Study of Some Reactions of Ethyl 4-Phenyl-3-benzoyl-2-pyrazoline-5-carboxylate

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Several reactions of the pyrazoline **1a** were investigated. With bromine water, potassium permanganate, hydrogen peroxide, or potassium hydroxide, different pyrazole derivatives were formed. While the reaction with hydroxylamine or some hydrazines gave the corresponding pyrazoline Schiff bases, with aroylhydrazines, pyrazole Schiff bases were formed.

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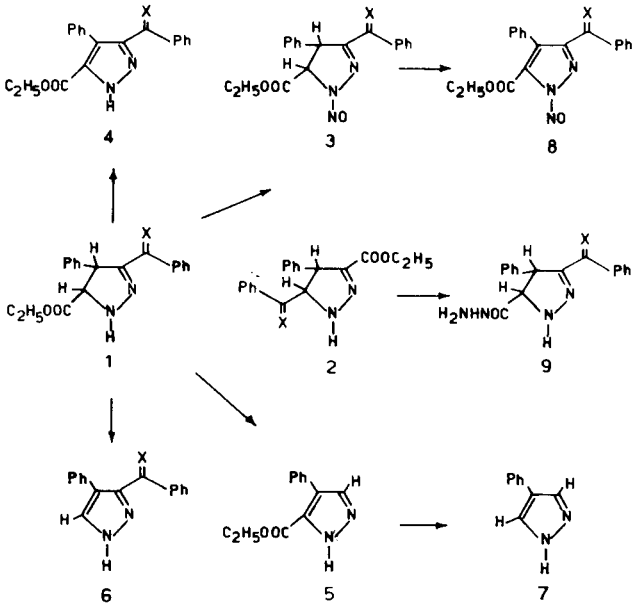
Pyrazolines are useful intermediates in the synthesis of certain cyclopropane derivatives such as fluorinated (1) and steroidal (2) cyclopropanes. Suitably substituted pyrazolines are sometimes used for the preparation of other ring systems such as 2*H*-pyran-2-ones (3,4). While the chemistry as well as stereochemistry of the decomposition of pyrazolines has received considerable attention (5), other reactions of pyrazolines are less encountered in the literature. In the present work the structure of ethyl 4-phenyl-3(5)benzoyl-2-pyrazoline-5(3)-carboxylate (**1a** or **2a**) as well as its conversion into certain pyrazoles, which are otherwise difficult to obtain, are discussed.

Ethyl 4-phenyl-3(5)benzoyl-2-pyrazoline-5(3)carboxylate (**1a** or **2a**) was prepared from the reaction of benzalacetophenone with ethyl diazoacetate (4,6). The infrared spectrum of this pyrazoline showed a strong NH absorption while its electronic spectrum lacked the absorption maximum near 320 mμ observed for 1-pyrazolines (7). The ^{1}H nmr spectrum exhibited, besides the aromatic and ethyl ester protons, two doublets (J = 5.0 Hz) at δ 4.48 and 5.20 for the C-4 and C-5 protons, respectively, as well as an exchangeable NH signal at δ 7.00. While such spectral data completely rule out the 1-pyrazoline structure, it cannot differentiate between the two tautomeric 2-pyrazoline structures **1a** and **2a**. However, **1a** may be more favoured since it is expected to be more thermodynamically stable. Brey and Jones (8) in an attempt to differentiate between the two isomeric pyrazolines obtained from methyl diazoacetate with ethyl cinnamate and ethyl diazoacetate with methyl cinnamate (9), mentioned that the chemical shift for the methylene of the carboethoxy group appears at higher field when the group is in the 3-position than when it is in the 5-position. The observation of the ester methylene signal in the pyrazoline **1a** or **2a** in the usual region (δ 4.1) may further support the above assignment with the carboethoxy group at the 5-position (**1a**).

The pyrazoline **1a** gave the *N*-nitroso derivative **3a** on treatment with nitrous acid, a reaction which usually characterizes 2-pyrazolines (10). The ^{1}H nmr spectrum of the *N*-nitrosopyrazoline **3a** exhibited two doublets (J = 5.0 Hz) at δ 4.42 and 5.90 for the C-4 and C-5 protons, respectively, while the signal due to the NH proton disappeared. The appreciable deshielding (about 0.7 ppm) observed for the signal of the C-5 proton compared to the parent pyrazoline **1a** can be attributed to the electronic effects of the nitroso group, which are probably enhanced by its magnetic anisotropy.

