Syntheses of Substituted 1-(2-Phenethyl)pyrazoles [1]

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Alkylation of 3-methylpyrazole with 2-phenethyl *p*-toluenesulfonate gave 3-methyl-1-(2-phenethyl)pyrazole (**2a**) and 5-methyl-1-(2-phenethyl)pyrazole (**3a**) in low yield. Reaction of 5-chloro-1,3-dimethylpyrazole (**5**) with substituted-benzaldehydes afforded compounds **7**. Reduction of the latter afforded compound **2** in high yield. Compound **3** could be obtained from the reaction of substituted-2-(phenethyl)hydrazine hydrochloride **9** with acetoacetaldehyde dimethylacetal in moderate yield.

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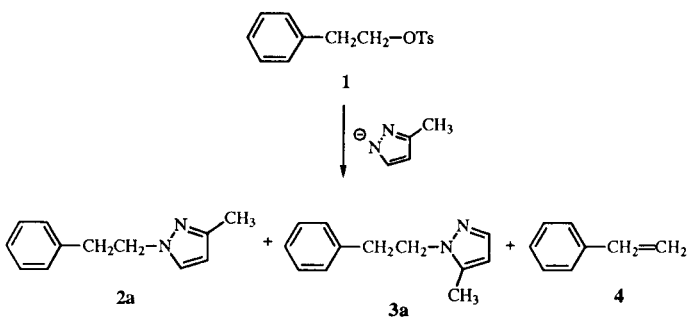
Recently the synthesis of pyrazole derivatives as potential bioisoteres of thromboxane-synthetase is reported [2]. In continuation of our research program for the synthesis of possible effective compounds against tropical diseases [3-4] the syntheses of the title compounds was of our interest.

The synthesis of 3-(or 5-)methyl-1-(2-phenethyl)pyrazole was studied according to Scheme 1.

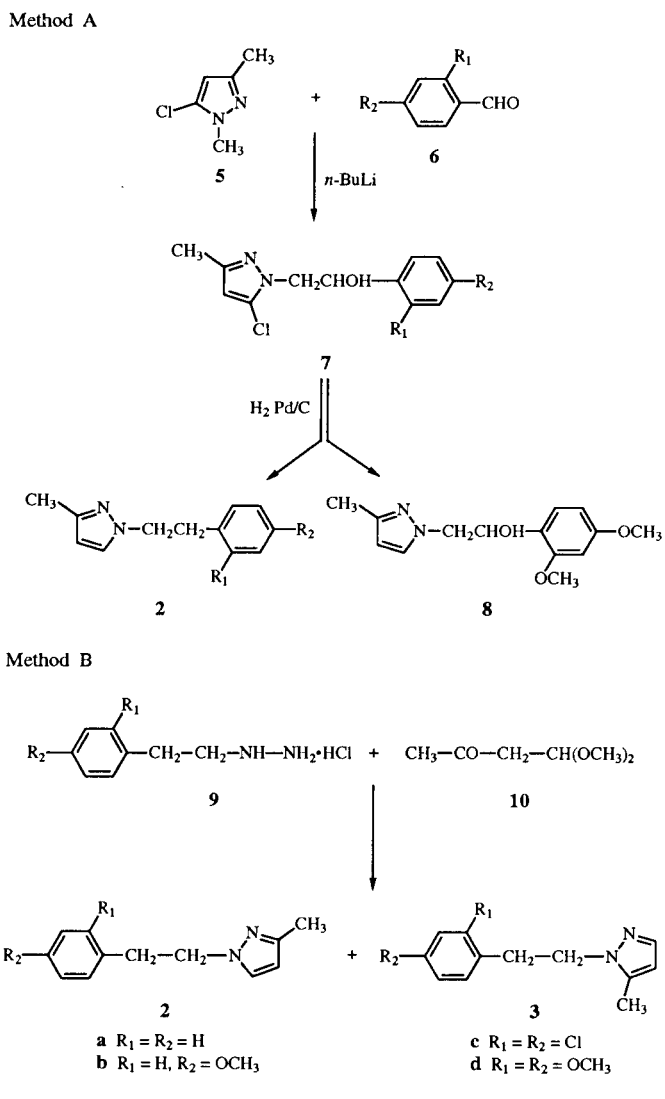
Scheme 1



The reaction of 3-methylpyrazole with 2-phenethyl *p*-toluenesulfonate in tetrahydrofuran in the presence of sodium hydride afforded a mixture of 3-methyl-1-(2-phenethyl)pyrazole (**2a**), 5-methyl-1-(2-phenethyl)pyrazole (**3a**) and styrene as a major product. The direct method of alkylation of 3-methylpyrazole gave low yields of the desired compounds **2a** and **3a**. In addition, the assignment of structures of *N*-alkyl derivatives of unsymmetrical pyrazoles is not an easy problem. The alkylation method for the preparation of substituted pyrazoles are usually ambiguous with respect to the location of the 3- or 5-position [5-10]. However, we could establish the structures of compounds **2** and **3** unambiguously according to the method A (Scheme 2).

