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Reaction of Aryl and Heterocyclylhydrazines with 2-Methylchromone: Structural Investigation of the Products

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REACTION OF ARYL AND HETEROCYCLYLHYDRAZINES WITH 2-METHYLCHROMONE : STRUCTURAL INVESTIGATION OF THE PRODUCTS

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Abstract : Reaction of 2-methylchromone (**2**) with phenylhydrazine provides 3-methyl-5-(o-hydroxyphenyl)-1-phenylpyrazole (**6**) as a major product. In contrast under similar conditions, heterocyclylhydrazines (**8a-c**) yield exclusively 5-ethyl-3-(o-hydroxyphenyl)-1-heterocyclylpyrazoles (**9a-c**). The structural assignments are based on an unambiguous synthesis and an analysis of NMR (^{1}H & ^{13}C) spectral data,

Reaction of chromone (**1**) and 2-methylchromone (**2**) with hydrazine has been reported to give 5(3)-(o-hydroxyphenyl)pyrazole[1] (**3**) and 5(3)-(o-hydroxyphenyl)-3(5)-methylpyrazole[2], respectively. Existence of tautomerism in the products does not lead to any structural ambiguity. However, treatment of **2** with monosubstituted hydrazines can, in principle, generate two isomeric products. Reaction of **2** with phenylhydrazine was first investigated by Alberti[3] who assigned the structure of the pyrazole (**5**) as having methyl group located at position-5. On the other hand, in a recent report, the reaction was

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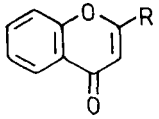
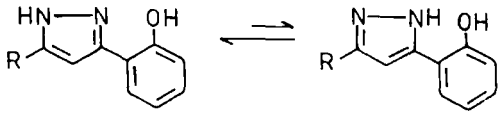
reinvestigated and a pyrazole (**6**) was assigned having methyl group located at position-3[4].



1; R = H
2; R = Me



3; R = H
4; R = Me

Interestingly in both the cases, structural assignment was not supported by any spectral evidence. In view of these contradictory literature reports and our continued interest in the structural investigation of heterocyclylpyrazoles[5,6], we focussed our attention to these structures. Thus reaction of **2** with phenylhydrazine in ethanediol containing a few drops of conc. HCl resulted in the formation of two isomeric pyrazoles in the ratio 4:1, which were separated by column chromatography. The isomers, **5** and **6** could not be differentiated on the basis of chemical shifts of methyl protons in their ^{1}H NMR spectra.

However, a careful inspection of ^{1}H NMR data reveals the following :

(i) In structure **5** there exists strong intramolecular hydrogen bonding (=N----H-O-) resulting in the significant deshielding of -OH proton (δ 10.93) as compared to **6** (δ 5.96).

(ii) Due to the presence of intramolecular hydrogen bonding in structure **5**, the pyrazole and o-hydroxyphenyl moieties exist in planar conformation about the C'$_3$-C"$_1$ bond. This leads to interaction between C'$_4$-H (pyrazole) and C"$_6$ (o-hydroxyphenyl) which get deshielded whereas in structure **6**, the

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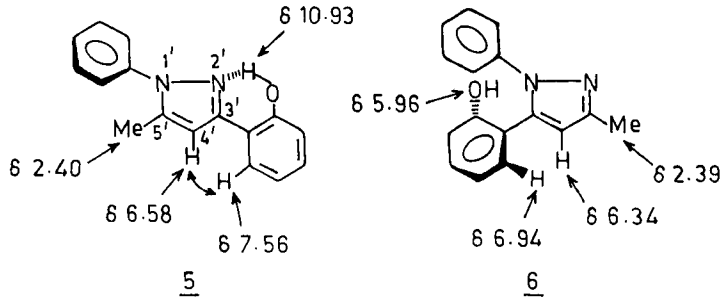

5 6

(Fig. 1)

pyrazole and o-hydroxyphenyl moieties may exist in near perpendicular geometry about C'5-C"1 bond and C'4-H and C"6-H are far removed for intraction to occur (Fig. 1). Such an assignment explains the observed chemical shift and is in line with a recent report by Elguero *et al.* while assigning the structure of similarly constituted molecules[7].

(iii) While the aromatic protons of **5** resonate at normal positions, similar protons in **6** are relatively shielded. This may be explained because of the presence of the mutual shielding effect of N-phenyl and C'5-(o-hydroxyphenyl) in **6**, caused by the geometery of the molecule.

Thus ^{1}H NMR spectral data are consistent with structures **5** and **6**. These isomers can also be differentiated by their ^{13}C NMR spectra. In case of **5** C'4 carbon resonantes at, δ 103.89 while in the case of **6** it resonates at δ 108.38 (Δδ = 4.49).

