

Search for physiologically active compounds

Part XXVII. Synthesis of 2-[4-(1, 3-diphenyl)-pyrazolyl]-3-methoxychromones

K. R. S. REDDY, G. SRIMANNARAYANA AND N. V. SUBBA RAO

Department of Chemistry, University College of Science, Osmania University,
Hyderabad 500007

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ABSTRACT

The synthesis of 2-[4-(1, 3-diphenyl)-pyrazolyl]-3-hydroxychromones has been carried out by AFO oxidation of 2-hydroxy-[4-(1, 3-diphenyl)-pyrazolylidene]-acetophenones. The pyrazolylidene acetophenones have been prepared by the condensation of *o*-hydroxyacetophenones with 1, 3-diphenyl-pyrazole-4-carboxaldehyde under alkaline conditions. The 3-hydroxy chromones have been converted to their methyl ethers for testing their physiological properties. The structures of these compounds have been established by their analytical and spectral characteristics. All the compounds have been tested against bacteria and fungi and among them, 2-[4-(1, 3-diphenyl)-pyrazolyl]-3-methoxy chromone is found to be active at 20 ppm against *Bacillus subtilis*.

A NUMBER of 2-heterocyclic substituted chromones were found to have interesting physiological properties. Devitt and coworkers¹ found that some 2-(2-furyl) and 2-(3-pyridyl) chromones possess anti-tumor, cardio vascular and coronary vasodilating properties. 6-chloro-2-(2-quinolyl)-chromone (I) exhibited anti-cancer activity² against *Sarcoma-180*. A number of aza-chalcones were also found to be active against *Staphylococcus aureus* and *Bacillus coli*³. These considerations prompted us to synthesise a number of 2-(4-pyrazolylidene)-acetophenones and 2-(4-pyrazolyl)-3-hydroxychromones along with their methyl ethers to evaluate their bacteriostatic and fungistatic activity. It may be mentioned that antipyrene (II), possessing pyrazole ring, is widely used as an antipyretic and analgesic.

Algar-Flynn-Oyamada (AFO)^{4, 5} oxidation is a widely used reaction for the conversion of 2'-hydroxychalcones to 3-hydroxyflavones. AFO reaction has also been successfully applied to the synthesis of a number of 2-heterocyclic-3-hydroxychromones from the corresponding heterocyclic

substituted chalcones^{6, 7}. However, 2-pyrazolyl chromones do not seem to have been synthesised.

AFO reaction has now been employed to synthesise 2-[4-(1, 3-diphenyl)-pyrazolyl]-3-hydroxychromones. 1,3-Diphenyl-pyrazole-4-carboxaldehyde (IV) has been prepared, following the procedure⁸ reported earlier, by the treatment of acetophenone phenylhydrazone with two moles of phosphorous oxychloride-dimethyl formamide adduct, followed by hydrolysis with dilute alkali. Condensation of the aldehyde (IV) successively with simple 2-hydroxy acetophenone (III A), 5- or 4- or 3-methyl-substituted-2-hydroxyacetophenones (III B-III D) respectively and 2-hydroxy-4-methoxyacetophenone (III E) under Claisen reaction conditions in 50% aq. alkaline medium at room temperature furnished the corresponding 2-hydroxy-[4-(1, 3-diphenyl)pyrazolyldine]-acetophenones (VA-VE) in good yields. The pyrazolyldine acetophenones on oxidation with hydrogen peroxide in 20% alkali at room temperature, under AFO reaction conditions have been found to give rise to appropriately substituted 3-hydroxychromones (VI A-VI E) in fairly good yields (35-50%) which on subsequent methylation with dimethyl sulphate, potassium carbonate and acetone gave the corresponding 3-methoxychromones (VII A-VII E). However, 4, 6-dimethoxy-2-hydroxyacetophenone, on adopting the same procedure of condensation with pyrazole aldehyde (IV) yielded 2-hydroxy-4, 6-dimethoxy-[4-(1, 3-diphenyl)-pyrazolyldine]-acetophenone (VIII), which on subsequent alkaline hydrogen peroxide oxidation (AFO) resulted in the formation of 4, 6-dimethoxy-2-[4-(1, 3-diphenyl)-pyrazolyldine]-coumaran-3-one (IX). The spectral characteristics presented in table 1 support the assigned structures to the various compounds synthesised in the investigation⁹.

