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Synthesis and Antifungal Properties of Some *N,N'*-Bis-azolylarylmethanes

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A series of 1,1'-bis-azolylarylmethanes has been prepared by reaction of azoles and their benzoderivatives with *ortho*-, and *para*-chlorobenzaldehydes, thiophene-2-carbaldehyde and furan-2-carbaldehyde in the presence of zinc chloride as catalyst. The antifungal activity has been tested, *in vitro*, against *Botrytis cinerea*, *Aspergillus flavus*, *Mucor rouxii* and *Candida albicans*. All 1,1'-bis-azolylarylmethanes have minima inhibitory concentrations (MIC) higher than that of chlotrimazol, used as positive control.

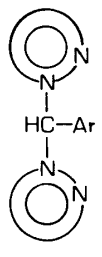
Keywords——1,1'-bis-azolylarylmethane; indazole; pyrazole; chlorobenzaldehyde; thiophene-2-carbaldehyde; furan-2-carbaldehyde; NMR analysis; antifungal activity

N,N'-Bis-azolylarylmethanes I are structurally related to the powerful antifungal drug chlotrimazol II,[1] thus a similar biological activity could be expected.

Despite their interest,[2,3] only few pyrazolyl and imidazolyl derivatives have been described. They were prepared from *N,N'*-carbonyldiazoles[3a,4] or by alkylation of pyrazole with benzal chloride.[5] We have found that they can also be obtained by reaction of some pyrazoles and indazoles with benzaldehyde in the presence of zinc chloride.[6] The reaction seemed to be specific for those indazoles and pyrazoles with basic pK_a's in the range from −0.7 to 2.2.

The present work is a further study on the reactivity of azoles and benzazoles toward chlorobenzaldehydes and some heteroaldehydes with the purpose to explore the specificity and scope of this new reaction. At the same time, the antifungal activity of some of the reaction products and other *N,N'*-bis-azolylphenylmethanes, previously prepared,[6] is analyzed.

According to the results shown in Table I, indazole **1a**, 4-bromopyrazole **1b** and 3-methyl-4-bromopyrazole **1c** reacted with chlorobenzaldehydes **2a** and **2b** to give the corresponding *N,N'*-bis-azolylphenylmethanes **3**—**10** with good to moderate yields. Similarly to unsubstituted benzaldehyde,[6] the reaction gave only 1,1'-derivatives **3** and **4** in the case of



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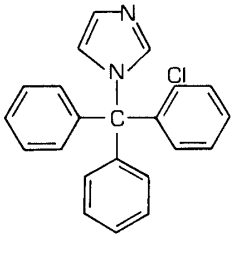
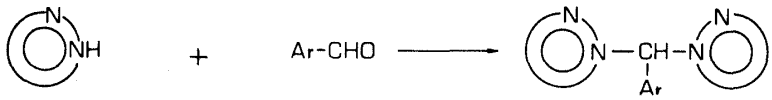


II

Fig. 1

TABLE I. Reactions of Azoles and Benzazoles **1a**—**f** with Chlorobenzaldehydes **2a**, **b** and Heteroaldehydes **2c**—**e**



1 **2** **3**—**16**

1a: indazole, $pK_a = 1.36$
1b: 4-bromopyrazole, $pK_a = 1.31$
1c: 3-methyl-4-bromopyrazole, $pK_a = 1.46$
1d: 3-methylindazole, $pK_a = 2.17$
1e: pyrazole, $pK_a = 2.32$
1f: benzotriazole, $pK_a = 1.6$

2a: *o*-chlorobenzaldehyde
2b: *p*-chlorobenzaldehyde
2c: thiophene-2-carbaldehyde
2d: furan-2-carbaldehyde
2e: *N*-methylpyrrole-2-carbaldehyde