In order to provide additional evidence in favour of structure **6**, it was synthesized unambiguously by an alternate procedure involving the reaction of 1-(o-hydroxyphenyl)-1,3-butanedione (**7**) and phenylhydrazine. The product was

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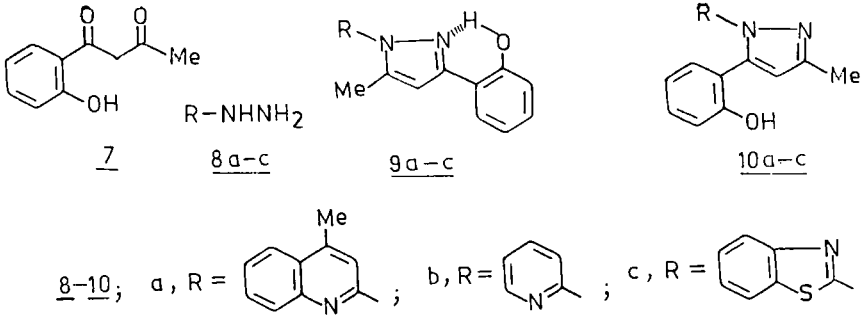
found to be identical in all respects with **6**. This reaction is based on our earlier experience of synthesizing 4,5'-bipyrazoles exclusively by treating 1-(5-hydroxy-3-methyl-1-substitutedpyrazol-4-yl)-1,3-butanedione with mono substituted hydrazines[8].

After distinguishing the isomeric structures **5** and **6** through NMR spectroscopy and the unambiguous synthesis of **6**, it was thought of interest to replace phenylhydrazine with heterocyclylhydrazines in order to extend the scope of this reaction. It is relatively much simpler to locate the position of the methyl group in heterocyclylpyrazoles through our recently observed upfield - downfield phenomenon[9].

The reaction of heterocyclylhydrazines (**8a-c**) with **2** in ethanediol afforded a single product which may be one of the two possible isomeric structures **9** or **10**. However, the products were easily chracterized as **9** on the basis of their ^{1}H NMR spectra which display the presence of the methyl group at position-5' (δ 2.66-2.85). This observation is in consonance with our earlier findings that methyl protons at position-5' resonate downfield as compared to those at position-3'.

The other isomeric products **10a-c** were obtained by the reaction of **7** and **8a-c** in ethanol containing a few drops of acetic acid which displayed the methyl protons appearing at δ 2.34-2.42 which were assigned to C'_3-CH_3.



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The structure of isomeric pairs **9a** & **10a** were further confirmed by their ^{13}C NMR spectra, which displayed a signal at δ 106.14 due to C'_4 carbon atom in **9a**. The same carbon resonates at δ 112.80 in the case of **10a** ($\Delta\delta = 6.66$).

Experimental

The melting points are uncorrected. ^1H & ^{13}C NMR spectra were recorded on Bruker-300 (300 MHz) and R-32 Perkin-Elmer (90 MHz) spectrometers. 2-Hydrazino-4-methylquinoline[10], 2-hydrazino-benzothiazole[11] and 2-methylchromone[12] were prepared according to the literature procedures, whereas 2-hydrazinopyridine was purchased from Aldrich.

Synthesis of 5-methyl-3-(o-hydroxyphenyl)-1-substituted pyrazoles (5, 9a-c)

General Procedure

To a warm solution of **2** (5 mmol) in ethanediol (40 ml), appropriate hydrazine (5 mmol) was slowly added with shaking. After the addition of a few drops of conc. HCl, the reaction mixture was heated under reflux for 4 hrs, cooled, diluted with water and extracted with chloroform (3 x 20 ml). The combined extract was dried over sodium sulfate and chloroform was distilled off. Residue so obtained was purified by a column of neutral alumina using pet. ether : ethyl acetate (9:1) as an eluent.

5 : m.p. 92°C; yield 64%; ^1H NMR ($CDCl_3$) : δ 2.40 (s, 3H, C'_5-CH_3), 6.58 (s, 1H, C'_4-H), 6.91 (t, 1H, J=7.8 & 8.2 Hz, C''_5-H), 7.02 (d, 1H, J=8.0 Hz, C''_3-H), 7.21 (t, 1H, J=7.6 & 7.8 Hz, C''_4-H), 7.39-7.43 (m, 1H, C_4-H), 7.46-7.49 (m, 4H, Ar-H), 7.56 (dd, 1H, J=7.7 & 1.5 Hz, C''_6-H), 10.94 (s, 1H, C''_2-OH, exchangeable with D_2O); ^{13}C NMR ($CDCl_3$) : δ 12.51 (C'_5-CH_3), 103.89 (C'_4),

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116.50 (C"$_1$), 117.14 (C"$_3$), 119.26 (C"$_5$), 124.66 (C_2 & C_6), 126.44 (C"$_6$), 127.98 (C_4), 129.28 (C"$_4$, C_3 & C_5), 139.19 (C_5), 139.99 (C_1), 151.59 (C'$_3$), 156.21 (C"$_2$).

The minor isomer **6** was also separated.