In the nmr spectrum of one of the compounds, 2-[4-(1, 3-diphenyl)-pyrazolyl]-3-methoxychromone (VII A) taken in trifluoro acetic acid, the methoxy protons appear at δ 3.60 (s, 3H) and the aromatic protons appear at δ 7.24-7.27 (m, 15H) as a complex multiplet. The ratio between methoxy protons and aromatic protons, which is 1 : 5, is in good agreement with the proposed structure.

In the mass spectrum of 2-[4-(1, 3-diphenyl)-pyrazolyl]-3-methoxychromone (VII A) (Chart 2), the molecular ion peak has been observed at M^+ 394, which itself is the base peak. The most significant breakdown is due to retro-Diels Alder fragmentation with proton transfer, of the parent molecular ion giving rise to two fragments m/e 121 and m/e 273. The other prominent peak of structural significance is an even electron ion m/e 393, ($M-1$). The fragment ion m/e 317 may be due to the loss of phenyl group from the parent molecular ion. The ion m/e 351 is likely to arise by the successive loss of methyl radical and carbon monoxide from the molecular ion.

Table 1. Compounds reported in this paper and their spectral characteristics

Compound and Structure	mp °C	Yield %	Molecular formula	Found			Required			uv data		ir C=O $\nu_{\text{cm}^{-1}}$
				C%	H%	N%	C%	H%	N%	Band-II $\lambda_{\text{EtOH}}^{\text{max}}$	Band-I nm (log ϵ)	
I. 2-Hydroxy-[4-(1, 3-di-phenyl)-pyrazolylidene]-acetophenones:												
(a) Unsubstituted	.. (V A)	80	C ₂₄ H ₁₈ N ₂ O ₂	78.42	4.62	7.64	78.68	4.92	7.65	275 (4.32)	363 (4.37)	1630
(b) 5-methyl	.. (V B)	80	C ₂₅ H ₂₀ N ₂ O ₂	78.80	5.13	7.35	78.94	5.26	7.37	259 (4.58)	370 (4.32)	1630
(c) 4-methyl	.. (V C)	75	C ₂₅ H ₂₀ N ₂ O ₂	78.85	5.10	7.36	78.94	5.26	7.37	278 (4.19)	365 (4.34)	1650
(d) 3-methyl	.. (V D)	75	C ₂₅ H ₂₀ N ₂ O ₂	78.85	5.25	7.36	78.94	5.26	7.37	277 (4.39)	367 (4.35)	1640
(e) 4-methoxy	.. (V E)	70	C ₂₅ H ₂₀ N ₂ O ₂	75.68	4.95	7.00	78.75	5.05	7.07	277 (4.44)	365 (4.47)	1645
(f) 4, 6-dimethoxy	.. (VIII)	75	C ₂₆ H ₂₂ N ₂ O ₄	73.11	4.98	6.53	73.24	5.16	6.57	252 (4.71)	365 (4.45)	1634
II. 2-[4-(1, 3-diphenyl)-pyrazolyl]-3-hydroxy-chromones:												
(a) unsubstituted	.. (VI A)	50	C ₂₅ H ₁₆ N ₂ O ₃	75.75	4.28	7.37	75.78	4.21	7.35	248 (4.83)	355 (4.68)	1610
(b) 6-methyl	.. (VI B)	35	C ₂₅ H ₁₈ N ₂ O ₃	76.02	4.45	7.01	76.14	4.57	7.11	250 (4.65)	353 (4.27)	1623
(c) 7-methyl	.. (VI C)	40	C ₂₅ H ₁₈ N ₂ O ₃	76.05	4.40	7.04	76.14	4.57	7.11	248 (4.53)	348 (4.25)	1626
(d) 8-methyl	.. (VI D)	35	C ₂₅ H ₁₈ N ₂ O ₃	76.03	4.45	7.04	76.14	4.57	7.11	249 (4.56)	354 (4.30)	1624
(e) 7-methoxy	.. (VI E)	50	C ₂₅ H ₁₆ N ₂ O ₄	73.00	4.21	6.81	73.16	4.39	6.83	272 (4.48)	364 (4.03)	1621
III. 2-[4-(1, 3-diphenyl)-pyrazolyl]-3-methoxy-chromones:												
(a) unsubstituted	.. (VII A)	90	C ₂₅ H ₁₈ N ₂ O ₄	76.00	4.41	7.15	76.14	4.57	7.11	242 (4.56)	325 (4.28)	1620
(b) 6-methyl	.. (VII B)	75	C ₂₅ H ₂₀ N ₂ O ₄	76.39	4.70	6.87	75.47	4.90	6.86	249 (4.59)	324 (4.35)	1629
(c) 7-methyl	.. (VII C)	85	C ₂₆ H ₂₀ N ₂ O ₄	76.41	4.75	7.83	76.47	4.90	6.85	242 (4.46)	317 (4.25)	1634
(d) 8-methyl	.. (VII D)	70	C ₂₆ H ₂₀ N ₂ O ₄	76.45	4.70	6.85	76.47	4.90	6.86	247 (4.43)	321 (4.16)	1631
(e) 7-methoxy	.. (VII E)	90	C ₂₆ H ₂₀ N ₂ O ₄	73.42	4.62	6.65	73.58	4.72	6.60	274 (4.35)	345 (4.26)	1618
IV. 4, 6-dimethoxy-2-[4-(1, 3-diphenyl)-pyrazolyl]-idene]-coumaran-3-one												
(IX)	245-6	45	C ₂₈ H ₂₀ N ₂ O ₄	73.43	4.62	6.54	73.58	4.72	6.60	284 (4.21)	394 (4.36)	1701

