(100 mL) was added dropwise to a well-stirred suspension of lithium aluminum hydride (0.10 mol) in either solvent (400 mL). After the addition, the reaction mixture was refluxed for 12 h, cooled to 0 °C, and decomposed by adding water (3.8 mL), 20% sodium hydroxide (11.4 mL), and again water (3.8 mL). The precipitate was filtered and washed 3 times with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated to dryness. The residue was dissolved in anhydrous ether, filtered to remove insoluble material, and treated with dry hydrogen chloride gas. The amine hydrochlorides were filtered and recrystallized from aqueous ethanol.

***3-(4-Methylphenyl)-1-adamantanemethylamine Hydrochloride* (4a).** **4a** was synthesized from the corresponding amide (*8*) (75%): mp 214–216 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.59 (br s, CH_2N), 7.11–7.29 (m, ArH), 7.97 (br s, NH_3^+); mass spectrum, *m/e* (relative intensity) 256 (20), 255 (M^+ – HCl, 60), 238 (41), 225 (100), 183 (128), 168 (92).

***3-(4-Methoxyphenyl)-1-adamantanemethylamine Hydrochloride* (4b).** **4b** was prepared (77%): mp 237–238 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.55 (br s, CH_2N), 6.77–7.36 (AA′BB′, ArH), 8.06 (br s, NH_3); mass spectrum, *m/e* (relative intensity) 273 (8), 272 (41), 271 (M^+, 70), 242 (57), 241 (100), 185 (62), 149 (25), 121 (30).

***3-(4-Fluorophenyl)-1-adamantanemethylamine Hydrochloride* (4c).** **4c** was obtained in 76% yield: mp 208–210 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.56 (br s, CH_2N), 6.95–7.5 (m, ArH), 8.06 (br s, NH_3); mass spectrum, *m/e* (relative intensity) 259 (M^+ – HCl, 32), 238 (100), 229 (67), 173 (59), 153 (21), 109 (50).

***3-(4-Methylthiophenyl)-1-adamantanemethylamine Hydrochloride* (4).** **4d** was produced (65%): mp 210–212 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.44 (s, SCH_3), 2.56 (br s, CH_2N), 7.26 (br s, ArH); mass spectrum, *m/e* (relative intensity) 290 (6), 289 (21), 288 (100), 287 (M^+ – HCl, 19), 257 (48), 201 (47), 169 (21), 165 (25), 137 (26).

***3-(2-Thienyl)-1-adamantanemethylamine*.** This compound was isolated as a pale yellow oil from the reduction of pure **3d** (81%): 180-MHz ^{1}H NMR ($CDCl_3$) δ 2.41 (d, CH_2N), 6.74 (dd, H-3 of thiophene), 6.83 (dd, H-4 of thiophene), 7.06 (dd, H-5 of thiophene), $J_{4,5}$ = 5.1, $J_{3,4}$ = 3.6, $J_{3,5}$ = 1.2 Hz. It was converted to the hydrochloride (**4e**): mp 255–260 °C (dec); mass spectrum, *m/e* (relative intensity) 249 (3), 248 (9), 247 (M^+ – HCl, 48) 218 (100), 217 (62), 135 (22), 134 (52), 133 (23); ^{1}H NMR (Me_2SO-d_6) δ 2.59 (br s, CH_2N), 6.90–7.46 (m, ArH), 8.01 (br s, NH_3^+).

Acknowledgment

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Registry No. **1**, 21816-08-0; **2** (Ar = H), 828-51-3; **2** (Ar = 4-$CH_3OC_6H_4$), 56531-56-7; **2a**, 88358-11-6; **2b**, 88358-12-7; **2c**, 88358-13-8; **2d**, 88358-14-9; **3** (Ar = 4-$CH_3C_6H_4$), 61051-22-7; **3a**, 61051-24-9; **3b**, 88376-63-0; **3c**, 88358-15-0; **3d**, 88358-16-1; **3e**, 88358-17-2; **4a**, 88358-18-3; **4b**, 88358-19-4; **4c**, 88358-20-7; **4d**, 88358-21-8; **4e**, 88358-22-9; 3-(2-thienyl)-1-adamantanemethylamine, 88358-23-0; fluorobenzene, 462-06-6; thioanisole, 100-68-5; thiophene, 110-02-1.

