

A theoretical study of the mechanism of oxidation of 1*H*-pyrazolines to 1*H*-pyrazoles by molecular bromine

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Dedicated to Professor Rosa M. Claramunt on the occasion of her 65th anniversary

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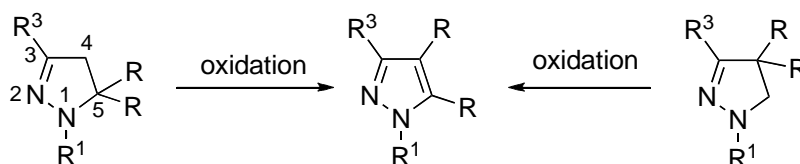
Abstract

The bromine oxidation of NH-pyrazolines to pyrazoles involves a bromo substituted 2- or 1-pyrazoline. The present paper explores theoretically the different possibilities comparing the published NMR results to the experimental ones. Besides, geometries and energies are reported and discussed.

Keywords: Dihydropyrazoles, pyrazolines, bromination, DFT calculations, GIAO, coupling constants

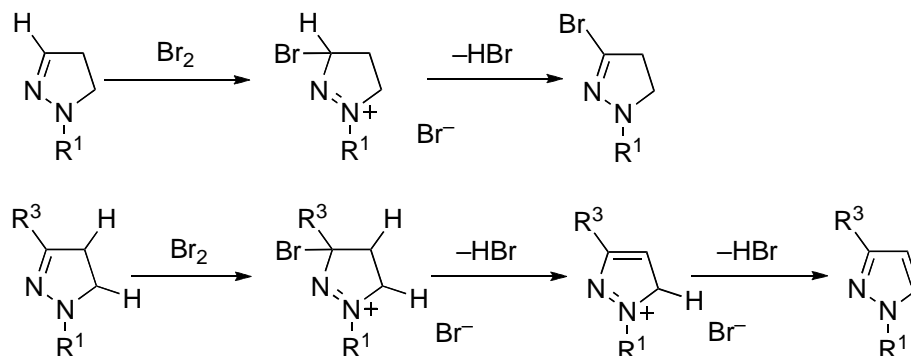
Introduction

Oxidation of 2-pyrazolines (4,5-dihydro-1*H*-pyrazoles) is one of the classical methods to prepare pyrazoles.¹⁻⁴ Several oxidizing agents have been used, amongst them bromine in different solvents. Bromine is an efficient and inexpensive agent but in some cases the resulting pyrazole is further brominated on the ring or in a substituent, for instance an aryl group. If one of the C4 or C5 carbon atoms is disubstituted the oxidation to pyrazole is accompanied by a retropinacol rearrangement with migration of one of the substituents to the adjacent position (Scheme 1).^{1a,2a,4a}



Scheme 1. The retropinacol rearrangement of 2-pyrazolines.

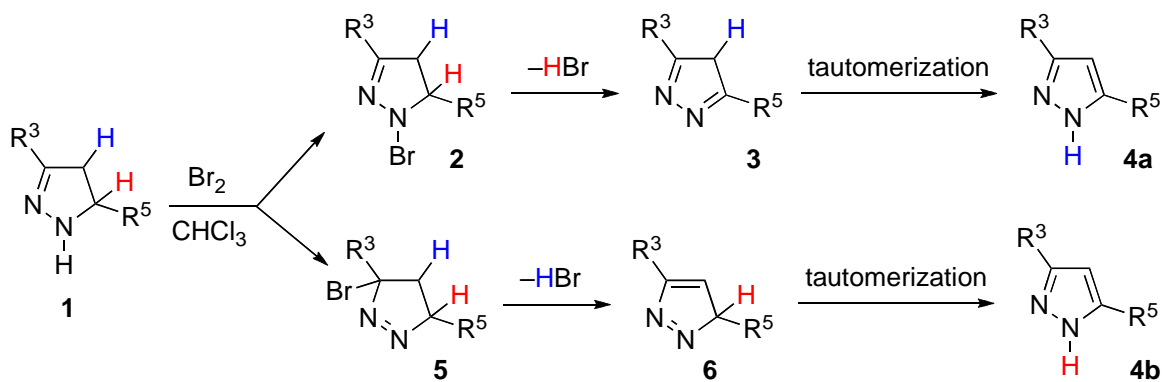
In what concerns bromination of 1-substituted-2-pyrazolines, the accepted mechanism is represented in Scheme 2.



Scheme 2. Bromination of 1-substituted-2-pyrazolines.

