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Binuclear Pyrazoles. I. Synthesis and Cytotoxic Activity of 1,1'-Dibenzyl and 1,1'-Dihydroxymethyl 4,4'-Bispyrazoles

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From 3,3',5,5'-tetramethyl-4,4'-bis-1*H*-pyrazole, 3,3',5,5'-tetramethyl-4,4'-methylenebis-1*H*-pyrazole and 4,4'-methylenebis-1*H*-pyrazole, the corresponding 1,1'-dibenzyl and 1,1'-dihydroxymethyl derivatives have been obtained. Benzylation of 1*H*-bispyrazoles was carried out by treatment with benzyl chloride under phase transfer conditions. Hydroxymethylation was done by treatment with 37% aqueous formaldehyde either in acidic or in neutral medium. All the products obtained have been evaluated as cytotoxic, and 1,1'-dibenzyl-3,3',5,5'-tetramethyl-4,4'-bispyrazole is a powerful cytotoxic agent ($ED_{50} = 7 \mu M$).

Keywords—4,4'-bispyrazole; 1,1'-dibenzyl derivative; 1,1'-dihydroxymethyl derivative phase transfer catalysis; cytotoxicity

Introduction

Interesting ligand properties of three 1*H*-4,4'-bispyrazoles **1a—c** (see Chart 1) towards Co(II), Ni(II) and Rh(I) have recently been described.^{1–3)} In this paper we wish to report the cytotoxic properties of these bispyrazoles together with their *N*-benzyl **2a—c** and *N*-hydroxymethyl **3a—c** derivatives. It has been shown recently that 1-benzyl-3,5-dimethylpyrazoles yield two-coordinate copper (I) complexes.⁴⁾

Chemistry

The three 1*H*-derivatives, **1a—c**, were prepared according to Mosby,⁵⁾ Knöevenhagel⁶⁾ and Trofimenko,⁷⁾ respectively (see Chart 1). Both tetramethyl compounds, **1a** and **1b**, were obtained from acetylacetone **7** in two steps. In the first step, 2 mol of **7** reacted with sodium hydride and iodine, affording 3,4-diacylhexan-2,5-dione (**8**). In a similar way, condensation of 2 mol of acetylacetone (**7**) and formaldehyde, using either diethyl- or triethylamine as a catalyst, yielded 3,5-diacylheptan-2,6-dione (**9**). In the second step, cyclization of both ketones with hydrazine hydrate in ethanol solution led to the bispyrazoles **1a** and **1b** in yields higher than 75%. A different method was employed for the preparation of 4,4'-methylenebis-1*H*-pyrazole (**1c**). The reaction between pyrazole and methylene bromide at 200 °C in a sealed tube afforded **1c** in 45% yield. The bispyrazoles **1** were characterized on the basis of analytical data, the molecular peak in mass spectrometry (MS), infrared (IR) and proton nuclear magnetic resonance (¹H-NMR) spectra.

The NMR spectra of these bispyrazoles are quite simple, since the prototropic exchange makes the four positions 3,3', 5 and 5' magnetically equivalent. Thus only one signal at δ 2.0 ppm corresponding to the four methyl groups and another broad signal at about 12.5 ppm corresponding to the NH protons is observed in the ¹H-NMR spectra of **1a** and **1b** (CH₂ at δ 3.3 ppm).

