ACTA CHEMICA SCANDINAVICA 27 (1973) 2930–2940

# Reactions between Azolium Salts and Nucleophilic Reagents

## X. The Reaction of 1,2-Disubstituted Pyrazolium Salts with *N*-Bromoacetamide and Sodium Hydroxide or Methoxide

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1,2-Disubstituted pyrazolium salts *8* (X=H) with *N*-bromoacetamide and sodium methoxide, *via* bromination and substitution produce the four 1,2-disubstituted pyrazol-4-in-3-ones *3* and *16* (X=H or Br). The ratio between *3* and *16* (X=H), as expected, is reflected by the ratio between the base-catalyzed deuterium exchange rates of the heteroaromatic protons of the corresponding starting material *8*. The 4-halo-pyrazolium compounds *8* (X=Hal) with *N*-bromoacetamide and sodium methoxide, analogously, afford the halo-pyrazol-4-in-3-ones *3* and *16* (X=Hal), but in a ratio different from the relative D-exchange rate of the heteroaromatic protons of the starting material *8* (X=Hal). This difference is due to equilibration between the intermediate dihalo-compounds *1* and *14* (X=Hal). Thus, pure *1e* and sodium methoxide produces *3e* together with the *tele*-substitution product *16e*. The 4-halo-pyrazolium compounds *8* (X=Hal) with *N*-bromoacetamide and sodium hydroxide, *via* two successive brominations, giving rise to *9* (X=Hal), and subsequent substitution give the dihalo-pyrazol-4-in-3-ones *7* and *13* (X=Hal) in a ratio different from the relative substitution rates of the corresponding monohalo-compounds *1* and *14* (X=H), presumably for steric reasons.

When 1,3-disubstituted [1,2] or 1,2-disubstituted [3] 1,2,3-triazolium salts were treated with *N*-bromoacetamide in sodium hydroxide or methoxide a bromination of the heterocyclic ring, followed by substitution of the bromine atom with hydroxide or methoxide, took place. When the formation of isomeric products was possible the relative rates of the base-catalyzed deuterium exchange of the heteroaromatic protons of the starting material could usually be used to predict the product distribution. The reaction of some pyrazolium salts with *N*-bromoacetamide and sodium hydroxide or methoxide has now been investigated in order to examine if similar predictions about product distribution can be made in this series.

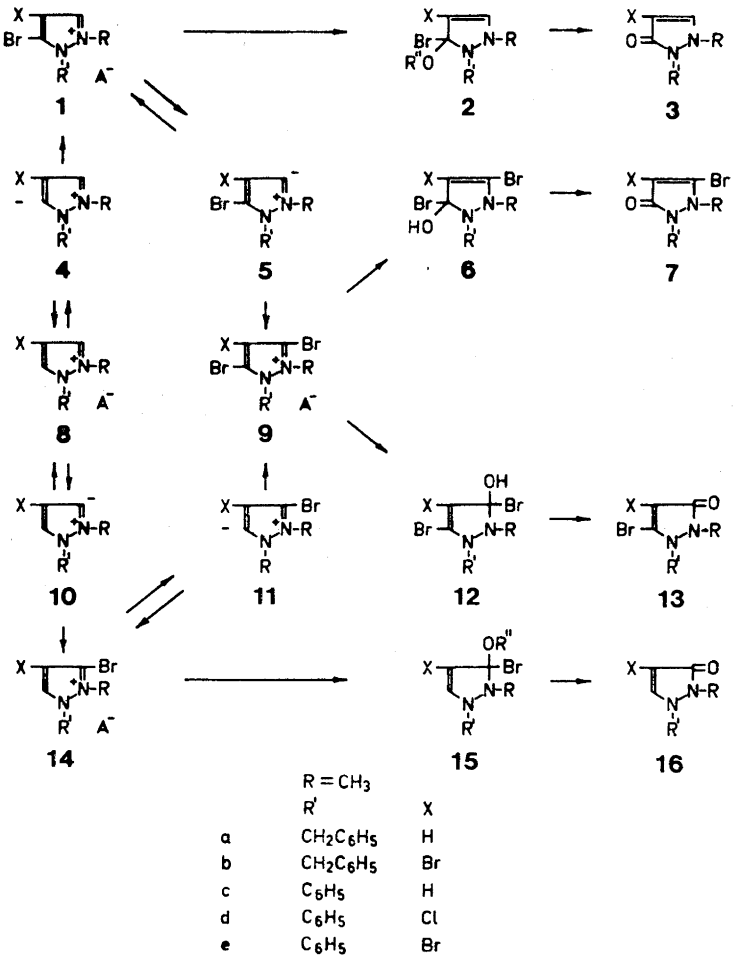
1-Methyl-2-benzyl-pyrazolium tosylate *8 a*, like the 1,2-dimethyl compound *8* ($R' = CH_3$)[4] did not react with *N*-bromoacetamide and aqueous sodium hydroxide. When the stronger base sodium methoxide in methanol was used a mixture of 1-methyl-2-benzyl-pyrazol-4-in-3-one *3a* and 1-benzyl-2-methyl-pyrazol-4-in-3-one *16a* was formed (total yield 21 %). Small amounts of the bromo-derivatives *3b* and *16b* were also isolated (total yield 4 %). Similarly, 1-methyl-2-phenyl-pyrazolium tosylate *8c*, *N*-bromoacetamide, and sodium methoxide produced 1-methyl-2-phenyl-pyrazol-4-in-3-one *3c* and 1-phenyl-2-methyl-pyrazol-4-in-3-one *16c* (total yield 6 %) together with the bromo-derivatives *3e* and *16e* (total yield 9 %).

