.72
1-Methyl-2-benzyl-4-bromo-	H-3	9.86[g]	5.8	501
1e	H-5	9.86[g]	6.7	426
1-Methyl-2-phenyl-	H-3	11.67[e]	13.7[c]	3.47
1e	H-4			
	H-5	11.67[e]	13.7[d]	3.47
1,3-Dimethyl-2-phenyl-	H-4			
10f	H-5	12.63[e]	7.0[d]	0.76
1,5-Dimethyl-2-phenyl-	H-3	12.63[e]	5.4[d]	0.98
12f	H-4			
1-Methyl-2-phenyl-3-chloro-	H-5	9.86[g]	92	34
8f, X = Cl	H-4	12.63[e]	80	0.066
1-Methyl-2-phenyl-3-bromo-	H-5	9.86[g]	109	28
8f	H-4	12.44[e]	148	0.055
1-Methyl-2-phenyl-4-chloro-	H-3	7.96[f]	26.2	9430
1f, X = Cl	H-5	7.96[f]	32.1	7710
1-Methyl-2-phenyl-4-bromo-	H-3	9.86[g]	6.0[c]	513
1f	H-5	9.86[g]	6.0[c]	513
1,3-Dimethyl-2-phenyl-4-bromo-	H-5	9.86[g]	8.6	3.64
11f				
1,5-Dimethyl-2-phenyl-4-bromo-	H-3	9.86[g]	6.3	490
13f				
1-Methyl-2-phenyl-5-chloro-	H-3	9.86[g]	78	40
4f	H-4	12.63[e]	99	0.046
1-Methyl-2-phenyl-5-bromo	H-3	9.86[g]	87.5	36
4f	H-4	12.44[e]	133	0.062

[a] The rates were measured by NMR at 33°C except in the cases of *8f* and *4f* which were studied at 40°C. [b] In comparison to 1,2-dimethyl-pyrazolium tosylate.[1] [c] Mean value for the 3- and 5-proton, since these signals almost coincide. [d] No exchange after 60 days at room temperature at pD 12. [e] Glycine buffer. [f] Phosphate buffer. [g] Borate buffer. [h] H-3 and H-5 were separated in the basic solution.

* It is noteworthy that the exchange rates of pyrazolium tosylates are less influenced by *N*-substituents or 4-substituents than 1,3-disubstituted 1,2,3-triazolium tosylates.[28] This indicates that the transmission of inductive effects is less efficient through the C=N and C=C bonds of pyrazolium ions than of triazolium ions. Probably, the bond order of these bonds are higher in the triazolium salt series. The exchange rate ratio between H-3 and H-5 of unsymmetric pyrazolium ions is less than that between H-4 and H-5 of the corresponding triazolium ions.[28]

Table 4. Reaction of 3-halogeno-substituted pyrazolium salts with sodium hydroxide.

Starting material	Product	Yield %	Melting point °C	Melting point after recrystallization [a] °C	Reported melting point °C	Analytical data C %	H %	Found: Calculated: N %
1,2-Dimethyl-3-chloro-pyrazolium tosylate *16* (X=Cl)	1,2-Dimethyl-pyrazol-4-in-3-one *5b*	100	72–73	72–73	47–63 [1]			
1-Methyl-2-benzyl-3-chloro-pyrazolium tosylate *8d* (X=Cl)	1-Methyl-2-benzyl-pyrazol-4-in-3-one *9d*	93	91–93	93–94		69.93 70.20	6.33 6.42	14.58 14.88
1-Methyl-2-benzyl-5-chloro-pyrazolium tosylate *4d* (X=Cl)	1-Benzyl-2-methyl-pyrazol-4-in-3-one *5d*	82	61–62	61–62		66.31 70.20	6.54 6.42	14.56 14.88
1-Methyl-2-phenyl-3-chloro-pyrazolium tosylate *8f* (X=Cl)	1-Methyl-2-phenyl-pyrazol-4-in-3-one *9f*	85	117–119	117–119	117 [29,30]	68.92 68.95	5.65 5.79	16.09 16.08
1-Methyl-2-phenyl-3-bromo-pyrazolium tosylate *8f*	1-Methyl-2-phenyl-pyrazol-4-in-3-one *9f*	76	96–98	117–119				
1-Methyl-2-phenyl-5-chloro-pyrazolium tosylate *4f* (X=Cl)	1-Phenyl-2-methyl-pyrazol-4-in-3-one *5f*	45	118	123–124		69.09 68.95	5.95 5.79	16.24 16.08
1-Methyl-2-phenyl-5-bromo-pyrazolium tosylate *4f*	1-Phenyl-2-methyl-pyrazol-4-in-3-one *5f*	31	118	123–124				

[a] All compounds were colourless and hygroscopic.

Table 5. NMR-spectra in deuteriochloroform with TMS as an internal standard and infrared absorptions of the carbonyl groups of 1,2-disubstituted pyrazol-4-in-3-ones.

Compound	IR[a] cm^{-1}	Phenyl group	NMR H-4 ppm	NMR H-5 ppm	NMR N-CH_3 ppm	NMR N-CH_2 ppm	NMR $J_{^{13}C\text{-}H_3}$ Hz	NMR J_{H4H5} Hz
1-Methyl-2-benzyl-pyrazol-4-in-3-one *9d*	1620	broad singlet	5.50	7.17	3.23	5.07	141	3.4
1-Benzyl-2-methyl-pyrazol-4-in-3-one *5d*	1625	multiplet	5.46	7.39[b]	3.30	4.83	141	3.4
1-Methyl-2-phenyl-pyrazol-4-in-3-one *9f*	1645	broad singlet	5.56	7.45	3.14		142	3.6
1-Phenyl-2-methyl-pyrazol-4-in-3-one *5f*	1630	broad multiplet	5.64	7.57[b]	3.28		142	3.7

[a] IR-spectra obtained in potassium discs. [b] The H-5 doublet was detected by homonuclear INDOR.

pyrazol-4-in-3-one *5d* and 1-methyl-2-benzyl-pyrazol-4-in-3-one *9d*, were formed in the ratio 1.62 (total yield 51 %). The pyrazolones *5d* and *9d* were identified through their spectra (Table 5). The IR-spectra showed a carbonyl absorption in the region where other 1,2-disubstituted pyrazol-4-in-3-ones absorb.[1] The NMR-spectra confirmed the structures exhibiting a CH_3-signal, a CH_2-signal, two doublets due to the 4- and 5-protons, and a phenyl group. In *5d* the doublet arising from H-5 was hidden by the multiplet of the phenyl group but was detected by homonuclear INDOR. All δ-values agreed well with the corresponding signals of other 1,2-disubstituted pyrazol-4-in-3-ones.[1] One of the pyrazolones isolated was identical with that formed by treatment of 1-methyl-2-benzyl-3-chloro-pyrazolium tosylate *8d* (X = Cl) with sodium hydroxide and therefore has the structure *9d*. The other pyrazolone was identical with that formed by similar treatment of 1-methyl-2-benzyl-5-chloro-pyrazolium tosylate *4d* (X = Cl) and therefore has the structure *5d*.

As a further proof of the structures, 1-methyl-2-benzyl-pyrazol-4-in-3-one *9d* was treated with benzoyl chloride; this produced 1-methyl-3-benzoyloxy-pyrazole, identified through its hydrolysis to 1-methyl-3-hydroxy-pyrazole. Similarly, 1-benzyl-2-methyl-pyrazol-4-in-3-one *5d* and benzoyl chloride afforded 1-methyl-5-benzoyloxy-pyrazole which, in turn by hydrolysis, gave 1-methyl-5-hydroxy-pyrazole.[6]

When 1-methyl-2-benzyl-4-iodo-pyrazolium tosylate *1d* (X = I) was treated with sodium hydroxide, the pyrazolones *5d* and *9d* were formed in the same ratio (1.66) and in a total yield of 20 %. When the chloro compound *1d* (X = Cl) was used as the starting material, the total yield of *5d* and *9d* dropped to 4 % (product ratio 1.99).

When 1-methyl-2-phenyl-4-bromo-pyrazolium tosylate *1f* was treated with 1 N sodium hydroxide or methoxide only one pyrazol-4-in-3-one was isolated. The compound was identified through its spectra (Table 5).