Literature Cited

(1) Westland, R. D.; Merz, M. M.; Alexander, S. M.; Newton, L. S.; Bauer, L.; Conway, T. T.; Barton, J. M.; Khullar, K. K.; Devdhar, P. B.; Grenan, M. M. *J. Med. Chem.* **1972**, *15*, 1313.
(2) Koch, H.; Haaf, W. "Organic Syntheses"; Wiley: New York, **1973**; Collect. Vol. V, p 20.
(3) Aigami, K.; Inamoto, Y.; Takaishi, N.; Hattori, K. *J. Med. Chem.* **1975**, *18*, 713.
(4) Stetter, H.; Schwarz, M.; Hirschhorn, A. *Chem. Ber.* **1959**, *92*, 1629.
(5) Perkins, R.; Bennett, S.; Bowering, E.; Burke, J.; Reid, K.; Wall, D. *Chem. Ind. (London)* **1980**, 790.
(6) Newman, H. *Synthesis* **1972**, 692.
(7) Weiss, J.-V.; Wray, V.; Schmutzler, R. *Z. Naturforsch. B* **1979**, *34*, 1286.
(8) Danilenko, G. I.; Votyakov, V. I.; Andreeva, O. T.; Boreko, E. I.; Denisova, L. V.; Shashikhina, M. N.; Timofeeva, M. N.; Dikolenko, E. I.; Utochka, T. N. *Khim.-Farm. Zh.* **1976**, *10*, 37.
(9) Fischer, V. W.; Grob, C. A.; Katayama, H. *Helv. Chim. Acta* **1976**, *59*, 1953.
(10) Pines, S. H.; Czaja, R. F.; Abramson, N. L. *J. Org. Chem.* **1975**, *40*, 1920.
(11) Hoek, W.; Strating, J.; Wynberg, H. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 1045.
(12) Bhacca, N. S.; Johnson, L. F.; Schoolery, J. N. "NMR Spectra Catalog"; Varian Associates: Palo Alto, CA, 1962.
(13) "The Sadtler Standard Spectra"; Sadtler, Research Laboratories, Inc.: Philadelphia, PA, 1975.
(14) Stetter, H.; Mayer, J. *Chem. Ber.* **1962**, *95*, 667.

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Heterocycles. 3. Synthesis and Spectral Data of Some 2-Pyrazolines

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The reaction of 1,3-diaryl-2-propen-1-ones (Ia–o) with hydrazine and methyl- and phenylhydrazine produced different substituted 2-pyrazolines (III). The structures of these products were evident from their chemical and spectroscopic analysis.

The aim of the present work is to prepare different substituted 2-pyrazolines and to substantiate their structure by chemical and spectral tools. The importance of these pyrazoline derivatives arises from their wide applications for different purposes. Thus, the 1,3-diaryl-2-propen-1-ones (Ia–o) were condensed with hydrazines hydrate, phenylhydrazine, and methylhydrazine to produce 1*H*-3,5-diaryl-2-pyrazolines ($IIIa_1$–I_1), 1,3,5-triaryl-2-pyrazolines ($IIIf_2$–I_2), and 3,5-diaryl-1-methyl-2-pyrazolines ($IIId_3$–n_3), respectively (cf. Scheme I). The structures of all products were evident from their chemical and spectral data (cf. Tables I–IV).

The electronic spectra of all the 2-pyrazolines exhibit similar absorption patterns. Thus, the pyrazolines $IIIa_1$–I_1 absorb in the regions 302–273 and 238–221 nm, the pyrazolines $IIIf_2$–I_2 show two major maxima in the regions 364–350 and 253–222

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Table I. Electronic Spectral Data (Ethanol) of the 2-Pyrazolines (III)

compd	yield, %	mp, °C	λ_{max}, nm	ϵ_{max}	compd	yield, %	mp, °C	λ_{max}, nm	ϵ_{max}
IIIa$_1$			287	8060	IIIi$_2$	90	134	358	13 010
			222	8100				312 (sh)	4 840
b$_1$			273	8750				242	14 580
			224	11880	j$_2$	90	173	365	19 690
								253	21 520
c$_1$			296	8550				225	20 600
			278 (sh)	7830	k$_2$	91	152	366	20 720
			227	6010				253	21 450
d$_1$	90	85	290	10370				226	17 085
			284	10740	l$_2$	86	132	364	13 350
			224	13460				252	15 515
e$_1$	92	94	285	14840					
			225	5270	d$_3$	88	87	304	11 720
								286 (sh)	8 320
f$_1$	85	72	302	10020				226	12 040
			239	6935	e$_3$	84	94	299	10 370
g$_1$	88	69	284	7010				221 (sh)	3 780
			229	6080					
h$_1$	87	65	287	13670	f$_3$	85	83	320	11 835
			224	9580				235	10 590
i$_1$	91	80	274	7740	g$_3$	87	91	300	11 835
								228	14 990
			238	7590					
j$_1$	88	89	305	12315	h$_3$	89	140	299	17 565
								228	14 650
			257	6160					
			220	12860					
k$_1$	87	75	304	9040	i$_3$	82	95	307	10 850
								231	11 320
			257	5160					
			222	10010					
l$_1$	82	83	287	5970	j$_3$	90	88	290	7 195
								264	7 195
			224	4500					
f$_2$	90	155	364	12830	k$_3$	86	84	223	10 795
								302	13 620
			252	16300				260	12 160
g$_2$	89	126	350	15140					
			300 (sh)	8390				224	12 646
			241	19960	l$_3$	82	121	300	9 560
								221	1 140
h$_2$	92	120	346	9340					
			258	18690					
					m$_3$	80	128	318	7 980
								274 (sh)	850
								223	2 510
					n$_3$	81	118	300	11 000
								220	15 180