When the reaction between *8* (X = H), *N*-bromoacetamide, and sodium methoxide was carried out in monodeuteriomethanol the 3- and 5-protons of *8* (X = H) were quantitatively, and almost instantaneously, exchanged with deuterium before any further reaction took place. This indicates that the solution contains a certain amount of the anions *4* and *10*.* These anions can react with either deuterons or with bromine cations delivered from the *N*-bromoacetamide.[1-4] The latter reaction, in analogy to previous considerations,[1-4] produces the bromo compounds *1* and *14*, respectively. Neither these, nor other intermediates, could, however, be observed in the reaction mixture by NMR-spectroscopy, most likely because they undergo a rapid substitution by a normal addition-elimination mechanism.[5] Subsequent *O*-demethylation then produces the pyrazol-4-in-3-ones *3* and *16*[2-4] (Scheme 1).

Since the anions *4* and *10* are very reactive the attack of bromine cations on a mixture of these anions is probably unselective. The ratio between the bromo compounds *1* and *14* will therefore be determined by the relative concentration of *4* and *10* and, hence, by their relative stability. This, in turn, is reflected by the relative deuterium exchange rate of the 3- and 5-protons of the starting material *8*.

Isomerizations between 3-halo-pyrazolium salts *1* (X = H) and *14* (X = H) have never been observed.[5] Thus, 1-methyl-2-phenyl-3-bromo-pyrazolium tosylate *1c* and base afforded the pyrazolone *3c* as the sole product. The isomeric pyrazolone *16c* was not formed. Similarly, the isomeric bromo compound *14c* produced the pyrazolone *16c*, exclusively.[5] Thus, in the present case, the ratio between the bromo compounds *1* and *14* will in its turn reflect the ratio between the final products *3* and *16*. Since the ratio of the exhange rates of the 3- and 5-protons of *8a* was found to be 1.13[5] the expected distribution between the pyrazol-4-in-3-ones *3a* and *16a* is 1.13. The distribution found was 1.04. According to the ratio of the exchange rates of the 3- and 5-protons of *8c*[5] the expected distribution between the pyrazol-4-in-3-ones *3c* and *16c* is 1.29. The distribution found was 1.53. The minor deviations between the predicted and obtained product ratio may be due to decomposition of the 3-bromo-pyrazolium salts *1* and *14*. Thus, considerable decomposition took place when the methylphenylbromopyrazolium tosylate *14c* was treated with potassium hydroxide.[5] The simultaneous formation of the bromo-pyrazol-4-in-3-ones may also influence the product distribution.

* The 3- and 5-protons of the starting material *8* (X = H) are replaced readily with deuterium in aqueous solution at pD = 12, whereas the 4-proton is not replaced at pD = 13 during three months.[5] This explains the lack of reactivity of the 4-position.




*Scheme 1.*

The 4-bromo-pyrazolones *3* (X = Br) and *16* (X = Br) do not arise *via* bromination of the initially formed pyrazolones *3* (X = H) and *16* (X = H) since separate experiments indicated that the latter compounds are not brominated by *N*-bromoacetamide under the conditions of the reaction. Since bromination at C-4 of the starting material *8* (X = H) is highly unlikely due to the slow deuterium exchange of H-4 of *8* (X = H) the bromopyrazolones probably arise *via* the initially formed 3-bromo-pyrazolium salts *1* (X = H) and *14* (X = H). In fact, pure 1-methyl-2-phenyl-3-bromo-pyrazolium tosylate *1c*, when treated with *N*-bromoacetamide and sodium methoxide, affords a mixture of 1-methyl-2-phenyl-pyrazol-4-in-3-one *3c* and the 4-bromo derivative *3e*. Similarly, 1-methyl-2-phenyl-5-bromo-pyrazolium tosylate *14c* gives rise to

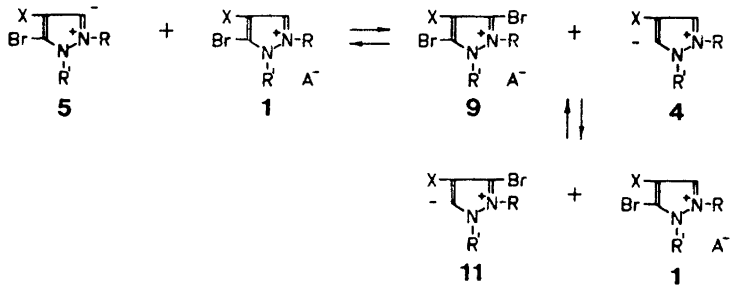
the pyrazolones *16c* and *16e*. The mechanism of formation of the 4-bromo-pyrazolones *3e* and *16e* from the 3-bromo-pyrazolium compounds, *1c* and *14c*, is not evident. Apparently, *1c* and *14c*, *via* the 4-anions, are brominated at *C*-4 giving rise to *1e* and *14e* which in turn, by substitution, produce the bromopyrazolones *3e* and *16e*, respectively. According to the exchange rates of *1c* and *14c*, however, the 3-anions *5c* and *11c* are more stable than the 4-anions.[5] Consequently, the 3-bromo-pyrazolium compounds *1* (X = H) and *14* (X = H) should preferently, *via* *5* (X = H) and *11* (X = H) give rise to the 3,5-dibromo compound *9* (X = H). However, no pyrazolones *7* (X = H) or *13* (X = H) derived from *9* (X = H) could be detected. It is possible that *9* (X = H) decomposes or undergoes further bromination followed by debromination and subsequent substitution to give the isolated bromopyrazolones *3* (X = Br) and *16* (X = Br). This possibility is only speculative as yet. Since the mechanism of the formation of the bromo pyrazolones *3* (X = Br) and *16* (X = Br) from *8* (X = H) is unknown the ratio between *3* (X = Br) and *16* (X = Br) cannot be predicted.