If the position 3 is unsubstituted a 3-bromopyrazoline is obtained that can be further oxidized to a 3-bromopyrazole. When there is a substituent at position 3, then two molecules of hydrogen bromide are eliminated and a pyrazole was isolated. The behavior depicted in Scheme 2 was referred to "enamine-like"⁵ and the kinetic parameters determined (order 2, $k = 2.2 \times 10^6 \text{ l.mol}^{-1}.\text{s}^{-1}$ for 1-phenyl-2-pyrazoline).⁶

When in position 1 there is an H atom, 1*H*-2-pyrazolines, there is another possibility, that the bromination occurs on the N1 nitrogen atom, somewhat related to the bromination of succinimide to affords NBS (*N*-bromosuccinimide).⁷ In Scheme 3 we have represented two possible mechanisms.



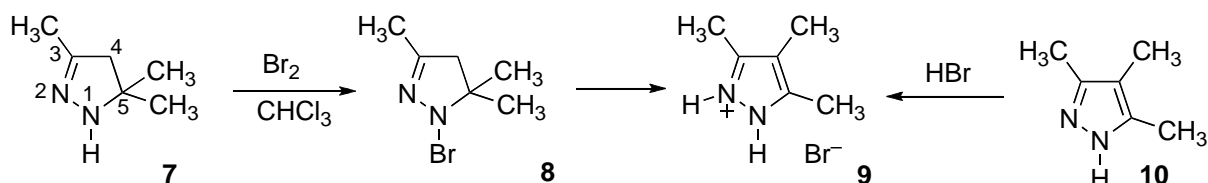
Scheme 3. The two mechanisms of oxidation of 1*H*-2-pyrazolines to 1*H*-pyrazoles.

In the present paper we will report our results concerning the mechanisms of Scheme 3.

Results and Discussion

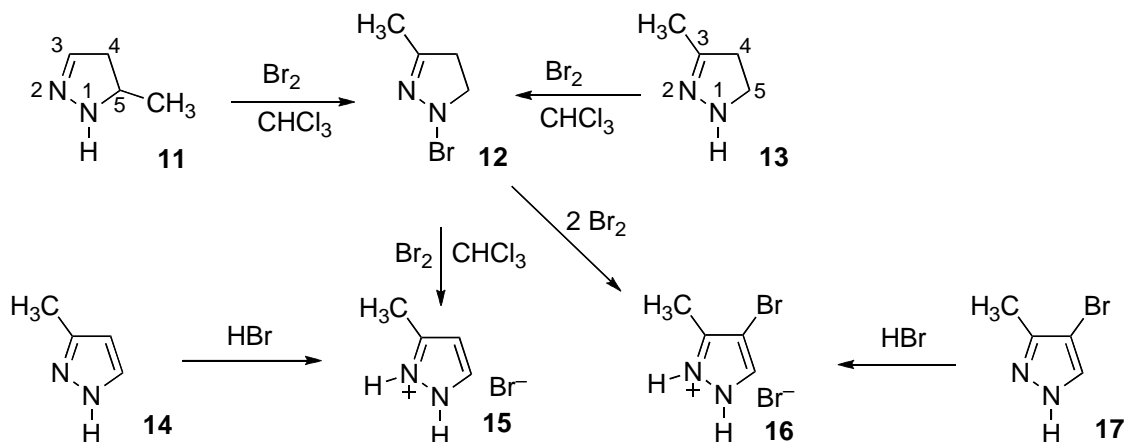
In 1962 and then, in more detail, in 1963 we proposed a mechanism involving an *N*-bromination.^{8,9} We maintain this mechanism in subsequent papers of 1964 and 1965,^{10,11} and corrected it in 1967.⁵ In the meantime, in 1966 a paper by Closs and Heyn appeared in which they prove conclusively that the intermediate was a 3-bromo-1-pyrazoline **5** and not a 1-bromo-2-pyrazoline **2**.¹²

The experiments were carried out on 3,5,5-trimethyl-2-pyrazoline (**7**, Scheme 4) and on 5-methyl (**11**) and 3-methyl-2-pyrazoline (**13**, Scheme 5).



Scheme 4. The mechanism we proposed for the bromination of **7**.

