

J. O. Oluwadiya\*

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Ife, Ile-Ife, Nigeria

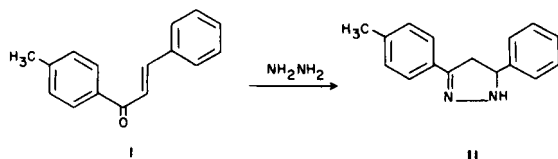
Received February 12, 1981

2'-Hydroxychalcones react with hydrazine hydrate in water to form phenolic 4,5-dihydro-3,5-diphenyl-1*H*-pyrazoles. Condensation of the pyrazoles with toluenesulphonylchloride in pyridine gave 4,5-dihydro-3,5-diphenyl-1-toluenesulphonylpyrazoles.

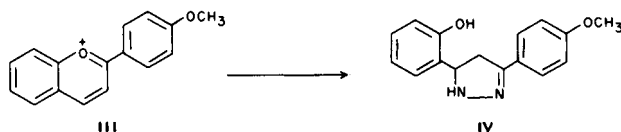
*J. Heterocyclic Chem.*, **18**, 1293 (1981).

The reported anticonvulsant (2) and monoamine oxidase (MAO) inhibitory properties, and bactericidal and fungicidal activities of pyrazoles stimulated the search for newer pyrazole derivatives in this laboratory.

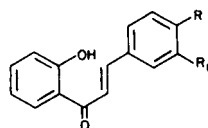
Hydrazine and its derivatives react with  $\alpha,\beta$ -unsaturated carbonyl systems to give pyrazoles or hydrazones depending on the substituent attached to the  $\alpha,\beta$ -unsaturated carbonyl moiety (3). The reaction of hydrazine and its derivatives in acidic methanol with 4'-substituted chalcone (I) has been demonstrated by Sammour (4) to give the pyrazole (II).



Jurd (5) reacted the flavylum salt (III) with hydrazine in pyridine to form the pyrazole (IV).

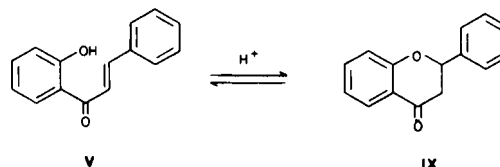


In the current work, it has been found that hydrazination of 2'-hydroxychalcones (V-VIII) in water proceeds smoothly without any side reactions.

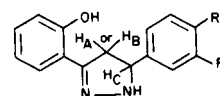


- (V)  $\text{R} = \text{R}_1 = \text{H}$   
 (VI)  $\text{R} = \text{OCH}_3$ ;  $\text{R}_1 = \text{H}$   
 (VII)  $\text{R} = \text{R}_1 = \text{OCH}_3$   
 (VIII)  $\text{R} = \text{N}(\text{CH}_3)_2$ ;  $\text{R}_1 = \text{H}$

When methanol-hydrochloric acid (4) was reacted with V under reflux, the main product was the flavanone (IX), in agreement with the fact that 2'-hydroxychalcones cyclise easily in acidic medium to give flavanones.

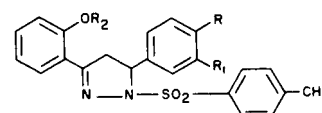


The structures of the pyrazoles were unequivocally assigned by the use of physical methods, *i.e.*,  $^1\text{H}$  nmr and elemental analysis. The pyrazoles (X-XIII) absorbed strongly in the ir spectra with bands at  $3350\text{ cm}^{-1}$  due to the  $-\text{NH}$  group and also at  $1625\text{--}1615\text{ cm}^{-1}$  due to the presence of a conjugated  $-\text{C}=\text{N}-$  group (6a).



