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Synthesis of Some New 2-[2-(5-Phenyl-3-isoxazolyl) phenoxy methyl]-4*H*-1-benzopyran-4-ones

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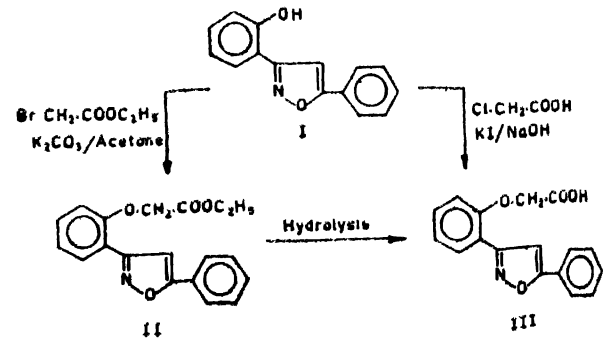
The synthesis of a few new 4*H*-1-benzopyran-4-ones having substituents containing heterocyclic systems starting from [2-(5-phenyl-3-isoxazolyl)phenoxy]-acetic acid and 2-hydroxy, 2,4-dihydroxy, 2,4,6-trihydroxy acetophenones has been described.

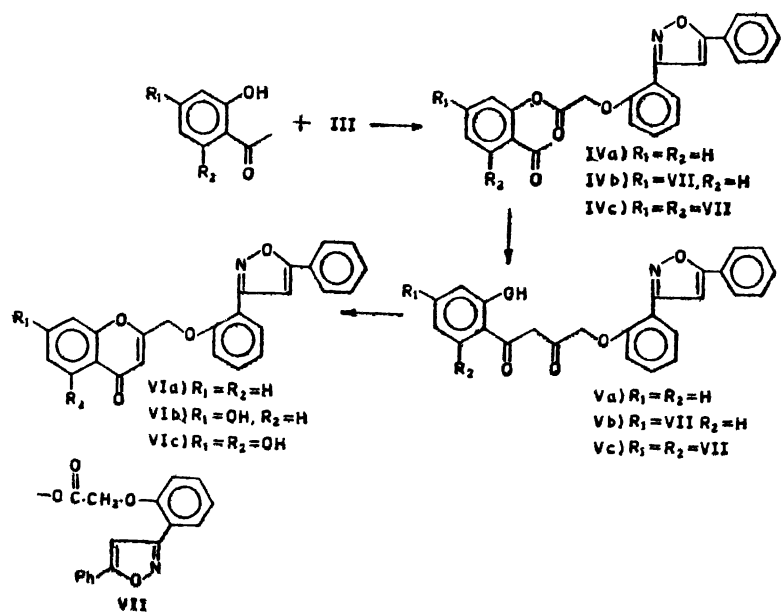
A review of chemical literature reveals that no hetero substituted derivatives at 2-position of 4*H*-1-benzopyran-4-one have been reported except a few chromones[1-7] with aliphatic substituents at 2- or 3-position of 4*H*-benzopyran-4-one.

In the previous communications we described the syntheses of chromones having substituents with pyrazole[8] and pyrazoline[9] moieties attached at 2-position of 4*H*-1-benzopyran-4-one. As a part of our continuing interest we now describe another series of chromone having [2-(5-phenyl-3-isoxazolyl) phenoxy methyl] group attached to 2-position of 4*H*-1-benzopyran-4-one.

2-(5-Phenyl-3-isoxazolyl) phenol (**I**), starting material for the present synthesis, was prepared by the action of hydroxylamine hydrochloride either on flavone[10] or its parent compound, β-diketone[11] in presence of pyridine. The acid[12] (**III**) required for the preparation of the chromones was prepared either directly by the condensation of isoxazole (**I**) with chloroacetic acid in presence of potassium iodide and alkali or *via* its ester (**II**) prepared similarly (Scheme 1). [2-(5-Phenyl-3-isoxazolyl) phenoxyl] acetic acid (**III**) was condensed with appropriate hydroxy acetophenone using phosphorus oxychloride[10] in pyridine to obtain phenoxy esters (**IVa-IVc**). These phenoxy esters were subjected



Scheme 1



Scheme 2

to Baker-Venkataraman rearrangement to yield 1,3-diketo compounds (Va-Vc), which on cyclisation yielded the 2-substituted heteroanalogues of 4*H*-1-benzopyran-4-ones or chromones (VIa-VIc) (Scheme 2).

Experimental

M.ps. were determined in open capillary tubes and are uncorrected. The structures were supported by elemental analysis, tlc and VI (a-c) by uv (MeOH) and ir (KBr, nujol) spectral data as well.