Table II. Infrared Spectral Data (CCl_4) of Some of the 2-Pyrazolines (III)

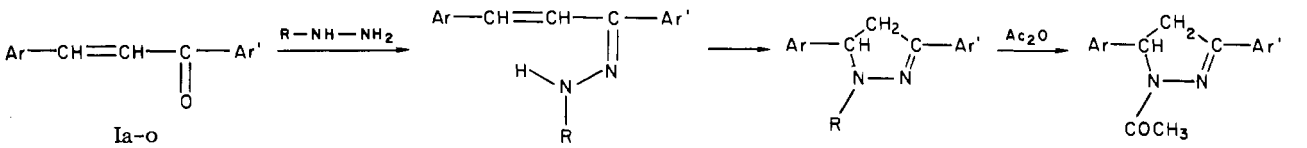
compd	νC=N,C=C	νC=C	δCH_2	νPh–N	νCH_3–N	νN–H
IIIf$_1$	1660 (s)	1465 (s)	1380 (m)			2950 (vs)
	1600 (s)	1420 (s)				2980 (vs)
g$_1$	1695 (w)	1500 (w)	1360 (s)			3050 (w)
	1600 (m)	1450 (s)				3080 (m)
h$_1$	1680 (m)	1520 (m)	1360 (m)			3030 (m)
	1608 (vs)					3100 (m)
f$_2$	1590 (vs)	1493 (vs)	1375 (s)	1312 (s)		
g$_2$	1600 (vs)	1508 (vs)	1395 (s)	1325 (m)		
h$_2$	1596 (vs)	1496 (vs)	1390 (s)	1325 (m)		
f$_3$	1575 (w)	1500 (w)	1380 (m)		1450 (s)	
g$_3$	1590 (w)	1500 (w)	1360 (m)		1450 (s)	
h$_3$	1610 (s)	1520 (vs)	1360 (m)		1455 (s)	

nm (*1–3*), and the pyrazolines IIId$_3$–n$_3$ absorb in the regions 307–299 and 235–220 nm (cf. Table I) (*4*). The long-wavelength band in all the above pyrazolines is due to the chromophore, X(1)—N—N=C—Ar (*3*). This band is affected by the nature of both substituents at positions 1 and II3. The effect of the methyl group on the electronic environment of N-1 was also detected by X-ray photoelectron spectroscopy (*5*).

The infrared spectra of all pyrazolines were examined in the region from 200 to 4000 cm^{-1}, and the results are tabulated in Table II. It can be envisaged that the 2-pyrazolines show absorption bands which can be ascribed to the conjugated C=N and C=C aromatic stretching vibrations as well as the asymmetric deformation frequencies of the CH_2 group. Other observations were noticed and correlated to the elongation vibrations of the Ph–N (*2*, *3*) or CH_3–N (*6a*) groups, as well as the stretching vibrations of the N–H group.

Further insight concerning the structure of the 2-pyrazolines (III) can be gleaned from the consideration of their NMR spectral data (cf. Table III). The aromatic protons of the 1,3,5-substituents in IIIa$_2$–l$_2$ show multiplet signals in the range