Azole	Aldehyde	Reaction product	Yield[a] (%)	mp (°C)
1a	**2a**	**3**	72	115—117 (methanol)
	2b	**4**	74	117—119 (methanol)
1b	**2a**	**5**	26	151—152 (ethanol)
	2b	**6**	32	96—98 (ethanol)
1c	**2a**	**7**	13	116—118 (ethanol)
		8	7	86—88[b]
	2b	**9**	15	112—114[b]
		10	6	111—113[b]
1a	**2c**	**11**	17	128—130 (ethanol)
	2d	**12**	20	135—137 (ethanol)
	2e	N.R.		
1d	**2c**	**13**	65	184—185 (ethanol)
	2d	**14**	23	163—165 (ethanol)
1e	**2c**	**15**	14	73—75[b]
1f	**2c**	**16**	13	135—137 (ethanol)

a) Yield is given in chromatographed product. *b*) Melting point from chromatographed product without recrystallization.

indazole, and two isomers, 3,3′- and 3,5′-methyl-4-bromopyrazole derivatives **7**—**10**, when **1c** was used as starting material.[7]

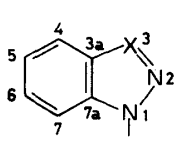
Unlike benzaldehydes, thiophene-2-carbaldehyde **2c** was able to react not only with indazoles **1a** and **1d** but also with pyrazole **1e** and benzotriazole **1f** giving the corresponding 1,1′-bis-azolylthiophen-2-yl derivatives **11**, **13**, **15** and **16**, although in low yield in most of the cases. Due to the low reactivity shown by furan-2-carbaldehyde **2d** and *N*-methylpyrrole-2-carbaldehyde **2e** with indazoles, further reactions with other azoles were not attempted.

Structures of compounds **3**—**16** were established by proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectroscopy, the data being in agreement with those previously described in the literature.[6,8] (Tables II and III). In order to obtain first-order spectra of thiophene and furan protons, easy to analyze and to assign, the spectra of compounds **11**—**16** were recorded at 360 MHz. Chemical shift and coupling constant values were in accordance with those reported for thiophene and furan.[9] Proton at the 3 position in the thiophene ring was easily recognized since it is coupled with protons H_4, H_5 and also with the C_{sp^3} proton with a ^4J value of *ca.* 1.3 Hz.

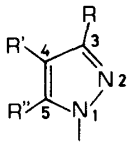
Antifungal Activity

Compounds **3**, **4**, **17**—**22**[10] were tested *in vitro* against *Botrytis cinerea* PERS. *ex* FR. obtained from Dr. J. A. Leal (Centro de Investigaciones Biologicas, Marid, Spain); *Aspergillus flavus* LINK *ex* FR. 113.32 CBS; *Mucor rouxii* 2654 CECT and *Candida albicans* 1001 CECT by using an agar dilution procedure.[11] Compounds were dissolved in ethylene

TABLE II. ^{1}H-NMR Data of Compounds **3**—**16** in Deuterochloroform[a)]