The brominated pyrazoline **8** was isolated (Bp_{0.5} = 58 °C, m.p. 16 °C) and characterized by its reactivity with potassium iodide, silver nitrate and sulfur dioxide. In IR, there is no NH band and presents a doublet at 1360-1370 cm⁻¹ characteristic of a gem-dimethyl group. Its ¹H NMR in CDCl₃ at 56.4 MHz shows bands at δ 1.45 (s, gem-dimethyl), 2.14 (s, 3-methyl) and a quartet centered at 1.99 ppm (*J* = 14.7 Hz) corresponding to the protons of the 4-position.⁹

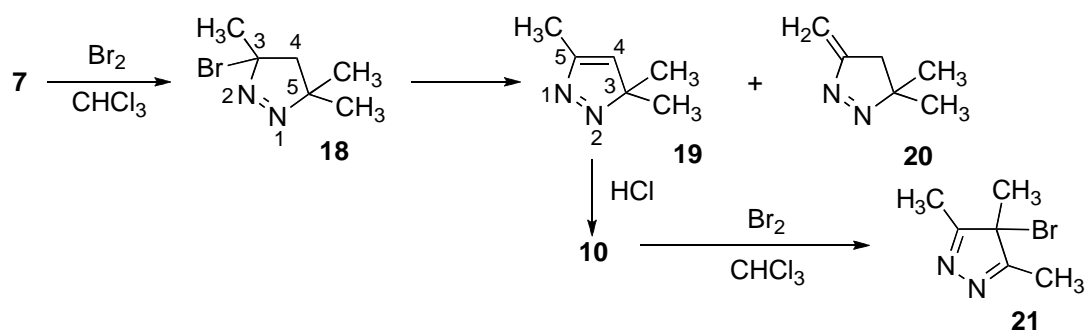


Scheme 5. The mechanism we proposed in 1962-1963 for the bromination of **11** and **13**.

In the same papers we reported that the bromination of 5-methyl-2-pyrazoline (**11**) affords **12** because the coupling between the 5-methyl and the 5-H disappears (in **11**, ³*J*₅₅ = 6.8 Hz) while a signal appears at 2.68 that we assigned to a 3-methyl group (in **13**, 3-methyl at 1.97 ppm). Thus,

the bromination was accompanied by an isomerization of **11** to **13**. It was verified that the bromination of **13** affords **12**.

In 1966, Closs and Heyn working at 60 MHz in CCl₄ interpreted the NMR spectrum of the compound obtained by bromination of **7** as belonging to structure **18** (Scheme 6). The signals appeared at δ 1.41 (s, gem-dimethyl), 2.09 (s, 3-methyl) and an AB system at 2.26 and 1.65 ppm ($J = 14.6$ Hz) corresponding to the protons of the 4-position. They concluded that the molecule does not have a plane of symmetry and therefore cannot be **8**. Besides, in toluene the methyl groups of the gem-dimethyl displays two signals ($\Delta\delta = 0.08$ ppm) and also in pyridine ($\Delta\delta = 0.02$ ppm).¹² Additional evidence against the *N*-bromo structure **8** was the lack of coupling between the methyl protons at position 3 and the methylene protons at C-4 that in other pyrazolines amount to approximately 1 Hz.¹²



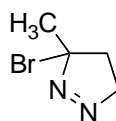
Scheme 6. The mechanism proposed by Closs and Heyn in 1966 for the bromination of **7**.

These arguments are convincing; we have also reported the small $^4J_{34}$ coupling of about 1 Hz, for instance for **13**, the methyl group appears as a triplet with a J of 0.9 Hz.¹¹ Afterwards, we reported that this coupling is dependent on the 1-substituent and that in some cases vanished.¹³ It cannot be excluded that the bromine substituent affects $^4J_{34}$ to the point to be not observable.

However, the main argument was that **8** was planar on average leading to the isochrony of the protons of the 4-position and of that of the methyl groups. At about the same time that these papers appeared, the very slow inversion process for *N*-halogenoaziridines was discovered¹⁴⁻¹⁷ providing a possible explanation based on structure **8**.

The structure of the products of direct bromination of 2-pyrazolines

We have published papers concerning the NMR properties of 2-pyrazolines, ^1H ,¹⁸⁻²⁰ ^{13}C ,^{21,22} and ^{15}N .²³ Results from other authors can be found in references^{4,24,25}. Also the geometries of these five-membered heterocycles related to the envelope of cyclopentane have been discussed and compared with crystallographic data from the CSD.²⁷

**22**

In Table 1 are some data of the calculated geometries of pyrazolines and in Figure 1 a view of **8** and **18** showing that the bromine atoms are clearly out-of-plane. The only structure related to **18** found in the CSD, BHXMPZ (3-bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3*H*-pyrazole),^{27,28} is also represented.

