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New heterocyclic derivatives of 3-formyl-4-hydroxycoumarin

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Condensation of 4-hydroxy-2-oxo-2*H*-[1]benzopyran-3-carboxaldehyde **1** with triacetic acid lactone **2,** 5, 5-dimethylcyclohexan-1,3-dione **5** and 3-methyl-1-phenyl-5-pyrazolone **7** in refluxing ethanol affords 3-acetoacetylpyrano[3,2-*c*][1]benzopyran-2,5-dione **3**, 7-(4-hydroxycoumarin-3-yl)-10,10-dimethyl-8-oxo-8,9, 10,11-tetrahydropyrano [3,2-*c*] coumarin **6** and methylidine-bis-4,4' -[3-methyl-5-oxo-1-phenylpyrazole] **9**. Pyrazoles **4a**,**b** and isoxazole **4c** are obtained by treatment of **3** in acetic acid with hydrazine, phenylhydrazine and hydroxylamine. Structures of all these compounds have been established by IR, ^{1}H NMR and mass spectral data.

Keywords: 3-Formyl-4-hydroxycoumarin, 3-acetoacetylpyrano[3,2-*c*][1]benzopyran-2,5-dione, pyranopyrazoles, isoxazole, 7-(4-hydroxycoumarin-3-yl)-10,10-dimethyl-8-oxo-8,9, 10,11-tetrahydropyrano [3,2-*c*] coumarin

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Much interest has been shown in pyranocoumarin and 3-substituted coumarin derivatives due to their pronounced pharmacological activities[1-3]. Pyranocoumarins are important heterocycles and various natural analogues have been isolated from plants[4]. Pyranopyrones have been much studied by Scott *et al.*[5] who converted it to biogenetically important compounds such as orcinol and other phenolic compounds under basic conditions. Dimeric coumarins such as dicoumarols have been shown to possess anticoagulant properties[6].

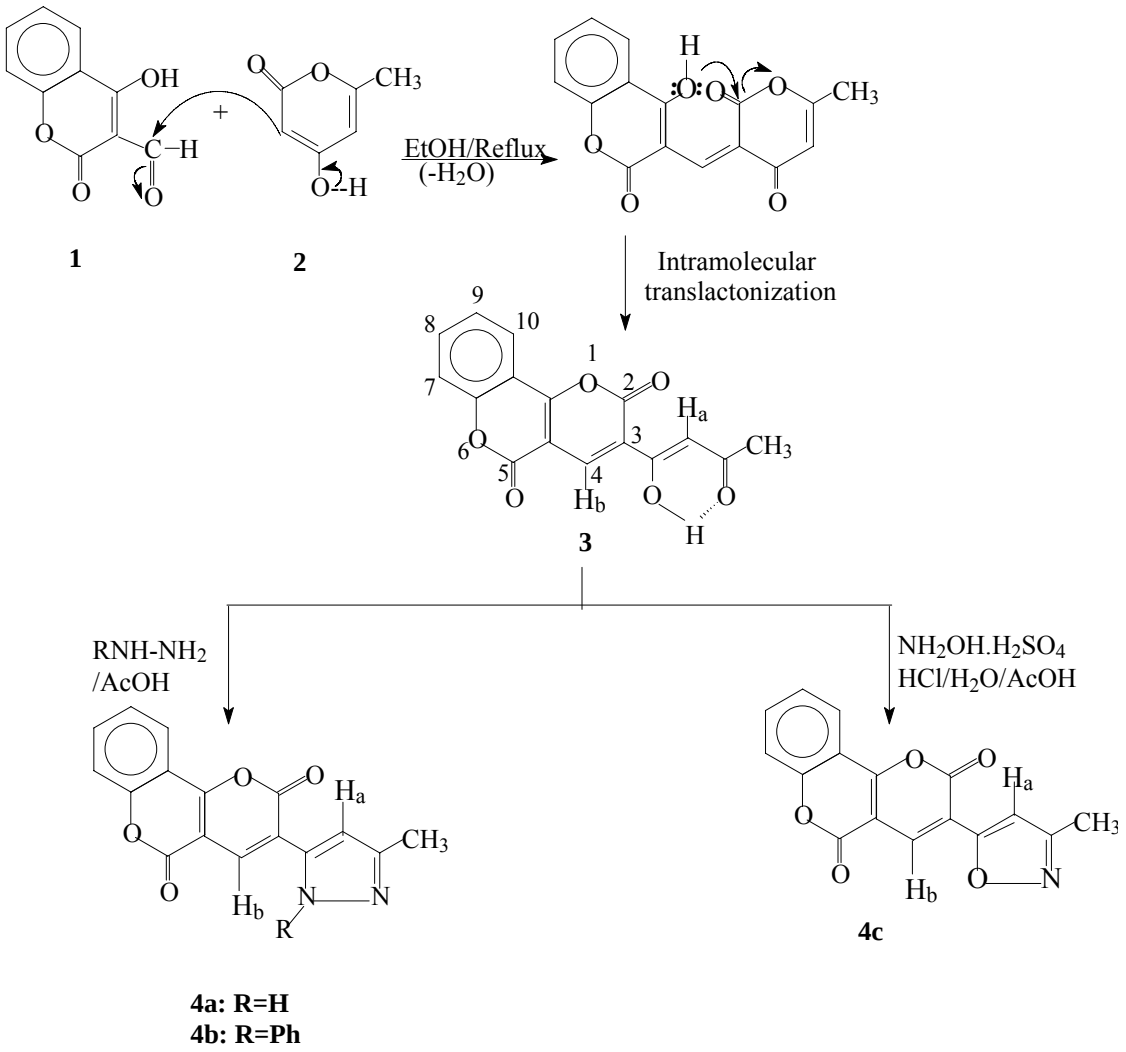
In continuation of the work on functionalization of coumarins and chromones[7-8], it was of interest to synthesize new heterocycles incorporating pyrazole and isoxazole moieties in pyranocoumarins which may exhibit much better or different types of biological properties. It is pertinent to mention that pyrazoles and isoxazoles exhibit a variety of biological properties such as antipyretic[9], analgesic[9], fungicidal[10], antimicrobial[11] and peptide deformylase inhibitor[12]. 4-Hydroxycoumarins possessing a formyl group in the 3-position are useful synthons for the synthesis of heterocyclic compounds[13]. In the present study 3-formyl-4-hydroxycoumarin was selected for the synthesis of pyranocoumarin, pyranopyrazoles, pyranoisoxazole and dimeric coumarin derivatives with the involvement of active methylene compounds.