- (X)  $\text{R} = \text{R}_1 = \text{H}$   
 (XI)  $\text{R} = \text{OCH}_3$ ;  $\text{R}_1 = \text{H}$   
 (XII)  $\text{R} = \text{R}_1 = \text{OCH}_3$   
 (XIII)  $\text{R} = \text{N}(\text{CH}_3)_2$ ;  $\text{R}_1 = \text{H}$

The  $^1\text{H}$  nmr signals for the pyrazole ring of (X) showed  $\text{H}_A$ ,  $\text{H}_B$  and  $\text{H}_C$  protons as well defined double doublets centred at  $\delta$  3.23, 3.30 and 4.80, respectively, with  $J_{AB} = 17.00\text{ Hz}$ ,  $J_{AC} = 14.00\text{ Hz}$  and  $J_{BC} = 10.00\text{ Hz}$ . In the case of XI and XII, the double doublets observed for the  $\text{H}_B$  protons were partially masked by the methoxy signals, while with XIII, the  $\text{H}_A$  double doublets were also obscured by the methyl group signal. However, the coupling constant for  $J_{BC}$  remained constant at  $10.00\text{ Hz}$  for XI-XIII.



- (XIV)  $\text{R} = \text{R}_1 = \text{R}_2 = \text{H}$ ; (XV)  $\text{R}_1 = \text{R}_2 = \text{H}$ ;  $\text{R} = \text{OCH}_3$   
 (XVI)  $\text{R} = \text{R}_1 = \text{OCH}_3$ ;  $\text{R}_2 = \text{H}$ ; (XVII)  $\text{R} = \text{N}(\text{CH}_3)_2$ ;  $\text{R}_1 = \text{R}_2 = \text{H}$   
 (XVIII)  $\text{R} = \text{R}_1 = \text{H}$ ;  $\text{R}_2 = \text{COCH}_3$ ; (XX)  $\text{R} = \text{OCH}_3$ ;  $\text{R}_1 = \text{H}$ ;  $\text{R}_2 = \text{COCH}_3$   
 (XXI)  $\text{R} = \text{R}_1 = \text{OCH}_3$ ;  $\text{R}_2 = \text{COCH}_3$ ; (XXII)  $\text{R} = \text{N}(\text{CH}_3)_2$ ;  $\text{R}_1 = \text{H}$ ;  $\text{R}_2 = \text{COCH}_3$

Table I

Compound	Molecular Formula	Anal. Calcd. %				Anal. Found %			
		C	H	N	S	C	H	N	S
	C <sub>15</sub> H <sub>14</sub> N <sub>2</sub> O	75.59	5.93	11.76	-	75.40	5.84	12.00	-
XI	C <sub>16</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>	71.60	6.02	10.45	-	71.60	6.11	10.40	-
XII	C <sub>17</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub>	68.42	6.09	9.40	-	68.29	6.10	9.47	-
XIII	C <sub>17</sub> H <sub>19</sub> N <sub>3</sub> O	72.55	6.81	14.95	-	72.40	6.76	15.10	-
XIV	C <sub>22</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> S	67.31	5.14	7.14	8.17	67.40	5.19	7.09	8.16
XVI	C <sub>23</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub> S	65.36	5.25	6.63	7.59	65.60	5.11	6.69	7.75
XVI	C <sub>24</sub> H <sub>24</sub> N <sub>2</sub> O <sub>5</sub> S	63.68	6.35	6.19	7.09	63.80	5.45	6.34	7.34
XVII	C <sub>24</sub> H <sub>25</sub> N <sub>3</sub> O <sub>5</sub> S	66.16	5.79	9.65	7.31	66.20	5.75	9.69	7.30

The toluenesulphonyl pyrazoles and their acetates (XIV-XXI) showed characteristic absorption bands in their ir spectra.

The phenolic pyrazoles (XIV-XVIII) exhibited broad -OH absorption band at 3400-3160 cm<sup>-1</sup>, the -C=N band appeared at 1625 cm<sup>-1</sup>, while the -SO<sub>2</sub>N- absorptions are at 1370 and 1175 cm<sup>-1</sup>, the pyrazole acetates (XVIII-XIX) showed an intense band at 1760 cm<sup>-1</sup>, which was due to the presence of an ester group. The <sup>1</sup>H nmr spectra of XIV-XVII showed the presence of a replacable proton at δ 0.36, giving evidence of a phenolic hydroxyl proton. The signal for the methyl group of toluene is characteristic of these compounds at δ 2.36. The coupling constants for the H<sub>A</sub>, H<sub>B</sub> and H<sub>C</sub> protons of the pyrazole ring in XIV-XXI were similar to those obtained for X-XIII. The acetates showed the acetyl signal as singlets at δ 2.46.