Mild oxidation of the pyrazoline **1a** with bromine water led to the formation of the corresponding pyrazole **4a**. However, treatment with potassium permanganate or hydrogen peroxide resulted in the formation of ethyl 4-phenylpyrazole-3(5)carboxylate (**5**) and benzoic acid. On the other hand, the reaction of the pyrazoline **1a** with

Scheme I



	X
a	O
b	N-NH$_2$
c	N-OH
d	N-NH-Ph
e	N-NH-C$_6$H$_4$-NO$_2$-p
f	N-NH-CO-Ph
g	N-NH-CO-C$_6$H$_4$-OCH$_3$-p
h	N-NH-CO-C$_6$H$_4$-NO$_2$-p

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potassium hydroxide or sodium carbonate gave 4-phenyl-3(5)benzoylpyrazole (**6a**) which is evidently formed by the oxidation of the pyrazoline accompanied by hydrolysis and decarboxylation of the ester group. It is worthy to mention that the pyrazole **6a** was reported (11) to be formed as a by-product in the pyrolysis of 4-phenyl-5-benzoyl-2-pyrazoline. While ethyl 4-phenylpyrazole-3(5)carboxylate (**5**) readily gave 4-phenylpyrazole (**7**) on treatment with potassium hydroxide, the latter could not be obtained from potassium permanganate or hydrogen peroxide treatment of 4-phenyl-3(5)benzoylpyrazole (**6a**). In contrast to the pyrazoline **1a**, the pyrazole **4a** failed to give the *N*-nitroso derivative **8a** by direct nitrosation. However, the latter, **8a**, was obtained by the bromine water oxidation of the *N*-nitrosopyrazoline **3a** (Scheme I).

The spectral data of the above pyrazole derivatives are consistent with the proposed structures. It is worthy to mention that in the ^{1}H nmr spectra of these compounds, generally no separate signals could be assigned for the C-3 or C-5 protons of the pyrazole ring. These protons usually resonate in the same region as the complex multiplet of the side chain aromatic protons (12).

The reactions of the pyrazoline **1a** with hydroxylamine and hydrazines were also investigated. Except for hydrazine hydrate, in which the ester group was involved giving the hydrazide **9a**, the attack was always at the carbonyl group. Thus, the reaction of **1a** with hydrazine hydrochloride, hydroxylamine, phenylhydrazine and *p*-nitrophenylhydrazine led to the formation of the corresponding 2-pyrazoline Schiff bases **1b-e**. Yet, the reaction with the aroylhydrazines: benzoylhydrazine, *p*-nitro- and *p*-methoxybenzoylhydrazines led to the formation of the pyrazole Schiff bases **4f-h**, which were also obtained from the pyrazole **4a** and the respective aroylhydrazines.

The direct formation of the pyrazole derivatives in the reaction with aroylhydrazines may be due to the prolonged heating, since in some instances pyrazolines undergo dehydrogenation on distillation (13). The 2-pyrazoline Schiff base **1c** could be converted to the analogous

