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The Reaction of Aroylacetaldehydes with Aroylhydrazines

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Abstract. A series of aroylacetaldehyde aroylhydrazones were prepared and characterized. Their uv and ^{1}H nmr spectra suggest the enol-imine structure rather than the keto-imine form. The *pKa* values of these aroylhydrazones were measured and correlated with the Hammett substitution constants. It was observed that benzoylacetaldehyde substituted in the *p*-position could be cyclized to form the 5-hydroxy-2-pyrazolines by refluxing in acidified ethanol, while formyldeoxybenzoin only gives the corresponding pyrazole due to steric requirements of the two phenyl groups.

Keywords. Aroylacetaldehyde aroylhydrazones; 5-Hydroxy-2-pyraazolines; Pyrazoles; UV; Tautomerism.

Die Reaktion von Aroylacetaldehyden mit Aroylhydrazinen

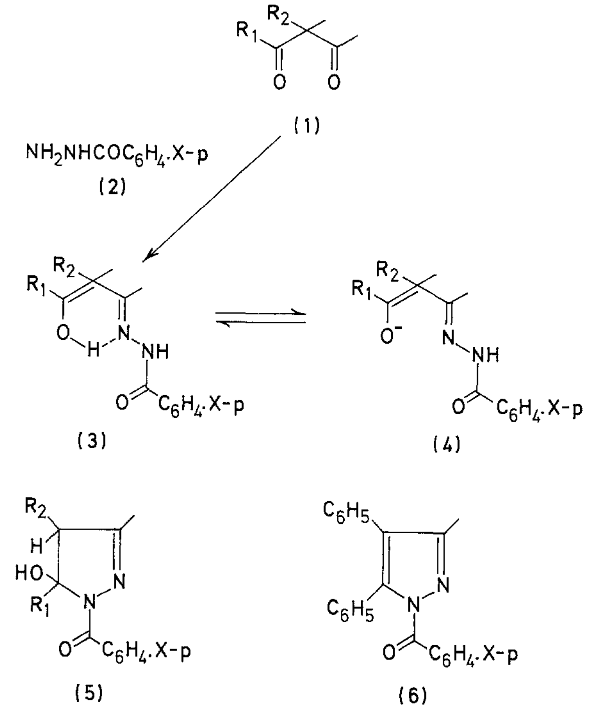
Zusammenfassung. Es wurde eine Reihe von Aroylacetaldehyd-aroylhydrazonen hergestellt und charakterisiert. Ihre UV- und ^{1}H-NMR-Spektren sprechen eher für eine Enol-imin-Struktur und nicht für die Keto-imin-Form. Die *pKa*-Werte für die Aroylhydrazone wurden bestimmt und über die Hammett-Beziehung korreliert. Es wurde festgestellt, daß *p*-substituierte Benzoyl-acetaldehyde durch Rückflußkochen in angesäuertem Ethanol zu 5-Hydroxy-2-pyrazolinen cyclisiert werden können, während Formyldeoxybenzoin wegen der sterischen Gegebenheiten der zwei Phenylgruppen lediglich die entsprechenden Pyrazole ergibt.

Introduction

The formation of pyrazoles from hydrazine and hydrazine derivatives with β-dicarbonyl compounds proceeds via the intermediate formation of hydrazones and 5-hydroxy-pyrazolines [1–4]. In a previous publication [2] we have found that the reaction of benzoylacetaldehyde with aroylhydrazines proceeds via the formation of the open-chain hydrazones which on refluxing in an acidified methanolic solution yielded 5-hydroxy-5-phenyl-1-aroylpyrazolines. All attempts for cyclization of the pyrazoline have failed to form the corresponding pyrazole.

We new present a study on the structural factors of the conditions leading to the formation of pyrazolines from the reaction of β-dicarbonyl compounds with acyl hydrazines.

The reaction of *p*-substituted benzoylacetaldehydes (**1**, $R^1 = p - Me\mathrm{C_6H_4}$, $R^2 = \mathrm{H}$) and (**1**, $R^1 = p - Me\mathrm{OC_6H_4}$, $R^2 = \mathrm{H}$) as well as formyldeoxy benzoin (**1**, $R^1 = R^2 = \mathrm{C_6H_5}$) with aroylhydrazines (**2**, $X = \mathrm{H}$, Me, $\mathrm{O}Me$, Cl, $\mathrm{NO_2}$) will be discussed.