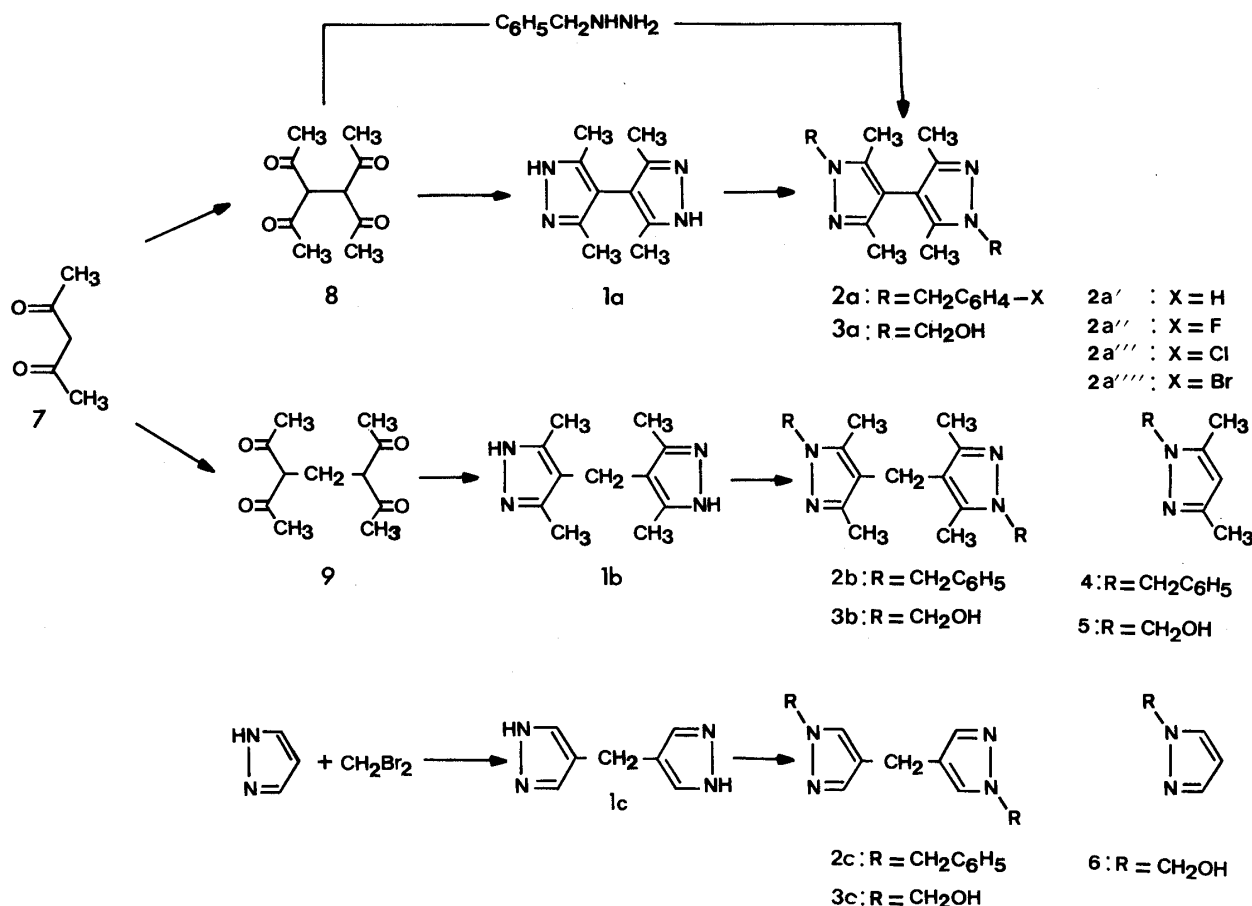
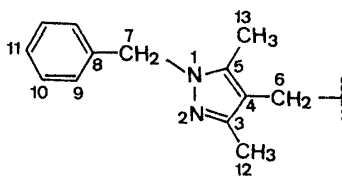


Chart 1

There are references in the literature to *N,N'*-disubstituted 4,4'-bispyrazoles, when both substituents are methyl,⁸⁻¹² ethyl,¹¹ phenyl,¹³⁻¹⁷ acetyl,⁵ benzoyl⁵ or 2-cyanoethyl¹⁸ groups, but, to the best of our knowledge, there has been no report on the 1,1'-dibenzyl or 1,1'-dihydroxymethyl derivatives of compounds 1a—c.

In order to evaluate the cytotoxic activity of a series of 4,4'-bispyrazoles we have prepared the 1,1'-dibenzyl, 2a', 2b, 2c, the 1,1'-di(*p*-halobenzyl), 2a'' ($\text{X} = \text{F}$), 2a''' ($\text{X} = \text{Cl}$), 2a'''' ($\text{X} = \text{Br}$), and the 1,1'-dihydroxymethyl, 3a—c, derivatives. The first ones were obtained from pyrazoles 1a—c, by benzylation with benzyl chloride under phase transfer conditions. They show no NH absorption in the IR spectrum, and show different signals for the substituents (CH_2 or H) in positions 3(3') and 5(5') in the ^1H -NMR spectrum. The CH_2 protons of the benzyl groups (4H) appear between 5.2 and 5.3 ppm and those of the CH_2 bridge (2H) between 3.45 and 3.6 ppm. One of the benzyl derivatives, 2b, was also obtained by condensation of 9 with benzylhydrazine, but the overall yield of the two-step procedure ($8 \rightarrow 1a \rightarrow 2b$) was far better. The 1,1'-dihydroxymethyl derivatives, 3a—c, were obtained by reaction of bispyrazoles, 1a—c, with formalin, either in acidic medium¹⁹ (3a) or in neutral medium²⁰ (3b and 3c). In the IR spectrum, they show the $3100\text{--}3200\text{ cm}^{-1}$ absorption of the OH group. In the ^1H -NMR spectrum (solvent: $\text{DMSO-}d_6$) the CH_2OH groups give rise to a doublet at 5.2 ppm corresponding to 2 protons. The coupling and the signal at 6.4 ppm (OH group) disappear on exchange with deuterium oxide.

