Synthesis of Benzopyran-4-one and Phloroglucinol Monomethyl Ether Derivatives from the Naturally Occurring Compound (Visnagin)

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The reaction of 6-formyl-7-hydroxy-5-methoxy-2-methylbenzopyran-4-one with dimethyl acetylenedicarboxylate and benzil gave the respective 4H,6H-pyrano[3,2-g]chromene and imidazolylbenzopyran derivatives. Treatment of the imidazolylbenzopyran with hydrazine hydrate or hydroxylammonium chloride yielded imidazolylpyrazolyl- or imidazolylisoxazolylbenzenes, while the alkaline hydrolysis of imidazolylbenzopyran afforded imidazolylacetophenone that reacted with some aromatic aldehydes to give the corresponding chalcones. Oxidation of the chalcone with hydrogen peroxide led to the formation of 6-hydroxy-4-methoxy-5-[4,5-diphenylimidazol-2-yl]-2-(4-methoxybenzylidene)coumaran-3-one, while the reaction with hydrazine hydrate gave the corresponding imidazolylpyrazolinylbenzene. Also, the imidazolylacetophenone was reacted with phenylhydrazine and hydroxylammonium chloride to give the respective hydrazone and oxime products. Fischer indolization of the above hydrazone yielded the corresponding indole derivative.

Numerous imidazole derivatives have been prepared and investigated for therapeutic and prophylactic application [1—3]. Also benzopyran derivatives possess coronary vasodilating [4], spasmyloytic [5], and antiatherogenic and antiatherosclerotic activity [6]. In the light of this report, compounds having a combination of benzopyran and imidazole moieties can be expected to exhibit marked biological activity. Thus this investigation deals with the synthesis of such type of compounds.

The naturally occurring furobenzopyran “visnagin” (I) yields 6-formyl-7-hydroxy-5-methoxy-2-methylbenzopyran-4-one (II) upon oxidation with potassium dichromate and sulfuric acid by rupture of furan ring [7]. The reaction of II with dimethyl acetylenedicarboxylate (DMAD) in the presence of anhydrous potassium carbonate gave 7,8-bis(methoxycarbonyl)-6-hydroxy-5-methoxy-2-methyl-4H,6H-pyrano[3,2-g]-chromen-4-one (III). The 1H NMR spectrum of compound III showed the presence of two singlets for two methyl ester groups at δ = 3.90 and 3.99, the IR spectrum showed the absence of aldehyde absorption (~ν = 1710 cm⁻¹), also the mass spectrum revealed a molecular ion [M⁺] at m/z = 376, which was in agreement with its molecular mass.

When the aldehyde II was refluxed with benzil in the presence of ammonium acetate in glacial acetic acid, it gave 7-hydroxy-5-methoxy-2-methyl-6-[4,5-diphenylimidazol-2-yl]benzopyran-4-one (IV). The 1H NMR spectrum showed the presence of 10 aromatic protons at δ = 7.5—8.0 of imidazole moiety, and the IR spectrum revealed the presence of NH group at ~ν = 3250 cm⁻¹.

Treatment of IV with hydrazine hydrate or hydroxylammonium chloride led to the formation of the only regioisomers: 1,3-dihydroxy-5-methoxy-6-[4,5-diphenylimidazol-2-yl]-4-[5-methyl-3-pyrazolyl or isoxazolyl]benzene (V) and (VI), respectively, via the opening of the chromone ring followed by reaction with the above reagents. The mass spectrum of V revealed molecular ion peak [M⁺] at m/z = 439 as the base peak, which was in agreement with its molecular mass, also two daughter peaks at m/z = 220 and 140 from the rupture of the diphenylimidazole and methylpyrazole rings, respectively.

Bromination of IV using an excess of bromine led to the formation of 8-bromo-5,7-dihydroxy-2-methyl-6-[4,5-diphenylimidazol-2-yl]benzopyran-4-one (VII). Demethylation of 5-methoxy group was accomplished from the effect of the hydrogen bromide formed during the reaction as reported in the case of khellin and visnagin with several reagents such as dilute hydrogen halides [8, 9].

On the other hand, nitration of compound IV gave 8-nitrobenzopyranone derivative VIII. IR spectrum revealed the vibrations ~ν(NO₂) = 1350 cm⁻¹ and ~ν(NO₂) = 1530 cm⁻¹. The mass spectrum of VIII revealed molecular ion [M⁺] at m/z = 470 which cor-
responded with its molecular mass.