3-Formyl-4-hydroxycoumarin is comparable in acidity to acetic acid. It is labile under strongly acidic or basic conditions. Therefore, condensation reactions with active methylene compounds such as triacetic acid lactone, 5,5-dimethylcyclohexan-1,3-dione and 3-methyl-1-phenyl-5-pyrazolone could be carried out under mild conditions.

Results and Discussion

In a series of papers Spanish workers have discussed that salicylaldehyde reacts with enol lactones to give rearranged product through intramolecular translactonization[14].. Similar type of rearrangement was observed when 3-formyl-4-hydroxycoumarin **1** was treated with triacetic acid lactone **2** in alcohol and the reaction mixture afforded **3** (**Scheme I**).

The structure of compound **3** was established on the basis of IR, ^{1}H NMR and MS studies. It showed strong bands at 1760, 1730 cm^{-1} due to enol lactone, coumarin carbonyl groups and at 1640 cm^{-1} due to chelated carbonyl group. In the ^{1}H NMR spectrum three singlets at δ 2.30, 7.11 and 8.52 were assigned to a methyl group, and olefinic protons H_a and H_b respectively. Four aromatic protons of coumarin moiety appeared as a multiplet between δ 7.2-8.2. The presence of acetoacetyl group at 3-position was confirmed by characteristic test with ferric chloride, a broad