The behaviour of 4-bromo-pyrazolium compounds *8* (X = Br) was now studied. When 1-methyl-2-benzyl-4-bromo-pyrazolium tosylate *8b* was treated with *N*-bromoacetamide and sodium methoxide 1-methyl-2-benzyl-4-bromo-pyrazol-4-in-3-one *3b* and 1-benzyl-2-methyl-4-bromo-pyrazol-4-in-3-one *16b* were produced (total yield 76 %). In analogy to the previous experiment, it is assumed that the dibromo compounds *1b* and *14b* arise initially *via* the anions *4b* and *10b* , respectively. Halogen in the 3-position of 1,2-disubstituted pyrazolium salts is replaced readily with nucleophilic reagents in contrast to halogen in the 4-position.[4,5] Therefore, the dibromo compounds *1b* and *14b* are expected to give *3b* and *16b*.

Provided that the conversion of the dibromo compounds to the bromo-pyrazol-4-in-3-ones *3b* and *16b* is kinetically controlled, the distribution between *3b* and *16b* should, as before, be reflected by the relative stability of the anions *4b* and *10b* and, hence, by the relative exchange rate of the 3- and 5-protons of the starting material *8b*. This exchange rate was determined to be 1.16. In contrast, the ratio between the methylbenzylbromopyrazolones *3b* and *16b* was found to be 0.74.

A similar difference between expected (1.35) and found (0.84) ratio was observed between the methylphenylbromopyrazolones *3e* and *16e*, produced by treatment of 1-methyl-2-phenyl-4-bromo-pyrazolium tosylate *8e* with *N*-bromoacetamide and sodium methoxide. The total yield of *3e* and *16e* was 59 %. Analogous results were obtained using 1-methyl-2-phenyl-4-chloro-pyrazolium tosylate *8d* as the starting material (see Experimental). These discrepancies may be explained by assuming that equilibration between the intermediate dihalo compounds *1* (X = Br) and *14* (X = Br) takes place. The ratio found being due to a net conversion of *1* (X = Br) to *14* (X = Br).

In order to investigate this possibility, pure 1-methyl-2-phenyl-3,4-dibromo-pyrazolium tosylate *1e*, prepared from 1-phenyl-4,5-dibromo-pyrazole and methyl tosylate, was treated with sodium methoxide. In fact, *1e* produced a mixture of the 4-bromo-pyrazol-4-in-3-one *3e* and the *tele*-substitution product *16e* in the ratio 8.2. A proposed mechanism for the *tele*-substitution of the dibromo compound *1e* is sketched in Scheme 2. Initially, *1e* loses a proton.



*Scheme 2.*

Since 3,4-di-bromo-pyrazolium salts may donate bromonium ions from the 3-position under basic conditions,[4] the anion *5e* may receive a bromonium ion from unchanged *1e*. The new anion *4e* thus produced may now receive a bromonium ion from the tribromo compound *9e*. If *9e* offers the bromine adjacent to the phenyl group the result is isomerization of the dibromo compound *1e* to *14e* as shown in Scheme 2. As a result a complex mixture arises. The highly different ratios between *3e* and *16e*, obtained from the monobromo compound *8e* or the dibromo compound *1e*, indicate that complete equilibration between the dibromo compounds is not reached. Therefore, predictions about the distribution between *3e* and *16e* in these cases are impossible. In the same way, the ratio between the methylphenylchloro-pyrazolones *3d* and *16d*, formed from *8c*, and analogously, the ratio between the methylbenzyl-bromo-pyrazolones *3d* and *16b*, formed from *8b*, cannot be predicted.

When 1-methyl-2-benzyl-4-bromo-pyrazolium tosylate *8b* was treated with *N*-bromoacetamide and sodium hydroxide 1-methyl-2-benzyl-4,5-dibromo-pyrazol-4-in-3-one *7b* and 1-benzyl-2-methyl-4,5-dibromo-pyrazol-4-in-3-one *13b* were obtained as the sole pyrazolones (total yield 28 %). Most likely, the dibromo compounds *1b* and *14b* are formed, as in the preceding experiment, *via* proton abstraction and bromination. The intermediates *1b* and *14b* then abstract a proton before substitution occurs producing the anions *5b* and *11b*, respectively. The latter species finally take up bromine cations to give the same tribromo-pyrazolium salt *9b*. This course is analogous to that found in the 1,2,3-triazolium salt series where substitution is slower than further bromination when the weaker nucleophile sodium hydroxide is used as the base.[1,3] The tribromopyrazolium salt *9b* in its turn, by substitution of the more reactive 3- and 5-halogen atoms, yields the dibromo-pyrazol-4-in-3-ones *7b* and *13b*, respectively. Since the latter process is product determining the distribution between *7b* and *13b* must depend on the relative reactivity of the 3- and the 5-halogens of the tribromo compound *9b* towards substitution. This ratio is expected to be reflected by the relative substitution rate of 1-methyl-2-benzyl-3-bromo-pyrazolium tosylate *1a* and 1-methyl-2-benzyl-5-bromo-pyrazolium tosylate *14a*, respectively, or by the rate of the chloro-analogs, as well. The latter substitution rate ratio was determined to be 0.30.[5] This ratio deviates somewhat from the ratio (0.21) between the dibromo-pyrazolones *7b* and *13b*, obtained by treatment of 1-methyl-2-benzyl-4-bromo-

pyrazolium tosylate *8b* with *N*-bromoacetamide and sodium hydroxide.