Preparation of 2-(5-phenyl-3-isoxazolyl) phenol (I): A mixture of flavone (1 g) and hydroxylamine hydrochloride (1.5 g) in pyridine (10 ml) was refluxed for 6 h on a sand bath. It was then poured over ice and neutralized with cold dilute hydrochloric acid. The solid separated, was filtered and washed with water. It was purified by dissolving in sodium hydroxide solution and reprecipitating with hydrochloric acid. The solid obtained was filtered, washed with water, and crystallised from acetone to yield the product as colourless needles (62%), m.p. 235° (Found: C, 75.76; H, 4.71; N, 5.99. $C_{15}H_{11}NO_2$ requires C, 75.95; H, 4.64; N, 5.91%).

The compound was also prepared by a similar condensation using 2-hydroxydibenzoylmethane instead of flavone.

Preparation of ethyl [2-(5-phenyl-3-isoxazolyl)-phenoxy] acetate (II): 2-(5-Phenyl-3-isoxazolyl) phenol (0.01 mol), and ethylbromoacetate (0.012 mol) were dissolved in dry acetone (20 ml). To this solution fused potassium carbonate (3 g) was added, and the reaction mixture was refluxed overnight on a water bath maintaining anhydrous conditions. The mixture was filtered and the residue washed with acetone. From the total extract acetone and excess of ethyl bromoacetate were removed by distilling under vacuum. The solid residue left behind was crystallised from ethanol to yield the product (82%), m.p. 95°.

Preparation of [2-(5-phenyl-3-isoxazolyl)-phenoxy] acetic acid (III): [2-(5-Phenyl-3-isoxazolyl)-phenoxy] acetate (0.005 mol) was dissolved in ethanol (5 ml) and sodium hydroxide (1%, 25 ml) was added. The mixture was refluxed for 2 h. The reaction mixture was cooled and neutralized with cold dilute hydrochloric acid. The precipitate was filtered, washed with water, dried and crystallised from methanol to yield the product (56%), m.p. 178° (Found: C, 69.21; H, 4.35; N, 4.79. $C_{17}H_{13}NO_4$ requires C, 69.15; H, 4.41; N, 4.75%).

Method B: To a solution of monochloroacetic acid (0.0025 mol) in sodium hydroxide solution (0.005 mol) was added powdered potassium iodide (0.0025 mol) and refluxed for 0.5 h. To this solution I (0.002 mol) was added and the solution was refluxed for 1.5 h. It was filtered and the filtrate acidified with cold dilute hydrochloric acid. The solid separated was filtered, washed with water and crystallised from methanol to yield the product (50%).

The acid obtained by both the methods were identical by their m.p., and m.m.p. was undepressed in admixture with the sample prepared from method A and method B and in co- tlc.

Preparation of the esters (IVa-IVc) (*general procedure*): III (0.007 mol) and substituted hydroxy acetophenone (0.0065 mol) were dissolved in dry pyridine (10-12 ml) and phosphorus oxychloride (0.4 ml) was added dropwise with constant stirring in cold condition. The mixture was stirred at room temperature maintaining the anhydrous condition with warming at intervals for 8 h. It was then treated with cold dilute hydrochloric acid. The solid separated was filtered, washed with cold sodium hydroxide solution followed by water. The solid obtained was crystallised from suitable solvents to yield the respective products.

2-[5-Phenyl-3-(2-phenoxyacetyloxy) isoxazole] acetophenone (IVa): The solid obtained in the general procedure was crystallised from ethanol to yield the product (63%), m.p. 110° (Found: C, 72.58; H, 4.63; N, 3.44. $C_{25}H_{19}NO_5$ requires C, 72.64; H, 4.60; N, 3.39%).

2,4-Di-[5-phenyl-3-(2-phenoxyacetyloxy)isoxazole] acetophenone (IVb): The solid obtained was crystallised from ethanol giving the product (71%), m.p., 101° (Found: C, 71.48; H, 4.18; N, 3.96. $C_{42}H_{30}N_2O_9$ requires C, 71.39; H, 4.25: N, 3.97%).

2,4,6-Tri-[5-phenyl-3-(2-phenoxyacetyloxy)isoxazole] acetophenone (IVc): The solid obtained was crystallised from methanol to yield the product (75%), m.p. 145° (Found: C, 70.91; H, 4.12; N, 4.16. $C_{59}H_{41}N_3O_{13}$ requires C, 70.87; H, 4.10; N, 4.20%).