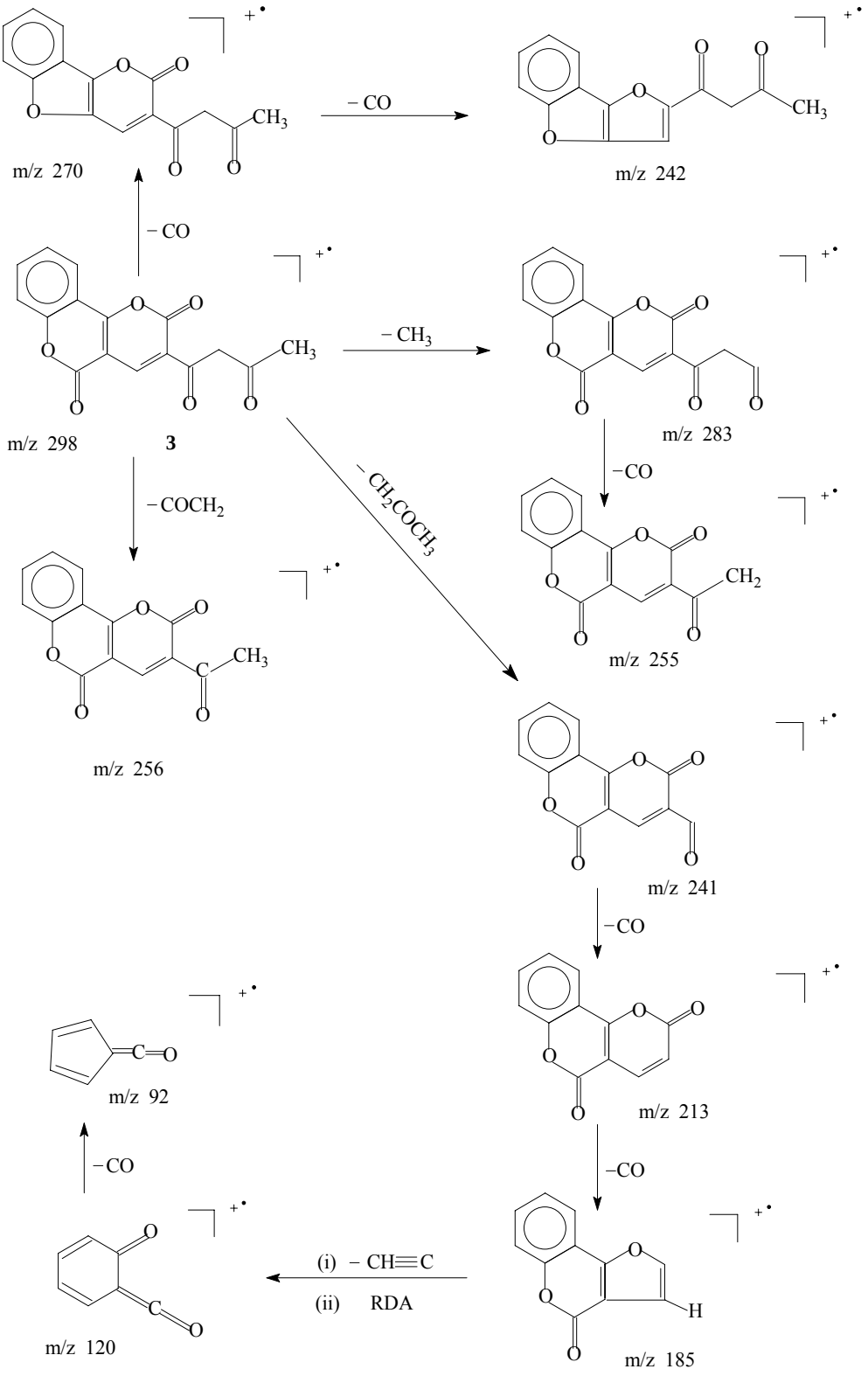


Scheme I

singlet at δ 10.5 due to OH group in the ^{1}H NMR spectrum and loss of -CH_2COCH_3- grouping from M^+ m/z 298 to give base peak at m/z 241. **(Scheme II** for mass fragmentation)

Refluxing of compound **3** in acetic acid with hydrazine hydrate, phenyl hydrazine and hydroxylammonium sulfate yielded pyrazoles **4a**,**b** and isoxazole **4c**. The IR spectra of these compounds showed strong bands for lactone and coumarin carbonyl groups at 1760 and 1726 cm^{-1}. This suggested that during the reaction with nitrogen bases, only acetoacetyl group participated in the formation of these compounds. The ^{1}H NMR spectrum of compound **4a** showed methyl singlet at δ 2.35 and two singlets for olefinic protons H_a and H_b at δ 6.75 and 7.71 respectively. A broad singlet for NH was clearly shown at δ 8.61 which was D_2O exchangeable. Further confirmation of structures **4a-c** was provided by their mass spectra showing M^+ at m/z 294, 370 and 295.