Scheme I



Ia-o

IIa-c, R = C_6H_5

IIIa$_1$-l$_1$, R = H
a$_2$-l$_2$, R = C_6H_5
d$_3$-n$_3$, R = CH_3

IVa-c

compd	Ar	Ar′	compd	Ar	Ar′
Ia	C_6H_5	C_6H_5	IIIa$_1$,a$_3$	C_6H_5	C_6H_5
b	p-ClC_6H_4	C_6H_5	b$_1$,b$_3$	p-ClC_6H_4	C_6H_5
c	C_6H_5	p-ClC_6H_4	c$_1$,c$_3$	C_6H_5	p-ClC_6H_4
d	p-$CH_3OC_6H_4$	C_6H_5	d$_1$,d$_3$	p-$CH_3OC_6H_4$	C_6H_5
e	C_6H_5	p-$CH_3OC_6H_4$	e$_1$,e$_3$	C_6H_5	p-$CH_3OC_6H_4$
f	C_4H_3S	C_4H_3S	f$_1$,f$_3$	C_4H_3S	C_4H_3S
g	C_4H_3S	C_6H_5	g$_1$,g$_3$	C_4H_3S	C_6H_5
h	C_4H_3S	p-$CH_3OC_6H_4$	h$_1$-h$_3$	C_4H_3S	p-$CH_3OC_6H_4$
i	C_4H_3S	p-ClC_6H_4	i$_1$-i$_3$	C_4H_3S	p-ClC_6H_4
j	p-ClC_6H_4	C_4H_3S	j$_1$-j$_3$	p-ClC_6H_4	C_4H_3S
k	p-$CH_3OC_6H_4$	C_4H_3S	k$_1$-k$_3$	p-$CH_3OC_6H_4$	C_4H_3S
l	C_4H_4N	C_6H_5	l$_1$,l$_3$	C_4H_4N	C_6H_5
m	C_4H_3S	C_4H_3S	l$_2$	C_4H_3S	C_4H_3O
n	C_4H_4N	C_4H_3N	m$_3$	C_4H_4N	C_4H_3O
o	C_5H_4N	C_6H_5	n$_3$	C_5H_4N	C_6H_5
IIa	C_6H_5	C_6H_5	IVa	C_6H_5	C_6H_5
b	p-ClC_6H_4	C_6H_5	b	p-ClC_6H_4	C_6H_5
c	C_6H_5	p-$OCH_3C_6H_4$	c	C_6H_5	p-ClC_6H_4

Table III. Nuclear Magnetic Resonance Spectral Data ($CDCl_3$) of Some 2-Pyrazolines (III)

compd	chemical shift (ppm), multiplicity	assignment (no. of H)	J,[a] Hz
IIIa$_1$	2.92, dd	H_A (1 H)	J_{AB} = 16
	3.43, dd	H_B (1 H)	J_{BX} = 10
	4.81, t	H_X (1 H)	J_{XA} = 9
	5.18, S (br)	N-H (1 H)	
	7.00-7.85, m	Ar-H (10 H)	
IIIe$_1$	2.94, dd	H_A (1 H)	J_{AB} = 18
	3.45, dd	H_B (1 H)	J_{BX} = 10
	4.88, t	H_X (1 H)	J_{XA} = 9
	3.79, s	O-CH_3 (3 H)	
	4.82, s (br)	N-H (1 H)	
	6.88, d	Ar-H (α to O-CH_3) (2 H)	J = 8
	7.03-7.46, m	Ar-H (5 H)	
	7.62, d	Ar-H (β to O-CH_3) (2 H)	J = 8
f$_1$	2.90, dd	H_A (1 H)	J_{AB} = 16
	3.30, dd	H_B (1 H)	J_{BX} = 10
	5.03, t	H_X (1 H)	J_{XA} = 10
	6.1, s (br)	N-H (1 H)	
	6.8-7.2, m	Ar-H (6 H)	
h$_1$	3.00, dd	H_A (1 H)	J_{AB} = 16
	3.40, dd	H_B (1 H)	J_{BX} = 9
	5.10, t	H_X (1 H)	J_{XA} = 9
	6.2, s (br)	N-H (1 H)	
	6.80-7.38, m	Ar-H (3 H)	
h$_1$	6.87, d	Ar-H (α to O-CH_3) (2 H)	J = 8
	7.63, d	Ar-H (β to OCH_3) (2 H)	J = 8
l$_1$	2.93, dd	H_A (1 H)	J_{AB} = 16
	3.38, dd	H_B (1 H)	J_{BX} = 8
	4.92, dd	H_X (1 H)	J_{XA} = 11
	4.02, s (br)	N-H (1 H)	
	6.10, m	β-H (pyrrole) (2 H)	
	6.65, m	α-H (pyrrole) (1 H)	
	7.25-7.70, m	Ar-H	
f$_2$	3.5, dd	H_A (1 H)	J_{AB} = 17
	3.78, dd	H_B (1 H)	J_{BA} = 12
	5.48, dd	H_X (1 H)	J_{XA} = 7
	6.75-7.35, m	Ar-H (11 H)	
h$_2$	3.13, dd	H_A (1 H)	J_{AB} = 17
	3.73, dd	H_B (1 H)	J_{BX} = 12
	5.43, dd	H_X (1 H)	J_{XA} = 7
	3.75, s	O-CH_3 (3 H)	
	6.88, d	Ar-H (α to OCH_3) (2 H)	J = 8
	7.02-7.48, m	Ar-H (8 H)	
	7.68, d	Ar-H (β to OCH_3) (2 H)	J = 8
l$_2$	3.30, dd	H_A (1 H)	J_{AB} = 18
	3.75, dd	H_B (1 H)	J_{BX} = 10
	5.33, dd	H_X (1 H)	J_{XA} = 8
	6.28, d	Ar-H (α to O) (1 H)	J = 2
	6.9-7.45, m	Ar-H (10 H)	
e$_3$	2.78, s	N-CH_3 (3 H)	
	2.86, dd	H_A (1 H)	J_{AB} = 16
	3.43, dd	H_B (1 H)	J_{BX} = 9
	4.07, dd	H_X (1 H)	J_{XA} = 14
	3.78, s	O-CH_3 (3 H)	
	6.87, d	Ar-H (α to OCH_3) (2 H)	J = 8
	7.22-7.50, m	Ar-H (5 H)	
	7.60, d	Ar-H (β to OCH_3)	J = 8
f$_3$	2.88, s	N-CH_3	
	3.08, dd	H_A (1 H)	J_{AB} = 16
	3.55, dd	H_B (1 H)	J_{BX} = 9
	4.48, dd	H_X (1 H)	J_{XA} = 13
	6.88-7.42, m	Ar-H (6 H)	
h$_3$	2.84, s	N-CH_3 (3 H)	
	2.96, dd	H_A (1 H)	J_{AB} = 17
	3.48, dd	H_B (1 H)	J_{BX} = 9
	4.30, dd	H_X (1 H)	J_{XA} = 14
	3.80, s	O-CH_3 (3 H)	
	6.85, d	Ar-H (α to OCH_3) (2 H)	J = 8
	6.95-7.37, m	Ar-H (3 H)	
	7.57, d	Ar-H (β to OCH_3) (2 H)	J = 8
f$_3$	2.80, s	N-CH_3 (3 H)	
	2.85, dd	H_A (1 H)	J_{AB} = 16
	3.37, dd	H_B (1 H)	J_{BX} = 9
	4.18, dd	H_X (1 H)	J_{XA} = 13
	6.15, m	β-H (pyrrole) (2 H)	
	6.78, m	α-H (pyrrole) (1 H)	
	7.28-7.70, m	Ar-H (5 H)	
	8.80, s (br)	N-H (1 H)	

