

Synthesis of hydroxylated 3,5-diaryl-2-pyrazolines by the reaction of hydroxychalcones with hydrazines

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Dedicated to Professor Dr. Alexandru T. Balaban on the occasion of his 75th birthday
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Abstract

New 1-substituted 3,5-diaryl-2-pyrazolines **13-27** have been synthesized by the reaction of hydroxychalcones **1-12** and hydrazines in hot acetic acid solution. Structures of all new compounds have been elucidated by microanalyses, ¹H- and ¹³C-NMR spectroscopy.

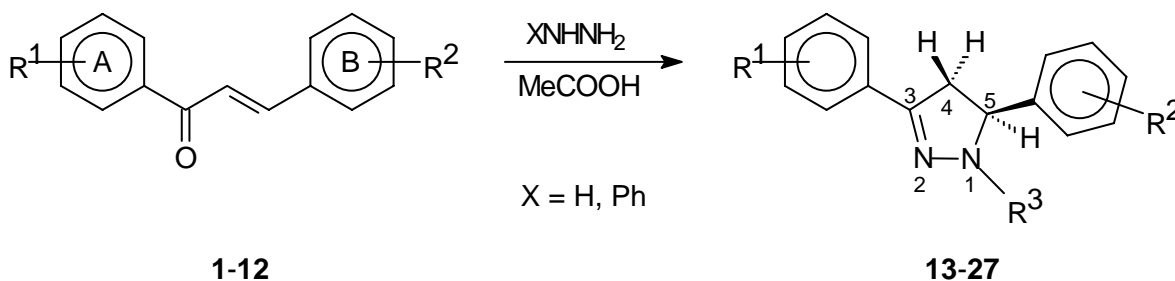
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Introduction

Pyrazolines are prominent nitrogen-containing heterocyclic compounds and, therefore, various procedures have been worked out for their synthesis.¹⁻⁴ Numerous pyrazoline type compounds have been found to possess useful bioactivity, *e.g.* antimicrobial,⁵ central nervous system⁶ and immunosuppressive.⁷ Among the various pyrazoline isomers, 2-pyrazolines appear to be the most frequently investigated compounds. As a consequence, a large number of 2-pyrazolines have been described in the chemical literature, using different synthetic methods for their preparation. An especially popular procedure is based on the reaction of α,β -unsaturated aldehydes and ketones with hydrazines.⁸⁻³⁷ However, series of specially substituted representatives have been prepared rarely. For this reason, the aim of our present study was to synthesize systematically hydroxylated 3,5-diaryl-2-pyrazolines for the study of their structure-activity relationships.

Results and Discussion

Formation of 2-pyrazolines by the reaction of α,β -unsaturated ketones and hydrazines may take place under various reaction conditions using ethanol,¹⁸ acetic acid^{8-10,16,21,25-27} or pyridine^{28,29} as solvent. After some preliminary experiments, acetic acid was found to be a convenient solvent in our present case. Hydroxychalcones **1-12** were allowed to react with hydrazine hydrate or phenylhydrazine in hot acetic acid (*cf.* Experimental Section) to afford 1-substituted 3,5-diaryl-2-pyrazolines **13-27** in high yields (Scheme 1). *N*-Acetylation of all 2-pyrazolines obtained by the reaction of the appropriate chalcones with hydrazine has taken place under these reaction conditions in each case. Formation of the *N*-acetyl derivatives is beneficial since the 1-substituted 2-pyrazolines are stable compounds and can be used for biological and pharmaceutical trials without the risk of undesirable decomposition.