Reaction of 5-chloro-1,3-dimethylpyrazole (**5**) with benzaldehyde (**6a**) in the presence of *n*-butyllithium gave 1-phenyl-2-(5-chloro-3-methyl-1-pyrazolyl)ethanol (**7a**) which was reduced with hydrogen in the presence of palladium to give compound **2a** [11]. In case of compound

Scheme 2



7d reduction at room temperature afforded 1-(2,4-dimethoxyphenyl)-2-(3-methyl-1-pyrazolyl)ethanol (**8**), while at 50° the desired compound **2d** was obtained.

Compound **3** could be obtained by method B in moderate yield (Scheme 2). Reaction of substituted phenethyl-

Table 1

Analytical Data of Compounds **2** and **3** as Hydrochlorides

Compounds	MP° C [a]	Yield %	Formula	Elemental Analysis % Calcd./Found C	H	N
2a	174-176 [b]	90	$C_{12}H_{15}ClN_2$	64.72 64.85	6.74 6.58	12.58 12.43
2b	92-94	85	$C_{13}H_{17}ClN_2O$	61.78 61.83	6.73 6.59	11.09 10.95
2c	[c]	35 [d]	$C_{12}H_{12}Cl_2N_2$	56.47 56.68	4.71 4.50	10.98 10.82
2d	110-113	75	$C_{14}H_{19}ClN_2O_2$	59.47 59.63	6.73 6.59	9.91 9.78
3a	110-112	35 [e]	$C_{12}H_{15}ClN_2$	64.72 64.91	6.74 6.62	12.58 12.39
3b	125-127	53	$C_{13}H_{17}ClN_2O$	61.78 61.64	6.73 6.85	11.09 11.21
3c	116-118	35 [d]	$C_{12}H_{13}Cl_3N_2$	49.40 49.52	4.46 4.61	9.61 9.80

[a] Unless otherwise mentioned the compound was crystallized as the hydrochloride from ethanol-ether. [b] bp 117-120° (10 mm), ref [11] bp 118-120° (10 mm). [c] The free base was an oil and the hydrochloride was hygroscopic, elemental analysis as the free base. [d] This compound was prepared by method B; the ratio of compound **2c** to **3c** was 1:1. [e] This compound was prepared by method B; the ratio of compound **2a** to **3a** was 1:2.

hydrazine hydrochloride **9** with acetoacetaldehyde dimethylacetal (**10**) in aqueous ethanol gave compounds **2** and **3** in a ratio of 1:2.

The structures of compounds **2** and **3** were also confirmed by nmr. The methyl group of compounds **2** appeared at 1.89 to 1.96 while the methyl group of compounds **3** had resonance at 2.21 to 2.27 ppm. Compounds **2** and **3** could be separated by preparative tlc on silica gel. The fast moving fraction was compound **2**. The tlc analysis of the compounds **2** and **3** was also in agreement with the suggested structure. In compound **3** the non-bonded electrons of nitrogen at position 2 could undergo a reaction with silica gel, while in compound **2** steric hindrance of the methyl and phenethyl groups with the latter electrons prevent their binding.

The analytical data of compounds **2** and **3** prepared are summarized in Table 1.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The uv spectra were recorded using a Perkin-Elmer Model 550 SE. The ir spectra were obtained using a Perkin-Elmer 781 spectrograph (potassium bromide disks). The ^1H nmr spectra were recorded on a Bruker FT-80 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. The mass spectra were run on a Varian Model MAT MS-311 spectrometer at 70 ev.

Reaction of 3-Methylpyrazole with 2-Phenethyl *p*-Toluenesulfonate.

To a stirring solution of 3-methylpyrazole (0.82, 0.01 mole) in tetrahydrofuran (20 ml), sodium hydride (0.24 g, 0.01 mole) was added. The stirring was continued for one half hour. This mixture was added dropwise to a stirring solution of compound **1** (2.76 g, 0.01 mole) in tetrahydrofuran (20 ml). After the addition was complete the stirring was continued for 12 hours. The solvent was evaporated. The residue was extracted with ether (50 ml). The ether was washed with concentrated hydrochloric acid (10 ml). The aqueous solution was made alkaline with sodium hydroxide and extracted with chloroform. The chloroform was dried (sodium sulfate), filtered and evaporated to give 0.093 g (5%) of compounds **2** and **3**. The mixture was purified by preparative tlc on silica gel using ether-petroleum ether (15:2) as the eluent. The fast moving fraction was compound **2a** (an oil, 0.062 g, 3.3%), as the hydrochloride mp 174-176°; ^1H nmr (deuteriochloroform, as the free base): 7.32-6.94 (m, 5H, C_6H_5), 7.00 (d, 1H, H_5 pyrazole, $J_{4,5}$ = 2 Hz), 5.90 (d, 1H, H_4 pyrazole, $J_{4,5}$ = 2 Hz), 4.22 (t, 2H, CH_2N), 3.09 (t, 2H, CH_2) and 2.28 ppm (s, 3H, CH_3); ms: m/z (%) 186 (M^+, 49), 104 (100), 95 (98), 91 (10) and 77 (10).