[a] Coupling constant.

Table IV. Electronic, Infrared, and Nuclear Magnetic Resonance Spectral Data of 1-Acetyl-2-pyrazolines (IVa-c)

			electronic spectra (ethanol)		infrared spectra (KBr)		NMR ($CDCl_3$)		
compd	yield, %	mp, °C	λ_{max}, nm	ϵ_{max}	cm^{-1}	ν	δ	assignment (no. of protons)	J, Hz
IVa	95	119	294	18 500	1650 (s)	C=O	2.4, s	$OCCH_3$ (3 H)	
			286	18 740	1595 (s)	C=N	3.08, dd	H_A (1 H)	J_{AB} = 18
							3.70, dd	H_B (1 H)	J_{BX} = 11
							5.60, dd	H_X (1 H)	J_{XA} = 5
							7.15-7.80, m	Ar-H (10 H)	
b	95	123	294	19 250	1650 (s)	C=O)	2.40, s	$OCCH_3$ (3 H)	
			286	19 590	1595 (s)	C=N	3.08, dd	H_A (1 H)	J_{AB} = 18
			221	21 250			3.75, dd	H_B (1 H)	J_{AB} = 12
							5.55, dd	H_X (1 H)	J_{XA} = 5
							7.20-7.90, m	Ar-H (9 H)	
c	98	104	295	28 010	1665 (s)	C=O	2.40, s	$OCCH_3$ (3 H)	
			222	16 180	1590 (s)	C=N	3.09, dd	H_A (1 H)	J_{AB} = 18
							3.73, dd	H_B (1 H)	J_{BA} = 11
							5.60, dd	H_X (1 H)	J_{XA} = 5
							7.25, s	Ar-H (5 H)	
							7.35, d	Ar-H (β to Cl) (2 H)	8
							7.63, d	Ar-H (α to Cl) (2 H)	8

6.28–7.80 ppm. The three protons at C-4 and C-5 of the 2-pyrazolines $IIIf_2$–l_2 and $IIId_3$–n_3 are represented by a typical (ABX) system (*3*, *7*, *8*). Each of the H_A, H_B, and H_X is represented by a double doublet. However, the H_X of the pyrazolines $IIIa_1$–l_1 appeared as a triplet, with the ratio 1:2:1.