When 1-methyl-2-phenyl-4-bromo-pyrazolium tosylate *8e* was treated with *N*-bromoacetamide and sodium hydroxide 1-phenyl-2-methyl-4,5-dibromo-pyrazol-4-in-3-one *7e* and 1-methyl-2-phenyl-4,5-dibromo-pyrazol-4-in-3-one *13e* were obtained as the sole pyrazolones (total yield 62 %). The ratio between the rate of substitution of 1-methyl-2-phenyl-3-bromo-pyrazolium tosylate *1c* and 1-methyl-2-phenyl-5-bromo-pyrazolium tosylate *14c* was found to be 0.18.[5] Thus, this is the expected ratio between the dibromo-pyrazolones *7e* and *13e*, formed from *8e*. However, the ratio found was 0.35. A similar deviation between expected (0.18) and found (0.35) product distribution was found in the reaction of 1-methyl-2-phenyl-4-chloro-pyrazolium tosylate *8d* with *N*-bromoacetamide and sodium hydroxide (see Experimental).

These discrepancies may be due to decomposition of the tribromo compound similar to the decomposition of 1-methyl-2-phenyl-5-bromo-pyrazolium tosylate *14c*.[5] Steric effects may also alter the relative substitution rate of the 3- and 5-halogen in the trihalo compound *9* (X = Br) as compared to the relative substitution rate of the 3- and 5-halogen in the monohalo compounds *1* (X = H) and *14* (X = H).

The results described in the present paper indicate that 1,2-disubstituted pyrazolium salts, when treated with *N*-bromoacetamide and base yield the expected products. However, the product distribution cannot be predicted exactly on basis of the base catalyzed deuterium exchange of the hetero-aromatic protons of the starting material or the substitution rates of simple model compounds. In the reaction of 4-halo pyrazolium compounds *8* (X = Br) with *N*-bromoacetamide and sodium methoxide the process is not kinetically controlled. In the other cases discussed above competing decomposition and steric factors may influence the product distribution.

The pyrazol-4-in-3-ones described in the present paper were identified through their IR- and NMR-spectra (Table 1) which showed absorption characteristics of other 1,2-disubstituted pyrazol-4-in-3-ones.[4,5] As described previously, the NMR-signal of the phenyl group of 1-methyl-2-benzyl-pyrazol-4-in-3-one *3a*, the structure of which has been proven by chemical transformation, turned out to be a broad singlet.[5] In contrast, the phenyl group of the isomeric 1-benzyl-2-methyl-pyrazol-4-in-3-one *16a* appeared as a multiplet. This difference may be explained in terms of deshielding of the *ortho*-phenyl-protons by the pyrazole-ring.[6] The isomeric pairs of bromo- and dibromo-pyrazolones *3b* and *16b*, or *7b* and *13b* showed a similar difference on which the structure identification was based. These assignments were proved by chemical transformation. Thus 1-benzyl-2-methyl-4-bromo-pyrazol-4-in-3-one *16b*, and 1-benzyl-2-methyl-4,5-dibromo-pyrazol-4-in-3- one *13b*, when treated with sodium borohydride and palladium on charcoal, both produced 1-benzyl-2-methyl-pyrazol-4-in-3-one *16a* in high yield.

As described previously, the NMR-signal of the phenyl group of 1-methyl-2-phenyl-pyrazol-4-in-3-one *3c*, the structure of which has been proven by chemical transformations, turned out to be a broad singlet.[5] In contrast, the phenyl group signal of the isomeric 1-phenyl-2-methyl-pyrazol-4-in-3-one *16c* appeared as a broad multiplet. Again, the difference may be explained in terms of deshielding of the *o*-phenyl protons by the pyrazole-ring.[6] This

*Table 1.* NMR-spectra in deuteriochloroform with TMS as an internal standard ($\delta$-values), and infrared absorptions of the carbonyl groups of 1,2-disubstituted pyrazol-4-in-3-ones.

