Some New Phenolic Pyrazoles from 2'-Hydroxychalcones

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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.

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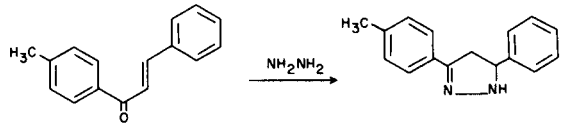
The reported anticonvulsant (2) and monoamine oxidase (MAO) inhibitory properties, and bactericidal and fungicidal activities of pyrazoles stimulated the search for newer pyrazole derivatives in this laboratory.

Hydrazine and its derivatives react with α,β-unsaturated carbonyl systems to give pyrazoles or hydrazones depending on the substituent attached to the α,β-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).

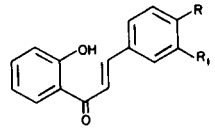


I II

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

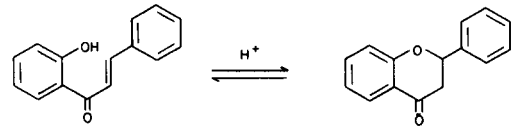
III IV

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



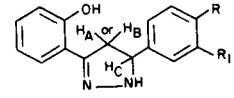
(V) R = R_1 = H
(VI) R = OCH_3; R_1 = H
(VII) R = R_1 = OCH_3
(VIII) R = $N(CH_3)_2$; R_1 = H

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.



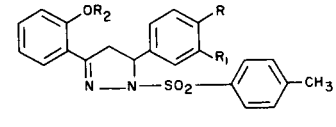
V IX

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



(X) R = R_1 = H
(XI) R = OCH_3; R_1 = H
(XII) R = R_1 = OCH_3
(XIII) R = $N(CH_3)_2$; R_1 = H

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



(XIV) R = R_1 = R_2 = H; (XV) R_1 = R_2 = H; R = OCH_3
(XVI) R = R_1 = OCH_3; R_2 = H; (XVII) R = $N(CH_3)_2$; R_1 = R_2 = H
(XVIII) R = R_1 = H; R_2 = $COCH_3$; (XX) R = OCH_3; R_1 = H; R_2 = $COCH_3$
(XX) R = R_1 = OCH_3; R_2 = $COCH_3$; (XXI) R = $N(CH_3)_2$; R_1 = H; R_2 = $COCH_3$

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Table I

Compound	Molecular Formular	Anal. Calcd. %				Anal. Found %			
		C	H	N	S	C	H	N	S
[illegible]	$C_{15}H_{14}N_2O$	75.59	5.93	11.76	-	75.40	5.84	12.00	-
XI	$C_{16}H_{16}N_2O_2$	71.60	6.02	10.45	-	71.60	6.11	10.40	-
XII	$C_{17}H_{18}N_2O_3$	68.42	6.09	9.40	-	68.29	6.10	9.47	-
XIII	$C_{17}H_{19}N_3O$	72.55	6.81	14.95	-	72.40	6.76	15.10	-
XIV	$C_{22}H_{20}N_2O_3S$	67.31	5.14	7.14	8.17	67.40	5.19	7.09	8.16
XVI	$C_{23}H_{22}N_2O_4S$	65.36	5.25	6.63	7.59	65.60	5.11	6.69	7.75
XVI	$C_{24}H_{24}N_2O_5S$	63.68	6.35	6.19	7.09	63.80	5.45	6.34	7.34
XVII	$C_{24}H_{25}N_3O_3S$	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^{-1}, the -C=N band appeared at 1625 cm^{-1}, while the -SO_2N- absorptions are at 1370 and 1175 cm^{-1}, the pyrazole acetates (XVIII-XIX) showed an intense band at 1760 cm^{-1}, which was due to the presence of an ester group. The ^1H 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_A, H_B and H_C 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. ^1H 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-1*H*-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-1*H*-pyrazole (X) (1.22 g), mp 85-86°, as colourless plates; ir: 3350 (NH), 1615 (-C=N-); 1600 cm^{-1} (C=C); ^1H nmr: δ 3.23 (dd, 1H, H_A, 17 Hz), 3.30 (dd, 1H, H_B, 14 Hz), 4.80 (t, 1H, H_C,10 Hz), 7.1 (m, 4H, 3_6H_4), 7.4 (s, 5H, C_6H_5). 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^{-1} (OH), 1625 cm^{-1} (-C=N-), 1600 cm−1 (C=C), 1370, 1175 cm−1 (-SO_2N-); ^1H nmr: δ 2.36 (s, 3H, CH_3), 3.40 (dq, 2H, CH_2), 4.60 (t, 1H, CH), 6.50-7.80 (m, 13H, 2 C_6H_4 + C_6H_5), -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 voilet needles from ethanol; ir: 1755 (-$COOCH_3$), 1610 (-C=N-), 1600 (C=C), 1380, 1170 cm^{-1} (-SO_2N-); ^1H nmr: δ 2.40 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.83-3.83 (dq, 2H, CH_2), 4.70-5.03 (t, 1H, CH), 6.83-7.91 (m, 13H, 2 C_6H_4 + C_6H_5).