When an ethanolic solution of **1** and 5,5-dimethylcyclohexan-1,3-dione **5** was refluxed for 30 min, it yielded **6**. The structure of compound **6** was determined on the basis of spectral studies. It showed bands at 1724 cm^{-1} for coumarin and 1612 cm^{-1} for C=C functional groups in IR spectrum. In the ^{1}H NMR spectrum, appearance of two methyl singlets at δ 1.11, 1.18, two double doublets of H-5', H-1 protons of coumarin moieties at δ 8.02, 7.92 and a singlet for


m/z 270
− CO
m/z 242
− CO
m/z 298
3
− CH3
m/z 283
−CO
m/z 255
−COCH2
− CH2COCH3
m/z 256
m/z 241
−CO
m/z 213
−CO
m/z 185
(i) − CH≡C
(ii) RDA
m/z 120
−CO
m/z 92

Scheme II

methine proton at δ 5.1 suggested involvement of two coumarin moieties in the formation of product **6**. Structure **6** was further confirmed by its mass spectrum which showed M^+ at m/z 456. Loss of 4-hydroxycoumarin fragment from M^+ led to the formation of base peak at m/z 295.

The condensation reaction of **1** with 3-methyl-1-phenyl-5 pyrazolone **7** in ethanol was carried out with the hope of getting **8**. The reaction, however, did not give the expected product; instead it afforded **9**. The IR spectrum of compound **9** did not show any band for coumarin carbonyl group. Besides, there was no characteristic signal for H-5 proton of coumarin moiety in its ^{1}H NMR spectrum. It seems that only aldehydic group of **1** reacted with **7** to give the dimeric product **9** which was further supported by its synthesis from **7** and triethylorthoformate containing a catalytic amount of *p*-toluenesulfonic acid (PTS) (**Scheme III**).

The work on analgesic, antipyretic, antiinflammatory and antibacterial activities of compounds **3** and **4a-c** is in progress.

Experimental Section

Melting points were taken in open capillaries and are uncorrected. The IR spectra were recorded on FT-IR spectrometer 2020. ^{1}H NMR spectra were recorded on Bruker DRX-300 spectrometer using TMS as internal standard and mass spectra on Jeol SX-102 (FAB).

3-Acetoacetylpyrano [3,2-*c*] [1] benzopyran-2,5-dione, 3.

1 (1.0 g, 5.3 mmoles) and **2** (0.65 g, 5.1 mmoles) were taken in ethanol (20 mL) and refluxed for 0.5 h. On cooling, a yellow solid **3** was obtained. It was filtered, washed with ethanol and purified by recrystallization from chloroform. Yield 1.2 g (72%), m.p. 242-43°C; IR (KBr): 3500, 1760, 1730, 1640 and 1550 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.30 (s, 3H, CH_3), 7.11 (s, 1H, H_a), 7.23-8.21 (m, 4H, Ar-H), 8.52(s, 1H, H_b), 10.5 (br s, 1H,); MS: m/z (%) 298 (M^+, 47), 283 (10), 270 (5), 256(10), 255(10), 242(20), 241(100), 213(10), 185(25), 120(35) and 92(30).

3-(3-Methyl pyrazol-5-yl)-pyrano [3, 2-*c*] [1] benzopyran-2,5-dione, 4a.

