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SYNTHESIS OF 4-[(BENZOPYRANYL, BENZOFURANYL) METHYLENE] -3-METHYL-1-(*P*-NITROPHENYL)-2-PYRAZOLIN-5-ONE.

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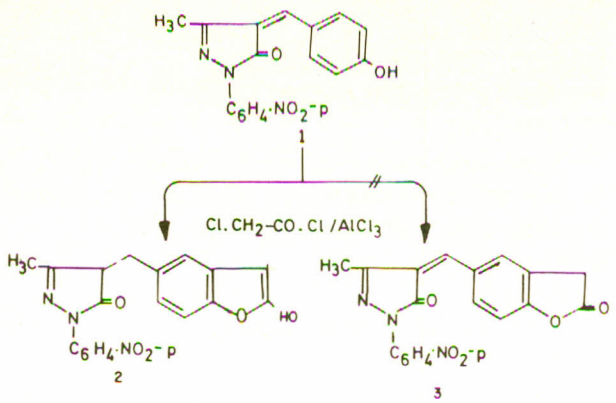
4-(p-Hydroxybenzylidene)-3-methyl-1-(p-nitro-phenyl)-2-pyrazolin-5-one (1) have been used as a key intermeditate for the introduction of benzofuranones (2 and 5) and chromenones (7) and (9) into the 4-position of 2-pyrazolin-5-one.

INTRODUCTION

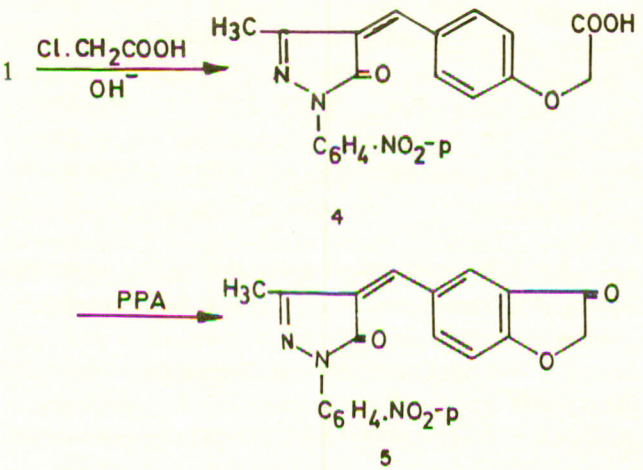
As a further extenstion of studies on the reaction of 4-(p-hydroxybenzylidene)-3-methyl-1-(p-nitrophenyl)-2-pyrazolin-5-one (1) with some reagents[1], reactions with mono- and trichloroacetic acid, chloroacetyl chloride, β-keto esters and *p*-nitrobenzylcyanide were investigated and many interesting results were obtained compairing with those reported in the literature[2-5].

Taking into account the usual procedure for the condensation of phenols, 4-(p-hydroxybenzylidene)-3-methyl-1-(p-nitrophenyl)-2-pyrazolin-5-one (1) was allowed to react with chloroacetyl chloride in the presence of aluminium chloride to give 4-[[(2-(hydroxy)-2H-benzofuran-5-yl] methylene] -3-methyl-1-(p-nitrophenyl)-2-pyrazolin-5-one (2).



1 → 2 and 3

Structure (3) was ruled out because of the presence of absorbtion band at 3400 cm^{-1} (free OH) in the IR spectrum of the product. On the other hand, the isomeric compound (5) was obtained via the intermediate phenoxyacetic acid derivative (4), which was obtained upon treating (1) with monochloroacetic acid.



1 → 4 → 5

The IR spectrum of (4) showed absorption bands at 1270 cm^{-1} (-O-CH_2-), 1600 cm^{-1} (C=N), 1630 and 1390 cm^{-1} (–C(=O)–O), 1660 cm^{-1} (C=C), 1720 cm^{-1} (C=O of COOH), 1740 cm^{-1} (C=O of pyrazolone) and 3310 cm^{-1} (OH of COOH). Compound (5) showed bands at 1825 and 1865 cm^{-1} (γ-lactone) in addition to the regular bands of C=N, C=C and C=O, at 1600, 1620 and 1720 cm^{-1}.