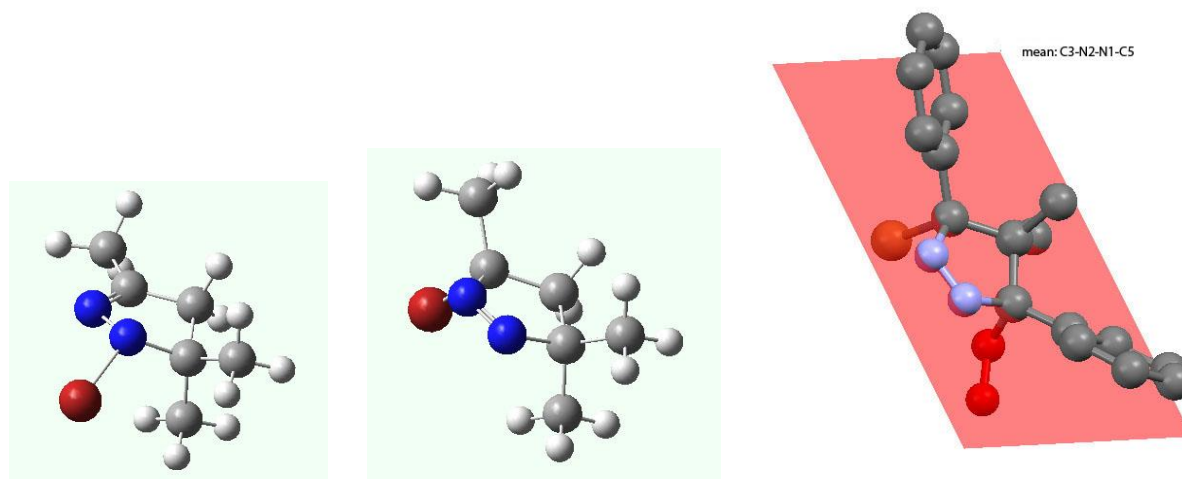


Figure 1. A view of the optimized geometries of bromopyrazolines **8** (left), **18** (center) and BHXMPZ (right) (C3-N2-N1-C5 mean plane in red).

Table 1. Some geometrical data of pyrazolines. X is the atom, H or Br, of the substituent on the out-of-plane atom, N or C, of the envelope

Comp.	Δ^2/Δ^1	N(C)-R	Folding (θ°)	$d_{\text{N(C)-mean plane}} (\text{\AA})$	$d_{\text{Br-mean plane}} (\text{\AA})$
7	Δ^2	NH	26.8	0.43	
8	Δ^2	NBr	32.4	0.53	0.89
11	Δ^2	NH	28.2	0.44	
12	Δ^2	NBr	31.1	0.49	1.08
13	Δ^2	NH	29.2	0.46	
18	Δ^1	CBr	13.1	0.22	1.84
22	Δ^1	CBr	13.9	0.33	1.90
BHXMPZ	Δ^1	CBr	28.0	0.46	1.85

Unsubstituted Δ^2 -pyrazoline and Δ^1 -pyrazoline have folding angles of $\theta = 28^\circ$ and 13.5° , respectively, in perfect agreement with the data of Table 1.²⁶ The NBr derivatives are more folded than the NH-ones, by about 4° . The X-ray structure, BHXMPZ, differs but it has special substituents like OOH.

In Table 2 are the calculated energies of pyrazolines **7**, **8**, **11**, **12**, **13**, **18** and **22**.

Table 2. Electronic energy values (hartree), relative values and inversion barriers (kJ mol⁻¹) and dipole moments (D)

Comp.	Δ^2/Δ^1	N-R	SCF Energy	Energy + ZPE	E _{rel} + ZPE	TS	TS+ZPE	Dipole
7	Δ^2	NH	-345.44074	-345.26459	----	16.7	13.0	2.51
8	Δ^2	NBr	-2918.95007	-2918.78510	8-18 : 65.1	33.4	31.7	4.02
11	Δ^2	NH	-266.78098	-266.65976	11-13 : 13.1	14.5	11.0	2.60
12	Δ^2	NBr	-2840.29754	-2840.18756	12-22 : 61.3	40.9	39.0	4.06
13	Δ^2	NH	-266.785913	-266.66476	13 most stable	18.0	14.0	2.45
22	Δ^1	----	-2840.32110	-2840.21090	22 most stable	----	----	3.72
18	Δ^1	----	-2918.97557	-2918.80989	18 most stable	----	----	3.76

The most important conclusion of Table 2 is that C-bromo- Δ^1 -pyrazolines are much more stable than N-bromo- Δ^2 -pyrazolines: 65.1 kJ mol⁻¹ for the 3,5,5-trimethyl derivatives (**8** and **18**) and 61.3 kJ mol⁻¹ for the 3-methyl series (**12** and **22**). Besides, 3-methylpyrazoline (**13**) is more stable than 5-methylpyrazoline (**11**) by 13.1 kJ mol⁻¹. We have shown experimentally, that **11** isomerizes into **13** in basic and acid conditions;¹¹ this explains how the same compound is formed from **11** and from **13** being it N-bromo **12** or C-bromo **22**.