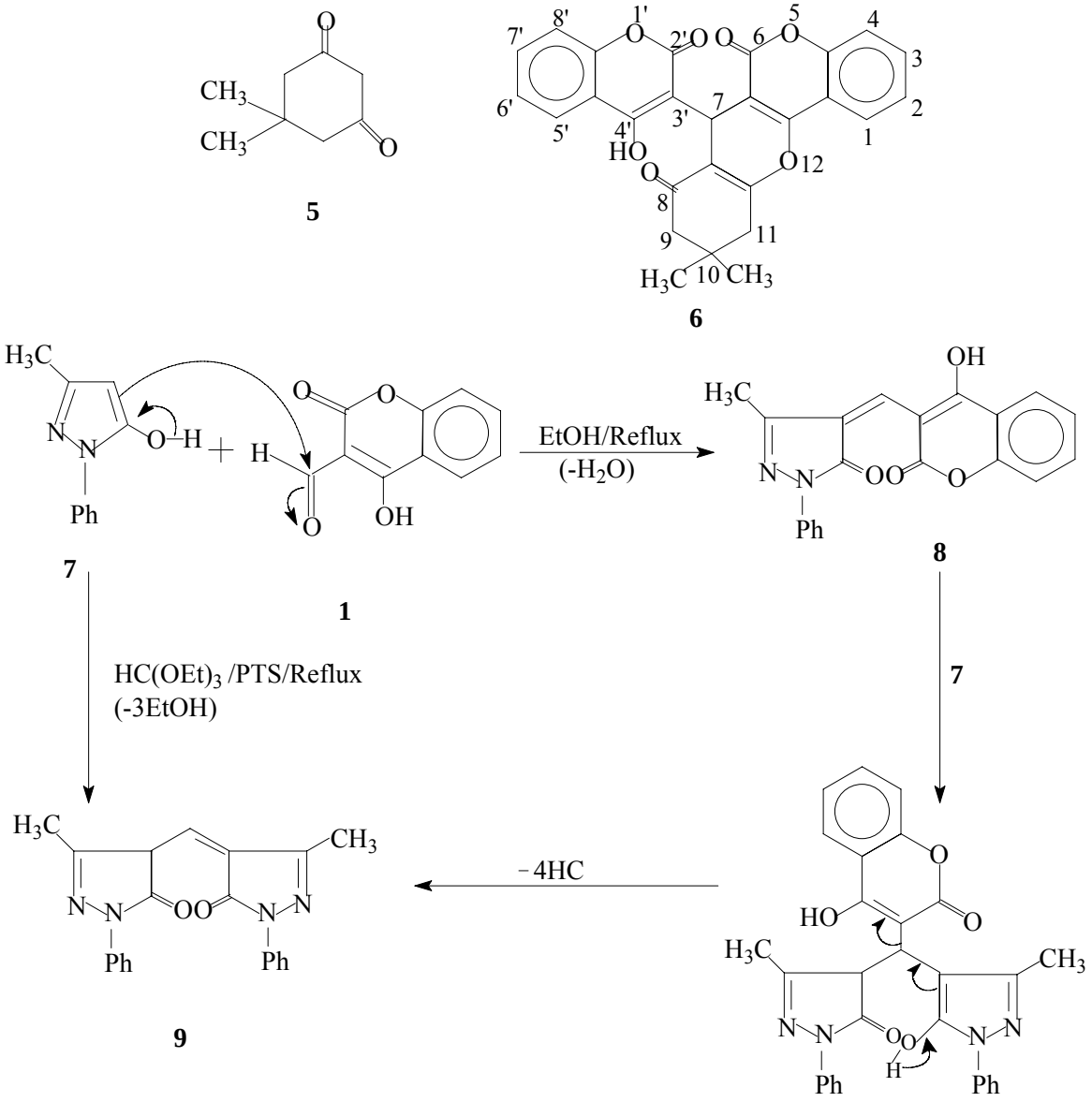
3 (1.0 g, 3.3 mmoles) was dissolved in acetic acid (20 mL) and hydrazine hydrate (1 mL, 20.2 mmoles) added to it. The reaction mixture was refluxed for 1 h on an oil bath. On cooling, a light yellow solid **4a** was obtained. It was filtered, washed with water and dried. The filtrate was poured into crushed ice-water (50 mL) when more **4a** was collected by filtration. The two solids were combined and purified by recrystallization from chloroform-benzene mixture as yellow shining needles. Yield 1.43 g (70%), m.p. 135-40°C; IR (KBr): 3250, 1767, 1711, 1628 and 1557 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, CH_3), 6.75 (s, 1H, H_a), 7.16-8.11 (m, 4H, Ar-H), 7.71 (s, 1H, H_b), 8.61 (br s, NH); MS: m/z (%) 294 (M^+ 20), 293 (20), 279 (5) 253 (5), 161 (20), 153 (100), 137 (50), 133 (40), 120 (20) and 104 (10).

3-(3-Methyl-1-phenyl pyrazol-5-yl)-pyrano [3,2-*c*] [1] benzopyran-2,5-dione, 4b.