| Compound | IR[a] $cm^{-1}$ | Phenyl group | H-4 ppm | H-5 ppm | N-$CH_3$ N-$CH_2$ ppm | $J_{^{13}C-H}$ Hz | $J_{H_4H_5}$ Hz |
|---|---|---|---|---|---|---|---|
| 1-Methyl-2-benzyl-pyrazol-4-in-3-one *3a*[b] | 1620 | broad singlet | 5.50 | 7.17 | 3.23<br>5.07 | 141 | 3.4 |
| 1-Benzyl-2-methyl-pyrazol-4-in-3-one *16a*[b] | 1625 | multiplet | 5.46 | 7.39 | 3.30<br>4.83 | 141 | 3.4 |
| 1-Methyl-2-benzyl-4-bromo-pyrazol-4-in-3-one *3b* | 1640 | broad doublet | | 7.32 | 3.25<br>5.07 | 142 | |
| 1-Benzyl-2-methyl-4-bromo-pyrazol-4-in-3-one *16b* | 1630 | multiplet | | 7.43 | 3.37<br>4.82 | 141 | |
| 1-Methyl-2-benzyl-4,5-dibromo-pyrazol-4-in-3-one *7b* | 1635 | broad singlet | | | 3.29<br>5.09 | | |
| 1-Benzyl-2-methyl-4,5-dibromo-pyrazol-4-in-3-one *13b* | 1655 | multiplet | | | 3.35<br>5.00 | | |
| 1-Methyl-2-phenyl-pyrazol-4-in-3-one *3c*[b] | 1645 | broad singlet | 5.56 | 7.45 | 3.14 | 142 | 3.6 |
| 1-Phenyl-2-methyl-pyrazol-4-in-3-one *16c*[b] | 1630 | broad multiplet | 5.64 | 7.57 | 3.28 | 142 | 3.7 |
| 1-Methyl-2-phenyl-4-chloro-pyrazol-4-in-3-one *3d* | 1670 | broad singlet | | 7.59 | 3.11 | 142 | |
| 1-Phenyl-2-methyl-4-chloro--pyrazol-4-in-3-one *16d* | 1635 | broad multiplet | 7.64 | 3.31 | | 142 | |
| 1-Methyl-2-phenyl-4-bromo--pyrazol-4-in-3-one *3e* | 1660 | broad singlet | 7.65 | 3.14 | | 142 | |
| 1-Phenyl-2-methyl-4-bromo--pyrazol-4-in-3-one *16e* | 1635 | broad multiplet | 7.65 | 3.32 | | 142 | |
| 1-Methyl-2-phenyl-4-chloro-5-bromo-pyrazol-4-in-3-one *7d* | 1680 | singlet | | 3.19 | | 142 | |
| 1-Phenyl-2-methyl-4-chloro-5-bromo-pyrazol-4-in-3-one *13d* | 1660 | multiplet | | 3.20 | | 142 | |
| 1-Methyl-2-phenyl-4,5-dibromo-pyrazol-4-in-3-one *7e* | 1675 | singlet | | 3.22 | | 142 | |
| 1-Phenyl-2-methyl-4,5-dibromo-pyrazol-4-in-3-one *13e* | 1670 | multiplet | | 3.22 | | 142 | |

[a] IR-spectra were obtained in potassium bromide discs. [b] The data have been described previously [5] but are shown here for comparison.

difference could be used in the structure determination of the isomeric pairs of bromo-pyrazolones *3e* and *16e*, chloro-pyrazolones *3d* and *16d*, dibromo-pyrazolones *7e* and *13e*, and chlorobromo-pyrazolones *7d* and *13d*, respectively. In one case the identification was controlled by chemical conversion. Thus, the supposed 1-phenyl-2-methyl-4,5-dibromo-pyrazol-4-in-3-one *13e* when treated with sodium borohydride and palladium on charcoal afforded the parent 1-phenyl-2-methyl-pyrazol-4-in-3-one *16c* in 96 % yield.

## 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 Häen, Leucht-

pigment ZS Super) was added to the silica gel and tubes 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 ($\delta$-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-4,5-dibromo-pyrazole.* 1-Phenyl-5-bromo-pyrazole [5] (1.00 g) was dissolved in glacial acetic acid (1.00 ml) and a solution of bromine (0.28 ml) in glacial acetic acid (1.9 ml) was added with stirring during 15 min. Stirring was continued for 1 h, and water (40 ml) was then added. Filtration yielded 1.29 g (94 %) of 1-phenyl-4,5-dibromo-pyrazole. Recrystallization from ethanol-water (1:1) afforded 1.17 g (84 %) of colourless crystals, m.p. 106°C. The compound was identical with that described previously.[5]

*1-Methyl-2-phenyl-3,4-dibromo-pyrazolium tosylate 1e.* 1-Phenyl-4,5-dibromo-pyrazole (1.54 g), methyl tosylate (0.95 ml), and dry acetonitrile (1.00 ml) were heated to 100°C for 3 h. Ether (20 ml) was then added and the precipitate was washed 4 times with ether (20 ml). This afforded 646 mg (26 %) of 1-methyl-2-phenyl-3,4-dibromo-pyrazolium tosylate *1e* as colourless crystals, m.p. 167 – 170°C. Recrystallization from methanol-ether raised the melting point to 180 – 184°C. (Found: C 41.96; H 3.33; N 5.63; S 6.61; Br 32.57. Calc. for $C_{17}H_{16}N_2O_3SBr_2$: C 41.82; H 3.31; N 5.74; S 6.57; Br 32.76). NMR-data in $D_2O$: *H*-5 8.69, *N*-$CH_3$ 3.94 ppm.