Scheme II

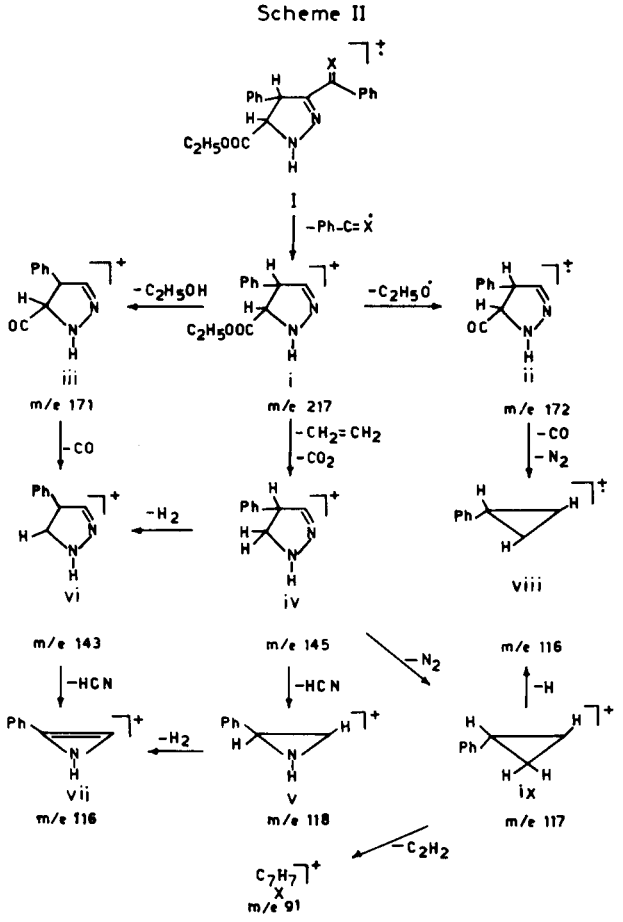

Table I

Analytical Data of the Pyrazolines and Pyrazoles

Compound	M.p. °C	Formula	Calcd. % C	H	N	Found % C	H	N
1b	145	$C_{19}H_{20}N_4O_2$	67.8	6.0	16.6	67.5	5.7	16.4
1c	140	$C_{19}H_{19}N_3O_3$	67.6	5.7	12.5	67.5	6.1	12.6
1d	152	$C_{25}H_{24}N_4O_2$	72.8	5.9	13.6	73.2	6.1	13.6
1e	192 (a)	$C_{25}H_{23}N_5O_4$	65.6	5.1	15.3	65.5	5.2	15.1
3a	136	$C_{19}H_{17}N_3O_4$	64.9	4.9	12.0	65.2	5.2	12.0
9a	49	$C_{17}H_{16}N_4O_2$	66.2	5.2	18.2	66.2	5.4	18.3
4a	98	$C_{19}H_{16}N_2O_3$	75.8	4.2	7.4	75.7	4.4	7.5
4c	136	$C_{19}H_{17}N_3O_3$	68.0	5.1	12.5	68.2	5.4	12.0
4f	193	$C_{26}H_{22}N_4O_3$	71.2	5.1	12.8	71.0	5.2	12.4
4g	176	$C_{27}H_{24}N_4O_4$	69.2	5.2	12.0	69.3	5.2	12.1
4h	135	$C_{26}H_{21}N_5O_5$	64.6	4.4	14.5	64.4	4.4	14.7
5	164	$C_{12}H_{12}N_2O_2$	66.6	5.6	12.9	66.6	5.3	12.9
8a	125	$C_{19}H_{15}N_3O_4$	65.3	4.3	12.0	65.0	4.5	11.8

(a) Melts with decomposition.

pyrazole **4c** on treatment with bromine water. The infrared spectra of the pyrazole aroylhydrazones **4f-h** exhibited two absorptions in the regions 1735-1685 and 1670-1650 cm^{-1} for ester and amide carbonyl absorptions, respectively, which exclude the possibility of a bicyclic structure for these compounds. The ^1H nmr spectra of the pyrazoline Schiff bases **1b-e** showed two doublets (J = 5.0 Hz) at δ 4.00-4.20 and 4.33-4.45 for the C-4 and and C-5 protons, respectively, which are lacking in the spectra of athe corresponding pyrazoles **4**.

Further evidence concerning the structure of the parent pyrazoline **1a** as well as the pyrazoline Schiff bases **1c,d** has been derived from their mass spectral data. The most common prominent peaks in their fragmentaiton patterns are observed at m/e 217, 172, 171, 145, 143, 118, 117, 116, 91 and 77, which could be assigned to some of the fragments shown in Scheme II. The moderately intense peak at m/e 217 is formulated as the ion *i* formed by loss of the C_6H_5-C=X radical from the molecular ion. Subsequent loss of the OC_2H_5 radical leads to the species *ii* at m/e 172, while loss of an ethanol molecule leads to a major peak at m/e 171, formulated as the ion *iii*. Loss of ethylene and carbon dioxide molecules from *i* leads to the moderately intense ion *iv* at m/e 145, which can be converted to the ion *v* (m/e 118) through loss of an HCN molecule. Elimination of a hydrogen molecule from *v* leads to the azirinium ion *vii* (m/e 116). The latter can also be formed from *iii via* elimination of a carbon monoxide molecule giving the relatively weak abundant ion *vi* at m/e 143, which subsequently eliminates an HCN molecule giving *vii*. Moreover, the species at m/e 116 may be formulated as the cyclopropyl radical ion *viii* arising by successive loss of a nitrogen molecule from *iv* leading to the moderately intense ion *ix* (m/e 117) and proton or loss of nitrogen and hydrogen molecules from *ii*. The tropylium cation *x* (m/e 91) is assumed to be formed from *ix* by fission of the cyclopropane ring and subsequent loss of acetylene molecule.

It is worthy to mention that the base peak in the spectrum of the phenylhydrazone **1d** was observed at m/e 93 due to an aniline molecule arising by fission of the N-N bond of the hydrazone moeity usually observed in the mass spectra of phenylhydrazones (14) and aroylhydrazones (15). Moreover, the observation of fragments of higher masses than m/e 217 (*cf.*, Experimental) indicates that the loss of the radical C_6H_5-C=X (X = N-NH-C_6H_5) from the phenylhydrazone **1d** is less favoured compared to the oxime **1c**.