3—**4**, **11**, **12**: X = CH_3
13, **14**: X = CCH_3
16: X = N



5—**10**, **15**

Compound	H_3	H_4	H_5	H_6	H_7	$C_{sp^3}H$	Aryl substituents
3[b)]	8.10 (s)	7.70 (d) $J_{4,5}=7.5$	7.45—7.05 (m)		7.40 (d) $J_{7,6}=8.0$	8.55 (s)	7.45—7.25 (m)
4[b)]	8.00 (d) $J_{3,7}=0.8$	7.65 (d) $J_{4,5}=7.0$	7.35—6.95 (m)		7.45 (d) $J_{7,6}=7.0$	8.40 (s)	7.35—6.95 (m)
5[b)]	7.57 (d) $J_{3,5}=0.6$	—	7.40 (s)	—	—	7.80 (s)	7.35—7.10 (m) 7.10—6.80 (m)
6[b)]	7.55 (s)	—	7.48 (s)	—	—	7.55 (s)	7.35 (d); $J=9.0$ 6.95 (d); $J=9.0$
7[b)]	—	—	7.35[c)]	—	—	7.70 (s)	7.45—7.25 (m) 7.03—6.83 (m) CH_3: 2.25 (s)
8[b)]	7.40	—	7.55 (s)	—	—	7.80 (s)	7.50—7.25 (m) 7.03—6.90 (m) $CH_3(3)$: 2.30 (s) $CH_3(5)$: 2.40 (s)
9[b)]	—	—	7.35 (m)	—	—	7.40 (s)	7.32 (d); $J=7.5$ 6.87 (d); $J=7.5$ CH_3: 2.25 (s)
10[b)]	7.28	—	7.43 (s)	—	—	7.50 (s)	7.32 (d); $J=7.5$ 6.92 (d); $J=7.5$ $CH_3(3)$: 2.25 (s) $CH_3(5)$: 2.35 (s)
11[d)]	8.01 (d)	7.69 (ddd)	7.15 (ddd)	7.34 (ddd)	7.65 (dddd)	8.60 (s)	H_3: 6.96 (ddd) H_4: 7.00 (dd) H_5: 7.41 (dd) $J_{3,4}=3.6$; $J_{3,5}=1.2$; $J_{3,CH}=1.3$; $J_{4,5}=4.9$
	$J_{3,7}=0.7$; $J_{4,5}=8.0$; $J_{4,6}=1.1$; $J_{4,7}=1.0$; $J_{5,6}=7.1$; $J_{5,7}=0.7$; $J_{6,7}=8.6$						
12[d)]	8.06 (d)	7.62 (ddd)	7.16 (ddd)	7.36 (ddd)	7.59 (dddd)	8.37 (s)	H_3,H_4: 6.44 (m) H_5: 7.49 (m) $J_{5,4}$—$J_{5,3}$—0.9
	$J_{3,7}=0.7$; $J_{4,5}=7.9$; $J_{4,6}=0.9$; $J_{4,7}=0.8$; $J_{5,6}=7.2$; $J_{5,7}=0.7$; $J_{6,7}=8.4$						
13[d)]	—	7.63—7.59 (m)	7.12 (ddd)	7.31 (ddd)	7.59—7.63 (m)	8.45 (s)	H_3: 6.90 (ddd) H_4: 6.97 (ddd) H_5: 7.37 (dd) $J_{3,4}=3.7$; $J_{3,5}=1.2$; $J_{3,CH}=1.3$ $CH_3=2.55$ (s)
	$J_{4,5}=7.5$; $J_{5,6}=7.5$; $J_{6,7}=8.3$						
14[d)]	—	7.53 (d)	7.11 (ddd)	7.31 (ddd)	7.53 (d)	8.21 (s)	H_3: 6.38 (dd) H_4: 6.41 (dd) H_5: 7.45 (br s) $J_{3,4}=3.5$; $J_{4,5}=1.8$ CH_3: 2.54 (s)
15[d)]	7.65 (d)	6.32 (t)	7.65 (d)	—	—	7.87 (s)	H_3: 6.98 (ddd) H_4: 7.01 (dd) H_5: 7.40 (dd) $J_{3,4}=3.6$; $J_{3,5}=1.3$; $J_{4,5}=5.0$; $J_{3,CH}=1.0$
	$J_{3,4}=1.6$; $J_{4,5}=2.5$						

TABLE II. (continued)

Compound	H_3	H_4	H_5	H_6	H_7	$C_{sp^3}H$	Aryl substituents
16[d]	—	8.06 (dd)	7.40 (ddd)	7.50 (ddd)	7.76 (d)	9.13 (s)	H_3: 7.11 (ddd) H_4: 7.07 (dd) H_5: 7.49 (dd) $J_{3,4}=3.6$; $J_{3,5}=1.2$; $J_{3,CH}=1.2$; $J_{4,5}=6.1$
	$J_{4,5}=8.4$; $J_{4,6}=0.9$; $J_{5,6}=8.4$; $J_{5,7}=0.8$; $J_{6,7}=8.4$						

a) Apparent multiplicity is given on the table: s, singlet; d, doublet; t, triplet; m, multiplet. *b*) At 90 MHz. *c*) Masked by the phenyl protons. *d*) At 360 MHz.