The Vilsmeier–Haack formylation of IV failed to give the corresponding 8-formyl derivative IX but demethylation of 5-methoxy group occurred affording 5,7-dihydroxy-2-methyl-6-[4,5-diphenylimidazol-2-yl]benzopyran-4-one (X).

Alkaline hydrolysis of IV gave a quantitative yield of imidazolylacetophenone derivative XI which was reacted with some aromatic aldehydes, namely benzaldehyde, p-anisaldehyde, p-chloro- and p-nitrobenzaldehyde to give the corresponding chalcones XIIa—XIIId. The IR spectra of XIIa—XIIId showed a charac-
characteristic α,β-unsaturated ketone band at ν = 1630—1640 cm⁻¹, also ¹H NMR spectra of XIIa showed a doublet signal of —CH=—CH—Ar at δ = 5.67 (J = 10 Hz).

Oxidation of the chalcone XIIb with hydrogen peroxide in sodium hydroxide led to the formation of 6-hydroxy-4-methoxy-5-[4,5-diphenylimidazol-2-yl]-2-(4-methoxybenzyldiene)coumaran-3-one (XIII). The assigned structure of XIII was established on the basis of the correct analytical and spectral data. Mass spectrum showed a molecular ion peak [M⁺] at m/z = 516 as the base peak which corresponded to its molecular mass. Also, when the chalcone XIIc was reacted with hydrazine hydrate, it gave the corresponding imidazolylpyrazolinylbenzene derivative XIV. The oxime derivative XV which was obtained from condensation of compound XI with hydroxylammonium chloride failed to give the isoxazole derivative XVII on treatment with acetic anhydride/pyridine mixture. On the other hand, on boiling phenyl hydrazone derivative XVI that was obtained from condensation of compound XI with phenyl hydrazine with polyphosphoric acid gave according to Fischer indole synthesis the corresponding indole product XVIII.

EXPERIMENTAL

Melting points were uncorrected. Elemental analysis was carried out in the Microanalytical Unit at the Faculty of Science, Mansoura and Cairo Universities. IR spectra were recorded on Mattson 5000 FTIR spectrometer using KBr wafer technique. ¹H NMR spectra were determined on Varian-Gemini 200 MHz and Jeol-Ex-270 MHz NMR spectrometers using TMS as an internal standard with δ = 0. Electron impact (EI) mass spectra were determined on a GC-MS QP-100 EX spectrometer Shimadzu (Japan). The purity of the synthesized compounds was tested by TLC.

Compound II was prepared adopting the published [7] procedure with the same m.p. = 189°C.

7,8-Bis(methoxycarbonyl)-6-hydroxy-5-methoxy-2-methyl-4H,6H-pyrido[3,2-g]-chromen-4-one (III)

A mixture of aldehyde II (1.0 g; 4 mmol), dimethyl acetylendicarboxylate (0.6 g; 4 mmol), and anhydrous potassium carbonate (0.5 g; 4 mmol) in dry benzene (50 cm³) was refluxed for 6 h. The reaction mixture was cooled, then diethyl ether (50 cm³) was added. The organic layer was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave a yellow viscous material, which was triturated with petroleum ether (b.p. = 60—80°C) and crystallized from dilute ethanol (60 %) to give III, m.p. = 80—81°C; yield = 20 %. For C₁₅H₁₀O₉ (Mᵣ = 376.32) w₁(found): 56.98 % C, 3.93 % H; w₁(calc.): 57.45 % C, 4.28 % H. IR spectrum: ν(C=O chromone)/cm⁻¹: 1658, ν(C=O ester)/cm⁻¹: 1723, 1750, ν(OH)/cm⁻¹: 3450. ¹H NMR spectrum (CDCl₃), δ: 2.3 (s, 3H, CH₃), 3.8 (s, 3H, OCH₃), 3.9 (s, 3H, COOCH₃), 3.99 (s, 3H, COOCH₃), 5.3 (s, 1H, H-4), 6.1 (s, 1H, H-7), 6.7 (s, 1H, OH), 8.1 (s, 1H, H-10). EI mass spectrum, m/z (Iᵣ/%): 376 (3, [M⁺]).