The structures of the above pyrazolines were further substantiated by acetylation of the 2-pyrazolines $IIIa_1$–c_1 with acetic anhydride to the corresponding 1-acetyl-3,5-diaryl-2-pyrazolines (IVa–C). Information concerning the structures of the acetylated products is derivable from spectroscopic and chemical analyses. The infrared spectra (cf. Table IV) show strong C=O stretching absorption bands in the region 1665–1650 cm^{-1} which can be ascribed to the *N*-acetyl groups (*6b*). The electronic spectra of the acetylated pyrazolines show that they absorb at a longer wavelength than the corresponding pyrazolines (cf. Table IV). Similar red shifts are observed in the absorption of indazolone (*9*) and pyrazoles (*10*) on acetylation. The NMR spectra lend further support to the structures of these acetylated pyrazolines (IVa–c). They show an ABX pattern (cf. Table IV) in which each of the A, B, and X protons is represented by a pair of doublets, with J_{AB} = 18 Hz, J_{AX} = 5 Hz, and J_{BX} = 11–12 Hz. The *N*-acetyl protons of each of the three compounds are characterized by a 3-H singlet at δ 2.40. The mechanism of the formation of the above 2-pyrazolines seems to proceed via the formation of the α,β-unsaturated ketone phenylhydrazones (IIa–c), which cyclize through a stereoselective enamine–imine tautomerism step (*11*, *12*).

Experimental Section

General Information. Microanalyses were performed b Prof. H. Malissa and G. Reuter, Analytisches Laboratorium BRD. Infrared spectra (KBr disk or carbon tetrachoride) were measured on a Perkin-Elmer 520B infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded for solutions in deuteriochloroform with tetramethylsilane as an external standard on a Varian T60A spectrometer. Electronic spectra were taken for solutions in ethyl alcohol on a Pye Unicam SP8-100 recording spectrometer. Melting points were determined by using a Bock-Monoscop M (thermal microscope).

Preparation of the Chalcones (Ia–o). General Procedure. A mixture of the aldehyde (0.1 mol) and methyl aryl ketone (0.1 mol) was dissolved in ethanol, and to this solution, with stirring, was added slowly an aqueous solution of 2 g of sodium hydroxide in 5 mL of water. The solution deveioped a yellow color and the solid began to separate after stirring for a further 2 h. The solution was chilled and filtered, and the solid was washed with cold alcohol, water, and finally cold alcohol. The product was crystallized from ethanol to give about 90% yield of the chalcones (Ia–o).

Preparation of 1H-3,5-Disubstituted-2-pyrazolines ($IIIa_1$–l_1). General Procedure. The chalcones were directly reacted with excess hydrazine hydrate by heating the mixture in a boiling water bath for 15 min. The mixture was left to cool and the solidified product was filtered off, washed with water, and then crystallized from hexane or cyclohexane to give the corresponding pyrazolines ($IIIa_1$–l_1).

Acetylation of the Pyrazolines ($IIIa_1$–c_1). Acetylation (*13*) was achieved by heating 1 g of the pyrazoline ($IIIa_1$,b_1,c_1) and 5 mL of acetic anhydride in a boiling water bath for 3 h and then leaving the solution to cool. The solid product was filtered off, washed with water, and crystallized from cyclohexane to give the corresponding 1-acetyl products (IVa–c).

Preparation of 1-Methyl- and 1-Phenyl-3,5-diaryl-2-pyrazolines ($IIId_3$–n_3 and $IIIf_2$–l_2). A mixture of 0.01 mol of 1,3-diaryl-2-propen-1-one (I) and methyl- or phenylhydrazine (2 mL) in 100 mL of ethanolic KOH solution (1 g/100 mL) was refluxed in a boiling water bath for 3 h and then left to cool. The solvent was evaporated, the residue extracted with ether, and the ethereal solution washed several times with water and dried over $CaCl_2$ (anhydrous). After the ether was evaporated, the residues were crystallized from hexane to give the corresponding 1-methyl- and 1-phenyl-3,5-diaryl-2-pyrazolines ($IIId_3$–n_3 and $IIIf_2$–l_2).

