Heterocycles. 7. Synthesis of New Pyrazolines

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The condensation of terephthalaldehyde with some aryl methyl ketones Ia–f such as acetophenone, *p*-methoxy-, *p*-bromo-, *p*-chloro-, *p*-fluoroacetophenones, as well as with 2-acetylthiophene gave the chalcones IIa–f. These were reacted with hydrazine and some of its derivatives to produce the corresponding pyrazolines IV–VI. The structure of these products was confirmed by chemical and spectral methods.

In a previous publication, new types of chalcones were prepared, and their brominated products were reacted with some nitrogen nucleophiles to produce substituted isoxazoles and pyrazoles (*1*). The present work intends to prepare other chalcone-type systems and to react them with different hydrazines to produce the corresponding pyrazoline systems (cf. Scheme I). Thus, terephthalaldehyde was reacted with acetophenone (Ia), *p*-methoxy- (Ib), *p*-bromo (Ic), *p*-chloro- (Id), *p*-fluoro- (Ie) acetophenones and with methyl 2-thienyl ketone (If). This resulted in the formation of terephthalbis(acetophenone) (IIa), *p*-methoxyacetophenone (IIb), *p*-bromoacetophenone (IIc), *p*-chloroacetophenone (IId), *p*-fluoroacetophenone (IIe), and methyl 2-thienyl ketone (IIf), respectively (1).

The structure of these α,β-unsaturated carbonyl systems was evident from their chemical and spectral analyses (cf. Table I and II) (*1–3*).

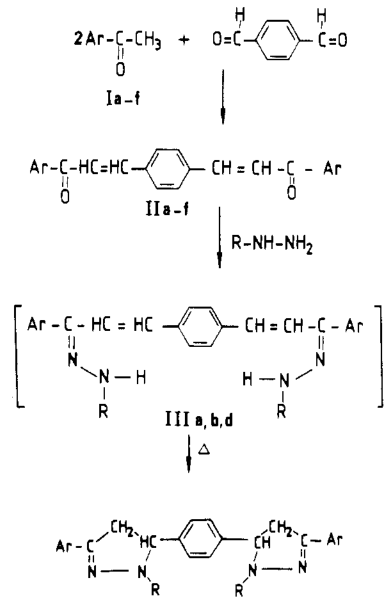
Condensation of the above systems II, with hydrazine hydrate, phenylhydrazine, and methylhydrazine, resulted in the formation of the corresponding 1*H*-pyrazoline (IV) as well as *N*-phenyl- and *N*-methylpyrazolines (V, VI), respectively. The structure of these systems was substantial by chemical and spectral methods (cf. Table I and II) (*4*, *5a*,*b*, *6*, *7*).

The mass spectra lend further support to the proposed structure and show molecular ion peaks corresponding to the molecular weights of these compounds (cf. Table I). It is noteworthy to mention that all the above compounds produced base peaks at *m/e* 28 (100%) and very intense peaks at *m/e* 32 with relative abundance ranging from 50–100%.

Chemical behavior of the above systems can be also adduced in favor of the proposed structure. Thus, acetylation of compounds IV led to the formation of the corresponding *N*-acetyl derivatives (VII). Their structure was corroborated by chemical and spectral methods (cf. Table I and II) (*4*, *5a*,*c*, *6–8*).

The formation of all the above products seems to proceed by a nucleophilic addition of the hydrazines on the carbonyl group to form the intermediate III, followed by cyclization to give the corresponding pyrazolines (*6*). Corroboration of this assumption is forthcoming from the preparation of the phenylhydrazones (IIa,b,d; R = C_6H_5). This was achieved by reacting the corresponding chalcone with phenylhydrazine under mild conditions. The structure of these hydrazones was evident from the chemical and spectral characteristics (cf. Tables I and II). Their infrared spectra indicates the disappearance of the absorption band of the carbonyl group and the presence of a new absorption band that can be correlated to the NH group. Heating of these hydrozones in ethanol led to their cyclization to the corresponding pyrazolines Va,b,d, which were similar in

Scheme I



IV (R = H) , V (R = C_6H_5)
VI (R = CH_3), VII (R = $COCH_3$)

Compound	Ar	Compound	Ar	Compound	Ar
a	C_6H_5	c	p-Br-C_6H_4	e	p-F-C_6H_4
b	p-OCH_3-C_6H_4	d	p-Cl-C_6H_4	f	C_4H_3S