Results and Discussion

The reaction of p-toluoyl-(**1**, $R^1 = p - Me\mathrm{C_6H_4}$, $R^2 = \mathrm{H}$), p-anisoylacetaldehyde (**1**, $R^1 = p - Me\mathrm{OC_6H_4}$, $R^2 = \mathrm{H}$) and formyldeoxybenzoin (**1**, $R^1 = R^2 = \mathrm{C_6H_5}$) with p-substituted aroylhydrazines (**2**) in water affords the corresponding open-chain hydrazones **3** (Table 1, Scheme 1). The ^{1}H nmr spectra (Table 2) are in accordance with the *cis-s-cis* enolimine structure [4].

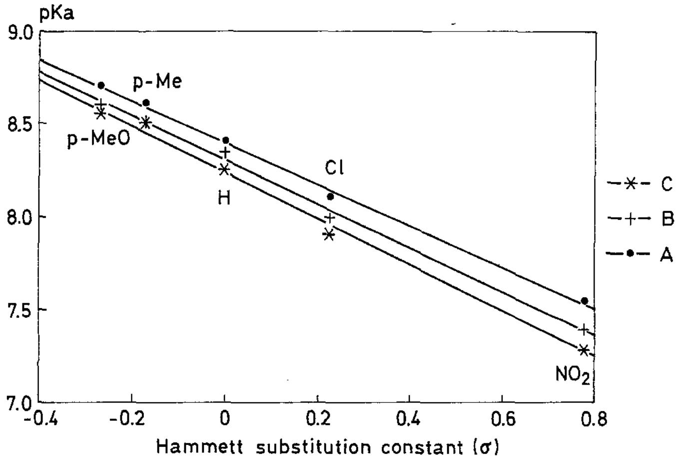


Fig. 1. A: 3, $\mathrm{R_1 = MeC_6H_4{-}p}$, $\mathrm{R_2 = H}$, X = H, Me, MeO, Cl, $\mathrm{NO_2}$
B: 3, $\mathrm{R_1 = MeOC_6H_4\text{-}p}$, $\mathrm{R_2 = H}$, X = H, Me, MeO, Cl, $\mathrm{NO_2}$
C: 3, $\mathrm{R_1 = R_2 = C_6H_5}$, X = H, Me, MeO, Cl, $\mathrm{NO_2}$

Table 1. Analytical data[a] of the prepared β-ketoaldehyde aroylhydrazones (**3**)

Compound			m.p.	C%	H%	N%	Cl%
R^1	*R*^{2}	*X*					
p-*Me*C_6H_4	H	H	136[b]	73.10 (72.86)	5.90 (5.71)	10.10 (10.10)	–
p-*Me*C_6H_4	H	*Me*	151[b]	73.40 (73.47)	6.10 (6.12)	9.31 (9.52)	–
p-*Me*C_6H_4	H	O*Me*	165[b]	69.60 (69.67)	5.90 (5.80)	9.40 (9.03)	–
p-*Me*C_6H_4	H	Cl	158[c]	64.90 (64.86)	4.60 (4.77)	8.70 (8.90)	11.50 (11.28)
p-*Me*C_6H_4	H	NO_2	181[c]	62.70 (62.77)	4.40 (4.61)	12.70 (12.92)	–
p-*Me*OC_6H_4	H	H	137[b]	69.00 (68.92)	5.30 (5.40)	9.20 (9.46)	–
p-*Me*OC_6H_4	H	*Me*	166[c]	69.40 (69.67)	5.40 (5.80)	9.10 (9.03)	–
p-*Me*OC_6H_4	H	O*Me*	167[d]	66.10 (66.25)	5.90 (5.52)	8.20 (8.59)	–
p-*Me*OC_6H_4	H	Cl	173[d]	61.80 (61.72)	4.40 (4.54)	8.18 (8.47)	10.71 (10.74)
p-*Me*OC_6H_4	H	NO_2	172[d]	59.96 (59.82)	4.35 (4.40)	12.18 (12.31)	–
C_6H_5	H	H	127[b]	77.50 (77.19)	5.20 (5.26)	8.32 (8.19)	–
C_6H_5	C_6H_5	*Me*	156[c]	77.60 (77.53)	5.90 (5.62)	7.60 (7.86)	–
C_6H_5	C_6H_5	O*Me*	152[c]	74.40 (74.19)	5.60 (5.37)	7.29 (7.53)	–
C_6H_5	C_6H_5	Cl	147[c]	70.20 (70.11)	4.20 (4.54)	7.10 (7.43)	9.28 (9.40)
C_6H_5	C_6H_5	NO_2	205[c]	68.30 (68.22)	4.32 (4.39)	10.80 (10.85)	–

[a] Values in brackets indicate the calculated results
[b] Benzene
[c] Ethanol
[d] Methanol

The uv absorption spectra of these aroylhydrazones in neutral methanol (Table 3) are more or less similar and show two maximum absorption bands at ca. 260 and 330 nm, besides a weak shoulder at 410 nm that disappears on acidification. In presence of sodium methoxide (0.1 mol/l) the spectra show maximum absorption bands at 260 and 410 nm due to the formation of the mononegative anion (**4**).