Study of the pyrolysis products from the 2-pyrazoline Schiff bases **1b-e**, which may prove to be of synthetic importance, is currently under investigation.

EXPERIMENTAL

Microanalyses were performed by Microanalysis Unit, Cairo University, Cairo. Infrared spectra were measured with a Unicam SP200 spectrophotometer for potassium bromide pellets or in Nujol and electronic spectra were measured for ethanolic solutions with a Unicam SP800 spectrophotometer. The ^1H nmr spectra were recorded on a Varian T-60 and Jeol 100 spectrometers for solutions in deuteriochloroform with TMS as an internal standard. Mass spectra were recorded on an LKB 9000 instrument.

Ethyl 4-Phenyl-3-benzoyl-2-pyrazoline-5-carboxylate (**1a**) (Tables II and III).

This compound, m.p. 162° (ethanol) was prepared from

Table II

Infrared and Electronic Spectral Data of the Pyrazolines and Pyrazoles

Compound	Ir (Cm^{-1}) C=O Ester	C=O Ketonic	C=N	NH	Uv λ Max, Nm, (ε)		
1a	1705	1679		3347	246 (14,130)	288 (9,908)	
1b	1690		1595	3350			
1c	1725		1595	3350	233 (2,035)	295 (2,453)	383 (2,712)
1d	1720		1605	3400	258 (1,407)	297 (1,580)	
1e	1700		1590	3350	240 (1,356) (a)	260 (1,175)	
3a	1738	1695			249 (2,168)	286 (1,373)	
9a	1650 (b)	1675		3350	265 (1,882) (a)	295 (2,664)	
4a	1725	1660		3500	254 (1,610)		
4c	1695		1600	3250	252 (1,472)		
4f	1735	1650 (b)	1605	3350		305 (1,930)	
4g	1685	1670 (b)	1602	3300		283 (2,698)	
4h	1700	1670 (b)	1602	3400		310 (1,536)	
5	1695			3300			
6a		1650		3400	250 (1,347)		
7				3330	264 (488) (a)		
8a	1730	1660					

(a) Shoulder. (b) C=O amide.

Table III

^{1}H Nmr Spectral Data of the Pyrazolines and Pyrazoles (a)

	^{1}H Nmr Chemical Shifts (δ/ppm)						
Compound	CH_3 (t) (3H)	CH_2 (q) (2H)	H-4 (d) (1H)	H-5 (d) (1H)	NH (s) (1H)	Ar-H (m)	Others (s)
1a	1.17	4.10	4.47	5.20	7.00	7.6	
1b	1.22	4.20	4.40	4.75	(b)	7.4	
1c	1.18	4.17	4.37	4.87	6.95	7.3	8.29 (1H, OH)
1d	1.22	4.18	4.45	4.82	(b)	7.3	
1e	1.17	4.00	4.33	4.77	(b)	7.4	
3a	1.23	4.20	4.42	5.90		7.5	
9a (c)			3.85	4.62	(b)	7.3	6.25 (2H, NH_2)
4a	1.12	4.23			(b)	7.6	
4f	1.23	4.33			8.33 (d)	7.5	
4h	1.18	4.22			(b)	7.6	
5	1.23	4.26			(b)	7.4	7.78 (1H, H-3)
6a (c)					(b)	7.5	
7 (c)					7.75	7.4	
8a	1.19	4.32				7.7	

(a) t: Triplet (J = 7.0 Hz), q: quartet (J = 7.0 Hz), d: doublet (J = 5.0 Hz), s: singlet and m: multiplet. (b) The NH proton is overlapped by the complex aromatic multiplet. (c) The ^{1}H nmr spectra was carried out in DMSO-d_6. (d) This signal is most probably due to the NH-CO proton rather than the NH pyrazole ring proton.

benzalacetophenone and ethyl diazoacetate according to the method reported by Kohler and Steele (6); ms: m/e (relative intensity) M^+ 322 (4), 249 (16), 217 (23), 216 (31), 173 (22), 172 (8), 171 (64), 146 (7), 145 (64), 144 (8), 143 (4), 118 (10), 117 (19), 116 (13), 115 (10), 106 (7), 105 (86), 95 (5), 91 (16), 90 (11), 89 (15), 78 (10), 77 (100), 65 (5), 51 (36).

Ethyl 1-Nitroso-3-benzoyl-4-phenyl-2-pyrazoline-5-carboxylate (**3a**) (Tables I, II and III).