#### EXPERIMENTAL

All melting points are uncorrected. The ir spectra were for Nujol mull and on a Perkin-Elmer 527 spectrophotometer. <sup>1</sup>H nmr were obtained in deuteriochloroform with a JEOL FX-60 spectrometer and TMS as the internal standard. The chemical shifts are in δ values. The elemental analysis for compounds X-XVII are as shown in Table I.

#### 3-(2-Hydroxyphenyl)-5-phenyl-4,5-dihydro-1H-pyrazole (X).

To 2'-hydroxychalcone (V) (2.24 g) was added hydrazine hydrate (8 ml, 50%). The mixture was warmed gently on a boiling waterbath until complete dissolution of the solid and a discharge of yellow colour was apparent (usually 15-20 minutes). The mixture was then left at room temperature overnight, and the crystalline precipitate was collected and recrystallised from ethanol to give 3-(2-hydroxyphenyl)-5-phenyl-4,5-dihydro-1H-pyrazole (X) (1.22 g), mp 85-86°, as colourless plates; ir: 3350 (NH), 1615 (-C=N-), 1600 cm<sup>-1</sup> (C=C); <sup>1</sup>H nmr: δ 3.23 (dd, 1H, H<sub>A</sub>, 17 Hz), 3.30 (dd, 1H, H<sub>B</sub>, 14 Hz), 4.80 (t, 1H, H<sub>C</sub>, 10 Hz), 7.1 (m, 4H, 3<sub>A</sub>H<sub>4</sub>), 7.4 (s, 5H, C<sub>6</sub>H<sub>5</sub>). Compound X (0.71 g) was dissolved in pyridine (15 ml), and toluenesulphonyl chloride (0.57 g) was added. After 3 hours at room temperature the mixture was diluted with excess water and thereafter acidified with dilute hydrochloric acid. The red precipitate was collected and crystallised from ethanol to give red needles of 3-(2-hydroxyphenyl)-5-phenyl-4,5-dihydro-1-toluenesulphonylpyrazole (XIV) (0.50 g), mp 219-221°; ir: 3400 cm<sup>-1</sup> (OH), 1625 cm<sup>-1</sup> (-C=N-), 1600 cm<sup>-1</sup> (C=C), 1370, 1175 cm<sup>-1</sup> (-SO<sub>2</sub>N-); <sup>1</sup>H nmr: δ 2.36 (s, 3H, CH<sub>3</sub>), 3.40 (dq, 2H, CH<sub>2</sub>), 4.60 (t, 1H, CH), 6.50-7.80 (m, 13H, 2 C<sub>6</sub>H<sub>4</sub> + C<sub>6</sub>H<sub>5</sub>), -0.33 (s, 1H, deuterium oxide exchangeable).

Compound XIV (50 mg) with acetic anhydride in pyridine gave the acetate (XVIII) (46 mg), mp 192-194°, as pale violet needles from ethanol; ir: 1755 (-COOCH<sub>3</sub>), 1610 (-C=N-), 1600 (C=C), 1380, 1170 cm<sup>-1</sup> (-SO<sub>2</sub>N-); <sup>1</sup>H nmr: δ 2.40 (s, 3H, CH<sub>3</sub>), 2.50 (s, 3H, CH<sub>3</sub>), 2.83-3.83 (dq, 2H, CH<sub>2</sub>), 4.70-5.03 (t, 1H, CH), 6.83-7.91 (m, 13H, 2 C<sub>6</sub>H<sub>4</sub> + C<sub>6</sub>H<sub>5</sub>).