From the spectral changes as a function of *pH*, the *pKa* values of these hydrazones were measured in aqueous buffered solution [5]. The *pKa* values (Table 3) measured for **3** can be correlated with the Hammett substitution constant σ (Fig. 1) with values of $\rho \approx -1.00$. It is quite apparent that the *pKa* values depend

Table 2. ^{1}H nmr data of β-ketoaldehyde aroylhydrazones **3** (δ/ppm, *J*/Hz)

Compound								
R^1	R^2	X	CH_3	CH_3O	$=C-H$	$N=C-H$	Aromatic	NH, OH
p-*Me*C_6H_4	H	H	2.23	–	6.00 (12)d	7.10 (12)d	7.33–8.00	9.4[b]
p-*Me*C_6H_4	H	*Me*	2.36	–	5.97 (12)d	[a]	7.06–7.97 m	9.5, 10.0[b]
p-*Me*C_6H_4	H	O*Me*	2.35	3.8	6.03 (12)d	6.95 (12)d	6.95–8.05 m	9.41, 10.71[b]
p-*Me*C_6H_4	H	Cl	2.26	–	6.00 (10)d	7.10 (10)d	7.30–8.00 m	10.9[b]
p-*Me*C_6H_4	H	NO_2	2.26	–	6.00 (12)d	[a]	7.00–8.40 m	9.5[b]
p-*Me*OC_6H_4	H	H	–	3.37	6.03 (10)d	6.86 (10)d	7.33–8.06 m	9.36[b]
p-*Me*OC_6H_4	H	*Me*	2.36	3.76	6.03 (12)d	6.92 (12)d	7.04–8.08 m	9.36, 10.70[b]
p-*Me*OC_6H_4	H	O*Me*	–	3.80	6.06 (12)d	[a]	6.80–8.06 m	9.36, 10.70
p-*Me*OC_6H_4	H	Cl	–	3.78	6.09 (12)d	6.96 (12)d	7.50–8.06 m	9.40, 10.78[b]
p-*Me*OC_6H_4	H	NO_2	–	3.73	6.00 (10)d	6.90 (10)d	7.40–8.13 m	9.26, 10.83[b]
C_6H_5	C_6H_5	H	–	–	–	[a]	6.86–8.33 m	9.06
C_6H_5	C_6H_5	*Me*	2.20	–	–	[a]	6.76–7.76 m	8.46, 12.10[b]
C_6H_5	C_6H_5	O*Me*	–	3.76	–	[a]	6.80–8.00 m	8.50, 10.66
C_6H_5	C_6H_5	Cl	–	–	–	[a]	7.01–8.28 m	9.42[b]
C_6H_5	C_6H_5	NO_2	–	–	–	[a]	6.93–8.53 m	8.66[b]

[a] Overlapped by aromatic signals

[b] Broad

Table 3. Electronic spectra and *pKa* values of β-ketoaldehyde aroylhydrazones (**3**)