Since carbon-13 NMR (^{13}C -NMR) spectra are useful to characterize new compounds, those of the twelve bispyrazoles were recorded (Table I). The assignment of signals was

TABLE I. ^{13}C -NMR Chemical Shifts of Bispyrazole Derivatives^{a)}

Compound	Solvent	C ₃	C ₄	C ₅	C ₆	C ₇	C ₈	C ₉	C ₁₀	C ₁₁	C ₁₂	C ₁₃
1a	DMSO- <i>d</i> ₆	141.7 ^{b)}	108.2	141.7 ^{b)}	—	—	—	—	—	—	11.0	11.0
1b	DMSO- <i>d</i> ₆	140.2 ^{b)}	112.6	140.2 ^{b)}	16.7	—	—	—	—	—	10.5	10.5
1c	DMSO- <i>d</i> ₆	132.3 ^{b)}	119.8	132.3 ^{b)}	18.6	—	—	—	—	—	—	—
2a'	Cl ₃ CD	147.4	110.8	137.6	—	53.0	137.5	127.0	128.6	126.5	12.3	10.1
2a''	Cl ₃ CD	147.4	110.9	137.6	—	52.4	133.3 ^{c)}	128.3 ^{c)}	115.6 ^{c)}	162.0 ^{c)}	12.4	10.1
2a'''	Cl ₃ CD	147.5	110.9	137.6	—	52.4	136.0	128.0	128.9	133.4	12.4	10.1
2a''''	Cl ₃ CD	147.5	110.9	137.6	—	52.5	136.5	128.3	131.9	121.5	12.4	10.1
2b	Cl ₃ CD	147.5	114.6	137.4	18.3	52.5	135.5	127.0	128.8	126.1	12.1	9.5
2c	Cl ₃ CD	138.9	121.1	128.6	19.3	55.7	136.8	127.8	127.7	127.5	—	—
3a	DMSO- <i>d</i> ₆	145.5	110.3	136.9	—	70.9	—	—	—	—	12.0	9.3
3b	DMSO- <i>d</i> ₆	146.0	115.8	136.5	18.5	71.8	—	—	—	—	13.0	10.0
3c	DMSO- <i>d</i> ₆	138.5	120.1	127.5	18.6	73.3	—	—	—	—	—	—

a) The numbering applies to all twelve compounds. b) Broad signal, due to a slow prototropic exchange. c) ^{13}C - ^{19}F coupling constants: $^1J=254.7$; $^2J=21.8$; $^3J=8.1$ and $^4J=2.9$ Hz.

straightforward based on the literature data on mononuclear pyrazoles²¹⁾ and amines.²²⁾ The main difference between the **a** series on the one hand and the **b** and **c** series on the other is the deshielding of carbon C₄ when both pyrazole rings are directly linked (X=nothing).

Cytotoxic Activity

The previously described methods²³⁾ were followed. Eagle's minimal medium²⁴⁾ (Difco code 5675) supplemented with 10% fetal calf serum (Difco) was used. HeLa cells (10⁵ cell/ml) were incubated at 37 °C in multiwell tissue culture plates (3008, Falcon). After 2–3 h, the cells had become attached to the glass, and a test compound, suspended in sterile saline containing 0.05% (v/v) Tween 80, was then added. The volume of this suspension was 10% of the final incubation mixture. Incubation was carried out at 37 °C for 72 h. As a positive control, 6-mercaptopurine was always included (ED₅₀ 0.1 μg/ml). Cell growth was estimated by measuring the cell proteins following the colorimetric method of Oyama and Eagle.²⁵⁾

The cytotoxic activity of the bispyrazoles **1a**–**c**, **2a'**, **2a''**, **2a'''**, **2a''''**, **2b**, **2c**, **3a**, **3b** and **3c** was measured. All the *N*-unsubstituted compounds (R=H), **1a**–**c**, are inactive. In order to determine the effect of the substituent R, three known pyrazoles, 1-benzyl-3,5-dimethylpyrazole (**4**), 1-hydroxymethyl-3,5-dimethylpyrazole (**5**) and 1-hydroxymethylpyrazole (**6**), were prepared (see Experimental) and their cytotoxic activities were evaluated (Table II).