7-Hydroxy-5-methoxy-2-methyl-6-[4,5-diphenylimidazol-2-yl]benzopyran-4-one (IV)

A mixture of aldehyde II (1.0 g; 4 mmol), benzil (0.9 g; 4 mmol), and ammonium acetate (3 g; 4 mmol) in glacial acetic acid (20 cm³) was refluxed for 2 h. The precipitate that formed was filtered off and washed several times with hot acetone to give IV, m.p. = 256—257°C; yield = 70 %. For C₂₆H₂₈O₇N₃ (Mᵣ = 424.45) w₁(found): 73.80 % C, 5.00 % H, 6.6 % N; w₁(calc.): 73.57 % C, 4.75 % H, 6.6 % N. IR spectrum, ν(C=N)/cm⁻¹: 1620, ν(C=O chromone)/cm⁻¹: 1658, ν(NH)/cm⁻¹: 3250, ν(OH)/cm⁻¹: 3500. ¹H NMR spectrum (DMSO-d₆), δ: 2.4 (s, 3H, CH₃), 3.9 (s, 3H, OCH₃), 6.1 (s, 1H, H-3), 7.1 (s, 1H, H-8), 7.5—8.0 (m, 12H, 10Ar—H, OH and NH). EI mass spectrum, m/z (Iᵣ/%): 424 (74.4, [M⁺]).

1,3-Dihydroxy-5-methoxy-6-[4,5-diphenylimidazol-2-yl]-4-[5-methylpyrazol-3-yl]benzene (V)

A mixture of IV (1.0 g; 4 mmol) and hydrazine hydrate (0.4 cm³, 8 mmol) in absolute ethanol (30 cm³) was refluxed for 8 h. The solid so obtained was filtered off, then washed several times with hot acetone to give compound V, m.p. = 299—300°C; yield = 97 %. For C₂₆H₂₂O₃N₄ (Mᵣ = 438.5) w₁(found): 71.50 % C, 5.00 % H, 12.5 % N; w₁(calc.): 71.22 % C, 5.05 % H, 12.78 % N. IR spectrum: ν(C=O)/cm⁻¹: 1630, ν(NH)/cm⁻¹: 3200—3450. EI mass spectrum, m/z (Iᵣ/%): 439 (100, [M⁺]).

1,3-Dihydroxy-5-methoxy-6-[4,5-diphenylimidazol-2-yl]-4-[5-methylisoxazol-3-yl]benzene (VI)

A solution of hydroxylammonium chloride (0.8 g) in water (5 cm³) was added to a solution of IV (1.0 g) in pyridine (10 cm³) and refluxed for 4 h, the mixture was cooled, then acidified with diluted acetic acid. The precipitate that formed was filtered off and crystallized from ethanol to give compound VI, m.p. = 120—121°C; yield = 93 %. For C₂₆H₂₁O₄N₃ (Mᵣ = 439.47) w₁(found): 71.20 % C, 4.9 % H, 9.66 % N; w₁(calc.): 71.06 % C, 4.82 % H, 9.56 % N. IR spectrum: ν(C=N)/cm⁻¹: 1630, ν(NH, OH)/cm⁻¹: 3200—3500. ¹H NMR spectrum (CDCl₃), δ: 2.4 (s, 3H, CH₃), 3.7 (s, 3H, OCH₃), 6.55 (s, 1H, isoxazolyl H), 6.56 (s, 1H, H-2), 7.3—7.6 (m, 12H, Ar—H, NH, OH), 10.4 (s, 1H, OH). EI mass spectrum, m/z (Iᵣ/%): 439 (100, [M⁺]).
8-Bromo-5,7-dihydroxy-2-methyl-6-[4,5-diphenylimidazol-2-yl]benzopyran-4-one (VII)

To a solution of IV (1 g; 2 mmol) in chloroform (8 cm³) was added bromine (1.88 g; 10 mmol) in chloroform (25 cm³). The reaction mixture was shaken and left to stand for 24 h. The precipitate that formed was filtered off, dried, then crystallized from chloroform to give VII, m.p. = 262—263°C; yield = 87 %. For C₂₂H₁₉O₄N₂Br (Mᵣ = 489) w₁(found): 60.93 % C, 36.32 % H, 16.2 % Br; w₁(calc.): 61.37 % C, 3.5 % H, 16.33 % Br. IR spectrum: ʋ(C=N)/cm⁻¹: 1614, ʋ(C=O)/cm⁻¹: 1655, ʋ(NH, OH)/cm⁻¹: 3200—3500. EI mass spectrum, m/z (Iᵣ/%)��: 489 (78.1, [M⁺]).