Compound			*Me*OH $\lambda_{max.}$/nm (log ε)			*Me*OH/NaOH $\lambda_{max.}$/nm (log ε)			*pKa*
R^1	R^2	X							
p-*Me*C_6H_5	H	H	260 (3.98)	327 (3.81)	410 sh	251 (3.94)	410 (4.22)		8.35
p-*Me*C_6H_5	H	*Me*	256 (4.05)	327 (3.89)	410	250 (4.02)	408 (4.22)		8.52
p-*Me*C_6H_5	H	O*Me*	259 (4.42)	327 (4.21)	402 sh	251 (4.34)	410 (0.63)		8.60
p-*Me*C_6H_5	H	Cl	250 (3.96)	325 (3.58)	390 sh	246 (3.88)	405 (4.22)		8.00
p-*Me*C_6H_5	H	NO_2	258 (3.94)	330 sh	430 (3.59)	262 (3.91)	438 (4.04)		7.40
p-*Me*OC_6H_5	H	H	273 (3.84)	325 (3.64)	402 (3.72)	262 (3.68)	407 (4.20)		8.40
p-*Me*OC_6H_5	H	*Me*	274 (4.08)	328 (3.90)	410 sh	260 sh	410 (4.30)		8.60
p-*Me*OC_6H_5	H	O*Me*	273 (4.01)	328 (3.73)	400 sh	265 (3.80)	408 (4.16)		8.70
p-*Me*OC_6H_5	H	Cl	274 (3.75)	335 sh	410 (3.73)	272 (3.61)	410 (4.14)		8.10
p-*Me*OC_6H_5	H	NO_2	271 (4.09)	330 sh	434 (3.84)	265 (4.05)	438 (4.19)		7.55
C_6H_5	C_6H_5	H	228 (3.99)	305 (3.79)	360 sh	305 (3.60)	390 (4.16)		8.25
C_6H_5	C_6H_5	*Me*	239 (3.86)	306 (3.60)	390 sh	303 (3.41)	391 (3.95)		8.50
C_6H_5	C_6H_5	O*Me*	256 (4.11)	300 (3.89)	370 sh	297 (3.77)	300 sh	398 (4.21)	8.55
C_6H_5	C_6H_5	Cl	276 (3.96)	327 (3.77)	400 sh	277 sh	410 (4.22)		7.90
C_6H_5	C_6H_5	NO_2	260 (3.98)	362 sh	438 (3.77)	259 (3.90)	439 (4.05)		7.30

mainly on the nature of *X* of the hydrazone residue rather than R^2 or R^3 of the β-ketoaldehyde moiety. This may suggest that *Ph*-*X* strongly interacts with the enolic oxygen via π-p conjugation [5].

Refluxing the open-chain hydrazones derived from **1** ($R^1 = p - Me\mathrm{C_6H_4}$, $R^2 = \mathrm{H}$) or **1** ($R^1 = p\text{-}Me\mathrm{OC_6H_4}$, $R^2 = \mathrm{H}$) in HCl acidified ethanol results in the formation of 1-aroyl-5-hydroxy-2-pyrazolines (**5**) (Table 3). The ^{1}H nmr spectra of these pyrazolines show ABX patterns due to the coupling between pyrazoline CH_2 and the azomethine proton. The CH_2 appears as a doublet at δ 3–4 ppm while the H-C = N proton appears as a triplet at δ 5.5–6.0 ppm. The uv spectra of the pyrazolines show maximum absorption bands at 305 and 255 nm. The spectra were found to be insensitive to *pH* variations, implying the stability of the cyclic pyrazoline structure and that no ring-chain tautomerism is observed. Attempts to prepare the corresponding pyrazoles from the hydroxy pyrazolines were unsuccessful.

On the other hand, refluxing the open-chain hydrazones (**3**) derived from formyldeoxybenzoin (**1**, $R^1 = R^2 = C_6H_5$) in acidified ethanol afforded the corresponding pyrazoles without the intervension of the 5-hydroxy-1-aroyl-pyrazoline (**5**) structure. This may be attributed to the steric requirements for the two phenyl groups. The ^{1}H nmr spectra of the isolated pyrazoles **6** (X = H, *Me*, *Me*O, Cl and NO_2) exhibit a singlet at δ 8.7 which is attributed to the C_3 proton.

Experimental

Electronic spectra were recorded on a Unicam SP 1800 spectrophotometer and some measurements were made on a Carl Zeiss PMQII spectrophotometer. ^{1}H nmr spectra were recorded on a Varian AGOA and a Varian 90 using *TMS* as internal standard at 30°.

pH values used in determination of *pKa* were measured on a digital Pye *pH* meter calibrated with buffers of *pH* 4.00 and 7.00. The *pH* values of different solutions were kept constant using KH_2PO_4-KOH buffer. The ionic strengths of all solutions were kept constant at 0.1 *M* using AR potassium chloride. All melting points are uncorrected and were determined on a Kofler block.

Preparation of Starting Material

The β-ketoaldehydes **1** were prepared as their sodium salts by the condensation of *p*-methyl and *p*-methoxy acetophenone and deoxybenzoin (1.0 mol) with ethyl formate (1.4 mol) in the presence of dry sodium ethoxide (1.0 mol) in ether according to the standard method [6].