3-(2-Hydroxyphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-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-1*H*-pyrazole (XI) (2.05 g), mp 92-94, as colourless needles from ethanol; ir: 3359 cm^{-1} (NH), 1610 cm^{-1} (-C=N-), 1600 cm^{-1} (C=C); ^1H nmr: δ 2.96-3.66 (dq, 2H, CH_2), 3.70 (s, 3H, CH_3), 4.66-5.00 (t, 1H, CH), 6.70-7.36 (m, 8H, 2 C_6H_4). Compound XI (0.80 g) with toluenesulphonyl chloride (0.57 g) in pyridine gave 3-(2-hydroxylphenyl)-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^{-1} (C=C), 1360, 1175 cm^{-1} (-SO_2N-); ^1H nmr: δ 2.35 (s, 3H, CH_3), 2.86-3.56 (bm, 2H, CH_2), 3.76 (s, 3H, CH_3), 4.70-5.06 (t, 1H, CH), 6.70-7.80 (m, 12H, 3 C_6H_4), -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 (-$COOCH_3$), 1610 (-C=N-), 1600 (C=C), 1370, 1170 cm^{-1} (-SO_2N-); ^1H nmr: δ 2.40 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.86-3.66 (m, 2H, CH_2), 3.88 (s, 3H, CH_3), 4.68-5.03 (t, 1H, CH), 6.83-7.83 (m, 12H, 3 C_6H_4).

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

2'-Hydroxy-3,4-dimethoxychalcone (VII) (2.84 g) and hydrazine hydrate (8 ml, 50%) gave 3-(2-hydroxyphenyl)-5-(3,4-diemthoxyphenyl)-4,5-dihydro-1*H*-pyrazole (XII) (2.10 g), mp 120-122° as colourless needles from ethanol; ir: 3359 (NH), 1625 (-C=N-), 1598 cm^{-1} (C=C); ^1H nmr: δ 3.00-3.60 (dq, 2H, CH_2), 3.86 (s, 6H, 2 CH_3), 4.70-5.03 (t, 1H, CH), 6.76-7.30 (m, 7H, C_6H_4 + C_6H_3).

Compound XII (0.89 g) with toluenesulphonylchloride (0.57 g) in pyridine gave 3-(2-hydroxy phenyl)-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^{-1} (-SO_2N-); ^1H nmr: δ 2.36 (s, 3H, CH_3), 2.60-3.60 (m, 2H, CH_2), 3.63 (s, 6H, 2 CH_3), 4.66-5.10 (t, 1H, CH), 6.70-7.80 (m, 11H, 2 C_6H_4 + C_6H_3), -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 (-$COOCH_3$), 1610 (-C=N-), 1600 (C=C), 1380, 1165 cm^{-1} (-SO_2N-); ^1H nmr: δ 2.40 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.03 (m, 2H, CH_2), 3.87 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 4.70-5.03 (t, 1H, CH), 6.86-7.83 (m, 11H, 2 C_6H_4 + C_6H_3).

3-(2-Hydroxyphenyl)-5-(4-dimethylaminophenyl)-4,5-dihydro-1*H*-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^{-1} (C=C); ^1H nmr: δ 2.96 (s, 6H 2 CH_3), 3.20-3.96 (m, 2H, CH_2), 4.70-5.03 (t, 1H, CH), 6.66-7.36 (m, 8H, 2 C_6H_4). 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^{-1} (OH), 1625 (-C=N-), 1600 (C=C), 1380, 1175 cm−1 (-SO_2N-); ^1H nmr: δ 2.33 (s, 3H, CH_3), 2.86 (s, 6H, 2 CH_3), 3.20-3.83 (m, 2H, CH_2) 4.73-5.10 (t, 1H, CH), 6.60-7.80 (m, 12H, 3 C_6H_4), -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^{-1} ($COOCH_3$), 1610 (-C=N-), 1600 C=C, 1370, 1170 cm^{-1} (-SO_2N-); ^1H nmr: 2.40 (s, 3H, CH_3), 2.46 (s, 6H, 2 CH_3), 3.00 (s, 3H, CH_3), 2.86-3.53 (m, 2H, CH_2), 4.66-5.03 (t, 1H, CH), 7.00-7.86 (m, 12H, 3 C_6H_4).

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