The pyrazolone isolated was identical with that formed by treatment of 1-phenyl-2-methyl-3-chloro-pyrazolium tosylate *4f* with sodium hydroxide and therefore has the structure *5f*. This was confirmed through its reaction with benzoyl chloride [6] which afforded 1-phenyl-3-benzoyloxy-pyrazole, identified through its hydrolysis to the previously described 1-phenyl-3-hydroxy-pyrazole.[7,8] The isomeric pyrazol-4-in-3-one *9f*, prepared independently by treatment of 1-methyl-2-phenyl-3-chloro-pyrazolium tosylate *8f* (X = Cl) with sodium hydroxide, was stable under the conditions of the reaction between the 4-bromo-pyrazolium salt *1f* and sodium hydroxide. The crude product from the latter process did not contain the pyrazol-4-in-3-one *9f*, as shown by NMR and TLC. It may therefore be concluded that the 5-position of 1-methyl-2-phenyl-4-bromo-pyrazolium salts differs markedly in reactivity from the 3-position. This agreed with the fact that 1,3-dimethyl-2-phenyl-4-bromo-pyrazolium tosylate *11f* reacted with sodium hydroxide to give 1-phenyl-2,5-dimethyl-pyrazol-4-in-3-one *14f* ("isoantipyrin"), whereas the isomeric pyrazolium salt *13f* decomposed under similar conditions and failed to give a pyrazol-4-in-3-one *15f*.

It was found that 1-methyl-2-phenyl-4-chloro-pyrazolium tosylate *1f* (X = Cl) gave a much lower yield of the pyrazol-4-in-3-one *5f* than the bromo and iodo compounds *1f* (X = Br) and *1f* (X = I).

DISCUSSION

The intramolecular halogen migration-substitution mechanism. The first step in an intramolecular halogen migration-substitution mechanism is a base-catalyzed abstraction of a proton adjacent to the halogen with formation of the 3-anion *2* (Fig. 1). If the halogen subsequently migrates as a halogen cation

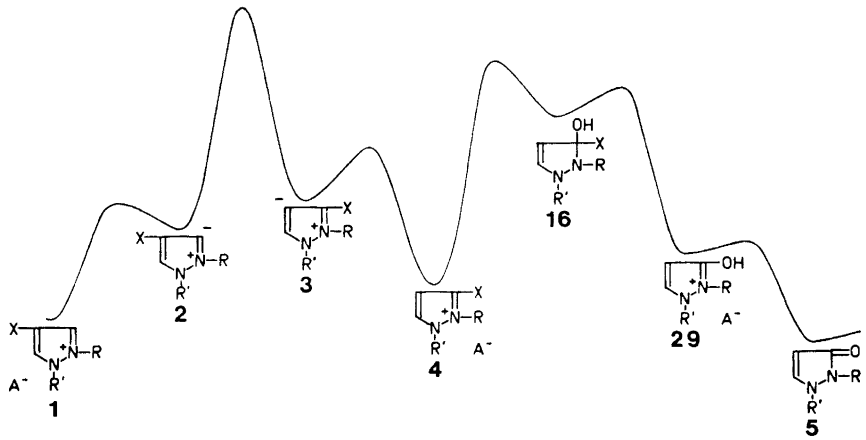
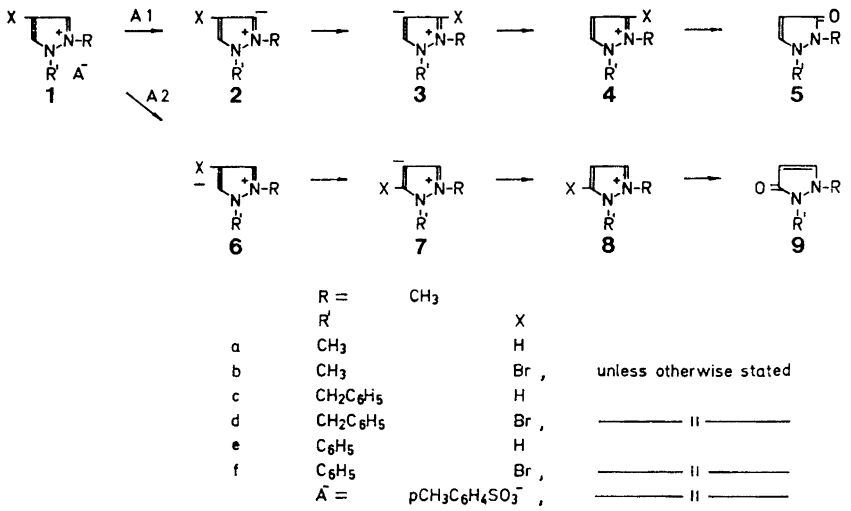


Fig. 1. The intrahalogenation-substitution mechanism of the reaction of 1,2-dimethyl-4-bromo-pyrazolium tosylate *1* (R = R′ = CH_3, X = Br) with sodium hydroxide. The energy diagram for the intrahalogenation (*1*→*2*→*3*→*4*) is discussed in the text. In the addition-elimination reaction with hydroxide ions the addition step is rate limiting,[32] the energy barrier between *4* and *16* being higher than that between *16* and *29*. The heteroaromatic protons of 3- and 4-bromo-pyrazolium tosylates are readily replaced by deuterium at pD's where no substitution of halogen takes place (Tables 3 and 6). Therefore, the barrier between *4* and *16* is considered to be higher than those between *1* and *2* and between *3* and *4*. Since transformation of 3- to 4-bromo-pyrazolium tosylates has never been observed, even under conditions where 3-bromo-pyrazolium tosylates undergo substitution, the barrier between *2* and *3* is considered to be higher than that between *4* and *16*. The barrier between *16* and *29* has arbitrarily been set higher than the *1*→*2* and *3*→*4* barriers. The barrier between *29* and *5* has been set low since 1,2-disubstituted pyrazol-4-in-3-ones *5* are very weak bases.

the 4-ion *3* is formed. Reprotonization gives the 3-halo compound *4*, which is expected to react readily with substitution, since halogen in the 3-position of pyrazolium salts react readily with nucleophilic reagents.[1] With hydroxide ions *4* gives rise to the hydroxy compound *16* which, in turn, by deprotonization produces the pyrazol-4-in-3-one *5*. The latter substitution is formulated as a normal addition-elimination mechanism.[2,3] When methoxide ions are used as the nucleophile *4* similarly gives a methoxypyrazolium salt which then, by loss of the *O*-methyl group yields *5*.[1]

Following this reaction course, a pyrazolium salt with two different *N*-substituents, *e.g. 1f*, could give rise to the two isomeric 3-anions *2f* and *6f* (Scheme 1, path A1 and A2). These anions would then rearrange to the 4-anions *3f* and *7f*, respectively, and the latter would by protonization, substitu-



Scheme 1.

tion, and deprotonization (or dealkylation when sodium methoxide is used as the nucleophile) yield the two isomeric pyrazol-4-in-3-ones *5f* and *9f* .

The pure 3-bromo-pyrazolium tosylate *4f* afforded *5f* as the sole pyrazolone when treated with sodium hydroxide. The isomeric pyrazolone *9f* was not found. Similarly, the 3-bromo-pyrazolium tosylate *8f* and sodium hydroxide produced the pyrazolone *9f*, exclusively. Since *1f* only gave *5f* with sodium hydroxide (see above) a halogen migration-substitution mechanism would imply that of the two possible anions *3f* and *7f* only *3f* was formed as an intermediate.

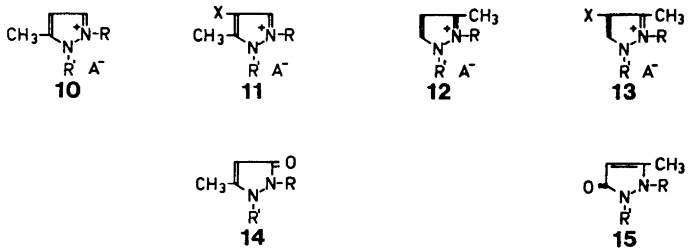
The base catalyzed deuterium exchange experiments indicated that the 3- and 5-protons of the 4-bromo-pyrazolium tosylate *1f* were exchanged *ca.* 8900 times faster than the 4-protons of the 3-bromo-pyrazolium tosylates *4f* or *8f* (see Table 3). Consequently, the transition states leading from the 3-bromo compounds *4f* or *8f* to the 4-anions *3f* or *7f* must have higher energy than the transition states involved in the conversion of the 4-bromo compound *1f* to the 3- and 5-anions *2f* and *6f*.