Preparation of Aroylacetaldehyde Aroylhydrazones (**3**)

A clear solution of the sodium salt (1.0 mol) of the β-ketoaldehyde **1**, in water (250 ml) was treated with an aqeuous solution (200 ml) of the aroylhydrazine (0.1 mol). The reaction mixture was then stirred for 20–30 min, then carefully acidified with cold 10% hydrochloric acid up to *pH* 5. Stirring was continued for further 30 min during which aroylhydrazone (**3**) separated out. The product was filtered, washed thoroughly with water, dried and then recrystallized from the appropriate solvent. The prepared aroylhydrazones together with their elemental analyses are listed in Table 1.

Preparation of 1-Aroyl-5-hydroxy-2-pyrazolines (**5**) *and 4,5-Diphenyl-1-aroyl pyrazoles* (**6**)

A solution of aroylacetaldehyde aroylhydrazone (3.0 g) in ethanol (50 ml) was refluxed with glacial acetic acid (5.0 ml) for 30 min. The solid which separated out on cooling was filtered, washed with ethanol and then crystallized. The prepared pyrazolines **5** and pyrazoles **6** are given in Tables 4 and 5.

Table 4. Analytical data[a] of the prepared 5-hydroxy-5-aryl-1-aroyl pyrazolines (**5**)

Compound			m.p.	C%	H%	N%	Cl%
R^1	R^2	X					
$p\text{-}Me\mathrm{C_6H_4}$	H	H	177^b	72.80	5.60	9.56	–
				(72.83)	(5.75)	(9.99)	–
$p\text{-}Me\mathrm{C_6H_4}$	H	Me	214^c	73.20	6.10	9.20	–
				(73.44)	(6.16)	(9.51)	–
$p\text{-}Me\mathrm{C_6H_4}$	H	$\mathrm{O}Me$	230^d	69.80	5.90	9.40	–
				(69.66)	(5.84)	(9.02)	–
$p\text{-}Me\mathrm{C_6H_4}$	H	Cl	219^d	64.90	4.70	9.01	11.47
				(64.86)	(4.77)	(8.90)	(11.28)
$p\text{-}Me\mathrm{C_6H_4}$	H	$\mathrm{NO_2}$	155^e	62.60	4.80	12.59	–
				(62.77)	(4.60)	(12.90)	–
$p\text{-}Me\mathrm{OC_6H_4}$	H	H	187^b	68.70	5.40	9.55	–
				(68.90)	(5.44)	(9.46)	–
$p\text{-}Me\mathrm{OC_6H_4}$	H	Me	244^b	69.60	5.80	9.00	–
				(69.60)	(5.84)	(9.02)	–
$p\text{-}Me\mathrm{OC_6H_4}$	H	$\mathrm{O}Me$	231^b	66.30	5.60	8.50	–
				(66.24)	(5.55)	(8.58)	–
$p\text{-}Me\mathrm{OC_6H_4}$	H	Cl	232^d	61.70	4.50	8.61	10.60
				(61.72)	(4.54)	(8.47)	(10.74)
$p\text{-}Me\mathrm{OC_6H_4}$	H	$\mathrm{NO_2}$	196^e	60.00	4.50	12.41	–
				(59.82)	(4.40)	(12.31)	

[a] Values in brackets indicate calculated results
[b] Ethanol
[c] Methanol
[d] Benzene/ethanol
[e] Benzene

Table 5. Analytical data[a] of 1-aroyl-4,5-diphenylpyrazoles (**6**)

Compound			m.p.	C%	H%	N%	Cl%
R^1	R^2	X					
$\mathrm{C_6H_5}$	$\mathrm{C_6H_5}$	H	183^b	81.20	5.20	8.50	–
				(81.45)	(4.97)	(8.63)	–
$\mathrm{C_6H_5}$	$\mathrm{C_6H_5}$	Me	152^c	81.44	5.50	8.00	–
				(81.63)	(5.36)	(8.27)	–
$\mathrm{C_6H_5}$	$\mathrm{C_6H_5}$	$\mathrm{O}Me$	163^c	77.76	5.40	8.11	–
				(77.94)	(5.11)	(7.90)	–
$\mathrm{C_6H_5}$	$\mathrm{C_6H_5}$	Cl	172^c	73.40	4.41	7.70	10.11
				(73.63)	(4.21)	(7.81)	(9.88)
$\mathrm{C_6H_5}$	$\mathrm{C_6H_5}$	$\mathrm{NO_2}$	168^d	71.83	4.13	11.10	–
				(71.53)	(4.09)	(11.37)	–

[a] Values in brackets indicate the calculated results
[b] Ethanol
[c] Benzene/ethanol
[d] Benzene

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