1, 13: R¹ = 2-OH, R² = 4-iPr, R³ = Ac

2, 14: R¹ = 2-OH, R² = 4-Cl, R³ = Ac

3, 15: R¹ = 2-OH, R² = 2,4-Cl₂, R³ = Ac

4, 16: R¹ = 2-OH, R² = 2,3-(MeO)₂, R³ = Ac

5, 17: R¹ = 2-OH, R² = 3,4,5-(MeO)₃, R³ = Ac

4, 18: R¹ = 2-OH, R² = 2,3-(MeO)₂, R³ = Ph

6, 19: R¹ = 2-OH, R² = 2-Cl, R³ = Ph

7, 20: R¹ = 2-OH, R² = 3-Cl, R³ = Ph

8, 21: R¹ = 3-OH, R² = 4-MeO, R³ = Ac

9, 22: R¹ = 3-OH, R² = 2,6-Cl₂, R³ = Ac

9, 23: R¹ = 3-OH, R² = 2,6-Cl₂, R³ = Ph

10, 24: R¹ = 4-OH, R² = 2,4-Cl₂, R³ = Ac

11, 25: R¹ = 4-OH, R² = 2,6-Cl₂, R³ = Ac

12, 26: R¹ = 4-OH, R² = 3,4-Cl₂, R³ = Ac

10, 27: R¹ = 4-OH, R² = 2,4-Cl₂, R³ = Ph

Scheme 1

Structures of all new compounds **13-27** have been elucidated by elemental analyses, ¹H- and ¹³C-NMR measurements. In the ¹H-NMR spectra of 2-pyrazolines **13-27**, the three hydrogen atoms attached to the C-4 and C-5 carbon atoms of the heterocyclic ring gave an ABX spin system. Measured chemical shift and coupling constant values (*cf.* Experimental Section) unequivocally prove the 2-pyrazoline structure. In the ¹H-NMR spectra of 1-acetyl-2-pyrazolines **13-17, 21, 22** and **24-36** a singlet signal at around 2.4 ppm refers to the presence of an *N*-acetyl group. In the ¹³C-NMR spectra of all new 1-substituted 3,5-diaryl-2-pyrazolines **13-27**, the

chemical shift values of carbon atoms C-3 (154-156 ppm), C-4 (42-44 ppm) and C-5 (56-58 ppm) corroborate the 2-pyrazoline structure determined by $^1\text{H-NMR}$ spectroscopic measurements. $^{13}\text{C-NMR}$ chemical shifts of the *N*-acetyl group also have been assigned in the case of compounds **13-17**, **21**, **22** and **24-26**.

In conclusion, we have synthesized systematically hydroxylated 3,5-diaryl-2-pyrazolines by the reaction of hydrazines and chalcones bearing an *ortho*-, *meta*- or *para*-hydroxy group in their ring A. These new substances allow the investigation of the possible linkage of the 2-pyrazolines to various sites in living organisms in the course of the investigation of their bioactivities. The new 1-substituted 3,5-diaryl-2-pyrazolines described in this paper are very stable compounds, a property which may render them especially useful substances in drug research.

Experimental Section

General Procedures. Melting points were determined with a Koffler hot-stage apparatus and are uncorrected. $^1\text{H-}$ and $^{13}\text{C-NMR}$ spectra were recorded on a Varian Gemini 200 spectrometer at 200/50 MHz in CDCl_3 (internal standard TMS, $\delta = 0.0$ ppm) at room temperature. Elemental analyses were measured in-house with a Carlo Erba 1106 EA instrument. TLC was performed on Kieselgel 60 F₂₅₄ (Merck) layer using hexane:acetone (7:3 v/v) or toluene:ethyl acetate (4:1 v/v) as eluents. Starting materials **1-12** were synthesized according to known procedures.³⁸⁻⁴¹

General procedure for the synthesis of compounds 13-27

A mixture of hydroxychalcone (**1-12**, 10.0 mmol), hydrazine hydrate (50.0 mmol) or phenylhydrazine (50.0 mmol) and acetic acid (40 ml) was refluxed for 3 hours then poured into water. The precipitate was separated by filtration, washed free of acid and crystallized from methanol to afford 2-pyrazolines **13-27** (Scheme 1).