TABLE III. ^{13}C-NMR Data of Compounds **3**—**16** in Deuterochloroform
(See Table II for Structural Formulae Numbering)

Compound	C_3	C_{3a}	C_4	C_5	C_6	C_7	C_{7a}	HC(sp^3)	Aryl substituents
3[a]	134.9	124.8	121.6	121.3	127.0	109.7	139.9	77.8	C_1, 133.6; C_2, 133.6; C_3, 129.1; C_4, 130.4; C_5, 129.9; C_6, 127.2
4[a]	134.9	124.9	121.6	121.1	126.9	110.7	139.8	74.2	C_1, 133.8; $C_{2(6)}$, 129.0; $C_{3(5)}$, 128.8; C_4, 133.8
5[a]	142.0	—	95.0	129.8	—	—	—	75.9	C_1, 133.5; C_2, 132.4; C_3, 128.6; C_4, 131.3; C_5, 130.3; C_6, 127.5
6[a]	141.9	—	95.1	129.8	—	—	—	75.5	C_1, 133.3; $C_{2(6)}$, 128.5; $C_{3(5)}$, 129.3; C_4, 133.3
8[b]	149.1 140.9 (CH)	—	95.4 95.5	130.9 (CH) 138.6	—	—	—	73.3	C_1, 132.8; C_2, 132.9; C_3, 128.7; C_4, 130.0; C_5, 129.8; C_6, 127.4; CH_3-3, 12.1; CH_3-5, 9.7
9[b]	149.5	—	95.8	130.0	—	—	—	77.6	C_1, 135.7; $C_{2(6)}$, 128.5; $C_{3(5)}$, 129.2; C_4, 133.6; CH_3-3, 12.1
10[b]	148.6	—	96.0 95.3	129.9 (CH) 135.6	—	—	—	75.0	C_1, 138.4; $C_{2(6)}$, 128.4; $C_{3(5)}$, 129.1; C_4, 133.7
11[c]	134.9	124.9	121.6	121.1	126.9	110.9	139.4	71.9	C_2, 137.4; C_3, 128.9; C_4, 127.4; C_5, 126.7
12[c]	134.9	124.9	121.6	121.0	127.1	110.5	139.4	70.1	C_2, 147.1; C_3, 111.4; C_4, 110.7; C_5, 143.5
13[c]	143.1	124.5	120.7	120.2	126.6	111.1	140.2	71.5	C_2, 138.5; C_3, 127.9; C_4, 127.0; C_5, 126.6; CH_3, 12.1
14[c]	143.3	124.5	120.7	120.2	126.8	110.7	140.3	69.7	C_2, 147.8; C_3, 111.1; C_4, 111.1
15[c]	140.8	—	106.7	129.3	—	—	—	74.4	C_2, 138.2; C_3, 127.7; C_4, 128.1; C_5, 126.8
16[c]	—	146.2	120.3	124.9	128.6	110.7	131.9	69.6	C_2, 134.1; C_3, 128.6; C_4, 127.2; C_5, 129.3

a) At 20 MHz. *b*) At 75 MHz. *c*) At 50 MHz.

glycol or acetone. These solutions were then diluted in sterile water and Czapeck Dox agar to give concentrations of 40, 80, 160, 320, 640 μg/ml. Inoculated Petri dishes were incubated at 30 °C until growth appeared in the growth control plate. All the products showed a higher minimum inhibitory concentration (MIC) than chlotrimazol used as reference. While the

MIC of chlotrimazol was lower than 1 μg/ml, the MIC values of the new compounds were higher than 640 μg/ml.

Experimental

Melting points were determined on a capillary Buchi 512 apparatus and are uncorrected. The infrared (IR) spectra were recorded on a Perkin Elmer model 257 spectrometer in potassium bromide. The ^{1}H-NMR spectra were performed on a Varian EM 390 (90 MHz) and a Bruker WH 360 (360 MHz) spectrometers in $CDCl_3$ using tetramethylsilane as an internal reference. The ^{13}C-NMR spectra were recorded on a Varian XL-300 (75.4 MHz) a Bruker AM-200 (50 MHz) and Bruker WP-80-SY (20 MHz) spectrometers in $CDCl_3$. Chemical shifts were measured in ppm (δ) and coupling constant (J) in Hz. Analyses were carried out using in-house facilities. Chromatographic purifications were performed through columns at normal pressure using silica gel Merck 60 (70—230 mesh). Azoles, benzazoles and aldehydes were purchased from commercial sources and aldehydes were distilled prior to use. Anhydrous $ZnCl_2$ was stored in a dessicator over P_2O_5 under vacuum prior to use. The following compounds were prepared by described procedures: 3-methylindazole,[12] 4-bromopyrazole,[13] 3-methyl-4-bromopyrazole,[14] 1-methylpyrrole-2-carbaldehyde,[15] and *ortho*- and *para*-chlorobenzaldehyde dimethylacetals.[16]