Anal. Calcd. for $C_{12}H_{15}ClN_2$: C, 64.72; H, 6.74; N, 12.58. Found: C, 64.85; H, 6.58; N, 12.43.

The slow moving fraction was compound **3a** (an oil, 0.031 g, 1.7%); ^1H nmr (deuteriochloroform): 7.40 (d, 1H, H_3 pyrazole, $J_{3,4}$ = 1.8 Hz), 7.27-6.90 (m, 5H, C_6H_5), 5.89 (dq, 1H, H_4 pyrazole, $J_{3,4}$ = 1.8 Hz, $J_{4,CH3}$ = 0.32 Hz), 4.20 (t, 2H, CH_2-N), 3.08 (t, 2H, CH_2) and 1.89 (d, 3H, CH_3, J = 0.32); ms: m/z (%) 186 (M^+, 63) 104 (100), 95 (95), 91 (12) and 77 (10).

Compound **3a** as the hydrochloride had mp 110-112°.

Anal. Calcd. for $C_{12}H_{15}ClN_2$: C, 64.72; H, 6.74; N, 12.58. Found: C, 64.91; H, 6.62; N, 12.39.

1-Phenyl-2-(5-chloro-3-methyl-1-pyrazolyl)ethanol (**7a**).

To a stirring solution of compound **5** (5.22 g, 0.04 mole) [10] in dry ether (70 ml) was added a solution of *n*-butyllithium (0.045 mole) in hexane at -20 to -10°. The solution was stirred at room temperature for 45 minutes and cooled to -20°. To this mixture benzaldehyde (4.24 g, 0.04 mole) in dry ether (40 ml) was added. The mixture was refluxed for 48 hours and cooled. To the mixture water (18 ml) was added. The organic layer was separated, dried (sodium sulfate), filtered and evaporated. The

residue was crystallized from petroleum ether to give 4.73 g (50%) of **7a**, mp 85-87° [lit [11] mp 85-87°].

Anal. Calcd. for $C_{12}H_{13}ClN_2O$: C, 60.89; H, 5.50; N, 11.84. Found: C, 60.95; H, 5.63; N, 11.98.

1-(2,4-Dichlorophenyl)-2-(5-chloro-3-methyl-1-pyrazolyl)-ethanol (**7c**).

This compound was prepared similarly to **7a** in 55% yield, mp 111-113° (ether-petroleum ether); uv (methanol): λ_{max} 220 nm (log ε = 4.21); ir (potassium bromide): ν 3180 (OH), 1590, 1520 (aromatic) and 1090 cm^{-1} (C-O); ^1H nmr (deuteriochloroform): 7.52-7.19 (m, 3H, aromatic), 5.99 (s, 1H, H_4 pyrazole), 5.35 (q, 1H *H*-C<(OH), J = 2.56; J = 7.30), 4.46 (q, 1H, *H*-CHN, J = 2.56, J = 14 Hz), 4.04 (q, 1H, *H*-CHN, J = 7.3, J = 14 Hz) and 2.26 ppm (s, 3H, CH_3); ms: m/z (%) 304 (M^+, 3), 177 (10), 175 (12), 132 (19), 131 (34), 130 (60), 129 (100), 111 (16) and 95 (10).

Anal. Calcd. for $C_{12}H_{11}Cl_3N_2O$: C, 47.14; H, 3.60; N, 9.17. Found: C, 47.01; H, 3.74; N, 9.02.

1-(2,4-Dimethoxyphenyl)-2-(5-chloro-3-methyl-1-pyrazolyl)-ethanol (**7d**).

This compound was made similar to **7a** in 40% yield, mp 82-84° (ether petroleum ether); uv (ethanol): λ_{max} 277 (log ε = 3.60), 227 nm (log ε = 4.17); ir (potassium bromide): ν 3410 (OH), 1615, 1590 and 1500 cm^{-1} (aromatic), ^1H nmr (deuteriochloroform): 7.30 (m, 1H, aromatic), 6.45 (m, 2H, aromatic), 5.96 (s, 1H, H_4 pyrazole), 5.23 (m, 1H, *H*-C<(OH)), 4.28 (m, 2H, CH_2N), 3.85 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.88 (brs, 1H, OH) and 2.25 ppm (s, 3H, CH_3); ms: m/z (%) 296 (M^+, 3), 167 (100), 151 (11), 137 (26) and 129 (57).

