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Synthesis and Spectroscopic Studies of Some Heterocyclic Compounds

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The reactions of aroylphenylacetylenes (I) with ethyl and phenyl hydrazinecarboxylates, benzoylhydrazine, phenylacetylhydrazine, α -naphthylacetylhydrazine, methylhydrazine, N,N-dimethylhydrazine, thiourea, guanidine and S-benzylisothiurea were reported.

The structure and configuration of the products are based on chemical and spectroscopic evidence.

Keywords— ω -aroylacetophenone-N-substituted hydrazone; 5-aryl-1-methyl-3-phenylpyrazole; α -aroyl- β -benzylthiostyrene; 2-amino-4-aryl-6-phenylpyrimidine; synthesis; spectroscopy

The reactions of the acetylenic ketones with hydrazine derivatives,²⁻⁶⁾ guanidine³⁻⁷⁾ and thiourea³⁾ have been reported.

In the present investigation aroylphenylacetylenes (Ia—c) were allowed to react with esters of hydrazine carboxylic acid, acyl- and aroyl-hydrazines, methylhydrazine, N,N-dimethylhydrazine, thiourea, guanidine and S-benzylisothiurea to study the structure and configuration of the products.

Treatment of acetylenic ketones (Ia—c) with hydrazine derivatives resulted in ω -aroylacetophenone-N-substituted hydrazones (IVa—m) (Chart 1).

The structures of the compounds (IVa—m) were established spectroscopically and chemically. Thus, their infrared spectra revealed the presence of a band in the region 3450—3340 cm^{-1} (νNH).^{8a)} They also showed a strong band in the region 1732—1630 cm^{-1} ($\nu_{\text{C=O}}$).^{8b)} (Table I). Their nuclear magnetic resonance (NMR) spectra (Table I) showed a quartet (2H) AB system ($J_{\text{AB}}=18-20$ Hz) due to the CH_2CO group.^{3,4)} The fact that the quartets collapsed to singlets when the NMR spectra of these compounds were measured in deuteriodimethyl sulfoxide (Table I) indicated that the AB system could be attributed to the restricted rotation of the (COAr) group by the weak hydrogen bonding between the NH and the carbonyl of the aroyl group. The highly polar solvent possibly cleaves the weak hydrogen bonding between the NH and CO group. The electronic spectra of these compounds (Table I) revealed their identity and showed absorption maxima in the range 298—278 nm attributable to $\pi-\pi^*$ transition bands.^{3,4)}

The compounds (IVa—m) are converted to the corresponding 3(5)-aryl-5-(phenyl)-pyrazoles (Va—c) when heated with 3% methanolic KOH. Compounds (IVc—e, h—m) gave, in addition, the acids (VIII). Compounds (IVa, f) were easily cyclized by refluxing with acetic

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anhydride to the corresponding 5-aryl-1-ethoxycarbonyl-3-phenylpyrazoles (VIa, f). The spectral data of these compounds is tabulated in Table I.

However, treatment of these ketones (Ia—c) with methylhydrazine, gave the corresponding 5-aryl-1-methyl-3-phenylpyrazoles (IXa—c) (*cf.* Chart 1). The spectral data of these compounds was in good resemblance with the spectra of substituted pyrazoles³⁾ and given in Table I. The identity of 5-(*m*-nitrophenyl)-1-methyl-3-phenylpyrazole (IXa) was established by its comparison with an authentic specimen prepared by the reaction of dibromide of *m*-nitrobenzalacetophenone with methylhydrazine in methanolic KOH.

The reaction of the acetylenic ketones (Ia, c) with N,N-dimethylhydrazine in boiling ethanol gave the corresponding 1,1-dimethyl-2-[β -(α -arylstyryl)]hydrazines (Xa, c)²⁾ (Chart 1). The latter compounds when heated with acetic anhydride, resulted in the corresponding 5-aryl-1-methyl-3-phenyl-pyrazoles (IXa, c), whose spectral data is included in Table I.