1-Acetyl-3-(2-hydroxyphenyl)-5-(4-isopropylphenyl)-2-pyrazoline (13). This compound was obtained as colourless needles in 65% yield, m.p. 163-164 °C; $^1\text{H-NMR}$ (δ): 1.22 (6H, d, $J = 6.9$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.38 (3H, s, CH_3), 2.89 (1H, m, $\text{CH}(\text{CH}_3)_2$), 3.31 (1H, dd, $J = 4.6, 17.8$ Hz, 4- H_{trans}), 3.85 (1H, dd, $J = 11.8, 17.8$ Hz, 4- H_{cis}), 5.57 (1H, dd, $J = 4.6, 11.8$ Hz, 5-H), 6.90-7.41 (m, 8 arom. H), 10.30 (1H, s, OH); $^{13}\text{C-NMR}$ (δ): 21.9, 23.7, 33.6, 42.6, 58.1, 115.3, 117.2, 119.8, 125.7, 127.2, 128.6, 132.4, 138.7, 148.8, 156.6, 157.9, 167.9. Anal. Calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$: C, 74.51; H, 6.88; N, 8.68. Found: C, 74.59; H, 6.84; N, 8.76.

1-Acetyl-5-(4-chlorophenyl)-3-(2-hydroxyphenyl)-2-pyrazoline (14). This material was isolated as colourless needles in 76% yield, m.p. 146-147 °C; $^1\text{H-NMR}$ (δ): 2.38 (3H, s, CH_3), 3.28 (1H, dd, $J = 4.8, 17.9$ Hz, 4- H_{trans}), 3.84 (1H, dd, $J = 12.0, 17.9$ Hz, 4- H_{cis}), 5.54 (1H, dd, $J = 4.8, 12.0$ Hz, 5-H), 6.92-7.41 (m, 8 arom. H), 10.21 (1H, s, OH); $^{13}\text{C-NMR}$ (δ): 21.8, 42.4, 57.7, 115.0, 117.2, 119.9, 127.2, 128.5, 129.3, 132.5, 133.9, 139.8, 156.3, 157.9, 167.9. Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O}_2$: C, 64.87; H, 4.80; N, 8.89. Found: C, 64.98; H, 4.83; N, 8.96.

1-Acetyl-5-(2,4-dichlorophenyl)-3-(2-hydroxyphenyl)-2-pyrazoline (15). This substance was prepared as pale yellow needles in 71% yield, m.p. 183-184 °C; ¹H-NMR (δ): 2.43 (3H, s, CH₃), 3.16 (1H, dd, J = 5.3, 18.0 Hz, 4-H_{trans}), 3.92 (1H, dd, J = 12.0, 18.0 Hz, 4-H_{cis}), 5.80 (1H, dd, J = 5.3, 12.0 Hz, 5-H), 6.86-7.42 (m, 7 arom. H), 10.17 (1H, s, OH); ¹³C-NMR (δ): 21.8, 41.6, 55.9, 114.9, 117.3, 119.9, 127.2, 127.8, 128.6, 130.1, 132.7, 134.4, 136.7, 156.8, 157.9, 168.1. Anal. Calcd. for C₁₇H₁₄Cl₂N₂O₂: C, 58.47; H, 4.04; N, 8.02. Found: C, 58.57; H, 4.07; N, 8.10.

1-Acetyl-5-(2,3-dimethoxyphenyl)-3-(2-hydroxyphenyl)-2-pyrazoline (16). This compound was prepared as colourless plates in 69% yield, m. p. 166-167 °C; ¹H-NMR (δ): 2.39 (3H, s, CH₃), 3.24 (1H, dd, J = 5.1, 17.8 Hz, 4-H_{trans}), 3.80 (1H, dd, J = 12.0, 17.8 Hz, 4-H_{cis}), 3.84 (3H, s, CH₃O), 3.89 (3H, s, CH₃O), 5.72 (1H, dd, J = 5.1, 12.0 Hz, 5-H), 6.72-7.37 (m, 7 arom. H), 10.34 (1H, s, OH); ¹³C-NMR (δ): 21.9, 42.0, 54.5, 55.6, 60.2, 112.1, 115.3, 116.9, 118.6, 119.7, 124.4, 128.6, 132.2, 134.9, 146.1, 153.1, 157.2, 157.9, 167.8. Anal. Calcd. for C₁₉H₂₀N₂O₄: C, 67.04; H, 5.92; N, 8.23. Found: C, 67.15; H, 5.86; N, 8.31.