When the pure 3-bromo compounds *4f* or *8f* were treated with base no isomerization to the 4-bromo isomer *1f* was observed. However, exchange of the 4-protons of *4f* and *8f* took place readily. Hence, the transition states leading from the 4-anions *3f* or *7f* to the 5- and 3-anions *2f* or *6f*, respectively, have a higher energy than the transition states leading from the 4-anions to the 3-bromo-pyrazolium tosylates *4f* or *8f*. Thus, the energy profile sketched in Fig. 1 may be proposed.

If the 4-anion is considered to be a valid representation of the transition state with the highest energy the distribution between the pyrazol-4-in-3-ones *5f* and *9f*, formed from *1f*, should depend on the difference in stability between the 4-anions *3f* and *7f*. This difference in turn is reflected by the relative

deuterium exchange rate of the 4-protons of the two 3-bromo-pyrazolium tosylates *4f* and *8f*. This ratio was found to be 1.1 (Table 3). A large difference in the stability between the 5- and 3-anions *2f* and *6f* could, however, influence the relative activation energy of the two transformations, *2f* to *3f*, and *6f* to *7f*, and hence, the distribution between the pyrazol-4-in-3-ones *5f* and *9f*.

The relative stability between the 5- and 3-anions *2f* and *6f* could not be determined accurately by deuterium exchange studies on the 4-bromo-pyrazolium tosylate *1e* (Table 3) since the 3- and 5-protons of this compound almost coalesced in NMR (Table 2). The relative stability could, however, be evaluated from deuterium exchange measurements in the 5- and 3-methyl-derivatives of *1f*. Thus, the 3-proton of 1,5-dimethyl-2-phenyl-4-bromo-pyrazolium tosylate *13f* was exchanged 1.36 times faster than the 5-proton of 1,3-dimethyl-2-phenyl-pyrazolium tosylate *11f* under identical conditions (Table 3). This ratio corresponds to the relative stability of the 3- and 5-anions *6f* and *2f*.



Scheme 2.

As a consequence, the distribution between the pyrazol-4-in-3-ones *5f* and *9f*, which could be formed from *1f via* an intrahalogenation-substitution mechanism, is expected to be *ca.* 1:1 and should never exceed 1:1.36.

Analogously, the distribution between the pyrazol-4-in-3-ones *5d* and *9d*, formed from *1d via* this mechanism, is expected to be *ca.* 1:1 and should never exceed 1:1.16. The formation of the pyrazol-4-in-3-one *5f* as the sole pyrazolone in the reaction between the pyrazolium salt *1f* and base excludes the intrahalogenation-substitution mechanism in this case.

The formation of the pyrazol-4-in-3-ones *5d* and *9d* in the ratio found *via* an intramolecular halogenation-substitution mechanism seems highly unlikely.

The elimination-addition mechanism. Of the previously discarded mechanisms[1] the elimination-addition mechanism is the only one which has to be analyzed again in the light of the present experimental results. The elimination-addition mechanism still remains unlikely for the previously mentioned reasons.[1] Furthermore, a rapid formation of a highly strained five-membered hetaryne in 1 N sodium hydroxide at only 100° seems unbelievable.* Superficially, the elimination-addition mechanism can, however, explain the formation of *5f* as the sole product arising from *1f*. Following an elimination-addition

* In fact, complete conversion of 1-methyl-2-phenyl-4-bromo-pyrazolium tosylate *1f* with 1 N sodium hydroxide may be performed even at room temperature, in the course of *ca.* 7 days.

mechanism, *1f* may give rise to the hetarynes *28f* and *30f* (Scheme 4) which then, by addition of water and subsequent deprotonization, could produce the pyrazol-4-in-3-ones *5f* and *9f*, respectively. The rate limiting step in an elimination-addition process is the elimination.[2,3,9] Therefore, the distribution of *5f* and *9f* should be reflected by the relative stability of the hetarynes *28f* and *30f*. In contrast to *30f*, the phenyl group and the triple bond are apparently conjugated in *28f*. However, the pyrazole ring and the benzene ring are presumably not coplanar in *28f*.[6] Therefore an overwhelming dominance of the pyrazol-4-in-3-one *5f* over the isomer *9f* is indeed not expected.

The anomalous addition-elimination mechanism. Thus, the only likely mechanism for the reaction of 1,2-disubstituted 4-halo-pyrazolium salts with base, is an anomalous addition-elimination reaction. In this case, the nucleophilic reagent initially attacks *1* (Fig. 2) at the electron deficient carbon atoms

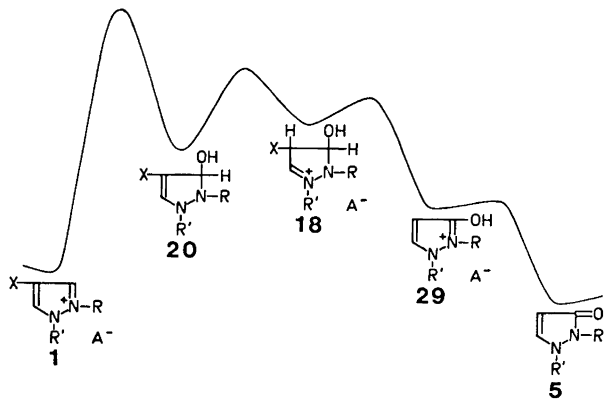
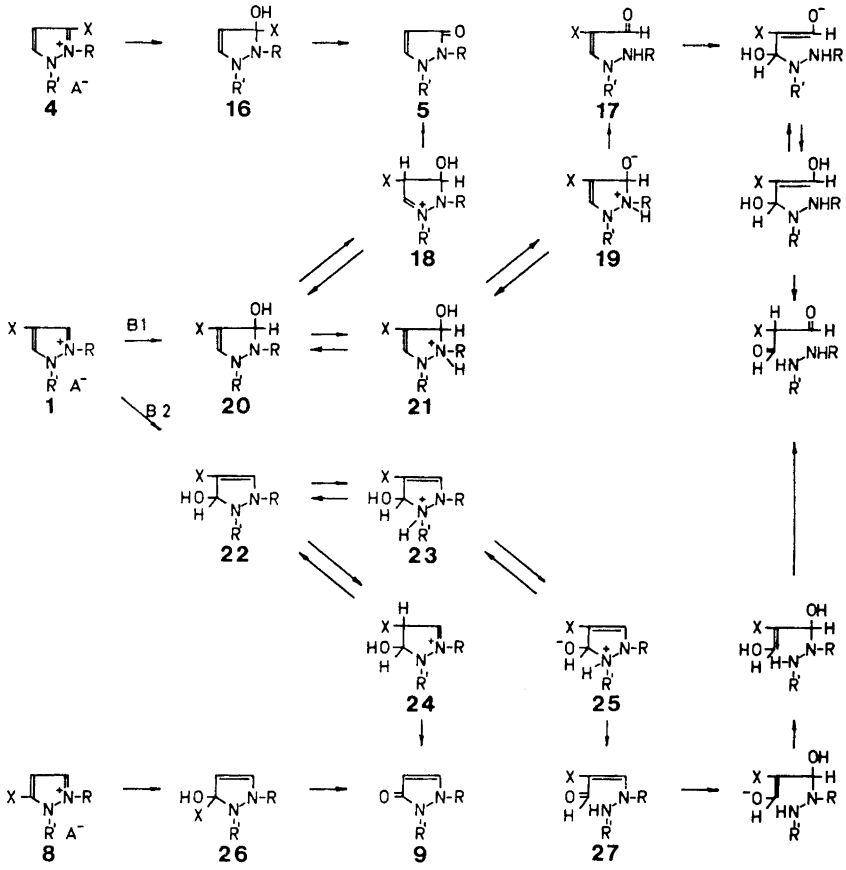