Replacement of substituted hydrazine derivatives with thiourea and its reaction with acetylenic kenones (Ib) afforded 4(6)-(m-nitrophenyl)-6(4)-phenyl-pyrimidine-2-thione (XIIb)

TABLE I. Physical Data for Compounds (IV—VII), (IX), (X), and (XII—XVII)

Compounds ^{a)}	mp (°C)	NMR ^{b)}			UV (EtOH) ^{c)}		IR (KBr) ^{d)}	
		δ (CDCl ₃)	δ (DMSO- <i>d</i> ₆)	Assignments	$\lambda_{\max}$ (nm)	$\epsilon \times 10^{-3}$	cm ⁻¹	ν
IVa	194—195 ^{e)}	8.24(m)	7.95(m)	ArH	286—282(sh)	21.63	3340(br)	NH
		4.80(br)	—	NH	276	23.08	1695(s)	C=O
		4.38(q), 1.32(t) (<i>J</i> = 7 Hz)	4.07(q), 1.03(t) (<i>J</i> = 7 Hz)	OCH ₂ CH ₃				
		3.82(d), 3.32(d) (<i>J</i> = 19 Hz)	3.67(s)	CH ₂ CO				
IVb	163—164 ^{e)}	7.75(m)	7.74(m)	ArH	278	25.01	3420(br)	NH
		4.73(br)	—	NH			1732(s)	C=O
		3.87(d), 3.36(d) (<i>J</i> = 18 Hz)	3.75(s)	CH ₂ CO				
IVc	161—162 ^{f)}	7.93(m)	7.95(m)	ArH	292	18.00	3350(br)	NH
		5.43(br)	—	NH	298—290(sh)	18.01	1632(s)	C=O
		3.83(d), 3.34(d) (<i>J</i> = 18 Hz)	3.67(s)	CH ₂ CO	283	18.43		
IVd	145—146 ^{g)}	7.74(m)	7.75(m)	ArH	304—297(sh)	13.46	3450(br)	NH
		5.38(br)	—	NH	282	21.71	1665(s)	C=O
		4.28(d), 3.73(d) (<i>J</i> = 14 Hz)	4.08(s)	CH ₂ CON				
		3.74(d), 3.22(d) (<i>J</i> = 19 Hz)	3.63(s)	CH ₂ COAr				
IVe	192—193 ^{e)}	7.72(m)	7.88(m)	ArH	296—290(sh)	25.99	3400(s)	NH
		5.13(br)	—	NH	282	28.74	1643(s)	C=O
		4.75(d), 4.42(d) (<i>J</i> = 14 Hz)	4.57(s)	CH ₂ CON				
		3.78(d), 3.76(d) (<i>J</i> = 18 Hz)	3.67(s)	CH ₂ COAr				
IVf	156—157 ^{h)}	7.6(m)	7.54(m)	ArH	280	22.15	3390(br)	NH
		5.02(br)	—	NH			1715(s)	C=O
		4.29(g), 1.32(t) (<i>J</i> = 7 Hz)	4.07(g), 1.05(t) (<i>J</i> = 7 Hz)	OCH ₂ CH ₃				
		3.76(d), 3.30(d) (<i>J</i> = 18 Hz)	3.27(s)	CH ₂ CO				
IVg	150—151 ^{e)}	7.47(m)	7.53(m)	ArH	280	17.63	3430(br)	NH
		4.67(br)	—	NH			1712(s)	C=O
		3.81(d), 3.34(d) (<i>J</i> = 19 Hz)	3.67(s)	CH ₂ CO				
IVh	127—128 ^{h)}	7.72(m)	7.61(m)	ArH	292	15.21	3410(br)	NH
		5.52(br)	—	NH			1630(s)	C=O
		3.68(d), 3.21(d) (<i>J</i> = 18 Hz)	3.62(s)	CH ₂ CO				
IVi	87—88 ^{h)}	7.35(m)	7.59(m)	ArH	295—289(sh)	19.84	3350(br)	NH
		5.22(br)	—	NH	283	20.33	1645(s)	C=O
		4.19(d), 3.82(d) (<i>J</i> = 14 Hz)	4.08(s)	CH ₂ CON				
		3.59(d), 3.08(d) (<i>J</i> = 18 Hz)	3.73(s)	CH ₂ COAr				
IVj	172—173 ^{h)}	7.57(m)	7.71(m)	ArH	293	32.57	3420(br)	NH
		5.03(br)	—	NH	284	33.97	1647(s)	C=O
		4.71(d), 4.40(d) (<i>J</i> = 15 Hz)	4.57(s)	CH ₂ CON				
IVk	129—130 ^{f)}	7.69(m)	7.67(m)	ArH	293	20.21	3418(br)	NH
		5.48(br)	—	NH			1632(s)	C=O
		3.68(d), 3.23(d) (<i>J</i> = 18 Hz)	3.66(s)	CH ₂ CO				
IVl	88—89 ^{f)}	7.70(m)	7.29(m)	ArH	293	23.01	3390(br)	NH
		5.07(br)	—	NH	284	23.97	1645(s)	C=O
		4.07(s)	4.07(s)	CH ₂ CON				
		3.77(d), 3.27(d) (<i>J</i> = 20 Hz)	3.70(d), 3.30(d) (<i>J</i> = 20 Hz)	CH ₂ COAr				
IVm	188—189 ^{e)}	7.52(m)	7.75(m)	ArH	294	27.11	3425(br)	NH
		5.00(br)	—	NH	283	28.26	1650(s)	C=O
		4.17(s)	4.57(s)	CH ₂ CON				
		3.76(d), 3.26(d) (<i>J</i> = 19 Hz)	3.60(s)	CH ₂ COAr				
Va	214—215 ^{e)}	8.00(m)	—	ArH	252	24.84	2950(br)	NH
Vb	182—183 ^{e)}	6.85(s)	—	CH=			1525(s)	NO ₂
		7.62(m)	—	ArH	254	25.70	3230(br)	NH
		6.83(s)	—	CH=				
		5.03(br)	—	NH				