Reaction of Azoles and Benzazoles with Aldehyde and $ZnCl_2$——A mixture of azole or benzazole, the corresponding aldehyde and anhydrous $ZnCl_2$ (2 : 1 : 1/20 molar ratio) was heated in an oil bath at 120—130 °C for 16—18 h. After cooling the crude reaction was purified by column chromatography. The eluent used is shown below individually for each compound.

1,1′-Bis-indazolyl-*ortho*-chlorophenylmethane (3)——Chromatographic eluent: methylene chloride, Rf=0.32. IR (KBr): 3050, 1615, 1500, 1470, 1425, 1340, 1330, 1190, 1045, 1020, 920, 915, 840, 810, 760, 750 cm^{-1}. *Anal.* Calcd for $C_{21}H_{15}ClN_4$: C, 70.28; H, 4.21; N, 15.61. Found: C, 70.01; H, 4.55; N, 15.28.

1,1′-Bis-indazolyl-*para*-chlorophenylmethane (4)——Chromatographic eluent: methylene chloride, Rf=0.48. IR (KBr): 3050, 1615, 1495, 1470, 1420, 1410, 1295, 1170, 1100, 1020, 920, 800, 750 cm^{-1}. *Anal.* Calcd for $C_{21}H_{15}ClN_4$: C, 70.28; H, 4.21; N, 15.61. Found: C, 70.37; H, 4.15; N, 15.31.

4,4′-Dibromo-1,1′-bis-pyrazolyl-*ortho*-chlorophenylmethane (5)——Chromatographic eluent: methylene chloride, Rf: 0.50. IR (KBr): 3110, 1440, 1415, 1385, 1330, 1315, 1250, 1170, 1055, 1000, 990, 965, 865, 820, 755 cm^{-1}. *Anal.* Calcd for $C_{13}H_9Br_2ClN_4$: C, 37.48; H, 2.18; N, 13.45. Found: C, 37.51; H, 2.49; N, 13.07.

4,4′-Dibromo-1,1′-bis-pyrazolyl-*para*-chlorophenylmethane (6)——Chromatographic eluent: hexane–ethyl acetate (95 : 5), Rf: 0.23. IR (KBr): 3100, 1495, 1430, 1410, 1390, 1325, 1310, 1170, 1100, 1025, 1000, 965, 870, 860, 820. 800 cm^{-1}. *Anal.* Calcd for $C_{13}H_9Br_2ClN_4$: C, 37.48; H, 2.18; N, 13.45. Found: C, 37.21; H, 2.16; N, 13.08.

3,3′-Dimethyl-4,4′-dibromo-1,1′-bis-pyrazolyl-*ortho*-chrorophenyl methane (7)——Chromatographic eluent: methylene chloride, Rf: 0.33. IR (KBr): 3100, 1470, 1445, 1430, 1415, 1330, 1250, 1165, 1150, 1065, 1045, 815, 750 cm^{-1}. *Anal.* Calcd for $C_{15}H_{13}Br_2ClN_4$: C, 40.52; H, 2.95; N, 12.60. Found: C, 40.23; H, 3.07; N, 12.45.

3,5′-Dimethyl-4,4′-dibromo-1,1′-bis-pyrazolyl-*ortho*-chlorophenylmethane (8)——Chromatographic eluent: methylene chloride, Rf: 0.62. IR (KBr): 3100, 2970, 1470, 1445, 1390, 1325, 1255, 1160, 1065, 1045, 865, 845, 810, 760 cm^{-1}. *Anal.* Calcd for $C_{15}H_{13}Br_2ClN_4$: C, 40.52; H, 2.95; N, 12.60. Found: C, 40.18; H, 3.22; N, 12.56.