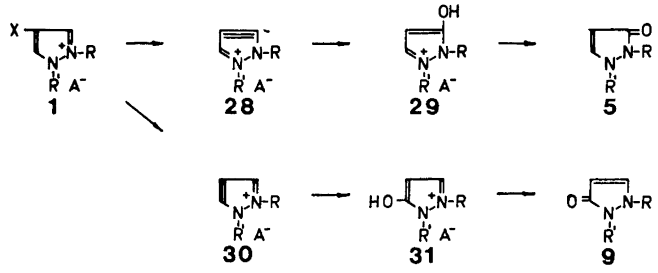
Fig. 2. The anomalous addition-elimination mechanism for the reaction of 1,2-dimethyl-4-bromo-pyrazolium tosylate *1* (R = R' = CH_3; X = Br) with sodium hydroxide. The addition step (*1* → *20*) is rate limiting, see the discussion in the text. The neutral intermediate *20* is considered more stable than the protonated derivative *18*. The elimination step (*18* → *29*) is assumed to be more favourable than the protonization (*20* → *18*) because it leads to a regain of aromaticity. The deprotonization (*29* → *5*) is discussed in the text to Fig. 1.

adjacent to the quaternary N-atoms giving rise to the neutral intermediate *20*. This is easily protonated at the 4-position, since the nitrogen atom may adopt the positive charge. This yields the species *18* which eliminates hydrogen halide producing the hydroxy-compound *29* which subsequently, by deprotonation, yields the pyrazol-4-in-3-one *5*. When methoxide ions are used as the nucleophile a similar reaction course takes place with formation of a methoxy-pyrazolium salt, which then, by cleaving off the *O*-methyl group, produces the pyrazolone *5*. Following the pathway depicted in Fig. 2, a pyrazolium salt with two different *N*-substituents, *e.g. 1f*, may be attacked in either the 5- or 3-position giving rise to the isomeric intermediates *20f* and *22f* and subsequently to the pyrazol-4-in-3-ones *5f* and *9f* (Scheme 3). It seems reasonable



Scheme 3.

that the rate limiting step in this sequence is either the addition of the nucleophile to *1* or the protonization of the intermediate *20*. The elimination step (*18*→*29*) is obviously more favorable than the protonization since it leads to a regain of aromaticity.



Scheme 4.

If the protonization step is rate limiting a kinetical H/D-isotope effect should be present. This is, however, not the case. Thus, 1-methyl-2-phenyl-4-bromo-pyrazolium tosylate *1f*, when heated with 1 N sodium hydroxide in a 1:1 mixture of water and deuterium oxide, gave the four H, D combinations of the pyrazolone *5f* and these were present in equal amounts as seen from the NMR-spectra. A separate experiment showed that the pyrazolone *5f* itself, when heated with 1 N sodium hydroxide in deuterium oxide under the usual reaction conditions, was deuterated quantitatively in the 5-position but only to an extent of a few per cent in the 4-position. Therefore, a kinetical H/D isotope effect is absent in the protonization of the 4-position. This protonization (and the elimination of hydrogen bromide from *18f*, as well) can therefore not be rate limiting. Consequently, the rate limiting step, if an anomalous addition-elimination mechanism is working, is the addition. In this case the intermediates *20f* and *20b* are similar to the intermediates *16f* (X = Cl) and *16b* (X = Cl), formed in the normal substitution reaction of 1-methyl-2-phenyl-5-chloro-pyrazolium tosylate *4f* (X = Cl) and 1,2-dimethyl-3-chloro-pyrazolium tosylate *4b* (X = Cl), respectively. Compound *4f* (X = Cl) reacts much faster with base than *4b* (X = Cl), (see Table 6). Therefore, *20f* is expected to react

Table 6. Rate of conversion of pyrazolium tosylate to pyrazol-4-in-3-ones in 1 N potassium hydroxide at 59.6°C.

Starting material	Product	$T_{1/2}$ min	Total amount of byproduct at the time of 50% conversion to pyrazol-4-in-3-one in %
1,2-Dimethyl-3-chloro-pyrazolium tosylate *16* (X = Cl)	1,2-Dimethyl-pyrazol-4-in-3-one *5b*	118.6	< 1
1-Methyl-2-benzyl-3-chloro-pyrazolium tosylate *8d* (X = Cl)	1-Methyl-2-benzyl-pyrazol-4-in-3-one *9d*	59.6	< 1
1-Methyl-2-benzyl-5-chloro-pyrazolium tosylate *4d* (X = Cl)	1-Benzyl-2-methyl-pyrazol-4-in-3-one *5d*	16.9	< 1
1-Methyl-2-phenyl-3-chloro-pyrazolium tosylate *8f* (X = Cl)	1-Methyl-2-phenyl-pyrazol-4-in-3-one *9f*	18.2	7.5
1-Methyl-2-phenyl-5-chloro-pyrazolium tosylate *4f* (X = Cl)	1-Phenyl-2-methyl-pyrazol-4-in-3-one *5f*	5.1	16
1-Methyl-2-phenyl-3-bromo-pyrazolium tosylate *8f*	1-Methyl-2-phenyl-pyrazol-4-in-3-one *9f*	31.0	< 1
1-Methyl-2-phenyl-5-bromo-pyrazolium tosylate *4f*	1-Phenyl-2-methyl-pyrazol-4-in-3-one *5f*	5.5	55

much faster than *20b* if the addition step is rate limiting. In fact, complete conversion of 1,2-dimethyl-4-bromo-pyrazolium tosylate *1b* required several hours heating to reflux with 1 N sodium hydroxide,[1] whereas 1-methyl-2-phenyl-4-bromo-pyrazolium tosylate *1f*, under identical conditions, was completely converted in 10 min.

The reason for the difference in reactivity between the dimethyl and the methylphenyl compounds is not clear. Mesomeric stabilization of the inter-

mediate by the phenyl group seems unlikely since the pyrazole and the benzene rings presumably are noncoplanar [6] and since an *N*-benzyl group exhibits a similar activation as a phenyl group (see Table 6). The activation decreases when the *N*-benzyl- or *N*-phenyl group is adjacent to the halogen (see Table 6), probably due to steric hindrance. Analogous results were found in the normal substitution of the 1-methyl-2-phenyl-5-bromo-1,2,3-triazolium ion, isosteric with *1f*, which is converted much faster than the 1,2-dimethyl-5-bromo-triazolium ion, isosteric with *1b*.[10]

If the addition step is rate limiting *and product determining*, the distribution between the pyrazol-4-in-3-ones *5f* and *9f* in the reaction of 1-methyl-2-phenyl-4-bromo-pyrazolium tosylate and base should be reflected by the relative stability of the intermediates *20f* and *22f*. No structural features justify that *20f* differs so markedly from *22f* in energy that only the former arises during the reaction. Indirectly, the *relative* energy of *20f* and *22f* can be roughly estimated by comparison with the *relative* stability of the structurally analogous compounds *16f* and *26f*, formed as intermediates in the normal substitution of the 3-bromo-pyrazolium tosylates *4f* and *8f*, respectively. The relative stability of *16f* and *26f* corresponds to the ratio between the substitution rates of *4f* and *8f* which was found to be 5.6. Therefore, 1-methyl-2-phenyl-4-bromo-pyrazolium tosylate *1f* should give the pyrazol-4-in-3-ones *5f* and *9f* in a ratio of *ca.* 5.6, in contrast to the fact that only *5f* arises. If an anomalous addition-elimination mechanism is working, the rate limiting addition step can therefore not be product determining.