## Reactions with sodium methoxide

*1-Methyl-2-benzyl-pyrazolium tosylate 8a* [5] (1.15 g), *N*-bromoacetamide (518 mg) and 1 N sodium methoxide (10.7 ml) were kept at room temperature for 14 days. Sodium thiosulfate (1.0 g) was then added. The solvent was removed, water (10 ml) was added, and the solution was extracted with methylene chloride (3 × 20 ml). The extract was dried (magnesium sulfate), the methylene chloride was removed and the residue was extracted with boiling ethyl acetate (50 + 20 + 2 × 10 ml). The ethyl acetate was removed and the residue was separated by preparative TLC using methylethyl ketone saturated with water as the eluent. This gave 20 mg (2.2 %) of 1-methyl-2-benzyl-4-bromo-pyrazol-4-in-3-one *3b* ($R_F = 0.66$) identical with the material described below. The next zone contained 13 mg (1.5 %) of 1-benzyl-2-methyl-4-bromo-pyrazol-4-in-3-one *16b* ($R_F = 0.53$) identical with the material described below. The last zone contained 134 mg (21 %) of a mixture of 1-methyl-2-benzyl-pyrazol-4-in-3-one *3a* and 1-benzyl-2-methyl-pyrazol-4-in-3-one *16a* in the ratio 1.04:1, as shown by an NMR-spectrum in deuteriochloroform solution. The pyrazolones were separated by preparative TLC as described previously [5] using methylethyl ketone as the eluent. The fast running fraction contained 35 mg (5.6 %) of 1-methyl-2-benzyl-pyrazol-4-in-3-one *3a*. The slow running fraction contained 44 mg (7.0 %) of 1-benzyl-2-methyl-pyrazol-4-in-3-one *16a*. The latter two compounds were identical with the materials described previously.[5]

*1-Methyl-2-phenyl-pyrazolium tosylate 8c* [5] *and N-bromoacetamide.* (1.03 g and 483 mg, respectively) were kept in 1 N sodium methoxide (9.7 ml) for 14 days. The mixture was then chromatographed on silica gel (50 g). Elution with ethyl acetate (200 ml) gave a mixture of 1-methyl-2-phenyl-4-bromo-pyrazol-4-in-3-one *3e* and 1-phenyl-2-methyl-4-bromo-pyrazol-4-in-3-one *16e* together with some impurities. The ratio between *3e* and *16e* was determined by NMR-spectroscopy in a 1:1 mixture of deuteriochloroform and benzene. The benzene causes upfield shifts of the *N*-methyl groups of 1,2-disubstituted pyrazol-4-in-3-ones. Methyl groups at *N*-1 are shifted much more than methyl groups at *N*-2.[6] The ratio between *3e* and *16e* determined in this way was 1:1.31. Preparative thin layer chromatography (ethyl acetate-ether 1:9) gave 25 mg (3.2 %) of *3e* ($R_F = 0.66$) as a yellow oil. Recrystallization from ethyl acetate-hexane afforded 21 mg of pure *3e*, m.p. 110 – 112°C. The compound was identical with the material described below. The next fraction ($R_F = 0.43$) from the thin layer chromatographically separation yielded 41 mg (5.3 %) of *16e*, m.p. 98 – 103°C. Recrystallization from ethyl acetate-hexane

raised the melting point to 117°C. The material was identical with that described below. The column was then eluted with ethyl acetate-methanol (1:1). This gave a mixture which was extracted with methylene chloride (5 × 8 ml). Removal of the solvent left 1-methyl-2-phenyl-pyrazol-4-in-3-one *3c* and 1-phenyl-2-methyl-pyrazol-4-in-3-one *16c* in the ratio 1.53:1 as shown by NMR-spectroscopy in a 1:1 micture of deuteriochloroform and benzene. The mixture was separated by preparative TLC using acetone as the eluent. The fast moving fraction contained 20 mg (3.6 %) of *3c*, m.p. 103 – 105°C. IR- and NMR-spectra were identical with those of the material described previously.[5] The slow moving fraction contained 11 mg (2.0 %) of *16c*, m.p. 104 – 105°C. IR- and NMR-spectra were identical with those of the material described previously.[5]

*1-Methyl-2-benzyl-4-bromo-pyrazolium tosylate 8b* [5] (743 mg), *N*-bromoacetamide (281 mg), and 1 N sodium methoxide (5.7 ml) were kept at room temperature for 14 days. Sodium thiosulfate (1.0 g) was then added. The methanol was removed, the residue was dissolved in water (5 ml), and the aqueous phase was extracted with methylene chloride (3 × 30 ml). The organic solution was dried (magnesium sulfate) and the methylene chlorid was removed. An NMR-spectrum of the residue dissolved in benzene-deuteriochloroform 1:1 indicated the presence of 1-methyl-2-benzyl-4-bromo-pyrazol-4-in-3-one *3b* and 1-benzyl-2-methyl-4-bromo-pyrazol-4-in-3-one *16b* in the ratio 1:1.36. The pyrazolones were separated on a column of silica gel (53 g) using ethyl acetate as the eluent. First, a minor amount of impurities left the column. Then, 112 mg (24 %) of 1-methyl-2-benzyl-4-bromo-pyrazol-4-in-3-one *3b* was collected. The compound was dissolved in ethyl acetate, filtered through activated carbon, and reprecipitated from ethyl acetate-hexane. This gave *3b* as a colourless oil. (Found: C 49.44; H 4.28; N 10.46; Br. 29.89. Calc. for $C_{11}H_{11}N_2OBr$: C 49.46; H 4.15; N 10.49; Br 29.92). The next fraction contained 242 mg (52 %) of 1-benzyl-2-methyl-4-bromo-pyrazol-4-in-3-one *16b* as colourless crystals, m.p. 98 – 103°C. Purification as described for the isomeric pyrazolone raised the melting point to 104 – 107°C. (Found: C 49.25; H 4.27; N 10.62; Br 29.79).