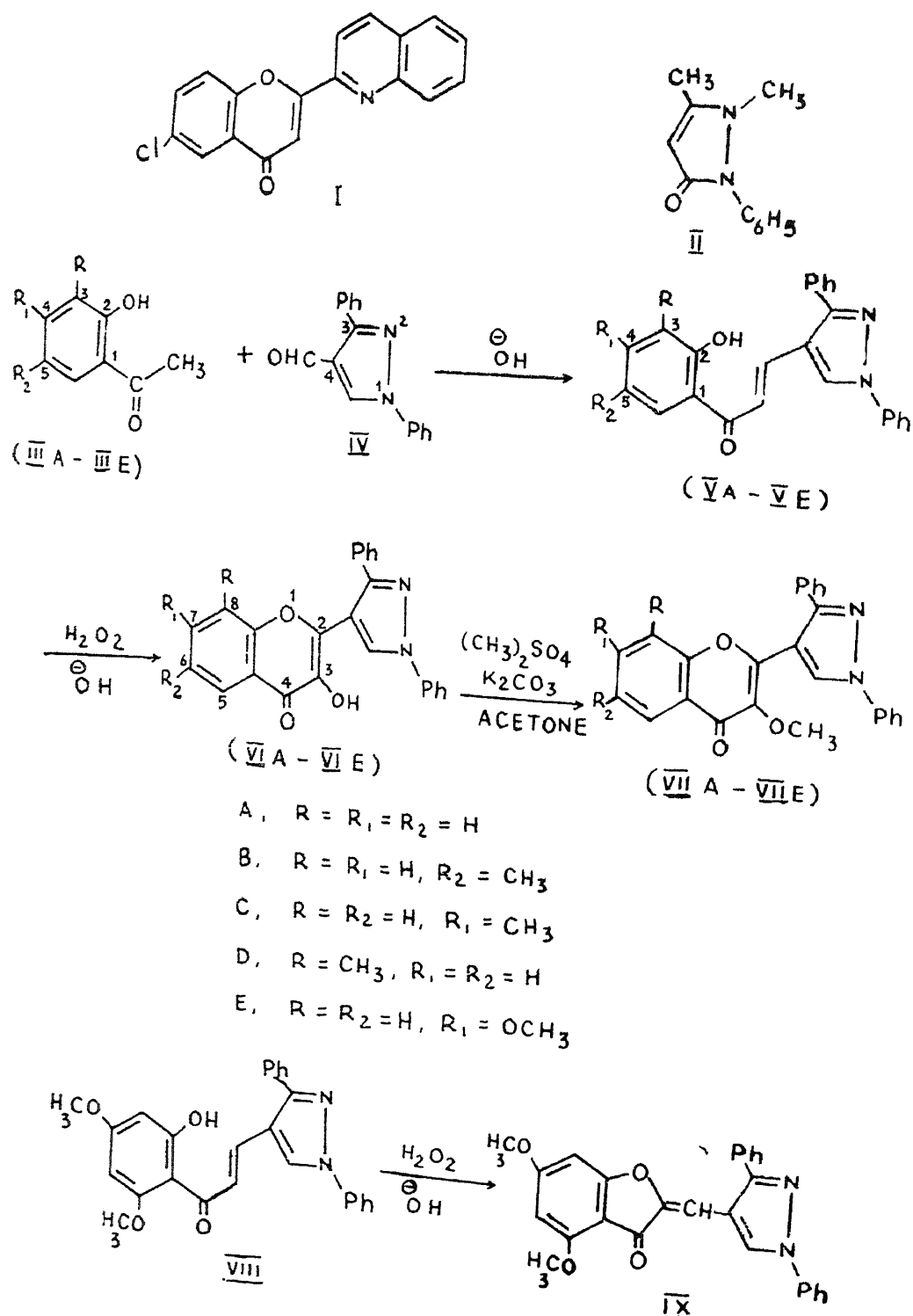


Chart 1

All the above compounds have been tested for antibacterial properties against *Staphylococcus aureus*, *Bacillus coli* and *Bacillus subtilis* as test organisms, using the tube dilution method. The compound VII A is found to be active even at 20 ppm concentration against *B. subtilis*. Some of the other compounds are active only at 100 ppm concentration. Fungistatic activity of all the compounds has been ascertained against *Aspergillus niger*