Preparation of the Phenylhydrazone Derivatives (IIa–c). Phenylhydrazine (0.01 mol) was added to a suspension of 0.01 mol of 1,3-diaryl-2-propen-1-one (Ia–c) in glacial acetic acid, and the mixtures were stirred at room temperature until the corresponding hydrazones were precipitated, then immediately collected by filtration, and washed with several portions of methyl alcohol to remove adhering acetic acid. The yield exceeded 95%; melting points were as followed (°C): IIa, 109–110; IIb, 111–112; and IIc, 120. Cyclization of these hydrazones to the corresponding 2-pyrazolines (III) was accomplished by treating them with glacial acetic acid at room temperature for a period 24 h.

Registry No. **Ia**, 94-41-7; **Ib**, 956-04-7; **Ic**, 956-02-5; **Id**, 959-33-1; **Ie**, 959-23-9; **If**, 59114-72-6; **Ig**, 89144-95-6; **Ih**, 89144-96-7; **Ii**, 89144-97-8; **Ij**, 89144-98-9; **Ik**, 89144-99-0; **Il**, 89145-00-6; **Im**, 89145-01-7; **In**, 89145-02-8; **Io**, 89145-03-9; **IIa**, 37799-62-5; **IIb**, 89144-71-8; **IIc**, 89144-72-9; $IIIa_1$, 16619-60-6; $IIIb_1$, 89144-73-0; $IIIc_1$, 89144-74-1; $IIId_1$, 76973-46-1; $IIId_3$, 86389-37-9; $IIIe_1$, 89144-75-2; $IIIe_3$, 86389-36-8; $IIIf_1$, 89145-05-1; $IIIf_2$, 89144-79-6; $IIIf_3$, 89144-86-5; $IIIg_1$, 89145-06-2; $IIIg_2$, 89144-80-9; $IIIg_3$, 89144-87-6; $IIIh_1$, 89145-07-3; $IIIh_2$, 89144-81-0; $IIIh_3$, 89144-88-7;

IIIl$_1$, 89145-08-4; IIIl$_2$, 89144-82-1; IIIl$_3$, 89144-89-8; IIIj$_1$, 89145-09-5; IIIj$_2$, 89144-83-2; IIIj$_3$, 89144-90-1; IIIk$_1$, 89145-10-8; IIIk$_2$, 89144-84-3; IIIk$_3$, 89144-91-2; IIIl$_1$, 89144-78-5; IIIl$_2$, 89144-85-4; IIIl$_3$, 89144-92-3; IIIm$_3$, 89144-93-4; IIIn$_3$, 89144-94-5; **IVa**, 30693-34-6; **IVb**, 89144-76-3; **IVc**, 89144-77-4; C_6H_5CHO, 100-52-7; *p*-ClC_6H_4CHO, 104-88-1; *p*-$CH_3OC_6H_4CHO$, 123-11-5; C_4H_3SCHO, 30583-13-2; C_4H_4NCHO, 89145-04-0; C_5H_4NCHO, 26445-06-7; C_6H_5COMe, 98-86-2; *p*-ClC_6H_4COMe, 99-91-2; *p*-$CH_3OC_6H_4COMe$, 100-06-1; C_4H_3SCOMe, 39709-34-7; C_4H_3OCOMe, 25154-45-4; NH_2NH_2, 302-01-2; $NHPhNH_2$, 100-63-0; $NHMeNH_2$, 60-34-4.

Literature Cited

(1) Duffin, G. F.; Kendall, J. D. *J. Chem. Soc.* **1954**, 408.
(2) Wiley, R. H.; Jarboe, C. H.; Hayes, F. N.; Hansbury, E.; Nielson, T.; Callahan, P. X.; Sellars, M. C. *J. Org. Chem.* **1955**, *23*, 732.
(3) Laude, B.; Khanh, Le Quoc. *Spectrochim. Acta, Part A* **1975**, *31*, 1121.
(4) Stamper, M.; Aycock, B. F. *J. Am. Chem. Soc.* **1954**, *76*, 2786.
(5) Katrib, A.; El-Rayyes, N. R.; Al-Kharafi, F. M. *J. Electron Spectrosc. Relat. Phenom.* **1983**, *31*, 317.
(6) (a) Bellamy, L. J. "The Infrared Spectra of Complex Molecules"; Chapman and Hall: London, 1975; p 289. (b) *Ibid.*, p 241.
(7) Oluwadiya, J. O. *J. Heterocycl. Chem.* **1981**, *1*,, 1293.
(8) Huisgen, R.; Huber, H. *Chem. Ber.* **1967**, *100*, 1802.
(9) Evands, N. A.; Whelan, D. J.; Johns, R. B. *Tetrahedron* **1965**, *21*, 3351.
(10) El-Rayyes, N. R.; Al-Hajjar, F. H. *J. Heterocycl. Chem.* **1977**, *14*, 367.
(11) Ferres, H.; Hamdam, M. S.; Jackson, W. R. *J. Chem. Soc., Perkin Trans. 2* **1973**, 936.
(12) Elguero, J.; Marzin, C. *Bull. Soc. Chim. Fr.* **1973**, 3401.
(13) Beech, S. G.; Turnbull, J. H.; Wilson, W. *J. Chem. Soc.* **1952**, 4686.