*1-Methyl-2-phenyl-4-bromo-pyrazolium tosylate 8e* [5] *and N-bromoacetamide* (1.05 g and 325 mg, respectively), were dissolved in 1 N methanolic sodium methoxide (8.2 ml). The solution was kept at room temperature for 14 days. It was then poured on a column of silica gel (50 g) packed with ethyl acetate. Elution with ethyl acetate gave 982 mg of brown crystals. An NMR-spectrum indicated the presence of 1-methyl-2-phenyl-4-bromo-pyrazol-4-in-3-one *3e* and 1-phenyl-2-methyl-4-bromo-pyrazol-4-in-3-one *16e* in the ratio 1:1.19. The two compounds were separated by preparative TLC eluting with ethyl acetate-ether (1:9). The fast moving fraction contained 218 mg (34 %) of 1-methyl-2-phenyl-4-bromo-pyrazol-4-in-3-one *3e*, m.p. 101 – 105°C. Filtration through activated carbon and recrystallization from ethyl acetate-hexane as above gave 160 mg (25 %), m.p. 119°C. (Found: C 47.62; H 3.60; N 11.17; Br 31.58. Calc. for $C_{10}H_9N_2OBr$: C 47.46; H 3.58; N 11.07; Br 31.57). The slow moving fraction contained 231 mg (36 %) of 1-phenyl-2-methyl-4-bromo-pyrazol-4-in-3-one *16e* as colourless crystals, m.p. 117C°. Filtration through activated carbon and recrystallization as above did not raise the melting point. (Found: C 47.59; H 3.67; N 11.14; Br 31.56).

*1-Methyl-2-phenyl-4-chloro-pyrazolium tosylate 8d* [5] *and N-bromoacetamide* (790 mg and 338 mg, respectively) were kept in 1 N sodium methoxide (7.0 ml) for 14 days at room temperature. Chromatography on silica gel (50 g) as described in the preceding experiment gave 479 mg of a mixture of the chloro-pyrazolones *3d* and *16d* in the ratio 1:1.37 as shown by NMR. Preparative TLC as described in the preceding experiment afforded a fast moving fraction containing 138 mg (31 %) of 1-methyl-2-phenyl-4-chloro-pyrazol-4-in-3-one *3d* as colourless crystals, m.p. 117 – 118°C. Filtration through activated carbon and recrystallization as above did not raise the melting point. (Found: C 57.60; H 4.20; N 13.26; Cl 16.85. Calc. for $C_{10}H_9N_2OCl$: C 57.54; H 4.35; N 13.42; Cl 16.99). The slow moving fraction contained 188 mg (42 %) of 1-phenyl-2-methyl-4-chloro-pyrazol-4-in-3-one *16d* as colourless crystals, m.p. 116 – 118°C. Filtration through activated carbon and recrystallization as before afforded 155 mg (34 %), m.p. 122°C. (Found: C 57.70; H 4.41; N 13.17; Cl 16.90).

*1-Methyl-2-phenyl-3,4-dibromo pyrazolium tosylate 1e* (322 mg) and 1 N sodium methoxide (2.10 ml) were kept at room temperature for 14 days. The mixture was then poured on a column of silica gel (30 g) packed with ethyl acetate. Elution with ethyl acetate gave a minor fraction which was not identified further. The second fraction contained 107 mg (41 %) of a mixture of 1-methyl-2-phenyl-4-bromo-pyrazol-4-in-3-one *3d* and

1-phenyl-2-methyl-4-bromo-pyrazol-4-in-3-one *16d* in the ratio 8.2:1 as shown by NMR in a mixture of deuteriochloroform and benzene (1:1). The compounds were identified by adding, one by the other, the pure substances to the solution. TLC (ethyl acetate-ether 9:1) confirmed the presence of *3d* and *16d*.

## Reactions with sodium hydroxide

*1-Methyl-2-benzyl-4-bromo-pyrazolium tosylate 8b* (622 mg), *N*-bromoacetamide (1.11 g) and 1 N sodium hydroxide (8.8 ml) were kept at room temperature for 14 days. Sodium thiosulfate (1.0 g) was then added and the mixture was extracted with methylene chloride (3 × 30 ml). After drying (magnesium sulfate) the methylene chloride was removed. An NMR-spectrum of the residue dissolved in deuteriochloroform-benzene (1:1) indicated the presence of 1-methyl-2-benzyl-4,5-dibromo-pyrazol-4-in-3-one *7b* and 1-benzyl-2-methyl-4,5-dibromo-pyrazol-4-in-3-one *13b* in the ratio 1:4.70. The compounds were separated on a column of silica gel (45 g) using ether as the eluent. First, a minor amount of impurities left the column. Then, 35 mg (7 %) of 1-methyl-2-benzyl-4,5-dibromo-pyrazol-4-in-3-one *7b* was collected. The material was dissolved in ethyl acetate and filtered through activated carbon. Two reprecipitations from ethyl acetate-hexane yielded the pure compound as a colourless oil. (Found: C 38.31; H 3.01; N 8.18; Br 46.40. Calc. for $C_{11}H_{10}N_2OBr_2$: C 38.17; H 2.92; N 8.10; Br 46.18). The next fraction contained a mixture of 1-benzyl-2-methyl-4,5-dibromo-pyrazol-4-in-3-one *13b* and *N*-methyl-*N'*-acetyl-urea. The urea derivative was removed by refluxing the mixture for 3 h with 1 N aqueous sodium hydroxide and subsequent extraction with methylene chloride (3 × 20 ml). Removal of the methylene chloride afforded 108 mg (21 %) of the dibromo-pyrazolone *13b* which was purified as described for the isomeric compound. This gave 1-benzyl-2-methyl-4,5-dibromo-pyrazol-4-in-3-one *13b* as a colourless oil. (Found: C 38.25; H 2.97; N 8.28; Br 45.98).