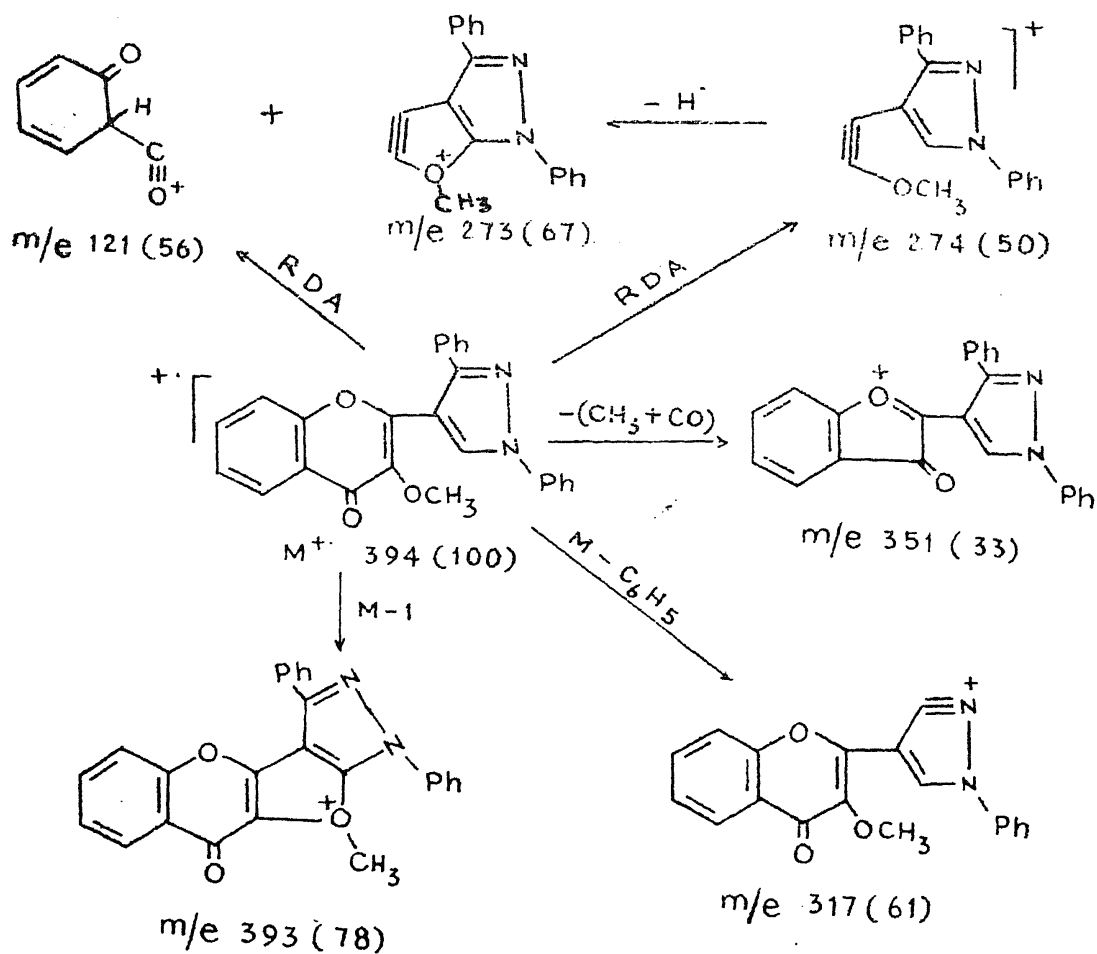


CHART-2

using *plate method*. Some of the compounds (VI B, VI E, VII B, VII E and VIII) inhibited the growth of *A. niger* to the extent of about 50% at 100 ppm.

EXPERIMENTAL

The mp's are uncorrected. The uv spectra of the compounds synthesised were recorded on Beckman-DB spectrophotometer using alcohol as solvent. The ir absorption spectra were recorded on Perkin-Elmer 337 Infrared double beam spectrophotometer equipped with sodium chloride cells using chloroform as a solvent. The nmr spectrum of VII A was run on Varian 60 MHz in trifluoro acetic acid using TMS as an internal standard.

- (1) 2-Hydroxy - [4-(1,3-diphenyl)-pyrazolylidene]-acetophenones (VA-VE and VIII) (General Procedure)

The 2-hydroxyacetophenones (0.01 mole) and 1, 3-diphenyl-pyrazole-4-carboxaldehyde (0.01 mole) were dissolved in alcohol (20 ml) and pyri-

dine (10 ml) and then sodium hydroxide (20 ml, 50%) was added drop wise, while shaking. After keeping the reaction mixture for 8 hr, at room temperature, it was acidified with acetic acid, filtered and washed with water. The bright yellow product was recrystallised from acetone-methanol (1 : 1) to give rise to yellow needles of the 2-hydroxy-[4-(1, 3-diphenyl)-pyrazolyli-dine]-acetophenones in 70-80% yield.

(2) 2-[4-(1, 3-Diphenyl)-pyrazolyl]-3-hydroxychromones (VIA-VIE) (*General Procedure*)