#### 3-(2-Hydroxyphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole (XI).

2'-Hydroxy-4-methoxychalcone (VI) (2.54 g) and hydrazine hydrate (8 ml, 50%) treated as above gave 3-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole (XI) (2.05 g), mp 92-94°, as colourless needles from ethanol; ir: 3359 cm<sup>-1</sup> (NH), 1610 cm<sup>-1</sup> (-C=N-), 1600 cm<sup>-1</sup> (C=C); <sup>1</sup>H nmr: δ 2.96-3.66 (dq, 2H, CH<sub>2</sub>), 3.70 (s, 3H, CH<sub>3</sub>), 4.66-5.00 (t, 1H, CH), 6.70-7.36 (m, 8H, 2 C<sub>6</sub>H<sub>4</sub>). Compound XI (0.80 g) with toluenesulphonyl chloride (0.57 g) in pyridine gave 3-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1-toluenesulphonylpyrazole (XV) (0.64 g), mp 209-210°, as red plates from ethanol; ir: 3200 (OH), 1625 (-C=N-), 1600 cm<sup>-1</sup> (C=C), 1360, 1175 cm<sup>-1</sup> (-SO<sub>2</sub>N-); <sup>1</sup>H nmr: δ 2.35 (s, 3H, CH<sub>3</sub>), 2.86-3.56 (bm, 2H, CH<sub>2</sub>), 3.76 (s, 3H, CH<sub>3</sub>), 4.70-5.06 (t, 1H, CH), 6.70-7.80 (m, 12H, 3 C<sub>6</sub>H<sub>4</sub>), -0.36 (s, 1H, deuterium oxide exchangeable).

Compound XV (50 mg) with acetic acid in pyridine gave the acetate (XX) (50 mg), mp 168-170°, as pale violet needles from ethanol; ir: 1765 (COOCH<sub>3</sub>), 1610 (-C=N-), 1600 (C=C), 1370, 1170 cm<sup>-1</sup> (-SO<sub>2</sub>N-); <sup>1</sup>H nmr: δ 2.40 (s, 3H, CH<sub>3</sub>), 2.50 (s, 3H, CH<sub>3</sub>), 2.86-3.66 (m, 2H, CH<sub>2</sub>), 3.88 (s, 3H, CH<sub>3</sub>), 4.68-5.03 (t, 1H, CH), 6.83-7.83 (m, 12H, 3 C<sub>6</sub>H<sub>4</sub>).

#### 3-(2-Hydroxyphenyl)-5-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazole (XII).

2'-Hydroxy-3,4-dimethoxychalcone (VII) (2.84 g) and hydrazine hydrate (8 ml, 50%) gave 3-(2-hydroxyphenyl)-5-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazole (XII) (2.10 g), mp 120-122° as colourless needles from ethanol; ir: 3359 (NH), 1625 (-C=N-), 1598 cm<sup>-1</sup> (C=C); <sup>1</sup>H nmr: δ 3.00-3.60 (dq, 2H, CH<sub>2</sub>), 3.86 (s, 6H, 2 CH<sub>3</sub>), 4.70-5.03 (t, 1H, CH), 6.76-7.30 (m, 7H, C<sub>6</sub>H<sub>4</sub> + C<sub>6</sub>H<sub>3</sub>).

Compound XII (0.89 g) with toluenesulphonylchloride (0.57 g) in pyridine gave 3-(2-hydroxyphenyl)-5-(3,4-dimethoxyphenyl)-4,5-dihydro-1-toluenesulphonylpyrazole (XVI) (0.73 g, mp 180-181°) as red needles from ethanol; ir: 3160 (OH), 1625 (-C=N-), 1600 (C=C), 1360, 1170 cm<sup>-1</sup> (-SO<sub>2</sub>N-); <sup>1</sup>H nmr: δ 2.36 (s, 3H, CH<sub>3</sub>), 2.60-3.60 (m, 2H, CH<sub>2</sub>), 3.63 (s, 6H, 2 CH<sub>3</sub>), 4.66-5.10 (t, 1H, CH), 6.70-7.80 (m, 11H, 2 C<sub>6</sub>H<sub>4</sub> + C<sub>6</sub>H<sub>3</sub>), -0.36 (s, 1H, deuterium oxide exchangeable).

Compound XVI (50 mg) with acetic acid in pyridine gave the acetate (XX), (65 mg), mp 158-159°, as pale violet needles from ethanol; ir: 1775 (COOCH<sub>3</sub>), 1610 (-C=N-), 1600 (C=C), 1380, 1165 cm<sup>-1</sup> (-SO<sub>2</sub>N-); <sup>1</sup>H nmr: δ 2.40 (s, 3H, CH<sub>3</sub>), 2.46 (s, 3H, CH<sub>3</sub>), 3.03 (m, 2H, CH<sub>2</sub>), 3.87 (s, 3H, CH<sub>3</sub>), 3.90 (s, 3H, CH<sub>3</sub>), 4.70-5.03 (t, 1H, CH), 6.86-7.83 (m, 11H, 2 C<sub>6</sub>H<sub>4</sub> + C<sub>6</sub>H<sub>3</sub>).