6 : m.p. 190°C; yield 10%; ^{1}H NMR ($CDCl_3$) : δ 2.39 (s, 3H, C'$_3$-CH_3), 5.96 (brs, 1H, C"$_2$-OH, exchangeable with D_2O), 6.34 (s, 1H, C'$_4$-H), 6.80 (t, 1H, C"$_5$-H), 6.88 (d, 1H, C"$_3$-H), 6.94 (dd, 1H, C"$_6$-H), 7.10-7.28 (m, 6H, Ar-H); ^{13}C NMR ($CDCl_3$) : δ 13.10 (C'$_3$-CH_3), 108.38 (C'$_4$), 115.59 (C"$_3$), 117.66 (C"$_1$), 118.75 (C"$_5$), 123.20 (C_2 & C_6), 125.85 (C"$_6$), 128.03 (C_4), 129.48 (C_3 & C_5), 130.59 (C"$_4$), 139.99 (C_1), 140.31 (C'$_5$), 148.51 (C'$_3$), 154.34 (C"$_2$).

9a : m.p. 130°C; yield 48%; ^{1}H NMR ($CDCl_3$) : δ 2.70 (s, 3H, C'$_5$-CH_3), 2.87 (s, 3H, C_4-CH_3), 6.55 (s, 1H, C'$_4$-H), 6.81-8.05 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$) : δ 15.19 (C'$_5$-CH_3), 19.13 (C_4-CH_3), 106.14 (C'$_4$), 114.65 (C_3), 116.26 (C"$_1$), 117.10 (C"$_3$), 119.45 (C"$_5$), 123.86 (C_5), 126.10 (C_6), 126.72 (C_{4a}), 126.89 (C"$_6$), 129.27 (C_7), 129.75 (C_8), 129.93 (C"$_4$), 142.75 (C'$_5$), 146.14 (C_4), 147.46 (C_{8a}), 151.12 (C_2), 151.99 (C'$_3$), 156.28 (C"$_2$); Found N, 13.43 $C_{20}H_{17}N_3O$ requires 13.33.

9b : m.p. 75°C; yield 48%; ^{1}H NMR ($CDCl_3$) : δ 2.66 (s, 3H, C'$_5$-CH_3), 6.48 (s, 1H, C'$_4$-H), 6.72-7.31 (m, 4H, Ar-H), 7.48 (ddd, 1H, C"$_6$-H), 7.71 (dd, 2H, C_3-H & C_4-H), 8.35 (dd, 1H, C_6-H); Found N, 16.67 $C_{15}H_{13}N_3O$ requires 16.73.

9c : m.p. 182-3°C; yield 59%; ^{1}H NMR ($CDCl_3$) : δ 2.85 (s, 3H, C'$_5$-CH_3), 6.58 (s, 1H, C'$_4$-H), 6.75-7.58 (m, 6H, Ar-H), 7.72-7.95 (m, C_4-H & C_7-H); Found N, 13.87 $C_{17}H_{13}N_3OS$ requires 13.68.

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Synthesis of 3-methyl-5-(o-hydroxyphenyl)-1-substituted pyrazoles (10a-c)

General Procedure

A mixture of an appropriate hydrazine (3 mmol) and 1-(o-hydroxyphenyl)-1,3-butanedione (7, 3 mmol) in ethanol (40 ml) containing a few drops of acetic acid was refluxed for 3 hrs. Excess of ethanol was distilled off and the residue was kept at room temperature. The solid so obtained was filtered and dried.

10a : m.p. 225°C; yield 79%; ^{1}H NMR ($CDCl_3$) : δ2.42 (s, 3H, C'$_3$-CH_3), 2.72 (s, 3H, C_4-CH_3), 6.28 (s, 1H, C'$_4$-H), 6.80-8.10 (m, 9H, Ar-H); ^{13}C NMR ($CDCl_3$) : δ 13.77 (C'$_3$-CH_3), 19.13 (C_4-CH_3), 112.80 (C'$_4$), 117.02 (C"$_3$), 120.63 (C"$_5$ & C_3), 122.18 (C"$_1$), 123.90 (C_5), 126.68 (C_6), 126.92 (C_{4a}), 127.43 (C"$_6$), 130.62 (C"$_4$), 131.03 (C_7), 132.50 (C_8), 142.72 (C_4), 144.43 (C'$_5$), 149.27 (C_{8a}), 150.73 (C_2), 151.39 (C'$_3$), 156.12 (C"$_2$); Found N, 13.03 $C_{20}H_{17}N_3O$ requires 13.33.

10b : m.p. 163°C; yield 65%; ^{1}H NMR ($CDCl_3$) : δ 2.36 (s, 3H, C'$_3$-CH_3), 6.24 (s, 1H, C'$_4$-H), 6.70-7.90 (m, 8H, Ar-H); Found N, 16.13 $C_{15}H_{13}N_3O$ requires 16.73.

10c : m.p. 177°C; yield 80%; ^{1}H NMR ($CDCl_3$) : δ 2.34 (s, 3H, C'$_3$-CH_3), 6.19 (s, 1H, C'$_4$-H), 6.77-7.40 (m, 6H, Ar-H), 7.73-7.59 (m, 2H, C_4-H & C_7-H); Found N, 13.57 $C_{17}H_{13}N_3OS$ requires 13.68.

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