The 2-hydroxy-[4-(1, 3-diphenyl)-pyrazolyldine]-acetophenones (0.005 moles) were dissolved in alcohol (20 ml), sodium hydroxide (20 ml, 26%) and pyridine (20 ml) and hydrogen peroxide (30%, 5 ml) was added dropwise with the continuous stirring. The reaction mixture, after keeping it overnight at room temperature, was acidified with acetic acid. The yellow solid was filtered, washed with water and recrystallised from alcohol to yield yellow needles of 2-[4-(1, 3-diphenyl)-pyrazolyl]-3-hydroxy-chromones in 35-50% yield.

(3) *Methylation of VIA-VIE*

The hydroxychromone (0.002 mole) was dissolved in dry acetone (200 ml) and to it were added dimethyl sulphate (1 ml) and freshly fused potassium carbonate (5 g). After refluxing for 10 hr acetone was filtered, the potassium salt was washed with anhydrous acetone. The combined acetone solutions were distilled under reduced pressure and water was added. The colourless precipitate, obtained, was filtered and recrystallised from benzene-petroleum ether (1:1) to yield colourless needles of 2-(4-(1, 3-diphenyl)-pyrazolyl)-3-methoxychromones (VII A-VII E) in 70-90% yield.

(4) 4, 6-Dimethoxy-2-[4-(1, 3-diphenyl)-pyrazolyldine]-coumaran-3-one (IX)

2-Hydroxy-4, 6-dimethoxy- [4- (1, 3-diphenyl) - pyrazolyldine) acetophenone (1.8 g) was dissolved in alcohol (20 ml), pyridine (10 ml), sodium hydroxide (20 ml, 20%) and subjected to AFO oxidation as in 2, with hydrogen peroxide (30%, 5 ml). The reaction mixture was left overnight and diluted with water and the product was recrystallised from alcohol, to give rise to bright yellow, prisms of IX (0.08 g, 45%). It was insoluble in alkali and did not respond to ferric chloride colour test.

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