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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-benzylisothiourea 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] guanidine[3–7] and thiourea[3] 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-benzylisothiourea 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} ($\nu_{C=O}$)[8b)] (Table I). Their nuclear magnetic resonance (NMR) spectra (Table I) showed a quartet (2H) AB system (J_{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 π—π* 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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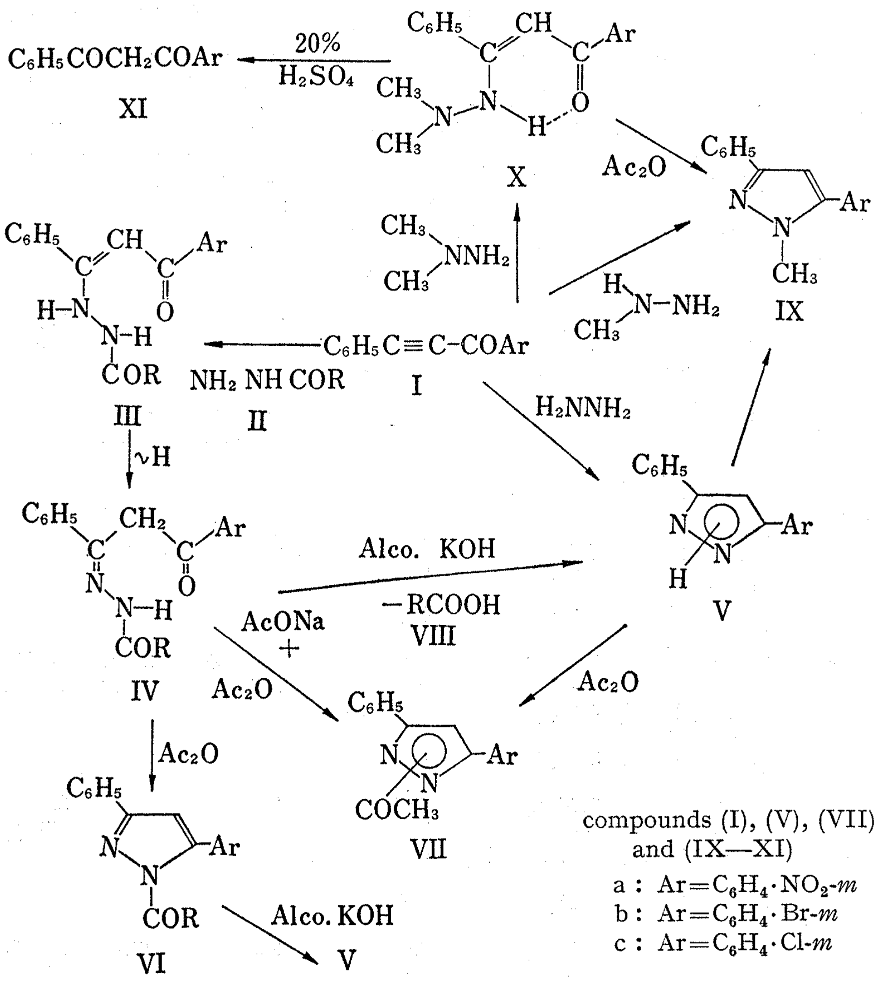

compounds (I), (V), (VII) and (IX—XI)
a : Ar=$C_6H_4 \cdot NO_2$-*m*
b : Ar=$C_6H_4 \cdot Br$-*m*
c : Ar=$C_6H_4 \cdot Cl$-*m*

compounds (III), (IV) and (VI)

	Ar	R
a	$C_6H_4 \cdot NO_2$-*m*	OC_2H_5
b	$C_6H_4 \cdot NO_2$-*m*	OC_6H_5
c	$C_6H_4 \cdot NO_2$-*m*	C_6H_5
d	$C_6H_4 \cdot NO_2$-*m*	$C_6H_5CH_2$
e	$C_6H_4 \cdot NO_2$-*m*	α-$C_{10}H_7CH_2$
f	$C_6H_4 \cdot Br$-*m*	OC_2H_5
g	$C_6H_4 \cdot Br$-*m*	OC_6H_5
h	$C_6H_4 \cdot Br$-*m*	C_6H_5
i	$C_6H_4 \cdot Br$-*m*	$C_6H_5CH_2$
j	$C_6H_4 \cdot Br$-*m*	α-$C_{10}H_7CH_2$
k	$C_6H_4 \cdot Cl$-*m*	C_6H_5
l	$C_6H_4 \cdot Cl$-*m*	$C_6H_5CH_2$
m	$C_6H_4 \cdot Cl$-*m*	α-$C_{10}H_7CH_2$

compounds (II) and (VIII)