In order to test this, the substitution of 1-methyl-2-phenyl-4-bromo-pyrazolium tosylate *1f* with sodium hydroxide was examined more carefully by following the reaction in NMR. The spectra indicated that 1-methyl-2-phenylhydrazine and the anion of bromomalonaldehyde were formed simultaneously with the pyrazolone. The crude product contained 33, 37, and 26 % of the three components, respectively. No other compounds or intermediates could be detected. The formation of the two byproducts is similar to the previously reported base induced ring cleavage of 1,2-dimethyl-pyrazolium iodide to give 1,2-dimethyl-hydrazine [11] and also to the cleavage of 1-methyl-2-phenyl-pyrazolium iodide [12] to 1-methyl-2-phenyl-hydrazine. These ring cleavages ,in analogy to the hydrolysis of immonium ions [13] and of 1,2-disubstituted pyrazolin-2-ium salts,[14] may be formulated as sketched in Scheme 3. Initially, a hydroxide ion attacks the carbon atom next to the positive N-atom, *1e* giving rise to *20f* and *22f*. Protonization at the ring-*N* and *O*-deprotonization followed by ring cleavage then produces *17f* and *27f*, respectively. By repetition of this sequence, *17f* and *27f* then afford bromomalonaldehyde and 1-methyl-2-phenyl-hydrazine. 1,2-Disubstituted hydrazines, when treated with 1,3-dicarbonyl compounds under acidic conditions, react with ring closure to give 1,2-disubstituted pyrazolium salts.[15] Therefore, bromomalonaldehyde and 1,2-dimethyl-hydrazine or 1-methyl-2-phenyl-hydrazine were treated with 1 N sodium hydroxide, both at room temperature and with prolonged heating to reflux. However, no pyrazol-4-in-3-ones, *5b* or *5f*, were produced. Consequently, ring-closure does not take place in basic solution, and hence, pyrazolone formation *via* a ring opening is unlikely. The intermediates *20f* and *22f* are common both for the pyrazolone generating

processes and for the ring cleavage. The formation of bromomalonaldehyde and of 1-methyl-2-phenyl-hydrazine demonstrates that the intermediate *20f* and/or *22f* are in fact formed. The product distribution may therefore depend on the relative ring cleavage rate of *20f* and *22f*. A faster ring cleavage of *22f* than of *20f* would cause a decrease in the relative yield of the pyrazol-4-in-3-one *9f*. If, on the other hand, *22f* is cleaved much faster than *20f*, virtually no pyrazol-4-in-3-one *9f* would arise in accordance with the experimental data. In contrast, the intrahalogenation-substitution process has no intermediate in common with the ring cleavage reaction. In this case, the latter is therefore not able to influence the distribution between the pyrazol-4-in-3-ones *5f* and *9f*.

This hypothesis is in excellent agreement with the results found by Maas *et al.* on the acid hydrolysis of tertiary enamines.[13]

Initially, the enamine is protonated producing an iminium ion which in turn is hydrated to an *N*-protonated α-amino alcohol analogous to *21* and *23*. The next steps are analogous to the sequence *23*→*25*→*27* (Scheme 3). It was found that the slowest step in the hydrolysis of the α-amino alcohol is the C–N cleavage reaction (corresponding to *25*→*27*). The rate of this step was found to be strongly dependent on the *N*-substituent. The more electron-attracting the *N*-substituent, the faster C–N-cleavage reaction. Thus the intermediate *23* is expected to undergo ring cleavage much faster than *21* due to the fact that a phenyl group is more electron attracting than a methyl group. Similarly, a more electron withdrawing halogen at C-4 may lead to a faster ring cleavage. At the same time, a more electron withdrawing 4-halogen will result in less protonization at the 4-position of *20f* and will therefore reduce the rate of formation of the pyrazol-4-in-3-one *5f*. The iodo compound *1f* (X = I) produces *5f* in a somewhat lower yield than the bromo compound *1f*. This is probably due to the fact that *1f* (X = I) gives off iodonium ions to a considerable extent during the reaction with formation of *1e*.

The differences between the 1-methyl-2-benzyl-4-chloro-, bromo-, and iodo-pyrazolium tosylates *1d* (X = Cl, Br, or I), respectively, are similar to those found between the phenyl analogs *1f* (X = Cl, Br, or I). This confirms that the reaction between 1-methyl-2-benzyl-4-halo-pyrazolium salts and sodium hydroxide follows an anomalous addition-elimination mechanism. If the addition step is product determining the ratio between *5d* and *9d* should be reflected by the relative substitution rates of 1-methyl-2-benzyl-5-chloro-pyrazolium tosylate *4d* and 1-methyl-2-benzyl-3-chloro-pyrazolium tosylate *8d*. This ratio was determined to be 3.35; therefore, the addition step is again not product determining. In the 1-methyl-2-benzyl substituted compounds the *N*-substituents are rather similar and the ring cleavage rates of the intermediates *20d* are therefore comparable. Consequently, the product ratio is only influenced to a minor extent by the ring cleavage reactions and both isomeric pyrazolones *5d* and *9d* arise. This may indicate that mesomeric delocalization of the nitrogen lone pair over the phenyl group plays a role during the rapid ring cleavage of the intermediate *22f*.

CONCLUSION

All experimental observations strongly support that 1-methyl-2-phenyl-4-halogeno-pyrazolium salts react with sodium hydroxide or sodium methoxide to form pyrazol-4-in-3-ones by an anomalous addition-elimination mechanism. The addition step is rate limiting (a proposed energy diagram is sketched in Fig. 2). The competition between pyrazol-4-in-3-one formation and ring cleavage is the product determining factor. The results obtained with 1-methyl-2-benzyl-4-halogeno-pyrazolium tosylates indicate that when the *N*-substituents are nonvinylic the ring cleavage processes influence the product distribution to a minor extent. The mechanism and the results are probably general for the reaction between 1,2-disubstituted 4-halogeno-pyrazolium tosylates *1* and sodium hydroxide or sodium methoxide.

EXPERIMENTAL

Column chromatography was carried out on silica gel (Merck, 0.05 – 0.2 mm). When non-aromatic eluents were used, 2 % of a fluorescent indicator (Riedl de Haën, Leuchtpigment ZS Super) was added to the silica gel and columns of clear quartz were used. The zones could then be visualized by illumination with a 254 mμ UV lamp. Preparative thin layer chromatography (TLC) was carried out on 20 × 40 cm plates with a 1 mm layer of silica gel (Merck, PF_{254}). Melting points are uncorrected. NMR-spectra were obtained on a Varian A-60 or a HA-100 instrument. Position of signals are given in ppm (δ-values) relative to tetramethylsilane (TMS) when deuteriochloroform was used as the solvent. When deuterium oxide was used as the solvent 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) was used as an internal standard. IR-spectra were measured in potassium bromide pellets. The purity of all non-ionic compounds were checked by TLC. All compounds were identified through their melting point, IR- and NMR-spectra.

1-Phenyl-3-hydroxy-pyrazole.[7] 1-Phenyl-pyrazolidon-3 (10.74 g) (commercially available) was dissolved in ethanol (50 ml) and 0.4 M aqueous iron(III) chloride solution, 0.25 N in HCl, (210 ml) was added with stirring and heating in a 100°C bath during 30 min. Stirring and heating was continued for 1 h. The solution was then diluted with water (1 l) and extracted with methylene chloride (3 × 200 ml). The organic layer was dried (magnesium sulfate) and the solvent was removed. The residue was dissolved in ethanol (40 ml) and boiling water (50 ml) was added. Cooling, filtration, and washing with water (5 × 20 ml) yielded 6.53 g (61 %) of 1-phenyl-3-hydroxy-pyrazole as light yellow crystals, m.p. 153 – 156°C (reported [7] m.p. 153°).

1-Methyl-5-chloro-pyrazole. 1-Methyl-5-hydroxy-pyrazole [16] (1.50 g) and phosphoryl chloride (3.06 ml) were heated in a sealed tube to 155°C for 8 h. The mixture was dissolved in methylene chloride (30 ml), water (30 ml) was added and the mixture was stirred at room temperature for 1 h. During this period hydrolysis takes place, and the heat evolution causes gentle reflux of the methylene chloride. The organic phase was isolated and the aqueous phase was extracted with two additional portions of methylene chloride (30 ml). The methylene chloride was distilled off through a steam distillation apparatus at a bath temperature of 100°C. The methylene chloride was kept in the receiver and the residue was steam distilled collecting 200 ml of distillate. The distillate was extracted with two additional portions of methylene chloride. The organic extract was dried (magnesium sulfate) and the methylene chloride was distilled off through a Vigreux column at bath temperature 85°C. The residue consisted of 817 mg (46 %) of 1-methyl-5-chloro-pyrazole as a highly volatile colourless oil. (Found: C 41.01; H 4.39; N 23.88; Cl 30.25. Calc. for $C_4H_4N_2Cl$: C 41.20; H 4.32; N 24.03; Cl 30.41.) NMR-data are given in Table 7.

1-Benzyl-5-chloro-pyrazole. Similarly, "1-benzyl-5-hydroxy-pyrazole"[17] (2.19 g) and phosphoryl chloride (2.3 ml) after the steam distillation afforded 1.49 g of a mixture of

Table 7. NMR-spectra of pyrazoles described in the experimental section.