Preparation of 1,3-diketones (Va-Vc) (*general procedure*): The esters IVa-IVc (0.01 mol) were dissolved in anhydrous pyridine (8 ml) and anhydrous powdered potassium hydroxide (0.001 mol) was added and the mixture stirred at room temperature. The stirring was continued (40-45 min) till the whole mass became quite viscous. The pasty mass was poured over cold water and acidified with cold dilute acetic acid (2*N*). The solid separated out was filtered, washed with water and crystallised from suitable solvents to yield the products.

Preparation of chromones (VIa-VIc) (*general procedure*): 1,3-Diketo compounds (Va-Vc) (0.001 mol) were dissolved in glacial acetic acid (10 ml) and a few drops of concentrated hydrochloric acid was added. The reaction mixture was refluxed for 2 h. The mass was then cooled and poured over crushed ice with stirring. The solid separated was filtered and washed with cold aquous sodium bicarbonate solution (5%), followed by water. It was crystallised from suitable solvents to yield the products.

2-[2-(5-Phenyl-3-isoxazolyl) phenoxy methyl]-4H-1-benzopyran-4-one (**VIa**) : The solid obtained in the general procedure was crystallised from methanol-dimethylformamide mixture to yield the product (52%), m.p. 210° (Found : C, 75.92 ; H, 4.32 ; N, 3.51. $C_{25}H_{17}NO_4$ requires C, 75.95 ; H, 4.30 ; N, 3.54%) ; λ_{max} 270 and 320 nm ; ν_{max} 1640 (C=O), 1600 (γ-pyrone), 1260, 1140 (ether linkage) and 1660 cm^{-1} (C=N, isoxazole).

7-Hydroxy-2-[2-(5-phenyl-3-isoxazolyl] phenoxy methyl]-4H-1-benzopyran-4-one (**VIb**) : The solid was crystallised from methanol-chloroform mixture to yield the product (69%), m.p. 161° (Found : C, 72.92 ; H, 4.11 ; N, 3.36. $C_{25}H_{17}NO_5$ requires C, 72.92 ; H, 4.14 ; N, 3.41%) ; λ_{max} 275 and 315 nm ; ν_{max} 3150 (O-H), 1640, 1620 (C=O), 1600 (γ-pyrone), 1250 (ether linkage) and 1660 cm^{-1} (C=N, isoxazole).

5,7-Dihydroxy-2-[2-(5-phenyl-3-isoxazolyl) phenoxy methyl]-4H-1-benzopyran-4-one (**VIc**) : The solid was crystallised from methanol to yield the product (65%), m.p. 181°(Found : C, 70.32 ; H, 3.95 ; N, 3.21. $C_{25}H_{17}NO_6$ requires C, 70.26 ; H, 3.98 ; N, 3.28%) ; λ_{max} 275 and 315 nm ; ν_{max} 3200 (O-H), 1590 (C=O), 1605 (γ-pyrone), 1220, 1150 (ether linkage) and 1640 cm^{-1} (C=N, isoxazole).

All the above compounds (**VIa-VIc**) gave single spot on tlc and showed bluish yellow fluorescence under uv light.

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References

1. E. Eiden and D. Dolcher, *Arch. Pharm.* (*Weinheim, Ger.*), 1975, **308**, 385.
2. J. Schmutz, R. Hirt, F. Kunzle, E. Eichenberger and H. Lauener, *Helv. Chim. Acta*, 1953, **36**, 620.
3. A. Wander, Brit. Pat. 728767 / 1956 (*Chem. Abstr.*, 1956, **50**, 7876).
4. J. Schmutz, R. Hist and H. Launer, *Helv. Chem. Acta*, 1952, **35**, 1168.
5. R. C. Johnston and D. Kidd, *J. Chem. Soc.*, 1964, 4730.
6. A. I. Tolmacher, V.P. Sribnaya and L. V. Sheheglova, *J. Gen. Chem. USSR* (*Engl. Transl.*), 1963, **33**, 433.
7. A. I. Kiprianov and A. I. Tolmacher, *J. Gen. Chem. USSR* (*Engl. Transl.*), 1960, **30**, 659.
8. P. S. Fernandes, D. Desai and V. V. Nadkarny, *J. Indian Chem. Soc.*, 1983, **50**, 165.
9. P. S. Fernandes and E. D. L. M. Mendes, *J. Indian Chem. Soc.*, 1983, **60**, 967.
10. P. N. Wadodkar and M. G. Marathy, *Indian J. Chem.*, 1972, **10**, 45.
11. W. Baker, J. Harborne and W. Ollis, *J. Chem. Soc.*, 1952, 1303.
12. N. Gawri, M.Sc. Thesis, University of Bombay, 1983.