3 (1.0 g, 3.3 mmoles) was taken in acetic acid (20 mL) and phenylhydrazine (1 mL, 10.2 mmoles) added to it. The reaction mixture was refluxed for 1 h on an oil bath. On cooling to RT a yellow solid was obtained. It was filtered, washed with water and dried. The filtrate was poured into crushed ice-water (50 mL) when more **4b** was obtained. The two solids were combined and purified by recrystallization from chloroform. Yield 1.36 g (65%), m.p. 225-30°C; IR (KBr): 1760, 1726, 1637 and 1565 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3), 6.59 (s, 1H, H_a), 7.35-8.04 (m, 9H, Ar-H), 7.81 (s, 1H, H_b); MS: m/z (%) 370 (M^+ 100), 369 (20), 329 (5), 213 (5), 185 (10), 181 (5), 161 (30), 157 (30), 153 (70), 137 (50), 133 (40), 120 (30), 104 (30) and 92 (35).

3-(3-Methyl isoxazol-5-yl)-pyrano [3,2-*c*] [1] benzopyran-2,5-dione, 4c.

Hydroxylammonium sulfate (0.54 g, 3.3 mmoles) was dissolved in 15 mL of water and 10 drops of dil HCl were added to it. This solution was added to **3** (1.0 g, 3.3 mmoles) dissolved in 10-12 mL of acetic acid. The reaction mixture was refluxed on an oil bath for 1 h. The pale yellow crystalline solid **4c** which was obtained on cooling was filtered, washed with cold water and dried. Yield 1.08 g (70%), m.p. 230°C; IR (KBr): 1765, 1725, 1628, 1603, 1566 and 1555 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 6.98 (s, 1H, H_a), 7.44-8.14 (m, 4H, Ar-H), 8.67 (s, 1H, H_b); MS: m/z (%) 295 (M^+, 50), 254 (20), 213 (10), 185 (10), 157 (100), 134 (75), 120 (25), 106 (40) and 76 (30).



Scheme III

7-(4-Hydroxycoumarin-3-yl)-10,10-dimethyl-8-oxo-8, 9, 10, 11-tetrahydro pyrano[3,2-*c*] coumarin, 6.

A mixture of **1** (1.0 g, 5.3 mmoles) and **5** (0.72 g, 5.1 mmoles) was refluxed in ethanol (20 mL) for 1 h. The cream coloured solid **6** which was obtained on cooling was filtered, washed with ethanol and purified by recrystallization from chloroform. Yield 1.03 g (60%), m.p. 240-45°C; IR (KBr): 1724, 1612, 1369, 1304, 1199, 1037 and 754 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.11 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 2.36 (s, 2H), 2.38 (s, 2H), 5.113 (s, 1H), 7.17-7.94 (m, 6H, Ar-H), 8.024 (dd, 1H, H-5', J = 7.8, 1.2 Hz), 7.92 (dd, 1H, H-1, J = 7.8, 1.2 Hz), 10.55 (br s, 1H); MS: m/z (%) 456 (M^+, 40), 335 (20), 307 (5), 295 (100), 239 (25), 121 (4) and 107 (10).

Methylidene-bis-4,4'-(3-methyl-5-oxo-1-phenyl pyrazole), 9.

1 (1 g, 5.3 mmoles) was dissolved in ethanol (15 mL) and **7** (0.9 g, 5.2 mmoles) added to it. The reaction mixture was refluxed for 10-12 h. The yellow

solid **9** which was obtained on cooling was filtered, washed with ethanol and purified by recrystallization from chloroform or benzene[15]. Yield 1.17 g (61.5%), m.p. 182-85°C; IR (KBr): 3350, 1627, 1592, 1550, 1498 and 1328 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.32 (s, 6H, CH_3), 7.26-7.92 (m, 11H, Ar–H + methylene proton); MS: m/z (%) 358 (M^+, 100), 357 (50), 340 (5), 281 (6), 117 (4), 104 (4), 90 (20) and 77 (35).

To refluxing moist triethylorthoformate (40 mL) containing a catalytic amount of *p*-toluene sulfonic acid, was added **7** (0.8 g) in portions during 0.5 h. The additions were so regulated that no solid remained before further addition was made. After complete addition the refluxing was continued for another 15 min, when yellow crystals of **9** were obtained on cooling. It was filtered, washed with ether and purified by recrystallization from benzene, 0.6 g (75%).

Conclusion

In the present study has been described synthesis of pyranocoumarin derivatives and dimeric coumarin derivative from 3-formyl-4-hydroxycoumarin. The method of synthesis is simple and convenient. Novel heterocyclic compounds are thus obtained in almost quantitative yield and short time period.

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