1-Acetyl-3-(2-hydroxyphenyl)-5-(3,4,5-trimethoxyphenyl)-2-pyrazoline (17). This substance was isolated as colourless needles in 68% yield, m.p. 154-155 °C; ¹H-NMR (δ): 2.42 (3H, s, CH₃), 3.31 (1H, dd, J = 5.0, 18.0 Hz, 4-H_{trans}), 3.80 (3H, s, CH₃O), 3.84 (6H, s, 2CH₃O), 3.90 (1H, dd, J = 11.8, 18.0 Hz, 4-H_{cis}), 5.49 (1H, dd, J = 5.0, 11.8 Hz, 5-H), 6.89-7.41 (m, 6 arom. H), 10.28 (1H, s, OH); ¹³C-NMR (δ): 21.7, 41.2, 55.3, 57.3, 111.7, 116.5, 119.3, 127.1, 127.7, 129.9, 132.5, 134.0, 137.4, 154.2, 160.0, 169.1. Anal. Calcd. for C₂₀H₂₂N₂O₅: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.92; H, 5.93; N, 7.64.

5-(2,3-Dimethoxyphenyl)-3-(2-hydroxyphenyl)-1-phenyl-2-pyrazoline (18). This material was prepared as yellow needles in 70% yield, mp. 127-128 °C; ¹H-NMR (δ): 3.23 (1H, dd, J = 6.9, 17.6 Hz, 4-H_{trans}), 3.90 (3H, s, CH₃O), 3.98 (3H, s, CH₃O), 4.02 (1H, dd, J = 11.3, 17.6 Hz, 4-H_{cis}), 5.02 (1H, dd, J = 6.9, 11.3 Hz, 5-H), 6.82-7.83 (m, 12 arom. H), 10.89 (1H, s, OH); ¹³C-NMR (δ): 42.8, 55.7, 58.1, 60.6, 111.9, 116.6, 118.7, 119.4, 119.8, 124.8, 127.3, 130.4, 135.5, 144.2, 146.0, 150.3, 153.1, 157.4. Anal. Calcd. for C₂₃H₂₂N₂O₃: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.89; H, 5.86; N, 7.57.

5-(2-Chlorophenyl)-3-(2-hydroxyphenyl)-1-phenyl-2-pyrazoline (19). This compound was prepared as pale yellow plates in 66% yield, m.p. 121-122 °C; ¹H-NMR (δ): 3.14 (1H, dd, J = 7.0, 17.6 Hz, 4-H_{trans}), 4.04 (1H, J = 12.1, 17.6 Hz, 4-H_{cis}), 5.58 (1H, dd, J = 7.0, 12.1, 5-H), 6.80-7.49 (m, 13 arom. H), 10.70 (1H, s, OH); ¹³C-NMR (δ): 42.2, 60.0, 113.2, 116.3, 116.7, 119.5, 120.1, 127.4, 127.9, 129.2, 129.4, 130.2, 130.7, 131.9, 138.8, 143.8, 150.2, 157.4. Anal. Calcd. for C₂₁H₁₇ClN₂O: C, 72.31; H, 4.91; N, 8.03. Found: C, 72.40; H, 4.87; N, 8.09.