Compounds ^{a)}	mp (°C)	NMR ^{b)}			UV (EtOH) ^{c)}		IR (KBr) ^{d)}	
		δ (CDCl ₃)	δ (DMSO- <i>d</i> ₆)	Assignments	$\lambda_{\max}$ (nm)	$\epsilon \times 10^{-3}$	cm ⁻¹	ν
VIa	139—140 ^{f)}	7.93(m) 6.83(s) 4.46(q), 1.37(t) (<i>J</i> = 7 Hz)		ArH CH= CH ₂ CH ₃	260	25.62	1772(s) 1535(s)	C=O NO ₂
VIb	130—131 ^{f)}	7.53(m) 6.67(s) 4.36(q), 1.36(t) (<i>J</i> = 7 Hz)		ArH CH= CH ₂ CH ₃	262	28.98	1768(s) 1560(s)	C=O C=N
VIIa	158—159 ^{f)}	7.43(m) 6.77(s)		ArH CH=	280—257(sh) 243	23.52 25.38	1741(s) 1537(s)	COCH ₃ NO ₂
VIIb	108—109 ^{g)}	7.58(m) 6.63(s) 2.77(s)		ArH CH= COCH ₃	272 243	23.78 26.47	1740(s)	COCH ₃
VIIc	114—115 ^{f)}	7.65(m) 6.65(s) 2.77(s)		ArH CH= COCH ₃	273 243	28.89 32.52	1738(s)	COCH ₃
IXa	98—99 ^{f)}	7.95(m) 6.57(s) 3.88(s)		ArH CH= NCH ₃	252	30.40	1540(s)	NO ₂
IXb	98—99 ^{f)}	7.80(m) 7.05(s) 3.40(s)		ArH CH= NCH ₃	253	28.81	1600(s) 1575(s)	C=N C=C
IXc	80—81 ^{g)}	7.54(m) 6.53(s) 3.90(s)		ArH CH= NCH ₃	253	27.86	1602(s) 1572(m)	C=N C=C
Xa	82—83 ^{f)}	11.83(br) 8.00(m) 5.67(s) 2.67(s)		NH ArH CH= N(CH ₃) ₂	347 226	18.33 22.00	1580(s)	C=O...NH
XIIb	194—195 ^{e)}	7.88(m)		ArH + NH + CH=	414 298 261	3.53 20.93 17.15	2900(br) 1600(s) 1581(s) 1550(s)	NH C=N and C=C
				Cyclohexane	320 257	15.11 41.47		
XIIIb	166—167 ^{h)}	7.73(m) 7.88(s) 2.57(s)		ArH CH= COCH ₃	307—290(sh) 259	13.32 35.85	1700(s) 1575(s) 1520(s)	COCH ₃ Pyrimidine ring
XIVb	186—187 ^{e)}	7.68(m) 7.73(s)		ArH CH=	320 263	30.78 86.36	1578(s) 1520(s)	Pyrimidine ring
XVa	185—186 ^{e)}	8.00(m) 5.17(br)		ArH NH ₂	341 245	12.51 39.48	3520(s) 3400(s) 1610(s) 1572(s) 1530(s)	NH ₂ C=N and C=C
XVb	116—117 ^{f)}	7.75(m) 5.5(br)		ArH NH ₂	337 353	13.34 30.53	3470(s) 3320(m) 3190(m) 1625(s) 1570(s) 1540(s)	NH ₂ C=N and C=C
XVIa	170—171 ^{e)}	10.12(br) 8.17(m)		NH ArH + CH=	317 252	10.00 31.75	3320(br) 1670(s) 1595(s) 1542(s)	NH NCOCH ₃ Pyrimidine ring
XVIb	170—171 ^{e)}	7.80(m) 2.73(s)		ArH COCH ₃	317 253	17.00 39.51	3300(br) 1670(s) 1600(s) 1542(s)	NH NCOCH ₃ Pyrimidine ring
XVIIa	130—131 ^{h)}	7.91(m) 3.63(s)		ArH SCH ₃	346 239	19.80 30.00	1635(s)	C=O
XVIIb	90—91 ^{h)}	7.45(m) 3.60(s)		ArH SCH ₃	344 269	21.85 13.98	1635(s)	C=O