Compound	NMR Phenyl group	H-3 ppm	H-4 ppm	H-5 ppm	N-CH_3 ppm	N-CH_2 ppm	$J_{H_3H_4}$ Hz	$J_{H_4H_5}$ Hz	$J_{H_3H_5}$ Hz
1-Benzyl-3-chloro-pyrazole	narrow multiplet		6.18	7.3		5.23		2.3	
1-Phenyl-3-chloro-pyrazole	broad multiplet		6.26	7.71				2.4	
1-Phenyl-3-bromo-pyrazole	broad multiplet		6.37	7.69				2.6	
1-Benzyl-4-chloro-pyrazole	narrow multiplet		7.3	7.43		5.14			0.7
1-Benzyl-4-iodo-pyrazole	narrow multiplet		7.54	7.37		5.27			
1-Phenyl-4-iodo-pyrazole	multiplet		7.92						0.7
1-Methyl-5-chloro-pyrazole		7.48	6.20		3.84		2.1		
1-Benzyl-5-chloro-pyrazole	singlet	7.49	6.19			5.30	1.9		
1-Phenyl-5-chloro-pyrazole [18]	narrow multiplet	7.65	6.35				1.9		
1-Phenyl-5-bromo-pyrazole	broad doublet	7.70	6.50				1.9		
1-Phenyl-5-methyl-pyrazole [22,31]	singlet	7.64	6.24				1.8		

1-benzyl-5-chloro-pyrazole and 1-benzyl-3-chloro-pyrazole.* The mixture was chromatographed on a column of silica gel (50 g) using benzene as the eluent. This gave 281 mg (12 %) of 1-benzyl-3-chloro-pyrazole, m.p. 63 – 65°C. Recrystallization from hexane did not raise the melting point. (Found: C 62.45; H 4.72; N 14.43; Cl 18.33. Calc. for $C_{10}H_9N_2Cl$: C 62.33; H 4.71; N 14.55; Cl 18.41.) The compound was identified through its NMR-spectrum (Table 7). Furthermore, the compound, when treated with methyl tosylate (see Table 1), produced 1-methyl-2-benzyl-5-chloro-pyrazolium tosylate *4d* (X = Cl) identical with the pyrazolium salt obtained by treatment of 1-methyl-5-chloro-pyrazole with benzyl bromide and subsequent exchange of the bromide ion with tosylate ion (see Table 1).

The next fraction contained 41 mg (2 %) of a mixture of 1-benzyl-3-chloro- and 5-chloro-pyrazole. The third fraction contained 661 mg (27 %) of 1-benzyl-5-chloro-pyrazole as a colourless oil. (Found: C 62.27; H 4.79; N 14.50; Cl 18.43.) NMR-data are given in Table 7.

1-Phenyl-3-chloro-pyrazole.[18] 1-Phenyl-3-hydroxy-pyrazole (3.52 g) and phosphoryl chloride (4.0 ml) were heated in a sealed tube to 200°C for 24 h. After hydrolysis, the organic phase was isolated and the aqueous phase was extracted with two additional portions of methylene chloride (30 ml). The extract was dried (magnesium sulfate) and the methylene chloride was removed. The residue was chromatographed on a column of silica gel (100 g) using benzene as the eluent. This gave 2.12 g (54 %) of 1-phenyl-3-chloro-pyrazole as a colourless oil which crystallized on cooling, m.p. 30 – 32°C (reported[18] m.p. 31.5°). NMR-data are given in Table 7.

* The presence of 1-benzyl-3-chloro-pyrazole in the product indicates that the starting material is contaminated with 1-benzyl-3-hydroxy-pyrazole. This explains the very large range of the melting point reported[17] for 1-benzyl-5-hydroxy-pyrazole. 1-Benzyl-3-hydroxy-pyrazole may arise if the initial benzoylation of pyrazolidone-3, in contrast to that supposed,[17] produces a mixture of N-benzoylated derivatives.

1-Phenyl-3-bromo-pyrazole.[27] 1-Phenyl-3-hydroxy-pyrazole (3.53 g) and phosphoryl bromide (3.5 ml) were mixed and heated in a sealed tube to 200°C for 24 h. The mixture was then worked up as described in the preceding experiment. The first fraction to leave the column contained 837 mg (13 %) of 1-phenyl-3,4-dibromo-pyrazole as colourless crystals, m.p. 46 – 48°C. Recrystallization from hexane raised the melting point to 50 – 51°C. (Found: C 35.84; H 2.10; N 9.32; Br 52.86. Calc. for $C_9H_6N_2Br_2$: C 35.79; H 2.00; N 9.28; Br 52.92.) The product was identical with that obtained by bromination of 1-phenyl-3-bromo-pyrazole.[6] The next fraction contained 584 mg of a mixture of 1-phenyl-3,4-dibromo-pyrazole and 1-phenyl-3-bromo-pyrazole. Finally, 1.39 g (29 %) of 1-phenyl-3-bromo-pyrazole came off the column. NMR-data are given in Table 7.

1-Phenyl-5-bromo-pyrazole.[18] 1-Phenyl-5-hydroxy-pyrazole [19] (3.03 g) and phosphoryl bromide (3.5 ml) were heated with stirring to 155°C for 8 h. The mixture was then worked up as in the preceding experiment. (After the hydrolysis, filtration of the mixture was necessary. The residue was washed with methylene chloride (3 × 10 ml). The aqueous phase was then extracted further with methylene chloride as before.) The first fraction contained 1.29 g (23 %) of 1-phenyl-4,5-dibromo-pyrazole as colourless crystals, m.p. 106 – 108°C. Recrystallization from ethanol-water (1:1) did not raise the melting point. (Found: C 35.58; H 2.02; N 9.11; Br 52.74.) The next fraction contained 1.96 g (47 %) of 1-phenyl-5-bromo-pyrazole as colourless crystals, m.p. 54 – 56°C. Recrystallization from ethanol-water did not raise the melting point (reported [18] m.p. 56°). NMR-data are given in Table 7.

1-Benzyl-4-chloro-pyrazole. 1-Benzyl-pyrazole [20] (4.00 g) was dissolved in ether (115 ml) and sulfuryl chloride (7.25 ml) was added with stirring and cooling in an ice-salt bath during 20 min. Stirring was continued for 30 min at 0°C and then for 1 h at room temperature. Water (30 ml) was then added with cooling in ice. The ether phase was isolated and the aqueous phase was extracted with ether (3 × 25 ml). The combined organic extracts were extracted with 4 N hydrochloric acid (30 ml), 20 % aqueous sodium carbonate (3 × 30 ml), dried (magnesium sulfate), and filtered through activated carbon. Removal of the ether gave 4.90 g (100 %) of 1-benzyl-4-chloro-pyrazole as colourless crystals, m.p. 32 – 33°C. Recrystallization from ethanol-water raised the melting point to 33 – 34°C. (Found: C 62.32; H 4.82; N 14.45; Cl 18.27. Calc. for $C_{10}H_9N_2Cl$: C 62.33; H 4.71; N 14.55; Cl 18.41.)

1-Benzyl-4-iodo-pyrazole. 1-Benzyl-pyrazole [20] (4.00 g) and sodium acetate (15.3 g) were dissolved in water (28 ml) and a solution of iodine (28.3 g) and potassium iodide (27.8 g) in water (56 ml) was added. The mixture was heated to reflux for 7 h. After cooling to room temperature a concentrated aqueous solution of potassium hydroxide was added until the solution turned clear light in colour. Sodium thiosulfate (10 g) was then added and the mixture was extracted with methylene chloride (4 × 50 ml). The organic phase was dried (magnesium sulfate) and the methylene chloride was removed. This afforded 6.40 g (89 %) of 1-benzyl-4-iodo-pyrazole, colourless crystals, m.p. 58 – 59°C. Recrystallization from ethanol-water did not raise the melting point. (Found: C 42.26; H 3.21; N 9.80; I 44.57. Calc. for $C_{10}H_9N_2I$: C 42.27; H 3.19; N 9.86; I 44.67.) NMR-data are given in Table 7.

1-Phenyl-4-iodo-pyrazole.[20] Similarly, 1-phenyl-pyrazole (3.99 g) afforded 6.90 g (92 %) of 1-phenyl-4-iodo-pyrazole, m.p. 82 – 84°C (reported [21] m.p. 77°).