A qualitative structure–activity study of the compounds in Table II shows that the most interesting compounds are those derived from the 4,4'-bispyrazole ring (X=nothing) and particularly **2a'**. When R=CH₂OH, in **3a**–**c**, **5** and **6**, the activity is almost independent of the ring and is probably related to formaldehyde liberation.^{19,20)} We attempted to improve the cytotoxicity of **2a'** by preparing three other similar derivatives but none of them is more cytotoxic than **2a'**: **2a''** (ED₅₀=250), **2a'''** (ED₅₀=230) and **2a''''** (ED₅₀=20 μM).

TABLE II. Cytotoxic Activity *in Vitro* of Bispyrazoles and Pyrazoles

Compound	R	R'	X	ED ₅₀ (μM)
1a	H	Me	Nothing	530
1b	H	Me	CH ₂	490
1c	H	H	CH ₂	680
2a'	Bz	Me	Nothing	7
2a''	<i>p</i> -FC ₆ H ₄	Me	Nothing	250
2a'''	<i>p</i> -ClC ₆ H ₄	Me	Nothing	230
2a''''	<i>p</i> -BrC ₆ H ₄	Me	Nothing	20
2b	Bz	Me	CH ₂	40
2c	Bz	H	CH ₂	230
3a	CH ₂ OH	Me	Nothing	40
3b	CH ₂ OH	Me	CH ₂	80
3c	CH ₂ OH	H	CH ₂	50
4	Bz	Me	—	540
5	CH ₂ OH	Me	—	80
6	CH ₂ OH	H	—	100

Experimental

Melting points are uncorrected. Proton and ¹³C-NMR spectra were recorded with a Varian XL-100 or a Varian EM 390 spectrometer using Me₄Si as an internal standard. MS were recorded on a Hitachi Perkin-Elmer RMU-6MG at 70 eV. The IR spectra were obtained on a Perkin-Elmer 257. Preparative layer chromatography was done on 20 × 20 cm glass plates coated with a 2 mm layer of Silica gel PF₂₅₄ (Merck).

The following compounds were prepared by using the reported procedures: 3,4-diacetylhexan-2,5-dione (**8**), mp 187–189 °C (from acetic acid) (76% yield) (lit.,⁵) mp 189–190 °C; 3,5-diacetylheptan-2,6-dione (**9**), mp 82–84 °C (from ethanol) (94% yield) (lit.,⁶) mp 85 °C; 1-benzyl-3,5-dimethylpyrazole (**4**), bp 139 °C (7 mmHg) (76% yield) (lit.,²⁶) bp 148 °C (13 mmHg); 1-hydroxymethyl-3,5-dimethylpyrazole (**5**), mp 108–109 °C (from benzene) (83% yield) (lit.,²⁰) mp 108–109 °C; 1-hydroxymethylpyrazole (**6**), mp 89–90 °C (from ether-*n*-hexane) (50% yield) (lit.,¹⁹) mp 89–90 °C. The 1*H*-bispyrazoles **1a–c** were also prepared by using the procedures described above.

Syntheses of 1,1'-Dibenzyl-4,4'-bispyrazoles 2a–c from 1*H*-derivatives 1a–c and Benzyl Halides in PTC Conditions—General Procedure: A solution of 0.04 mol of benzyl chloride and 0.0004 mol of tetrabutyl ammonium bromide in 100 ml of toluene was added, to a solution of 0.01 mol of the 4,4'-bispyrazole 1*H* derivative **1** in 20 ml of 50% aqueous sodium hydroxide. The mixture was stirred vigorously at 112 °C for 6 h. After cooling at room temperature, the organic layer was separated, washed repeatedly with water and then dried over magnesium sulfate. The resulting solution was evaporated to dryness under reduced pressure and the oily residue was purified as indicated in each case.

Compounds **2a''**, **2a'''** and **2a''''** were prepared analogously but using *p*-halogen substituted benzyl halides.

1,1'-Dibenzyl-3,3',5,5'-tetramethyl-4,4'-bispyrazole (**2a'**): An oily residue was obtained according to the general procedure from **1a** and benzyl chloride. From this oil, unreacted starting products were removed by distillation under a vacuum (100 °C/1 mm). The non volatile residue afforded **2a'** as a syrup (68% yield).