a) Elemental analyses in agreement with theoretical values were obtained and submitted for review. b) NMR were recorded on JEOL JNM-PMX60 NMR spectrometer using TMS as internal standard. c) Ultraviolet spectra were recorded on a pye-Unicam SP 8000 spectrometer. d) IR spectra were recorded using a Pye-Unicam SP 1000 and Beckman IR 12 spectrophotometers. e) Crystallised from benzene. f) Crystallised from cyclohexane. g) Crystallised from benzene-petroleum ether (30—60°). h) Crystallised from benzene-cyclohexane. i) Crystallised from petroleum ether (30—60°). j) Crystallised from ethanol. k) Crystallised from methanol.

which gave a colourless acetyl-mercaptopyrimidine derivative (XIIIb) with acetic anhydride. Oxidation of the thione (XIIb) with sodium nitrite and sodium hydrogen sulphate in ethanol gave 2,2-bis-[4-(*m*-bromophenyl)-6-phenylpyrimidinyl] disulphide (XIVb) from which the original thione (XIIb) could be obtained by reduction.

Chart 2

The acetylenic ketones (Ia, b) when treated with guanidine hydrochloride gave the corresponding 2-amino-6-aryl-4-phenylpyrimidines (XVa, b) (*cf.* Chart 2). The structures of these compounds and their acetylated products were established from the spectral data (Table I).