Table I. Melting Points and Yields of Compounds II–VII and Mass Spectra of Compounds VIa, b, d

compd	mp, °C	yield, %	compd	mp, °C	yield, %
IId[a]	250–252	92	Va	290–292	80
IIe	232–234	90	Vb	248–250	82
IIf	208–210	88	Vc	270–272	78
IIIa	210–212	70	Vd	230–232	81
IIIb	188–190	74	Ve	270–272	84
IIId	175–177	78	Vf	100–102	77
IVa	212–214	82	VIIa	288–290	91
IVb	173–175	84	VIIb	228–230	92
IVd	200–202	87	VIId	256–258	94
IVe	195–197	81	VIIe	280–282	93
IVf	190–191	85	VIIf	263–265	91

compd	mp, °C	yield, %	m/e	% of base peak	assign.
VIa	168–170	75	393	10.82	$M^{+\cdot}$
			391	1.56	$[M-H_2]^+$
			389	2.45	$[M-2H_2]^+$
			159	35.08	$[C_{10}H_{11}N_2]^+$
VIb	245–247	78	453	4.42	$M^{+\cdot}$
			189	5.33	$[C_{11}H_{13}N_2O]^+$
			265	1.53	$[C_{17}H_{17}N_2O]^+$
VIc	268–270	77			
VId	237–239	81	461	6.60	$M^{+\cdot}$
			463	4.52	$[M + 2]^+$
			193	12.77	$[C_{10}N_{10}N_2Cl]^+$
			270	1.9	$[C_{16}H_{14}N_2Cl]^+$
IVe	113–115	73			
IVf	178–180	71			

[a] Element analysis, IR and UV data of compounds IIa–c were previously reported (*1*).