From **2a'** and picric acid in ethanolic solution, the corresponding dipicrate derivative was obtained as a solid, mp 144.5–146 °C (ethanol). *Anal.* Calcd for C₂₄H₂₆N₄ · 2C₆H₃N₃O₇: C, 52.17; H, 3.89; N, 16.90. Found: C, 52.50; H, 4.08; N, 16.62.

1,1'-Di(*p*-fluorobenzyl)-3,3',5,5'-tetramethyl-4,4'-bispyrazole (**2a''**): The reaction of **1a** and *p*-fluorobenzyl chloride according to the general procedure afforded a solid residue, which was chromatographed on preparative thin layer chromatography (TLC) plates with C₆H₆-AcOEt (2:1, v/v) as the developer. From the main band (*R*_f=0.39), **2a''** was obtained as a white solid. mp 145.5–146.5 °C (*n*-hexane), (35% yield). *Anal.* Calcd for C₂₄H₂₄F₂N₄: C, 70.92; H, 5.95; F, 9.34; N, 13.74. Found: C, 71.10; H, 6.03; F, 9.23; N, 13.64.

1,1'-Di(*p*-chlorobenzyl)-3,3',5,5'-tetramethyl-4,4'-bispyrazole (**2a'''**): Compound **2a'''** (yield, 69%) was obtained

TABLE III. Spectroscopical Data (MS, IR and $^1\text{H-NMR}$) for **2a'**—**a''''**, **2b**, **c** and **3a**—**c**

Compound	MS m/e (%)	IR (KBr) ^{a)} ν_{max} (cm^{-1})	$^1\text{H-NMR}$ (Cl_3CD) ^{b)} δ (ppm)
2a'	370 (M^+ , 47)	1610, 1500, 1215, 1080, 1030, 720	1.95 (s, 6H), 2.10 (s, 6H), 5.30 (s, 4H), 7.00—7.50 (m, 10H)
2a''	406 (M^+ , 67)	1610, 1515, 1220, 1170, 1040, 820	1.95 (s, 6H), 2.07 (s, 6H), 5.22 (2, 4H), 6.95—7.15 (m, 8H)
2a'''	438 (M^+ , 100)	1495, 1315, 1095, 1035, 1020, 810	1.97 (s, 6H), 2.10 (s, 6H), 5.25 (s, 4H), 6.93—7.40 (m, 8H)
2a''''	528 (M^+ , 100)	1495, 1318, 1080, 1035, 1018, 805	1.97 (s, 6H), 2.10 (s, 6H), 5.25 (s, 4H), 7.65—6.85 (m, 8H)
2b	384 (M^+ , 10)	1500, 1310, 1240, 1038, 835, 750	1.98 (s, 6H), 2.10 (s, 6H), 3.45 (s, 2H), 5.25 (s, 4H), 7.00—7.50 (m, 10H)
2c	328 (M^+ , 27)	1500, 1160, 1000, 750, 735, 710	3.60 (s, 2H), 5.20 (s, 4H), 7.05—7.40 (m, 14H)
3a	190 ($\text{M}^+ - 2 \text{CH}_2\text{O}$, 100)	3180 (OH), 1495, 1220, 1080, 1035, 730	1.94 (s, 6H), 2.06 (s, 6H), 5.30 (d, 4H), 6.45 (t, 2H) ^{c)}
3b	204 ($\text{M}^+ - 2 \text{CH}_2\text{O}$, 100)	3190 (OH), 1475, 1385, 1310, 1080, 760	1.90 (s, 6H), 2.10 (s, 6H), 3.30 (s, 2H), 5.15 (d, 4H), 6.30 (t, 2H) ^{c)}
3c	148 ($\text{M}^+ - 2 \text{CH}_2\text{O}$, 100)	3200 (OH), 1330, 1160, 1075, 995, 780	3.50 (s, 2H), 5.17 (d, 4H), 6.50 (t, 2H), ^{c)} 7.23 (s, 4H)

a) Except **2b**—**c**, which were measured in Nujol. b) Except **3a**—**c**, which were measured in $\text{DMSO}-d_6$. c) Exchangeable with D_2O .

according to the general procedure from **1a** and *p*-chlorobenzyl chloride as a white solid after preparative TLC with a mixture of benzene–ethyl acetate–acetone (1 : 1 : 0.5, v/v) as the developer mp 165—167 °C (*n*-hexane). *Anal.* Calcd for $\text{C}_{24}\text{H}_{24}\text{Cl}_2\text{N}_4$: C, 65.61; H, 5.51; Cl, 16.14; N, 12.75. Found: C, 65.65; H, 5.51; Cl, 15.92; N, 12.72.