The inversion barriers, ZPE (Zero-point energy) corrected, are much smaller for N-H than for N-Br, the first are between 11 and 14 kJ mol⁻¹ while the second are between 32 and 39 kJ mol⁻¹ (factor between 2.2 and 3.6). In any case, barriers in the range between 30-40 kJ mol⁻¹ are too low to justify the distereotopicity of methylene and methyl protons of the positions 4 and 5 in **8**.^{29,30}

We have calculated the inversion barriers including the ZPE correction of 1*H*-aziridine (62.9 kJ mol⁻¹), 1-chloroaziridine (101.8 kJ mol⁻¹) and 1-bromoaziridine (91.7 kJ mol⁻¹) corresponding to an increase of the barriers by halogenation of 1.6 (Cl) and 1.5 times (Br). Another calculation (cc-pVDZ, cc-pVTZ and cc-pVQZ extrapolated to focal-point) for the barrier of 1*H*-aziridine affords 79 kJ mol⁻¹.³¹ Experimental values are 73 kJ mol⁻¹ for 1*H*-aziridine (CCl₄)³² and much higher than 90 kJ mol⁻¹ for N-chloro and N-bromoaziridines.³³ Other authors estimate the barriers of these last compounds to 105-115 kJ mol⁻¹.³⁴ Our barrier for 1*H*-aziridine is underestimated ($73/62.9 = 1.16$), using this factor of proportionality, the values for N-chloro and N-bromoaziridines can be estimated to 118 and 107 kJ mol⁻¹, respectively, consistent with the experimental results previously discussed. In any case, the barriers of aziridines are much larger than those of pyrazolines. Therefore, the distereotopicity cannot be due to a N-Br blocked inversion.

In Table 3 are the calculated and experimental chemical shifts of pyrazolines **7**, **8**, **11**, **12**, **13**, **18** and **22**.

Table 3. ¹H, ¹³C and ¹⁵N chemical shifts (ppm) and some selected SSCC (Spin-Spin Coupling Constants, Hz). ¹H NMR values of reference ³⁵ that differ from those of references ^{8,9} have been determined anew

Comp.	Nuclei	Position	Calc.	Exp.	Ref.
7 , NH	¹ H	1 (NH)	4.25	4.4	35
		3 (Me)	2.09	1.89, $J_{34}=1.2$	
		4 (CH ₂)	2.26	2.42, $J_{34}=1.2$	
		5 (Me ₂)	1.14	1.25	
	¹³ C	3	147.2	151.5	21b
		4	49.4	49.6	
		5	65.4	61.5	
		3 Me	16.7	16.0	
		5 Me ₂	26.4	27.1	
		1 (NH)	-227.8	-228.2	
11 , NH	¹ H	1 (NH)	4.92	5.04	35
		3 (CH)	6.43	6.75, $J_{34}=1.9$	
		4 (CH)	2.21	2.31, $J_{44'}=-16.5$	
		4 (CH)	2.46	2.79, $J_c=10.2$	
		5 (CH)	3.69	3.79, $J_t=7.8$	
	¹³ C	5 (Me)	1.30	1.19, $J_{55'}=6.3$	21b
		3	139.7	141.4	
		4	42.0	40.6	
		5	59.0	53.5	
		5 Me	18.6	19.9	
¹⁵ N	1 (NH)	-233.6	----		
	2 (-N=)	-21.6	----		
13 , NH	¹ H	1 (NH)	4.56	----	35
		3 (Me)	1.92	1.95, $J_{34}=1.0$	
		4 (CH ₂)	2.38	2.58, $J_{45}=8.6$	
		5 (CH ₂)	3.22	2.96, $J_{45}=8.6$	
	¹³ C	3	148.6	150.8	21b
		4	36.7	36.0	
		5	49.2	46.9	
		3 Me	16.2	15.5	
		1 (NH)	-252.6	-255.0	
	¹⁵ N	2 (-N=)	-39.7	-49.6	