a	OC_2H_5
b	OC_6H_5
c	C_6H_5
d	$C_6H_5CH_2$
e	α-$C_{10}H_7CH_2$

Chart 1

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 pyrazoles[3] 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-aroylstyryl)]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 ($DMSO$-d_6)	Assignments	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	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) ($J=7$ Hz)	4.07(q), 1.03(t) ($J=7$ Hz)	OCH_2CH_3				
		3.82(d), 3.32(d) ($J=19$ Hz)	3.67(s)	CH_2CO				
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) ($J=18$ Hz)	3.75(s)	CH_2CO				
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) ($J=18$ Hz)	3.67(s)	CH_2CO	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) ($J=14$ Hz)	4.08(s)	CH_2CON				
		3.74(d), 3.22(d) ($J=19$ Hz)	3.63(s)	CH_2COAr				
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) ($J=14$ Hz)	4.57(s)	CH_2CON				
		3.78(d), 3.76(d) ($J=18$ Hz)	3.67(s)	CH_2COAr				
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) ($J=7$ Hz)	4.07(g), 1.05(t) ($J=7$ Hz)	OCH_2CH_3				
		3.76(d), 3.30(d) ($J=18$ Hz)	3.27(s)	CH_2CO				
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) ($J=19$ Hz)	3.67(s)	CH_2CO				
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) ($J=18$ Hz)	3.62(s)	CH_2CO				
IVi	87—88[i]	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) ($J=14$ Hz)	4.08(s)	CH_2CON				
		3.59(d), 3.08(d) ($J=18$ Hz)	3.73(s)	CH_2COAr				
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) ($J=15$ Hz)	4.57(s)	CH_2CON				
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) ($J=18$ Hz)	3.66(s)	CH_2CO				
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_2CON				
		3.77(d), 3.27(d) ($J=20$ Hz)	3.70(d), 3.30(d) ($J=20$ Hz)	CH_2COAr				
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_2CON				
		3.76(d), 3.26(d) ($J=19$ Hz)	3.60(s)	CH_2COAr				
Va	214—215[e]	8.00(m)		ArH	252	24.84	2950(br)	NH
		6.85(s)		CH=			1525(s)	NO_2
Vb	182—183[e]	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-d_6)	Assignments	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	cm^{-1}	ν
VIa	139—140[f]	7.93(m)		ArH	260	25.62	1772(s)	C=O
		6.83(s)		CH=			1535(s)	NO$_2$
		4.46(q), 1.37(t) (J=7 Hz)		CH$_2$CH$_3$				
VIf	130—131[f]	7.53(m)		ArH	262	28.98	1768(s)	C=O
		6.67(s)		CH=			1560(s)	C=N
		4.36(q), 1.36(t) (J=7 Hz)		CH$_2$CH$_3$				
VIIa	158—159[f]	7.43(m)		ArH	280—257(sh)	23.52	1741(s)	COCH$_3$
		6.77(s)		CH=	243	25.38	1537(s)	NO$_2$
VIIb	108—109[i]	7.58(m)		ArH	272	23.78	1740(s)	COCH$_3$
		6.63(s)		CH=	243	26.47		
		2.77(s)		COCH$_3$				
VIIc	114—115[f]	7.65(m)		ArH	273	28.89	1738(s)	COCH$_3$
		6.65(s)		CH=	243	32.52		
		2.77(s)		COCH$_3$				
IXa	98—99[f]	7.95(m)		ArH	252	30.40	1540(s)	NO$_2$
		6.57(s)		CH=				
		3.88(s)		NCH$_3$				
IXb	98—99[f]	7.80(m)		ArH	253	28.81	1600(s)	C=N
		7.05(s)		CH=			1575(s)	C=C
		3.40(s)		NCH$_3$				
IXc	80—81[i]	7.54(m)		ArH	253	27.86	1602(s)	C=N
		6.53(s)		CH=			1572(m)	C=C
		3.90(s)		NCH$_3$				
Xa	82—83[f]	11.83(br)		NH	347	18.33	1580(s)	C=O···NH
		8.00(m)		ArH	226	22.00		
		5.67(s)		CH=				
		2.67(s)		N(CH$_3$)$_2$				
XIIb	194—195[e]	7.88(m)		ArH	414	3.53	2900(br)	NH
				+NH+CH=	298	20.93	1600(s)	C=N and C=C
					261	17.15	1581(s)	
					Cyclohexane		1550(s)	
					320	15.11		
					257	41.47		
XIIIb	166—167[h]	7.73(m)		ArH	307—290(sh)	13.32	1700(s)	COCH$_3$
		7.88(s)		CH=	259	35.85	1575(s)	Pyrimidine ring
		2.57(s)		COCH$_3$			1520(s)	
XIVb	186—187[e]	7.68(m)		ArH	320	30.78	1578(s)	Pyrimidine ring
		7.73(s)		CH=	263	86.36	1520(s)	
XVa	185—186[e]	8.00(m)		ArH	341	12.51	3520(s)	NH$_2$
							3400(s)	
		5.17(br)		NH$_2$	245	39.48	1610(s)	C=N and C=C
							1572(s)	
							1530(s)	
XVb	116—117[f]	7.75(m)		ArH	337	13.34	3470(s)	NH$_2$
							3320(m)	
							3190(m)	
		5.5(br)		NH$_2$	353	30.53	1625(s)	C=N and C=C
							1570(s)	
							1540(s)	
XVIa	170—171[e]	10.12(br)		NH	317	10.00	3320(br)	NH
		8.17(m)		ArH+CH=	252	31.75	1670(s)	NCOCH$_3$
							1595(s)	Pyrimidine ring
							1542(s)	
XVIb	170—171[e]	7.80(m)		ArH	317	17.00	3300(br)	NH
		2.73(s)		COCH$_3$	253	39.51	1670(s)	NCOCH$_3$
							1600(s)	Pyrimidine ring
							1542(s)	
XVIIa	130—131[k]	7.91(m)		ArH	346	19.80	1635(s)	C=O
		3.63(s)		SCH$_3$	239	30.00		
XVIIb	90—91[k]	7.45(m)		ArH	344	21.85	1635(s)	C=O
		3.60(s)		SCH$_3$	269	13.98		