The reaction of the acetylenic ketones (Ia, b) with S-benzylisothiourea hydrochloride gave the corresponding α -aroyle- β -benzylthiostyrenes (XVIIa, b). These compounds were reacted with hydrazine hydrate in ethanol to give the corresponding 3(5)-aryl-5(3)-phenylpyrazoles (Va, b) and benzylthiol. The NMR spectra show signals in the range δ 3.63—3.60 attributed to the SCH_2 -group. The infrared and ultraviolet spectra of these compounds (Table I) lent a further support for the styrene derivatives (XVIIa, b) (Table I).

Experimental

Aroylphenylacetylenes (Ia, mp 134—135°; Ib, mp 90—91°; and Ic, mp 90—91°), ω -aroyleacetophenone-N-substituted hydrazones (IVa—m), 5-aryl-1-ethoxycarbonyl-3-phenylpyrazoles (IVa, f), 5-aryl-1-methylpyrazole (IXa—c), N,N-dimethyl-2-([β -[α -(*m*-nitrobenzoyl)styryl]]hydrazine (Xa), 4-(*m*-bromophenyl)-6-phenyl-(1H)-pyrimidine-2-thione (XIIb), 2-acetylmercapto-4-(*m*-bromophenyl)-6-phenyl-pyrimidine (XIIIb),

2,2-bis-[4-(*m*-bromophenyl)-6-phenyl-pyrimidinyl] disulphide (XIVb), 2-amino-4-aryl-6-phenyl-pyrimidines (XVa, b), 2-acetamido-4-aryl-6-phenylpyrimidine (XVIa, b) and α -aroyl- β -benzylthiostyrenes (XVIIa, b) were prepared according to the methods previously reported by our group.²⁻⁴⁾ The results are reported in Table I.

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Studies on Carbon-13 Magnetic Resonance Spectroscopy. IX.¹⁾ Carbon-13 Pulse Fourier Transform Nuclear Magnetic Resonance Chemical Shifts of 1-Substituted-3,4-dimethoxy- and -3,4-methylenedioxybenzene Derivatives

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C-13 nuclear magnetic resonance chemical shifts of 1-substituted-3,4-dimethoxy- and -3,4-methylenedioxybenzene derivatives were measured. Reliability of the additivity rule of the shielding parameters of monosubstituted benzenes, and the linear relations between the chemical shifts and shielding parameters or substituent constants were confirmed. Deviations from the additivity rule are mainly attributed to the *ortho* steric effect.

Keywords—C-13 NMR chemical shift; 1-substituted-3,4-dimethoxybenzenes; 1-substituted-3,4-methylenedioxybenzenes; substituent constants; additivity rule

Introduction

In the previous reports of this series,³⁾ carbon-13 chemical shifts of mono- (1) and disubstituted benzene derivatives were measured under the proton decoupled continuous wave mode, and the reliability of the additivity rule of the shielding parameters of monosubstituted benzenes was confirmed in the disubstituted series, and the correlations between the chemical shifts and substituent constants σ_i or σ_π ,⁴⁾ as empirical parameters of σ - and π -electronic effects, were also acknowledged.

In this work, the reliabilities of the above rule were examined for 1-substituted-3,4-dimethoxy- (2) and -3,4-methylenedioxy benzene (3) series, and the relationships between the chemical shifts and shielding parameters and/or with the substituent constants were confirmed as the basis of the assignment of the chemical shifts of complex natural products.

Experimental

All monosubstituted benzenes were commercially available, whereas 1-substituted-3,4-dimethoxy- and -3,4-methylenedioxybenzene derivatives were prepared by the authentic methods from vanilline, piperonal, etc.

All spectra were measured at 22.63 MHz on a Hitachi R-22 type NMR spectrometer with a HITAC 10-II computer system under pulse Fourier transform mode. 99.8% CDCl₃ (CEA) solutions of samples

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