5-(3-Chlorophenyl)-3-(2-hydroxyphenyl)-1-phenyl-2-pyrazoline (20). This substance was obtained as yellow plates in 72% yield, m.p. 122-123 °C; ¹H-NMR (δ): 3.22 (1H, dd, J = 7.6, 17.3 Hz, 4-H_{trans}), 3.96 (1H, dd, J = 12.1, 17.3 Hz, 4-H_{cis}), 5.20 (1H, dd, J = 7.6, 12.1 Hz, 5-H), 6.82-7.40 (m, 13 arom. H), 10.70 (1H, s, OH); ¹³C-NMR (δ): 43.8, 62.8, 113.5, 116.2, 116.8, 119.5, 120.4, 124.2, 126.2, 127.3, 128.3, 129.3, 130.8, 135.3, 144.1, 149.8, 157.5. Anal. Calcd. for C₂₁H₁₇ClN₂O: C, 72.31, H, 4.91; N, 8.03. Found: 72.22; H, 4.97; N, 7.94.

1-Acetyl-3-(3-hydroxyphenyl)-5-(4-methoxyphenyl)-2-pyrazoline (21). This material was prepared as colourless plates in 62% yield, m.p. 211-212 °C; ¹H-NMR (δ): 2.26 (3H, s, CH₃), 3.04 (1H, dd, J = 4.5, 18.0 Hz, 4-H_{trans}), 3.70 (3H, s, CH₃O), 3.80 (1H, dd, J = 11.7, 18.0 Hz, 4-H_{cis}), 5.47 (1H, dd, J = 4.5, 11.7 Hz, 5-H), 6.84-7.30 (m, 8 arom. H), 10.24 (1H, s, OH); ¹³C-NMR (δ): 21.6, 42.0, 55.0, 58.8, 112.9, 117.6, 117.8, 126.9, 129.9, 132.6, 134.6, 154.3, 157.8, 158.7, 167.5. Anal. Calcd. for C₁₈H₁₈N₂O₃: C, 69.66; H, 5.85; N, 9.02. Found: C, 69.78; H, 5.90; N, 9.09.

1-Acetyl-5-(2,6-dichlorophenyl)-3-(3-hydroxyphenyl)-2-pyrazoline (22). This compound was prepared as yellow needles in 70% yield, m.p. 252-253 °C; ¹H-NMR (δ): 2.38 (3H, s, CH₃), 3.27 (1H, dd, J = 8.5, 17.8 Hz, 4-H_{trans}), 3.67 (1H, dd, J = 12.8, 17.8 Hz, 4-H_{cis}), 6.21 (1H, dd, J = 8.5, 12.8 Hz, 5-H), 6.89-7.39 (m, 7 arom. H), 10.42 (1H, s, OH); ¹³C-NMR (δ): 21.2, 40.7, 56.2, 112.9, 117.6, 128.7, 129.7, 130.0, 130.2, 132.4, 133.0, 135.1, 135.5, 154.3, 157.8, 167.7. Anal. Calcd. for C₁₇H₁₄Cl₂N₂O₂: C, 58.47; H, 4.04; N, 8.02. Found: C, 58.41; H, 4.01; N, 8.07.

5-(2,6-Dichlorophenyl)-3-(3-hydroxyphenyl)-1-phenyl-2-pyrazoline (23). This substance was obtained as yellow plates in 73% yield, m.p. 206-207 °C; ¹H-NMR (δ): 3.31 (1H, dd, J = 7.3, 17.7 Hz, 4-H_{trans}), 3.79 (1H, dd, J = 11.4, 17.7 Hz, 4-H_{cis}), 6.08 (1H, dd, J = 7.3, 11.4 Hz, 5-H), 6.76-7.45 (m, 12 arom. H), 10.31 (1H, s, OH); ¹³C-NMR (δ): 39.7, 60.0, 112.3, 113.2, 115.8, 118.6, 119.5, 128.6, 129.1, 129.4, 129.9, 130.9, 134.4, 135.2, 135.3, 135.8, 144.6, 146.2, 155.9. Anal. Calcd. for C₂₁H₁₆Cl₂N₂O: C, 65.81; H, 4.21; N, 7.30. Found: C, 65.93; H, 4.27; N, 7.22.