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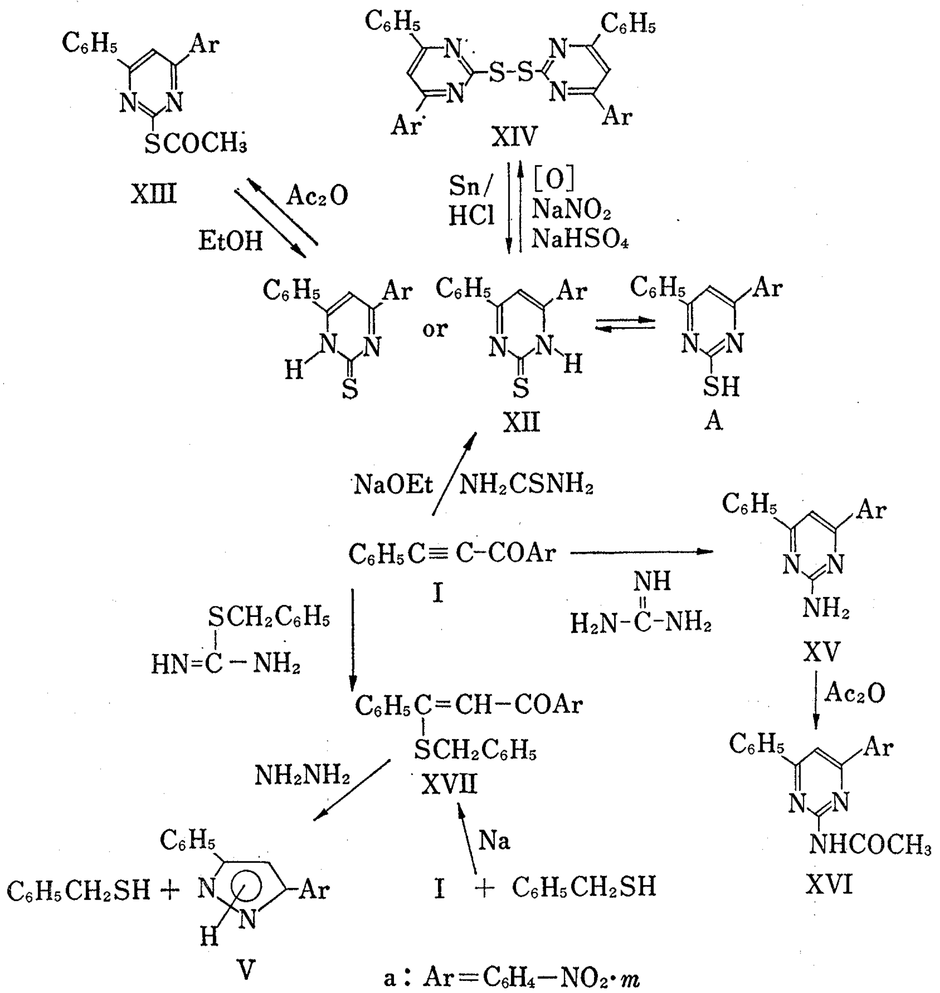
a) Elemental analyses in agreement with theoretical values were obtained and submitted for review. b) NMR were recorded on JEOL JNM-PMX60 NMR spectrometer using TMS as internal standard. c) Ultraviolet spectra were recorded on a pye-Unicam SP 8000 spectrometer. d) IR spectra were recorded using a Pye-Unicam 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.



a : Ar=$C_6H_4-NO_2\cdot m$
b : Ar=$C_6H_4-Br\cdot m$

Chart 2

The acetylenic ketones (Ia, b) when treated with guanidine hydrochloride gave the correponding 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-aroyl-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-aroylacetophenone-N-substituted hydrazones (IVa—m), 5-aryl-1-ethoxycarbonyl-3-phenylpyrazoles (IVa, f), 5-aryl-1-methyl-pyrazole (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% $CDCl_3$ (CEA) solutions of samples

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