*1-Methyl-2-phenyl-4-bromo-pyrazolium tosylate 8e and N-bromoacetamide* (1.72 g and 3.21 g, respectively) were dissolved in 1 N sodium hydroxide (25.0 ml) and the solution was kept at room temperature for 14 days. Sodium thiosulfate (1 g) was then added and the solution was extracted with methylene chloride (3 × 20 ml). Drying (magnesium sulfate), removal of the methylene chloride, dissolving in ethyl acetate, filtration through activated carbon, and removal of the solvent gave 1.00 g of yellow crystals. An NMR-spectrum, using chloroform-$d_1$-benzene-$d_6$ (1:1) as the solvent, indicated the presence of 1-methyl-2-phenyl-4,5-dibromo-pyrazol-4-in-3-one *7e* and 1-phenyl-2-methyl-4,5-dibromo-pyrazol-4-in-3-one *13e* in the ratio 1:2.82. The mixture was extracted with four 5 ml portions of boiling ethyl acetate. The extracts were poured into a column of silica gel (60 g) packed with ether. The column was then eluted with ether. The first fraction contained 307 mg (22 %) of 1-methyl-2-phenyl-4,5-dibromo-pyrazol-4-in-3-one *7e* as colourless crystals, m.p. 135 – 151°C. The compound was dissolved in ethyl acetate, filtered through activated carbon, and recrystallized from ethyl acetate-hexane giving 191 mg (14 %), m.p. 154 – 156°C. (Found: C 36.19; H 2.21; N 8.62; Br 48.03. Calc. for $C_{10}H_8N_2OBr_2$: C 36.18; H 2.43; N 8.44; Br 48.14). The next fraction contained 556 mg (40 %) of 1-phenyl-2-methyl-4,5-dibromo-pyrazol-4-in-3-one *13e* as colourless crystals, m.p. 150°C. Filtration through activated carbon and recrystallization from ethyl acetate-hexane did not raise the melting point. (Found: C 35.98; H 2.55; N 8.53; Br 48.05).

*1-Methyl-2-phenyl-4-chloro-pyrazolium tosylate 8d and N-bromoacetamide* (1.36 g and 2.84 g, respectively) dissolved in 1 N sodium hydroxide (23.0 ml) similarly gave 880 mg of a crude mixture of 1-methyl-2-phenyl-4-chloro-5-bromo-pyrazol-4-in-3-one *7d* and 1-phenyl-2-methyl-4-chloro-5-bromo-pyrazol-4-in-3-one *13d* in the ratio 1:2.85 as shown by NMR-spectroscopy. The product was dissolved in ethyl acetate and filtered through activated carbon. The ethyl acetate was removed and the mixture was chromatographed on silica gel (56 g) as described in the preceding experiment. This afforded 185 mg (17 %) of *7d*, m.p. 117 – 124°C, and 479 mg (45 %) of *13d*, m.p. 117 – 120°C. Filtration through activated carbon and recrystallization as described in the preceding experiment afforded 140 mg (13 %) of 1-methyl-2-phenyl-4-chloro-5-bromo-pyrazol-4-in-3-one *7d* as colourless crystals, m.p. 131°C. (Found: C 41.67; H 2.71; Br 27.95; Cl 12.28. Calc. for $C_{10}H_8N_2OBrCl$: C 41.75; H 2.81; N 9.74; Br 27.79; Cl 12.33). The yield of 1-phenyl-2-

methyl-4-chloro-5-bromo-pyrazol-4-in-3-one *13d* was 428 mg (40 %) after purification. Colourless crystals, m.p. 133 – 134°C. (Found: C 41.92; H 2.89; N 9.54; Br 27.85; Cl 11.25).

*Dehalogenation of 1-benzyl-2-methyl-4-bromo-pyrazol-4-in-3-one. 16b* (195 mg) was dehalogenated as described for [1-methyl-3-phenyl-5-bromo-4-(1,2,3-triazolio)]oxide [1] using 60 mg of palladium on charcoal and 119 mg of sodium borohydride. The acidification was omitted. The crude product was dissolved in ethyl acetate and filtered through activated carbon. Removal of the ethyl acetate afforded 123 mg (90 %) of 1-benzyl-2-methyl-pyrazol-4-in-3-one *16a*, m.p. 52 – 54°C. IR- and NMR-spectra proved the identity with the material described previously.[5]

*Dehalogenation of 1-benzyl-2-methyl-4,5-dibromo-pyrazol-4-in-3-one.* Similarly, *13b* (95 mg), palladium on charcoal (26 mg), and sodium borohydride (47 mg) produced 32 mg (62 %) 1-benzyl-2-methyl-pyrazol-4-in-3-one *16a*, identical with the material described previously.[5]

*Dehalogenation of 1-phenyl-2-methyl-4,5-dibromo-pyrazol-4-in-3-one.* Similarly, *13e* (287 mg), palladium on charcoal (71 mg), and sodium borohydride (137 mg) produced 145 mg (96 %) of 1-phenyl-2-methyl-pyrazol-4-in-3-one *16c*, m.p. 115 – 117°C, identical with the material described previously.[5]

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Received April 18, 1973.