1-Phenyl-4-bromo-5-methyl-pyrazole. 1-Phenyl-5-methyl-pyrazole [22] (1.03 g) was dissolved in acetic acid (1.0 ml) and a solution of bromine (0.39 ml) in acetic acid (2.0 ml) was added with stirring during 15 min. Stirring was continued for 1 h. Water (60 ml) was then added and the mixture was cooled to 0°C. The precipitate was isolated and the aqueous phase was extracted with methylene chloride (10 ml). The extract was combined with the separated material and the methylene chloride was removed. The residue was reprecipitated from ethanol-water. The product was then dissolved in ether and filtered through activated carbon. Removal of the ether gave 1.40 g (90 %) of 1-phenyl-4-bromo-5-methyl-pyrazole as a yellow oil which crystallized on cooling to – 30°C, m.p. 34 – 36°C. Recrystallization from 90 % ethanol raised the melting point to 38°C. (Found: C 50.48; H 3.91; N 11.68; Br 33.59. Calc. for $C_{10}H_9N_2Br$: C 50.67; H 3.83; N 11.80; Br 33.71.)

1-Phenyl-3-methyl-4-bromo-pyrazole. 1-Phenyl-3-methyl-pyrazole [23] (1.11 g) was brominated as described above. Water (60 ml) was then added and the mixture was extracted with methylene chloride (3 × 10 ml). The methylene chloride was removed and the crude product was chromatographed on a column of silica gel (100 g) using benzene

as the eluent. The first fraction contained 177 mg (8 %) of a compound which, on the basis of an NMR-spectrum, is assumed to be 1-(*p*-bromo-phenyl)-3-methyl-4-bromo-pyrazole. (NMR-data: δ 7.84, singlet, (1H); δ 7.53, singlet, (4H); δ 2.31, singlet (3H)). The compound melted at 102 – 105°C. The next fraction contained 1.34 g (81 %) of 1-phenyl-3-methyl-4-bromo-pyrazole as an oil which crystallized on cooling, m.p. 28°C. The compound was dissolved in ether and filtered through activated carbon. Removal of the ether and recrystallization from 90 % ethanol gave colourless crystals, m.p. 31°C. (Found: C 50.62; H 3.96; N 11.60; Br 33.45.)

Preparation of pyrazolium tosylates

The pyrazolium tosylates were prepared by one of the following six methods (see Table 4).

A. The pyrazole (*ca.* 5 g) and methyl tosylate (1.2 equiv.) were heated to 145°C for 3 h. The mixture was then washed with ether (5 × 20 ml) and recrystallized from methanol-ether to give the crude product which was crystallized once more from methanol-ether. The product was dried *in vacuo* at room temperature.

B. As *A*, but the mixture of pyrazole and methyl tosylate was heated to 100°C for 3 h.

C. As *A*, but the mixture of pyrazole and methyl tosylate was heated to 100°C for 3 h and then to 145°C for 3 h.

D. As *A*, but after the first recrystallization the product was dissolved in methanol and filtered through activated carbon. Evaporation of the methanol *in vacuo* afforded the crude product which was recrystallized once more from methanol-ether.

E. As *A*, but after the first recrystallization the product was dissolved in water (5 ml per g of product). The aqueous phase was extracted with ether (2 × 10 ml per g of product) and then with methylene chloride (5 × 15 ml per g of product). The methylene chloride solution was dried (magnesium sulfate) and the solvent was removed. The residue was dissolved in methanol and filtered through activated carbon. Evaporation of the methanol and recrystallization from methanol-ether afforded the pure compound.

F. The pyrazole (5 g), benzyl bromide (1.2 equiv.), and dry acetonitrile (3.0 ml) were heated to reflux for 3 h. The mixture was washed with ether (5 × 20 ml), dissolved in water and passed through a column of Amberlite IRA-400 (190 ml) as its salt with *p*-toluene-sulfonic acid. The water was removed *in vacuo* and the residue was recrystallized from methanol-ether.

Reaction of 4-halogeno-substituted pyrazolium tosylates with sodium hydroxide

1-Methyl-2-phenyl-4-bromo-pyrazolium tosylate 1f (994 mg) was added with stirring to boiling 1 N aqueous sodium hydroxide (8.00 ml). The solution was heated to reflux for 10 min and the water was then removed *in vacuo* at room temperature. The residue was extracted with boiling chloroform (50 ml + 4 × 10 ml). The chloroform was removed and the residue was dried *in vacuo* in a desiccator. The residue was then extracted with boiling ethyl acetate (30 ml + 4 × 10 ml), the extracts were filtered through activated carbon and the solvent was removed. The crude product could be purified by recrystallization but chromatography on a column of silica gel (10 g) using ethyl acetate as the eluent was considered to be more convenient. The first fraction contained a small amount of a brown oil which was not identified further. The column was then eluted with ethyl acetate-methanol (1:1). This gave 141 mg (33 %) of 1-phenyl-2-methyl-pyrazol-4-in-3-one *5f*, m.p. 108 – 109°C. The compound was dissolved in ethyl acetate and the solution was filtered through activated carbon. Removal of the ethyl acetate yielded 109 mg of *5f* as colourless crystals, m.p. 119 – 122°C. Recrystallization from ethyl acetate-hexane raised the melting point to 123 – 124°C. The compound is hygroscopic. Melting point, IR- and NMR-spectra proved the identity with the material described below.

In a separate experiment, 1-methyl-2-phenyl-4-bromo-pyrazolium tosylate *1f* (41 mg) was dissolved in 1 N sodium hydroxide (0.40 ml) in an NMR-tube. The tube was heated in the NMR probe to 90°C. After *ca.* 1 min three peaks at δ 2.62, 3.30, and 8.77, relative to DSS, appeared. In the following minutes these peaks grew at the expense of the peak at δ 3.84, corresponding to the starting material *1f*. After *ca.* 10 min no more starting material was present. The signals were identified by adding, one by one, the pure substances to the solution. The three signals corresponded to 1-methyl-2-phenylhydrazine, 1-phenyl-2-methyl-pyrazol-4-in-3-one *5f*, and bromomalonaldehyde, respectively. The yields, calculated on basis of the integral of the methyl group signal of the tosylate anion, were 33 %, 26 %, and 37 %, respectively. In a similar experiment, the solution was acidified with hydrochloric acid after the reaction. The NMR-spectrum of the acidic solution showed three singlets at δ 3.10, 3.55, and 8.73. Again, addition of the pure substances demonstrated the presence of the above mentioned products. In a third experiment, the alkaline reaction mixture was extracted with deuteriochloroform. The organic solution, in addition to phenyl group absorptions and signals due to impurities, exhibited a doublet at δ 5.64 and a singlet at δ 3.29 in the NMR-spectrum. The signals corresponded to 1-phenyl-2-methyl-pyrazol-4-in-3-one *5f* as shown by addition of the authentic substance to the solution.

Deuterium exchange experiments. 1-Methyl-2-phenyl-4-bromo-pyrazolium tosylate *1f* (868 mg) was heated in a mixture of 1 N aqueous sodium hydroxide (4.30 ml) and deuterium oxide (4.30 ml) and the mixture was worked up as described above. The NMR-spectrum of the product, obtained after column chromatography, showed three signals (intensity 1:2:1) symmetrically centered at δ 5.64. The distance between the peaks was 1.8 Hz. This proves the presence of 1-phenyl-2-methyl-pyrazol-4-in-3-one *5f*, (4H5H) and *5f*, (4H5D) in the ratio 1:1. The ratio between the intensity of the triplet and the *N*-methyl group was 1:6.0 indicating that 50 % of the total amount of pyrazol-4-in-3-one present had deuterium incorporated at the 4-position. The 5-proton doublet of *5f* was reduced in intensity and a new peak appeared in the center of the doublet. The relative intensities could not be determined accurately due to overlap with minor phenyl group signals. However, integration indicated that H-5 had been replaced with deuterium to an extent of *ca.* 50 %. Therefore *5f*, (4D5H) and *5f*, (4D5D) are present in the ratio 1:1 and in the same amount as *5f*, (4H5H) and *5f*, (4H5D). In a separate experiment 1-phenyl-2-methyl-pyrazol-4-in-3-one *5f* was heated with 1 N sodium deuteriooxide in deuterium oxide (5.1 ml) and the mixture worked up as described above. The NMR-spectrum of the product, obtained after column chromatography, showed a singlet at δ 5.64. The ratio between the intensity of this signal and the methyl group signal was 1:3.50 indicating that 14 % of H-4 in *5f* had been replaced by deuterium. The doublet corresponding to H-5 in *5f* had disappeared and integration confirmed that *ca.* 100 % of H-4 in *5f* had been replaced by deuterium.