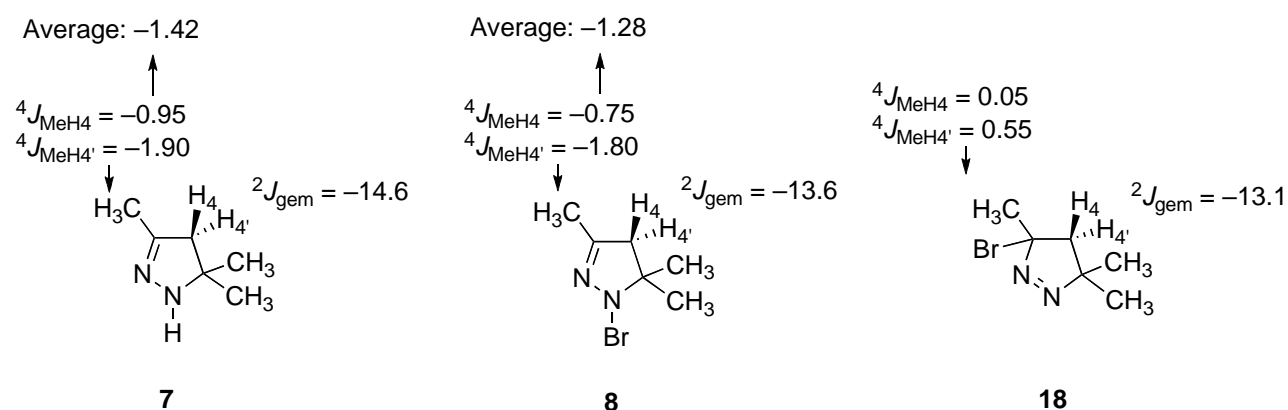
Table 3. (Continued)

8 , NBr	¹ H	3 (Me)	1.89	2.14	9	
		with	4 (CH ₂)	2.20 ^a		1.99, ^b $J_{44}=14.7$
		inversion	5 (Me ₂)	1.27		1.45
8 , NBr	¹ H	3 (Me)	1.89	2.14	9	
		without	4 (CH ₂)	2.12 & 2.28, $\Delta = 0.16$		1.99, ^b $J_{44}=14.7$
		inversion	5 (Me ₂)	1.20 & 1.34, $\Delta = 0.14$		1.45
With inv.	¹³ C	3	150.8	----		
		4	48.8	----		
		5	79.8			
		3 Me	17.1	----		
		5 Me ₂	23.9			
		Without	5 Me ₂	23.7 & 24.0, $\Delta = 0.3$		----
18 , CBr	¹⁵ N	1 (NH)	-158.3	----	12	
		2 (-N=)	-18.9	----		
		¹ H	3 (Me)	2.04		2.09
18 , CBr	¹³ C	4 (CH ₂)	1.24 & 2.05, $\Delta = 0.81$	1.65 & 2.26, $\Delta = 0.61$, $J_{44}=14.6$		
		5 (Me ₂)	1.39 & 1.45, $\Delta = 0.06$	1.41 ^c		
		3	113.3	----		
		4	47.7	----		
		5	94.3	----		
		3 Me	31.3	----		
18 , CBr	¹⁵ N	5 Me ₂	23.6 & 27.1, $\Delta = 3.5$	----		
		1 (NH)	132.9	----		
		2 (-N=)	105.0	----		
12 , NBr	¹ H	3 (Me)	1.96	2.68	9	
22 , C-Br	¹ H	3 (Me)	2.25	2.68	9	

^a 2.20 is the average of 2.28 and 2.12 ppm; ^b In the cited publication only the center of the AB system was reported while Δ_{AB} was not given; ^c In toluene the methyl groups of the gem-dimethyl appear different ($\Delta = 0.08$ ppm) as well as in pyridine ($\Delta = 0.02$ ppm).¹²

The calculations reproduce fairly well the known experimental values for NH-pyrazolines. Thus, we can be confident that in the case of **8** and **18** the predictions are accurate. The ¹H NMR data agree much better with **18** than with **8** even assuming no N-Br inversion in the latter. At that time (1962-1966), ¹³C and ¹⁵N NMR were not accessible preventing a straightforward identification. Although, the information on **12/22** is scarce (only ¹H NMR) it appears that the structure should be **22**.

We have calculated all the couplings involving the compounds of Tables 3 and 5, but we will report here only the ^1H - ^1H SSCC of compounds **7**, **8** and **18** (Scheme 7).



Scheme 7. Calculated [B3LYP/6-311++G(d,p)] ^1H - ^1H SSCC (in Hz).