0021-9568/85/1730-0500$01.50/0

Table II. Spectrometric Data of Compounds II-VII

compd	IR (KBr)		UV (dioxane)		NMR ($C_2F_3O_2D$)	
	ν, cm^{-1}	bond	λ_{max}, nm	ϵ_{max}	δ ppm	assignments
IIa					7.48–8.10	(m, 14, Ar–H + 2CH=CH)
IIb					7.04–8.20	(m, 12, Ar–H + 2CH=CH)
					4.02	(s, 6, OCH_3)
IIc					7.48–8.04	(m, 12, Ar–H + 2CH=CH)
IId	1658 (s)	C=O	245	16 535	7.56	(d, 4, Ar–H)
	1608 (s)	C=C	285	15 260	8.02	(d, 4, Ar–H, J = 4 Hz)
			352	55 610	7.65	(d, 2, =CH)
					8.00	(d, 2, =CH, J = 9 Hz)
IIe	1665 (s)	C=O	240	16 730	7.19–8.21	(m, 12, Ar–H + 2CH=CH)
	1605 (s)	C=C	289	14 760		
			384	66925		
IIf	1648 (s)	C=O	245	11 845	7.22–7.99	(m, 10, Ar–H + 2CH=CH)
	1587 (s)	C=C	290	12 890		
			355	57 125		
IIIa	1600 (m)	C=N	240	64 230		
	3420		300	21 840		
	3480 (br)	NH	356	17 985		
IIIb	1600 (s)	C=N	240	11 300		
	3400		350	80 970		
	3500 (br)	NH				
IIId	1605 (s)	C=N	239	67 315		
	3400		351	21 540		
	3500 (br)	NH				
IVa	1588 (m)	C=N	253	26 040	4.0–4.30	(m, 4, CH_2)
	3370 (s)	NH			5.63	(t, 2, CH)
					7.38–8.54	(m, 14, Ar–H)
					8.80	(br, 2, NH)
IVb	1608 (s)	C=N	265	27 325	3.6–4.25	(m, 4 CH_2)
	3320 (m)	NH	325	12 945	4.0	(s, 6, OCH_3)
					5.63	(t, 2, CH)
					7.10–8.0	(m, 12, Ar–H)
					8.20	(br, 2, NH)
IVd	1588 (m)	C=N	255	26 655	3.66–4.66	(m, 4, CH_2)
	3365 (m)	NH	289	10 660	5.92	(t, 2, CH)
			325	10 220	7.80–8.40	(m, 12, Ar–H)
					10.20	(s, 2, NH)
IVe	1604 (s)	C=N	250	21 535	3.10–3.40	(m, 4, CH_2)
	3362 (m)	NH	325	8 075	4.83	(t, 2, CH)
					7.09–7.70	(m, 12, Ar–H)
IVf	1630 (m)	C=N	260	20 065	4.0–4.25	(m, 4, CH_2)
	3310 (m)	NH	280	16 180	5.59	(t, 2, CH)
			325	6 475	7.18–7.90	(m, 10, Ar–H)
					8.35	(br, 2, NH)
Va	1600 (s)	C=N	236	50 495		
			277	32 670		
			356	5 940		
Vb	1610 (s)	C=N	245	36 125		
			353	110 780		
Vc	1654 (s)	C=C	261	44 360		
	1597 (s)	C=N	275	40 140		
			353	57 040		
Vd	1600 (s)	C=N	237	48 700		
			277	32 465		
			360	12 985		
Ve	1600 (s)	C=N	240	51 805		
			350	19 030		
Vf	1600 (s)	C=N	242	65 488		
			285	36 550		
			358	7 615		
VIa	1588 (s)	C=N	224	24 625	4.14[a]	(s, 6 H, N–CH_3)
			310	40 725	3.0–3.61	(m, 4 H, CH_2)
					4.12	(q, 2 H, CH)
					7.26–7.84	(m, 14 H, ArH)
VIb	1588 (s)	C=N	225	24 590	3.38	(s, 6 H, N–CH_3)
	1608 (s)		310	32 160	3.85	(s, 6 H, OCH_3)
					3.77–4.40	(m, 4 H, CH_2)
					5.36	(t, 2 H, CH)
					7.80–8.58	(m, 12 H, Ar–H)
VIc	1580 (m)	C=N	317	32 775	3.44	(s, 6 H, N–CH_3)
					0.82–4.40	(m, 4 H, CH_2)
					5.47	(t, 2 H, CH)
					7.70–8.80	(m, 12 H, Ar–H)
VId	1582 (s)	C=N	244	17 885	3.43	(s, 6 H, NCH_3)
					3.80–4.39	(m, 4 H, CH_2)
			315	35 770	5.45	(t, 2 H, CH)
					7.56–8.78	(m, 12 H, Ar–H)

Table II (Continued)

	IR (KBr)		UV (dioxane)		NMR (C$_2$F$_3$O$_2$D)	
compd	ν, cm^{-1}	bond	λ_{max}, nm	ϵ_{max}	δ ppm	assignments
VIe	1600 (m)	C=N	237	51 060		
			325	18 810		
VIf	1610 (m)	C=N	240	19 520		
			284	39 040		
VIIa	1660 (s)	C=O	225	59 140	2.80	(s, 6 H, NCOCH$_3$)
	1640 (s)	C=O	300	42 285	3.28–4.10	(m, 4 H, CH$_2$)
					5.76	(t, 2 H, CH)
	1595 (m)	C=N			7.30–7.95	(m, 14 H, Ar-H)
VIIb	1660 (s)	C=O	217	19 125	2.40^a	(s, 6 H, NCOCH$_3$)
	1609 (m)	C=N	250	6375	3.0–3.60	(m, 4 CH$_2$)
			300–310	51 000	3.50	(s, 6 H, OCH$_3$)
					5.53	(q, 2 H, CH)
					6.82–7.72	(m, 12 H, Ar-H)
VIId	1660 (s)	C=O	310	32 440		
	1600 (m)	C=N				
VIIe	1663 (s)	C=O	295	36 980	2.40	(s, 6 H, NCOCH$_3$)
	1650 (s)				3.0–3.68	(m, 4 H, CH$_2$)
	1607 (s)	C=N			5.66	(t, 2 H, CH)
					6.80–7.84	(m, 12 H, Ar-H)
VIIf	1650 (s)	C=O	255	16685	2.38^a	(s, 6 H, NCOOcH$_3$)
			315	32 510	3.0–4.0	(m, 4 H, CH$_2$)
					5.51	(q, 2 H, CH)
					7.03–7.80	(m, 10 H, Ar-H)

[a] Solvent CDCl$_3$.

every aspect to those prepared directly from the reaction of phenylhydrazine and the proper chalcone.