1-Acetyl-5-(2,4-dichlorophenyl)-3-(4-hydroxyphenyl)-2-pyrazoline (24). This material was obtained as yellow plates in 64% yield, m.p. 240-241 °C; ¹H-NMR (δ): 2.31 (3H, s, CH₃), 3.01 (1H, dd, J = 4.8, 18.0 Hz, 4-H_{trans}), 3.88 (1H, dd, J = 11.8, 18.0 Hz, 4-H_{cis}), 5.69 (1H, dd, J = 4.8, 11.8 Hz, 5-H), 6.83-7.66 (m, 7 arom. H), 10.01 (1H, s, OH); ¹³C-NMR (δ): 21.4, 40.8, 56.6, 115.7, 121.9, 127.9, 128.0, 128.6, 129.3, 131.9, 132.7, 138.5, 154.6, 159.9, 167.5. Anal. Calcd. for C₁₇H₁₄Cl₂N₂O₂: C, 58.47; H, 4.04; N, 8.02. Found: C, 58.53; H, 4.07; N, 8.09.

1-Acetyl-5-(2,6-dichlorophenyl)-3-(4-hydroxyphenyl)-2-pyrazoline (25). This compound was prepared as pale yellow needles in 70% yield, m.p. 261-262 °C; ¹H-NMR (δ): 2.20 (3H, s, CH₃), 3.15 (1H, dd, J = 7.9, 18.0 Hz, 4-H_{trans}), 3.80 (1H, dd, J = 12.9, 18.0 Hz, 4-H_{cis}), 6.06 (1H, dd, J = 7.9, 12.9 Hz, 5-H), 6.84-7.65 (m, 7 arom. H), 9.98 (1H, s, OH); ¹³C-NMR (δ): 21.2, 40.7, 56.0, 115.7, 122.1, 128.5, 128.8, 129.7, 130.2, 133.0, 135.1, 135.7, 154.3, 159.8, 167.4. Anal. Calcd. for C₁₇H₁₄Cl₂N₂O₂: C, 58.47; H, 4.04; N, 8.02. Found: C, 58.39; H, 3.99; N, 8.08.

1-Acetyl-5-(3,4-dichlorophenyl)-3-(4-hydroxyphenyl)-2-pyrazoline (26). This substance was isolated as yellow plates in 67% yield, m.p. 254-255 °C; ¹H-NMR (δ): 2.28 (3H, s, CH₃), 3.12 (1H, dd, J = 4.9, 18.1 Hz, 4-H_{trans}), 3.79 (1H, dd, J = 11.7, 18.1 Hz, 4-H_{cis}), 5.51 (1H, dd, J = 4.9, 11.7 Hz, 5-H), 6.83-7.64 (m, 7 arom. H), 10.01 (1H, s, OH); ¹³C-NMR (δ): 21.5, 41.8, 58.2, 115.7, 122.0, 126.1, 128.1, 128.7, 129.9, 131.1, 143.7, 154.6, 159.9, 167.6. Anal. Calcd. for C₁₇H₁₄Cl₂N₂O₂: C, 58.47; H, 4.04; N, 8.02. Found: C, 58.56; H, 4.07; N, 8.09.

5-(2,4-Dichlorophenyl)-3-(4-hydroxyphenyl)-1-phenyl-2-pyrazoline (27). This substance was prepared as yellow plates in 83% yield, m.p. 125-126 °C; ¹H-NMR (δ): 3.01 (1H, dd, J = 6.9, 17.2 Hz, 4-H_{trans}), 3.94 (1H, dd, J = 11.8, 17.2 Hz, 4-H_{cis}), 5.51 (1H, dd, J = 6.9, 11.8 Hz, 5-H),

6.75-7.62 (m, 12 arom. H), 10.30 (1H, s, OH); ^{13}C -NMR (δ): 41.9, 60.8, 113.2, 115.7, 119.4, 125.5, 127.7, 128.1, 128.6, 129.2, 129.8, 132.6, 134.0, 138.2, 144.8, 147.4, 156.6. Anal. Calcd. for $\text{C}_{21}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}$: C, 65.81; H, 4.21; N, 7.30. Found: C, 65.72; H, 4.17; N, 7.38.

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