A solution of **1a** (1 g., 0.0031 mole) in glacial acetic acid (10 ml.) was treated with 25% aqueous sodium nitrite (10 ml.). The nitroso derivative **3a** (85% yield) which separated, crystallized from ethanol as needles.

Ethyl 3-(5)-Benzoyl-4-phenylpyrazole-5(3)-carboxylate (**4a**) (Tables I, II and III).

To a suspension of **1a** (1 g., 0.0031 mole) in water (10 ml.), 5% bromine water (15 ml.) was gradually added (10 minutes) with stirring at 20°. The pyrazole **4a** which separated (80% yield), crystallized from 80% aqueous ethanol as needles.

The nitroso-pyrazoline **3a** was similarly converted into the nitroso-pyrazole **8a**.

Ethyl 4-Phenylpyrazole-3(5)carboxylate (**5**) (Tables I, II and III).

A solution of **1a** (1 g., 0.0031 mole) in acetone (20 ml.) was refluxed with potassium permanganate (0.5 g., 0.0031 mole) for one hour. The reaction mixture was then filtered and the product, separated after concentration, was extracted several times with boiling water. The pyrazole **5** (50% yield) crystallized from ethanol as needles. The aqueous solution gave, after concentration and cooling, benzoic acid.

The pyrazole **5** was also obtained (60% yield) when a solution of **1a** (0.5 g., 0.0016 mole) in glacial acetic acid (8 ml.) was treated with hydrogen peroxide (100 vol., 10 ml.) at 20°.

4-Phenyl-3(5)benzoylpyrazole (**6a**) (Tables II and III).

A solution of **1a** (1 g., 0.0031 mole) in 10% methanolic potassium hydroxide (15 ml.) was refluxed for 30 minutes. The pyrazole **6a** (45% yield) was obtained after dilution with water and crystallized from benzene as needles, m.p. 194° [lit. (11) m.p. 193-194°]. The pyrazole **6a** was also obtained (50% yield) when **1a** was refluxed with 20% aqueous sodium carbonate for two hours.

The pyrazole **6a** was recovered unchanged after refluxing its solution in acetone with potassium permanganate for one hour or treating its solution in glacial acetic acid with hydrogen peroxide.

4-Phenylpyrazole (**7**) (Tables II and III).

This compound was obtained (60% yield) by refluxing the pyrazole **5** (0.5 g., 0.0023 mole) with 10% methanolic potassium hydroxide (10 ml.) for 30 minutes. It crystallized from ethanol as needles, m.p. 232° [lit. (16) m.p. 229°].

3-Benzoyl-4-phenyl-2-pyrazoline-5-carbohydrazide (**9a**) (Tables I, II and III).

A solution of **1a** (0.5 g., 0.0016 mole) in ethanol (15 ml.) was refluxed with 98% hydrazine hydrate (2 ml., 0.04 mole) for two hours. The hydrazide **9a** (30% yield), which separated after concentration, crystallized from ethanol as needles.

Pyrazoline Schiff Bases (Tables I, II and III).

A solution of **1a** (0.5 g., 0.0016 mole) in ethanol (20 ml.) was refluxed with the proper reagent (0.04 mole) for 4 hours. The Schiff bases were obtained (60-70% yield) after concentration and were crystallized from ethanol.

The pyrazoline Schiff base **1c** was converted into the corresponding pyrazole Schiff base **4c** (45% yield) on treatment with bromine water at 20°; ms: m/e (relative intensity); **1c**: 218 (8), 217 (42), 173 (7), 172 (12), 171 (100), 145 (20), 144 (5), 143 (3), 118 (10), 117 (16), 116 (18), 115 (9), 105 (5), 104 (25), 103 (9), 91 (10), 90 (8), 89 (12), 77 (25), 51 (9); **1d**: M^+ 412 (19), 320 (5), 318 (9), 311 (9), 246 (7), 219 (8), 218 (7), 217 (14) 195 (8), 191 (7), 172 (7), 171 (59), 145 (9), 144 (5), 143 (2), 118 (9), 117 (16), 116 (9), 115 (7), 104 (17), 94 (8), 93 (100), 92 (26), 91 (14), 77 (16), 65 (14).

Pyrazole Schiff Bases (Tables I, II and III).

A solution of **1a** (0.5 g., 0.0016 mole) in ethanol (20 ml.) was refluxed with the aroylhydrazine (0.04 mole) for 15-18 hours. The product separated after concentration (50-65% yield) of the solvent and was crystallized from ethanol or benzene.

The pyrazole Schiff bases **4g,h** were also prepared (40-60% yield) by refluxing the pyrazole **4a** in ethanol with the proper aroylhydrazine for 15 hours.

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