The PMR spectrum of 4 displayed signals at δ1.1 (s, 3H, –N=C–CH_3), 4.4 (s, 2H, –O–CH_2–CO–) and 8 (s, 1H, –COOH). On the other hand compound 5 showed signals at δ1.2 (s, 3H, –N=C–CH_3), 3.8 (s, 2H, –)–CH_2 – CO) and no acidic protons.

When trichloroacetic acid was treated with three equivalents of (1), compound (6) was obtained in good yield. Its IR spectrum showed a regular absorption bands characteristic for C=N (1600), C=C (1640), C=O (1720), C=O of COOH(1740) and OH of COOH (3400 cm^{-1}).

The PMR spectrum or 6 displayed signals at δ1.1 (s, 3H, –N=C–CH_3) and 8.1 (s, 1H, –COOH).

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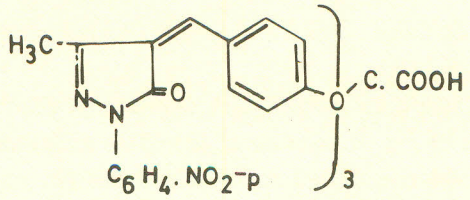

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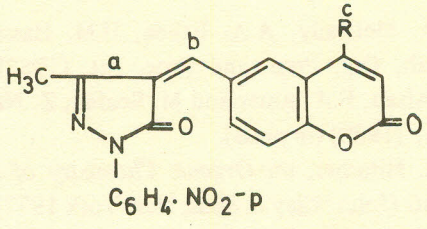
Since chromonar[3] shows activity as a coronary vasodilator. This prompted us to introduce such nucleus in the 4-position of (1), via the Pechmann reaction on its phenolic residue. Therefore, reaction of (1) with ethyl acetaocetate or ethyl benzoylacetate under the Pechmann conditions gave (7a-b).



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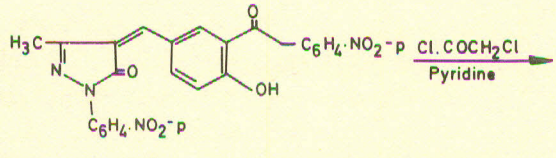
a: R = CH_3
b: R = C_6H_5

The PMR spectrum of (7a), showed the protons (a) 0.7 ppm, s, proton (b) at 5.8 ppm, s, while protons (c) appears at 2 ppm; s.

On the otherhand the spasmolytic activity of such chromones[3] is already a motive to synthesize the 4-chromenone analogue (9) via the phenacyle derivative (8).



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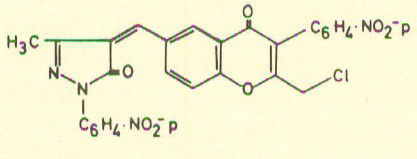

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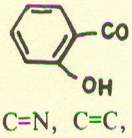
The IR spectrum of (8) showed a band at 1650 cm^{-1} () in addition to the characteristic bands of C=N, C=C, C=O and OH groups, while compound (9) showed a clear and sharp band at 750 cm^{-1} (C-Cl).

The PMR spectrum of 9 displayed signals at δ 1.2 (s, 3H, $-N=C-CH_3$) and 3.9 (s, 2H, $-CH_2-Cl$).

EXPERIMENTAL

Melting points were determined on Gallenkamp electric melting point apparatus and are uncorrected. IR spectra in KBr were determined on a Unicam SP 2000 Infrared Spectrophotometer. NMR spectra were recoreded on a varian Model T-60 NMR spectrometer, using TMS as internal standard.

4-(p-Hydroxybenzylidene)-3-methyl-1-(p-nitropphenyl)-2-pyrazolin-5-one (1). A mixture of 1-(p-nitrophenyl)-3-methyl-2-pyrazolin-5-one (0.01 mole) and p-hydroxybenzaldehyde (0.012 mole) was boiled in ethanol (20 ml), till a solid product precipitated, set aside at room temperature. The solid product, was crystallized from acetic acid to give compound (1) as a reddish yellow crystals, m.p. 245°, yield 95 %, Analysis: $C_{17}H_{13}N_3O_4$ (323.29); Calcd: C 63.15 H 4.05 N 12.99; Found: C 63.41 H 4.15 N 13.21.