#### 3-(2-Hydroxyphenyl)-5-(4-dimethylaminophenyl)-4,5-dihydro-1H-pyrazole (XIII).

2'-Hydroxy-4-dimethylaminochalcone (VIII) (2.67 g) and hydrazine hydrate (8 ml, 50%) gave 3-(2-hydroxyphenyl)-5-(4-dimethylaminophenyl)-4,5-dihydro-1*H*-pyrazole (XIII) (1.84 g), mp 110-112°, as colourless plates from ethanol; ir: 3330 (NH), 1620 (C=N-), 1595 cm<sup>-1</sup> (C=C); <sup>1</sup>H nmr: δ 2.96 (s, 6H, 2 CH<sub>3</sub>), 3.20-3.96 (m, 2H, CH<sub>2</sub>), 4.70-5.03 (t, 1H, CH), 6.66-7.36 (m, 8H, 2 C<sub>6</sub>H<sub>4</sub>). Compound XIII (0.84 g) with toluene sulphonylchloride (0.57 g) in pyridine gave 3-(2-hydroxyphenyl)-5-(4-dimethylaminophenyl)-4,5-dihydro-1-toluenesulphonylpyrazole (XVII), (0.60 g), mp 190-191°, as pale brown sandy prisms from ethanol. ir: 3160 cm<sup>-1</sup> (OH), 1625 (C=N-), 1600 (C=C), 1380, 1175 cm<sup>-1</sup> (-SO<sub>2</sub>N-); <sup>1</sup>H nmr: δ 2.33 (s, 3H, CH<sub>3</sub>), 2.86 (s, 6H, 2 CH<sub>3</sub>), 3.20-3.83 (m, 2H, CH<sub>2</sub>), 4.73-5.10 (t, 1H, CH), 6.60-7.80 (m, 12H, 3 C<sub>6</sub>H<sub>4</sub>), -0.50 (s, 1H, deuterium oxide exchangeable.)

Compound XVII (50 mg) with acetic acid in pyridine gave the acetate (XXI), (65 mg), mp 158-159°, as pale brown needles from ethanol; ir: 1765 cm<sup>-1</sup> (COOCH<sub>3</sub>), 1610 (C=N-), 1600 C=C, 1370, 1170 cm<sup>-1</sup> (-SO<sub>2</sub>N-); <sup>1</sup>H nmr: 2.40 (s, 3H, CH<sub>3</sub>), 2.46 (s, 6H, 2 CH<sub>3</sub>), 3.00 (s, 3H, CH<sub>3</sub>), 2.86-3.53 (m, 2H, CH<sub>2</sub>), 4.66-5.03 (t, 1H, CH), 7.00-7.86 (m, 12H, 3 C<sub>6</sub>H<sub>4</sub>).

#### Acknowledgement.

Thanks to Professor B. Wickberg (Organic Chemistry 2, Chemical Center, Lund) for the use of his facilities and for his stimulating discussions. The award of a fellowship by the International Seminar, University of Uppsala, is also acknowledged.

#### REFERENCES AND NOTES

- (1) Present address: Organic Chemistry 2, Chemical Center, University of Lund, Box 740, S-220 07 Lund, Sweden.
- (2) S. S. Parmar, B. R. Pandey, C. Dwivedi and R. D. Harbison, *J. Pharm. Sci.*, **63**, 1152 (1974).
- (3) V. I. Yakovenko, E. T. Oganessian, V. P. Zolniskii and V. F. Zakharov, *Khim-Farm Zh.*, **10**, 97 (1976).
- (4) A. Sammour and M. Elkasaby, *U. A. R. J. Chem.*, **13** 243 (1970).
- (5) L. Jurd, *Tetrahedron*, **31**, 2884 (1975).
- (6a) J. L. Bellamy, "The Infrared Spectra of Complex Molecules", John Wiley and Sons, Inc., New York, N. Y., 1958, p. 263; (b) p. 350.
- (7) A. Albert and R. Royer, *J. Chem. Soc.*, 1148 (1949).