Anal. Calcd. for $C_{14}H_{17}ClN_2O_3$: C, 56.66; H, 5.73; N, 9.44. Found: C, 56.53; H, 5.61; N, 9.27.

1-(2,4-Dimethoxyphenyl)-2-(3-methyl-1-pyrazolyl)ethanol (**8**).

A solution of compound **7d** (2.965 g, 0.01 mole), sodium acetate (0.82 g, 0.01 mole) in glacial acetic acid (15 ml) was hydrogenated for 6 hours at 50 psi using 10% pd/C (0.3 g) as catalyst. The mixture was filtered. The solvent was evaporated. To the residue dilute sodium hydroxide was added and extracted with chloroform. The organic layer was washed with water, dried (sodium sulfate) and evaporated. The residue was crystallized from petroleum ether to give 2.1 g (80%) of compound **8**, mp 46-47°; uv (methanol): λ_{max} 277 (log ε = 3.69), 226 nm (log ε = 4.33); ir (potassium bromide): ν 3340 (OH), 1615, 1590, 1500 (aromatic) and 1068 cm^{-1} (C-O); ^1H nmr (deuteriochloroform): 7.27 (m, 1H, aromatic), 7.17 (d, 1H, H_5 of pyrazole, $J_{4,5}$ = 2.1 Hz), 6.41 (m, 2H, aromatic), 5.95 (d, 1H, H_4 of pyrazole, $J_{4,5}$ = 2.1 Hz), 5.21 (q, 1H, *H*-C<(OH), J = 3.2, J = 7.5), 4.32 (q, 1H, *H*-CHN, J = 3.2, J = 13.8 Hz), 4.04 (q, 1H, *H*-CHN, J = 7.5 Hz, J = 13.8 Hz), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), and 2.26 ppm (s, 3H, CH_3); ms: m/z (%): 262 (M^+, 8), 245 (23), 168 (13), 167 (46), 151 (16), 137 (27), 121 (27), 96 (87), 95 (100), 83 (18) and 77 (17).

Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.12; H, 6.87; N, 10.69. Found: C, 64.26; H, 6.71; N, 10.52.

3-Methyl-1-(2-phenethyl)pyrazole (**2a**).

Method A.

A solution of compound **7a** (23.65 g, 0.1 mole), sodium acetate (8.2 g, 0.1 mole) and 10% Pd/C (1 g) in acetic acid (150 ml) was hydrogenated at 50 psi at 50° for 4 hours. The mixture was filtered. The solvent was evaporated. To the residue dilute sodium hydroxide was added and extracted with chloroform. The organic layer was washed with water, dried (sodium sulfate) and evaporated. The residue was distilled to give 16.7 g (90%) of compound **2a**, bp 117-120° (10 mm) [ref [11] bp 118-120° (10 mm)]. The hydrochloride was crystallized from ethanol-ether, mp 174-176°.

Compounds **2b** and **2d** were prepared similarly (Table 1).

5-Methyl-1-(2-phenethyl)pyrazole (**3a**).

Method B.

To a solution of acetoacetaldehyde dimethylacetal (396 mg, 3 mmoles) in water (13 ml) a solution of compound **9a** (518 mg, 1.5 mmoles) in ethanol (6 ml) was added. The mixture was heated on steam bath for 40 minutes. It was concentrated under reduced pressure. The mixture was made alkaline with 20% sodium hydroxide solution and extracted with chloroform. The organic layer was dried (sodium sulfate), filtered and evaporated. The residue was purified by preparative tlc on silica gel using ether-petroleum ether (2:15) as eluent. The fast moving fraction was compound **2a** (an oil, 195 mg, 35%); as the hydrochloride had mp 176-178°.

The slow moving fraction was compound **3a** (an oil, 195 mg, 35%); ^1H nmr (deuteriochloroform): 7.40 (d, 1H, H_3 pyrazole, $J_{3,4}$ = 1.8 Hz), 7.27-6-90 (m, 5H, C_6H_5), 5.89 (dq, 1H, H_4 pyrazole, $J_{3,4}$ = 1.8 Hz, $J_{4,CH3}$ = 0.32 Hz) and 1.89 ppm (d, 1H, CH_3, $J_{4,CH3}$ = 0.32 Hz); ms: m/z (%) 186 (M^+, 63), 104 (100), 95 (95), 91 (12) and 77 (10); as hydrochloride, mp 110-112°.

Anal. Calcd. for $C_{12}H_{15}ClN_2$: C, 64.72; H, 6.74; N, 12.58. Found: C, 64.91; H, 6.62; N, 12.39.

Compounds **3b** and **3c** were prepared similarly (Table 1).

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REFERENCES AND NOTES

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