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Syntheses and Antibacterial Activity of Some New *N*-(3-Methyl-2-quinoxaloyl) Amino Alcohols and Amine 1,4-Dioxides

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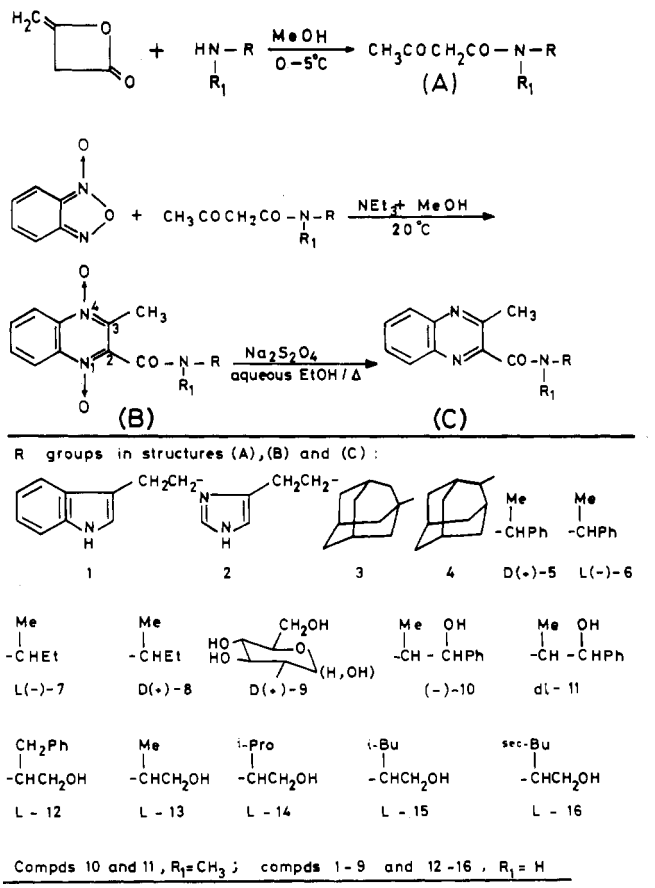
The syntheses and in vitro and in vivo antibacterial activities of a series of *N*-(3-methyl-2-quinoxaloyl) amino alcohols and amine 1,4-dioxides, and their deoxygenated analogues, are described. The quinoxaline 1,4-dioxide derivative of the naturally occurring (-)-ephedrine was found to be the most potent antibacterial agent of the series. The presence of a hydroxy group and a tertiary amide appears to be associated with enhancement of the antibacterial action.

The chemistry and biological activity of heterocyclic *N*-oxides have received considerable attention for the past two decades (*1*, *2*). In particular, various biological activities of several substituted quinoxaline 1,4-dioxides have been described in recent patent reports (*3*-*7*). These 1,4-dioxides are conveniently prepared via interaction of benzofuroxan (BFO) with enamines or enolate anions, "the Beirut reaction" (*8*).

As an extension to previous studies on quinoxaline amino acid *N*-oxides (*9*, *10*), we now report on the syntheses and in vitro and in vivo antibacterial activity of new quinoxaline 1,4-dioxide derivatives of some biologically interesting amino compounds.

The *N*-acetoacetyl precursors (A), quinoxaline 1,4-dioxides (B), and quinoxalines (C) are synthesized as depicted in Scheme I; their physical data are presented in Table I.

Scheme I



Biological Activity

The quinoxaline 1,4-dioxides (B) were tested for antibacterial activity. The results obtained showed that the quinoxaline 1,4-dioxide derivative of (-)-ephedrine (compound ***10B***) is the most effective bacteriostatic agent of the series. This compound exhibited in vitro bacteriostatic activity against *Mycobacterium tuberculosis*, *Escherichia coli*, and *Pseudomonus aeruginosa* at minimal inhibitory concentrations (MIC) of 1, 2, and 78 μg/mL, respectively. In vivo (mice) experiments indicated that ***10B*** was also active against *E. coli* (CD 50 = 35 mg/kg, po) but was inactive against *P. aeruginosa* (a species known to develop R-plasmid-mediated resistance to the penicillin derivatives (*11*)). Compound ***10B*** also exhibited a selective activity against *Staphylococcus aureus*, and *Proteus vulgaria*

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