Simultaneous NH inversion and ring inversion in the case of **7** transform the AB system of the 4- CH_2 into an A_2 system preventing the observation of the geminal $^2J_{44'}$. At the same time, the 4J is averaged to a -1.4 Hz, which compares well with the experimental $J_{34} = |1.2|$ Hz. In the case of the hypothetical **8** the values are very similar eliminating the possibility that the bromine atom at N1 could substantially reduce 4J . On the contrary, as assumed by Closs and Heyn,¹² J_{34} is almost zero for **18**.

The structure of the products formed after the direct bromination of 2-pyrazolines

We will obviate the geometrical aspects of pyrazoles **9**, **10**, **14**, **15**, **16** and **17**, because the geometry of pyrazoles has been discussed many times,³⁶⁻³⁹ and report in Figure 2 the three other compounds, a 3*H*-pyrazole **19**, and exomethylene tautomer of the precedent, **20**, and a 4*H*-pyrazole **21**.

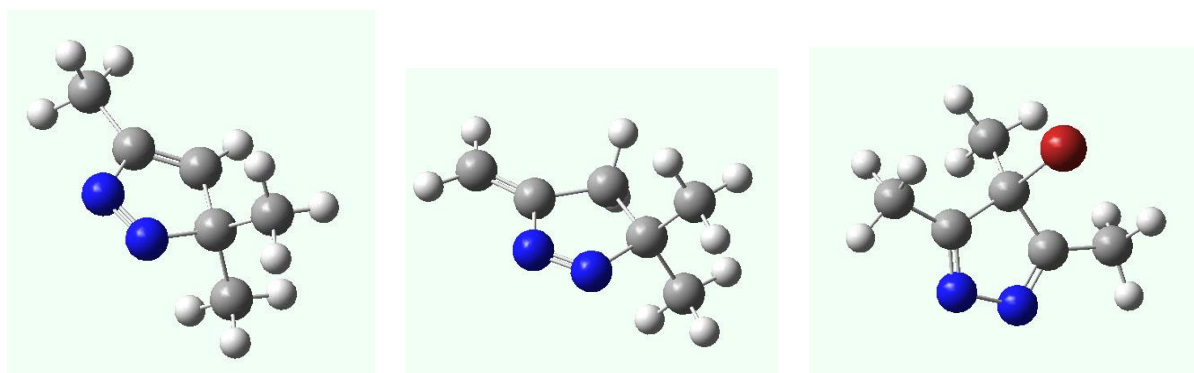


Figure 2. A view of the optimized geometries of 3*H*-pyrazole **19** (left), its exomethylene tautomer **20** (center) and the 4*H*-pyrazole **21** (right).

In what concerns the energies (Table 4) only three products have the same molecular formula and can be compared. Note that for pyrazolium salts, the anion bromide was not included in the calculations.

Table 4. Absolute values (hartree) and relative values (kJ mol⁻¹)

Comp.	Class	SCF Energy	Energy + ZPE	E _{rel} + ZPE
9	Pyrazolium	-344.62793	-344.46244	----
10	1 <i>H</i> -pyrazole	-344.25405	-344.10107	10 most stable
14	1 <i>H</i> -pyrazole	-265.59677	-265.49846	----
15	Pyrazolium	-265.95791	-265.84678	----
16	Pyrazolium	-2839.48860	-2839.38765	----
17	1 <i>H</i> -pyrazole	-2839.13615	-2839.04762	----
19	3 <i>H</i> -pyrazole	-344.20684	-344.05476	19-10: 121.6
20	Exo tautomer	-344.20153	-344.04909	20-10: 136.5
21	4 <i>H</i> -pyrazole	-2917.76061	-2917.61870	----

Of the three compounds with C₆H₁₀N₂ formula, the 1*H*-pyrazole **10** is by far the most stable; the exo tautomer **20** is slightly less stable than the 3*H*-pyrazole **19** (14.9 kJ mol⁻¹).

Concerning NMR, in general, we will report in Table 5 only the chemical shifts that have experimental counterparts.