1,1'-Di(*p*-bromobenzyl)-3,3',5,5'-tetramethyl-4,4'-bispyrazole (2a''''**):** According to the general procedure, the reaction of **1a** and *p*-bromobenzyl bromide afforded an oily residue, which was crystallized from a mixture of benzene–*n*-hexane to give **2a''''** as a white solid in 93% yield, mp 146—147 °C. *Anal.* Calcd for $\text{C}_{24}\text{H}_{24}\text{Br}_2\text{N}_4$: C, 54.56; H, 4.58; Br, 30.25; N, 10.60. Found: C, 54.69; H, 4.77; Br, 30.18; N, 10.56.

1,1'-Dibenzyl-3,3',5,5'-tetramethyl-4,4'-methylenbis-pyrazole (2b**):** The reaction of **1b** and benzyl chloride according to the general procedure gave a residue, which was crystallized from *n*-hexane to afford **2b** (79% yield). mp 107—108 °C. *Anal.* Calcd for $\text{C}_{23}\text{H}_{28}\text{N}_4$: C, 78.12; H, 7.29; N, 14.58. Found: C, 78.14; H, 7.33; N, 14.43.

1,1'-Dibenzyl-4,4'-methylenbis-pyrazole (2c**):** The residue obtained from the reaction of **1c** and benzyl chloride according to the general procedure was chromatographed on preparative TLC plates with $\text{Cl}_3\text{CH}-\text{AcOEt}-\text{EtOH}$ (7.5 : 7.5 : 0.5, v/v) as the developer. The intermediate band afforded **2c** as a solid, mp 41—42 °C (65% yield). *Anal.* Calcd for $\text{C}_{21}\text{H}_{20}\text{N}_4$: C, 76.82; H, 6.09; N, 17.07. Found: C, 76.76; H, 6.34; N, 16.91.

Synthesis of 1,1'-Dihydroxymethyl-4,4'-bispyrazoles **3a—**c** from 1H-Derivatives (**1a**—**c**)—Method A:** Acidic medium: **1,1'-Dihydroxymethyl-3,3',5,5'-tetramethyl-4,4'-bispyrazole (**3a**):** Formalin (4.1 ml) was added to a solution of **1a** (0.01 mol) in 12 ml of 20% hydrochloric acid. After being stirred at room temperature overnight and cooled with ice, the reaction mixture was made alkaline with concentrated sodium hydroxide. A white precipitate was formed at pH 12 and was filtered off. Crystallization from water gave 0.97 g of **3a** (39% yield), mp 200—201 °C. *Anal.* Calcd for $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}_2$: C, 57.58; H, 7.24; N, 22.38. Found: C, 57.31; H, 7.46; N, 22.12.

Method B: Neutral medium: A solution of **1** (0.002 mol) in 20 ml of 50% ethanol–water and 1 ml of formalin was stirred at 30 °C for 48 h. From the resulting solution, the product was purified as follows.

1,1'-Dihydroxymethyl-3,3',5,5'-tetramethyl-4,4'-methylenbis-pyrazole (3b**):** The precipitate obtained from **1b** by method B was crystallized from water to give **3b** as a white solid (91% yield), mp 212—214 °C. *Anal.* Calcd for $\text{C}_{13}\text{H}_{20}\text{N}_4\text{O}_2$: C, 59.09; H, 7.57; N, 21.21. Found: C, 59.17; H, 7.52; N, 21.14.

1,1'-Dihydroxymethyl-4,4'-methylenbis-pyrazole (3c**):** The solution obtained from **1c** by method B was evaporated under reduced pressure. The residue was washed with ethanol to give **3c** as a pure solid (51% yield), mp 130—132 °C. *Anal.* Calcd for $\text{C}_9\text{H}_{12}\text{N}_4\text{O}_2$: C, 51.92; H, 5.76; N, 26.92. Found: C, 51.89; H, 5.65; N, 26.76.

Spectroscopical data (MS, IR and $^1\text{H-NMR}$) for compounds **2a'**—**a''''**, **2b**, **c** and **3a**—**c** are given in Table III.

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