3,3′-Dimethyl-4,4′-dibromo-1,1′-bis-pyrazolyl-*para*-chlorophenylmethane (9)——Chromatographic eluent: methylene chloride, Rf: 0.23. IR (KBr): 3100, 2950, 1500, 1425, 1330, 1270, 1155, 1100, 1075, 1030, 830, 805 cm^{-1}. *Anal.* Calcd for $C_{15}H_{13}Br_2ClN_4$: C, 40.52; H, 2.95; N, 12.60. Found: C, 40.03; H, 2.89; N, 12.49.

3,5′-Dimethyl-4,4′-dibromo-1,1′-bis-pyrazolyl-*para*-chlorophenylmethane (10)——Chromatographic eluent: methylene chloride, Rf: 0.52. IR (KBr): 3120, 2960, 1500, 1330, 1270, 1100, 1075, 1025, 805 cm^{-1}. *Anal.* Calcd for $C_{15}H_{13}Br_2ClN_4$: C, 40.52; H, 2.95; N, 12.60. Found: C, 40.58; H, 3.30; N, 12.25.

1,1′-Bis-indazolyl-(thiophen-2-yl)methane (11)——Chromatographic eluent: hexane–ethyl acetate (95 : 5), Rf: 0.20. IR (KBr): 3100, 3070, 2940, 1620, 1500, 1470, 1420, 1300, 1165, 920, 910, 840, 800, 780, 755, 740, 720 cm^{-1}. *Anal.* Calcd for $C_{19}H_{14}N_4S$: C, 69.06; H, 4.27; N, 16.95. Found: C, 68.52; H, 4.27; N, 16.95.

1,1′-Bis-indazolyl-(fur-2-yl)methane (12)——Chromatographic eluent: methylene chloride, Rf: 0.32. IR (KBr): 3110, 3050, 1615, 1500, 1470, 1420, 1330, 1310, 1180, 1170, 1020, 920, 815, 805, 760 cm^{-1}. *Anal.* Calcd for $C_{19}H_{14}N_4O$: C, 72.59; H, 4.49; N, 17.82. Found: C, 72.87; H, 4.89; N, 17.42.

3,3′-Dimethyl-1,1′-bis-indazolyl-(thiophen-2-yl)methane (13)——Reaction product was crystallized from the crude mixture using ethanol as solvent. mp 172—175 °C. Rf: 0.41 (methylene chloride). IR (KBr): 3040, 2940, 1615, 1510, 1440, 1350, 1305, 1240, 1210, 1180, 1020, 815, 800, 750, 720, 700 cm^{-1}. *Anal.* Calcd for $C_{21}H_{18}N_4S$: C, 70.36; H, 5.06; N, 15.63. Found: C, 70.28; H, 5.10; N, 15.94.

3,3′-Dimethyl-1,1′-bis-indazolyl-(fur-2-yl)methane (14)——Chromatographic eluent: methylene chloride, Rf: 0.25. IR (KBr): 3060, 2940, 1620, 1515, 1350, 1300, 1290, 1185, 1015, 800, 760, 750, 740 cm^{-1}. *Anal.* Calcd for $C_{21}H_{18}N_4O$: C, 73.66; H, 5.30; N, 16.36. Found: C, 73.42; H, 5.44; N, 16.52.

1,1′-Bis-pyrazolyl-(thiophen-2-yl)methane (15)——Chromatographic eluent: methylene chloride, Rf: 0.06. IR (KBr): 3080, 1440, 1395, 1295, 1255, 1215, 1095, 1045, 830, 785, 760, 725 cm^{-1}. *Anal.* Calcd for $C_{11}H_{10}N_4S$: C, 57.43;

H, 4.38; N, 24.35. Found: C, 57.12; H, 4.67; N, 23.78.

1,1′-Bis-benzotriazolyl-(thiophen-2-yl)methane (16)——Chromatographic eluent: methylene chloride, *Rf*: 0.24. IR (KBr): 3070, 2950, 1495, 1450, 1360, 1290, 1240, 1160, 1150, 1090, 1080, 1070, 940, 820, 805, 750, 700 cm^{-1}. *Anal.* Calcd for $C_{17}H_{12}N_6S$: C, 61.43; H, 3.64; N, 25.28. Found: C, 61.06; H, 3.25; N, 24.97.

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