Table 5. ¹H, ¹³C and ¹⁵N chemical shifts (ppm)

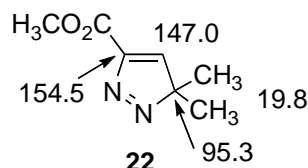
Comp.	Nuclei	Position	Calc.	Exp.	Ref.
9	¹ H	3,5	2.51	2.43	9
		4	2.19	1.98	
10	¹ H	3,5	2.10	2.20	9
		4	1.88	1.91	
	¹³ C*	3	148.5	147.4	40
		4	111.7	110.7	
		5	133.2	137.7	
		3 Me	12.8	11.4	
		4 Me	7.9	6.8	
		5 Me	8.0	8.9	
¹⁵ N ^a	1 (NH)	-195.6	-175.1	41	
	2 (-N=)	-85.8	-99.3		

Table 5. (Continued)

14	¹ H ^b	3 (Me)	2.29	2.32		
		4	6.06	6.06		
		5	7.20	7.48		
	¹³ C ^b	3	149.6	146.0		40
		4	104.2	103.2		
15	¹ H	5	125.8	128.3		
		3 Me	13.6	13.7		
		¹⁵ N	1 (NH)	-195.1		-173
	2 (-N=)	-80.1	-93			
	16	¹ H	3 (Me)	2.76		2.60
4			6.88	6.48		
5			7.94	7.98		
17	¹ H	3 (Me)	2.68	2.59	9	
		5	7.83	7.96		
		19	¹ H ^b	3 (Me)	2.24	2.31
5	7.17			7.50		
¹³ C ^b	3			149.2	140.8	40
	4 (C-Br)		113.6	92.2		
20	¹ H		5	126.7	134.7	
		3 Me	12.5	10.3		
		3 (Me ₂)	1.33	1.35	42	
	¹³ C	4	6.20	6.30		
		5 (Me ₂)	2.40	2.37		
		3	96.6	----		
		4	140.5	----		
		5	154.0	----		
		3 Me ₂	21.0	----		
		5 Me	13.4	----		
¹⁵ N	1	113.4	----			
	2	151.8	----			
21	¹ H	3 (=CH ₂)	5.45 & 5.93	5.52 & 6.18	12	
		4 (CH ₂)	2.09	1.89		
		5 (Me ₂)	1.30	1.32		
21	¹ H	3,5 (Me)	2.29	2.30	43	
		4 (Me)	1.62	1.73		

^a In solid state (CPMAS, Cross Polarization Magic Angle Spinning); ^b Due to prototropy, these products are mixtures of 3- and 5-methyl tautomers except in some solvents like HMPA (Hexamethylphosphoramide) or in the solid state.

Taking into account that data measured in the solid state deviate from those in solution,^{44,45} and that ¹³C C-Br signals need to be corrected,^{46,47} the results of Table 5 are satisfactory to the point that the predictions for **19** should be close to reality. The more similar structure found in the literature is **22**.⁴⁸ Its ¹³C chemical shifts are very similar to the calculated ones of Table 5 for **19**.



Conclusions

Theoretical calculations at the B3LYP/6-311++G(d,p) level for geometries, energies and coupling constants and GIAO (Gauge-Independent Atomic Orbital) over these geometries for chemical shifts provide a complete and consistent picture of the processes involved in the bromination of 1*H*-2-pyrazolines. Obviously the Closs and Heyn mechanism of 1966 was confirmed as we already recognized in 1967.

Computational Details

The geometry of the molecules has been fully optimized with the hybrid HF/DFT B3LYP (Becke, three-parameter, Lee-Yang-Parr)⁴⁹⁻⁵¹ computational method and the 6-311++G(d,p) basis set⁵²⁻⁵⁴ in gas phase. Frequency calculations have been carried out at the same computational level to verify that the structures obtained correspond to energetic minima and transition state (zero and one imaginary frequency, respectively). These geometries have been used for the calculations of coupling constants, SSCC, as well as for the absolute chemical shieldings with the GIAO method^{55,56} and the B3LYP/6-311++G(d,p) computational level. All the calculations have been carried out with the Gaussian-09 package.⁵⁷

The following equations obtained by statistical analysis of a great number of data have been used to transform absolute shieldings into chemical shifts:

$$\delta^1\text{H} = 31.0 - 0.97 * \sigma^1\text{H} \quad \text{eq. 1 (reference TMS, 0.00 ppm)}^{58}$$

$$\delta^{13}\text{C} = 175.7 - 0.963 * \sigma^{13}\text{C} \quad \text{eq. 2 (reference TMS, 0.00 ppm)}^{59}$$

$$\delta^{15}\text{N} = -152.0 - 0.946 * \sigma^{15}\text{N} \quad \text{eq. 3 (reference ext. neat MeNO}_2, 0.00 \text{ ppm)}^{59}$$

The chemical shifts and all the coupling constants not discussed in this manuscript are available from one of us (I.A.) on request.

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