1-Methyl-2-phenyl-4-chloro-pyrazolium tosylate 1f (X = Cl) (572 mg) was heated to reflux with 1 N sodium hydroxide (5.01 ml) and the mixture was worked up as described above for the bromo-compound *1f*. After chromatographic purification 7.6 mg (3 %) of 1-phenyl-2-methyl-pyrazol-4-in-3-one *5f*, identified through its spectra, was obtained.

1-Methyl-2-phenyl-4-iodo-pyrazolium tosylate 1f (X = I). Similarly, *1f* (X = I) (997 mg), after treatment with 1 N sodium hydroxide (4.37 ml) and working up as described above for the bromo-compound *1f* afforded 54 mg (14 %) of 1-phenyl-2-methyl-pyrazol-4-in-3-one *5f*, m.p. 108 – 111°C. Filtration through activated carbon and recrystallization from ethyl acetate-hexane raised the melting point to 123 – 124°C. IR- and NMR-spectra proved the identity with the material described above. As shown by an NMR-spectrum the residue from the ethyl acetate extraction contained, among other compounds, the 1-methyl-2-phenyl-pyrazolium salt *1e*. The latter was identified by addition of the pure substance to the solution.

1,3-Dimethyl-2-phenyl-4-bromo-pyrazolium tosylate 11f A. 11f (679 mg) and 1 N sodium hydroxide (3.2 ml) were heated to reflux for 3 h. The solvent was then removed *in vacuo* and the residue was extracted with boiling chloroform (50 + 4 × 10 ml). The chloroform was removed leaving 87 mg (29 %) of 1-phenyl-2,5-dimethyl-pyrazol-4-in-3-one *14f* ("isoantipyrin") as colourless crystals, m.p. 96 – 100°C. Recrystallization from ethyl acetate-hexane raised the melting point to 117°C (reported [11] m.p. 113°C). IR- and NMR-spectra were identical with those of an authentic sample.[24]

B. 11f (1.22 g) was treated with 1 N sodium hydroxide (5.8 ml) and the mixture worked up as described above for 1-methyl-2-phenyl-4-bromo-pyrazolium tosylate *1f*. The first fraction to leave the column (20 g of silica gel, elution with ethyl acetate) contained 128 mg of a brown oil. (NMR-data: δ 2.05, doublet, (3H) ($J = 1.2$ Hz); δ 2.80, singlet, (3H); δ 4.33, quartet, (1H) ($J = 1.2$ Hz); δ 7.2 – 7.5, multiplet, (*ca.* 7H)). The compound was unstable, even at room temperature, and attempts to purify it were unsuccessful.

Therefore, the material was not identified further. The column was then eluted with ethyl acetate-methanol (1:1). This gave 73 mg (13 %) of 1-phenyl-2,5-dimethyl-pyrazol-4-in-3-one *15f*, m.p. 104 – 106°C. Recrystallization from ethyl acetate-hexane raised the melting point to 117°C.

1-Phenyl-2,3-dimethyl-4-bromo-pyrazolium tosylate 13f (955 mg) was treated with 1 N sodium hydroxide (4.5 ml) as described above for 1-methyl-2-phenyl-4-bromo-pyrazolium tosylate *1f*. The water was then removed *in vacuo* and the residue was extracted with boiling chloroform ($50 + 4 \times 10$ ml). Removal of the chloroform and extraction with boiling ethyl acetate ($50 + 3 \times 20$ ml) gave a residue which was dissolved in water and passed through Amberlite IRA 400 (40 ml) in the *p*-toluenesulfonate form. Removal of the water gave 378 mg (40 %) of unchanged starting material as a brown oil. The ethyl acetate extract was filtered through activated carbon and the solvent was removed leaving 14 mg of a yellow oil. An NMR-spectrum indicated that no 1-methyl-2,5-dimethyl-pyrazol-4-in-3-one *15f* was present.

1-Methyl-2-benzyl-4-bromo-pyrazolium tosylate 1d (1.33 g) and 1 N sodium hydroxide (12.4 ml) were heated to reflux for 3 h. The solvent was evaporated and the residue was extracted with chloroform and with ethyl acetate as described above. The ethyl acetate extract contained 298 mg (51 %) of a mixture of 1-methyl-2-benzyl-pyrazol-4-in-3-one *9d* and 1-benzyl-2-methyl-pyrazol-4-in-3-one *5d* in the ratio 1.62 as shown by the NMR-spectrum in deuteriochloroform solution. The pyrazolones *9d* and *5d* were purified by preparative TLC using methylethyl ketone saturated with water as the eluent. The first fraction contained *9d* contaminated with *5d*. Rechromatography afforded the pure compounds. The second fraction contained pure *5d*. The total yield of *9d* was 93 mg (16 %) as a yellow oil which was dissolved in ethyl acetate and filtered through activated carbon. Removal of the solvent and two reprecipitations from ethyl acetate-hexane raised the melting point to 74 – 80°C. IR- and NMR-spectra proved the identity with the material described below. The total yield of *5d* was 178 mg (30 %) as yellow crystals, m.p. 53 – 55°C. Purification as described for the isomeric compound raised the melting point to 67 – 69°C. The compound was identical with the material described below.

1-Methyl-2-benzyl-4-chloro-pyrazolium tosylate 1d (X = Cl) (1.26 g) and 1 N sodium hydroxide (10.6 ml) similarly gave an ethyl acetate extract which was purified by preparative TLC (methylethyl ketone, one elution). The adjoining zones containing the pyrazolones *9d* and *5d* ($R_F = 0.29$) were combined. Yield 24 mg (3.8 %). An NMR-spectrum indicated that the ratio between *5d* and *9d* was 1.99.

1-Methyl-2-benzyl-4-iodo-pyrazolium tosylate 1d (X = I) (434 mg) and 1 N sodium hydroxide (3.0 ml) similarly gave an ethyl acetate extract which contained 34 mg (20 %) of a mixture of *5d* and *9d* in the ratio 1.66 as indicated by the NMR-spectrum. The residue from the extraction with ethyl acetate consisted of 58 mg (21 %) of 1-methyl-2-benzyl-pyrazolium iodide *1c* (A = I). The latter compound was identified by NMR with addition of the pure compound to the solution.

Reaction of 3-halogeno-substituted pyrazolium tosylates with sodium hydroxide

The pyrazolium salt (*ca.* 1 g) and 1 N aqueous sodium hydroxide (3.2 equiv.) were heated to reflux for 3 h. The solvent was then removed *in vacuo* and the residue was extracted with boiling methylene chloride (5×10 ml). The methylene chloride was removed and the residue was extracted with boiling ethyl acetate (4×10 ml). The solution was filtered through activated carbon. Removal of the ethyl acetate gave the crude pyrazolone which was crystallized from ethyl acetate-hexane. Yields, melting points, and analytical data are given in Table 4. IR- and NMR-data of the pyrazolones are presented in Table 5.

Reactions with sodium methoxide

1-Methyl-2-phenyl-5-bromo-pyrazolium tosylate 1f (250 mg) and 1 N sodium methoxide (2.0 ml) were heated to reflux for 10 min. The mixture was worked up as described for the reaction of *1f* with sodium hydroxide. The yield of 1-phenyl-2-methyl-pyrazol-4-in-3-one *5f* was 5.3 mg (5.0 %).

Kinetic experiments. The pyrazolium tosylate was dissolved in 1 N aqueous potassium hydroxide (0.88 ml per mmol of pyrazolium salt). The solution was placed in a bath the temperature of which was kept at 59.6°C. At intervals samples of 0.45 ml were taken; they were quenched immediately with three drops of conc. hydrochloric acid. The solvent was removed, the residue was dissolved in deuterium oxide and NMR-spectra were measured. The conversion of starting material to pyrazol-4-in-3-one was evaluated from mean-values of several integrations of the *N*-methyl signals. The results are given in Table 6. The total amount of byproducts was estimated by comparing the sum of the integrals of the *N*-methyl group signals of the starting material and of the pyrazol-4-in-3-one with the integral of the *C*-methyl group signal of the tosylate ion.

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