Experimental Section

Microanalyses were performed by Prof. H. Malissa and G. Reuter, Analytisches Laboratorium, West Germany. The infrared spectra (KBr) and electronic spectra (dioxane) were measured on Perkin-Elmer 520B and Pye Unicam SP8000 spectrophotometers, respectively. The NMR spectra were run on a Jeol JNM-MH 100 spectrometer in deuterated trifluoroacetic acid (C$_2$DF$_3$O$_2$) with Me$_4$Si as internal standard. The mass spectra were run on Varian MAT 311 A. *Melting points are uncorrected* and determined by a Bock-Monoscop M (thermal microscope).

Preparation of the Chalcones IIa–f. A mixture of terephthalaldehyde (0.1 mol and alkyl aryl ketone (0.2 mol) was dissolved in ethanol (50 mL). An aqueous solution of 2 g sodium hydroxide was added slowly and the mixture was stirred for 2 h and worked up as described before (*1*). The products were crystallized from acetic acid or chloroform.

Preparation of the Substituted 1,4-Dipyrazolinylbenzenes IV–VI. The α,β-unsaturated carbonyl compound II (0.01 mol) in ethanol (100 mL) was treated respectively with hydrazine hydrate, phenyl- and methylhydrazines, and then worked up as described previously (*1*, *5*). This gave in each case the corresponding substituted pyrazolines IV–VI. Thus, the reaction of II with hydrazine hydrate produced the corresponding 1,4-bis(3-aryl-1*H*-pyrazolin-5-yl)benzenes IVa–f crystallized from dilute acetic acid. Reaction with *N*-phenylhydrazine yielded the corresponding 1,4-bis(3-aryl-1-phenylpyrazolin-5-yl)benzenes Va–f crystallized from chloroform. Similarly, compounds II reacted with methylhydrazine to form the corresponding 1,4-bis(3-aryl-1-methylpyrazolin-5-yl)benzenes VIa–f, which were crystallized from benzene–petroleum ether (60–80°).

Acetylation of the 1,4-Bis-(3-aryl-1H-pyrazolin-5-yl)-benzenes IV. The 1*H*-pyrazolines (1 g) were refluxed with acetic anhydride (5 mL) for a period of 3 h, and the mixture was poured over ice. The solid product was crystallized from benzene-petroleum ether (60–80°) to give the corresponding 1,4-bis(1-acetyl-3-arylpyrozolin-5-yl)benzenes VIIa–f.

Preparation of the Phenylhydrazone Derivatives IIIa, b, d. Phenylhydrazine (0.015 mol) was added to a suspension of 0.01 mol of the chalcones IIa,b,d in glacial acetic acid, and the mixtures were stirred at room temperature until the corresponding hydrazones (IIIa,b,d) were precipitated. These were immediately collected by filtration and washed with several portions of methyl alcohol to remove adhering acetic acid.

Registry No. Ia, 98-86-2; Ib, 100-06-1; Ic, 99-90-1; Id, 99-91-2; Ie, 403-42-9; If, 88-15-3; IIa, 3251-38-5; IIb, 26483-84-1; IIc, 26473-71-2; IId, 26473-69-8; IIe, 6995-56-8; IIf, 26473-83-6; IIIa, 96503-99-0; IIIb, 96504-00-6; IIId, 96504-01-7; IVa, 96504-02-8; IVb, 96504-03-9; IVd, 96504-04-0; IVe, 96504-05-1; IVf, 96504-06-2; Va, 34135-42-7; Vb, 34765-71-4; Vc, 34765-76-9; Vd, 34135-46-1; Ve, 96504-07-3; Vf, 34135-49-4; VIa, 34135-51-8; VIb, 96504-09-5; VIc, 96504-10-8; VId, 96504-11-9; VIe, 96504-12-0; VIf, 96504-13-1; VIIa, 96504-14-2; VIIb, 96504-15-3; VIId, 96504-16-4; VIIe, 96504-17-5; VIIf, 96504-18-6; terepthalaldehyde, 623-27-8; hydrazine, 302-01-2; phenylhydrazine, 100-63-0; methylhydrazine, 60-34-4.

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Received for review May 21, 1984. Revised manuscript received October 8, 1984. Accepted December 12, 1984.