4-[[2(Hyroxy)-*2-H-benzofuran-5-yl] methylene]-3-methyl-1-(p-nitrophenyl)-2-Pyrazolin-5-one (2).* To a mixture of (1) (0.01 mole) and chloroacetyl chloride (0.012 mole) in dry benzene (30 ml), anhydrous aluminium chloride (0.02 mole) was added portion wise. The reaction mixture was refluxed for three hours, left to stand for overnight. The solvent was removed under suction, and the residue obtained was dissolved in ice-cold hydrochloic acid to give a brown precipitate. After crystallization from ethanol it gave a brown powder. m.p. > 360°. yield 45 %. Analysis: $C_{10}H_{13}N_3O_5$ (363.31); Calcd: C 62.8 H 3.6 N 11.56; Found: C 62.4 H 3.87 N 11.91

Interaction of (1) with Monochloroacetic Acid: Formation of (4). To a mixture of (1) (1 g) and (4 ml) of 33 % sodium hydroxide solution, (3 ml) of 50 % monochloroacetic acid was added, followed by addition of water (5 ml). The reaction mixture was refluxed for two hours, diluted with water, acidified with dilute hydrochloric acid. Crystalization of the solid from ethanol gave a brownish-red crystals m.p. 115-16°, yield 60 % Analysis: $C_{19}H_{15}N_3O_6$ (381.33); Calcd: C 59.84 H 3.96 N 11.01; Found: C 59.55 H 3.78 N 11.35.

Cyclization of (4) Into (5). A mixture of (4) (1 g) and polyphosphoric acid (10 g) was heated in an oil-bath at 90-110° for one hour, left to cool and poured into ice-cold water. The product so obtained was crystallized from ethanol to give (5) as buff crystals, m.p. > 360°, yield 60 %, Analysis: $C_{19}H_{13}N_3O_5$ (363.31); Calcd: C 62.8 H 3.6 N 11.66; Found: C 62.88 H 3.86 N 11.95

Interaction of (1) with Trichloroacetic Acid: Formation of (6). To a mixture of (1) (3 g) and (12 ml) of 33 % sodium hydroxide solution, (3 ml) of 50 % trichlo-

roacetic acid was added, followed by addition of water (5 ml). The reaction mixture was refluxed for four hours, diluted with (40 ml) of water and acidified with dilute hydrocholoric acid. Crystallization from ethanol gave (6) as a brown crystals, m.p. 170°, yield 70 %. Analysis: $C_{53}H_{37}N_9O_{14}$ (1023.902); Calcd: C 62.16 H 3.64 N 12.31; Found: C 62.63 H 4.2 N 12.51.

The Pechamnn Reaction with (1): Formation of (7a-b). A mixture of (1), ethyl acetoacetate or ethyl benzoylacetate and polyphosphoric acid (molar ratios 1:1:10), was heated at 90-100° for one hour. The reaction mixture was left to stand for five hours, poured into ice-cold water. The solid products that separated were recrystallized from ethanol to give:

Compound (7a) as dark-brown, m.p. 190°, yield 70 %. Analysis: $C_{21}H_{15}N_3O_5$ (389.35); Calcd: C 64.77 H 3.88; Found: C 65.11 H 4.00.

Compound (7b) as dark brown, m.p. 180° yield 65 %. Analysis: $C_{26}H_{17}N_3O_5$ (451.42); Calcd: C 69.17 H 3.79; Found: C 68.98 H 3.55.

Reaction of (1) with p-nitrobenzylcyanide: Formation of (8). A stream of dry HCl gas was passed into a mixture of (1) (0.01 mole) and *p*-nitrobenzylcyanide in absolute ethanol (30 ml) for three hours. The solvent was removed and the residue was treated with 5 % sodium carbonate solution (20 ml). The product was collected, washed with water and crystallized from ethanol to give compound (8) as red crystals, m.p. 235°, yield 40%. Analysis: $C_{25}H_{18}N_4O_7$ (486.42); Calcd: C 61.72 H 3.72 N 11.51; Found: C 62.11 H 3.42 N 11.11.

Cyclization of (8) with Choroacetyl Chloride: Formation of (9). A mixture of (8) (0.01 mole) and chloroacetyl chloride (0.012 mole) in pyridine (25 ml) was left to stand for one day at room temperature. The reaction mixture poured into ice-cold water, and the product obtained was recrystallized from ethanol to give compound (9) as a yellow powder, m.p. 205°, yield 55 %. Analysis: $C_{27}H_{17}N_4O_7Cl$ (544.897); Calcd: C 59.51 H 3.14 N 10.28; Found: C 60.01 H 3.13 N 10.70.

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