7-Hydroxy-5-methoxy-2-methyl-8-nitro-6-[4,5-diphenylimidazol-2-yl]benzopyran-4-one (VIII)

To a suspension of IV (1 g) in glacial acetic acid (2.5 cm³) was added a mixture of concentrated nitric acid (1 cm³) and glacial acetic acid (0.5 cm³). The reaction mixture was left at room temperature for 30 min, then poured onto water (50 cm³). The precipitate that formed was filtered off, dried and crystallized from ethanol to give compound VIII, m.p. = 145—146°C; yield = 50 %. For C₂₆H₁₉O₅N₃ (Mᵣ = 469.45) w₁(found): 66.14 % C, 3.80 % H; w₁(calc.): 66.52 % C, 4.08 % H. IR spectrum: ʋ(NO₂)/cm⁻¹: 1350, 1530, ʋ(C=N)/cm⁻¹: 1620, ʋ(C=O)/cm⁻¹: 1660, ʋ(NH, OH)/cm⁻¹: 3200—3600. EI mass spectrum, m/z (Iᵣ/%)藏: 470 (31.8, [M⁺]).

5,7-Dihydroxy-2-methyl-6-[4,5-diphenylimidazol-2-yl]benzopyran-4-one (X)

To a cold solution of IV (1 g) in N,N-dimethylformamide (6 cm³) phosphorous oxychloride (0.5 cm³) was added dropwise in the course of 30 min with shaking. The reaction mixture was then refluxed on water bath for 5 h and then left to cool. After pouring on crushed ice and decomposition with sodium acetate solution, the solid that separated was filtered off, dried, then crystallized from a mixture of ethanol—acetone (1 : 1) to give compound X, m.p. = 265°C; yield = 80 %. For C₂₅H₁₈O₄N₂ (Mᵣ = 410.43) w₁(found): 73.14 % C, 4.15 % H; w₁(calc.): 73.16 % C, 4.42 % H. IR spectrum: ʋ(C=N)/cm⁻¹: 1620, ʋ(C=O)/cm⁻¹: 1658, ʋ(NH)/cm⁻¹: 3250, ʋ(OH)/cm⁻¹: 3500. EI mass spectrum, m/z (Iᵣ/%)藏: 410 (100, [M⁺]).

4,6-Dihydroxy-2-methoxy-3-[4,5-diphenylimidazol-2-yl]acetophenone (XI)

To an ice-cooled mixture of XIb (15.5 g; 0.03 mol), sodium hydroxide (5.2 g; 0.13 mol), ethanol (200 cm³), and water (100 cm³) was added 30 % hydrogen peroxide (11.4 cm³, 0.1 mol). The reaction mixture was stirred at 0°C for 2 h and then at room temperature for 16 h. The crude product which separated on acidification with 2 M hydrochloric acid, was filtered off, washed with water, dried and crystallized from acetone to give compound XIIX, m.p. = 240—241°C; yield = 80 %. For C₃₂H₂₄O₄N₂ (Mᵣ = 516.5) w₁(found): 74.40 % C, 4.60 % H; w₁(calc.): 74.0 % C, 4.68 % H. IR spectrum: ʋ(C=N)/cm⁻¹: 1610, ʋ(C=O)/cm⁻¹: 1650, ʋ(NH, OH)/cm⁻¹: 3300—3500. EI mass spectrum, m/z (Iᵣ/%)藏: 516 (100, [M⁺]).
1,3-Dihydroxy-5-methoxy-6-[4,5-diphenylimidazol-2-yl]-4-[5-chlorophenylpyrazolin-3-yl]benzene (XIV)

A mixture of XlC (1.0 g; 2 mmol) and hydrazine hydrate (0.1 cm³, 2 mmol) in absolute ethanol (20 cm³) was refluxed for 2 h. The solid so obtained was filtered off and washed several times with hot acetone to give compound XIV, m.p. = 134–135; yield = 90 %. For C₃₁H₂₄O₄N₂Cl (Mᵣ = 536.01) w₁(found): 69.70 % C, 4.9 % H, 10.2 % N; w₁(calc.): 69.47 % C, 4.5 % H, 10.45 % N. IR spectrum: ν(Cl)/cm⁻¹: 760, ν(C≡N)/cm⁻¹: 1620, ν(NH, OH)/cm⁻¹: 3300–3500.

1H NMR spectrum (DMSO­-d₆): δ: 2.2 (s, 1H, NH), 3.8 (s, 3H, OCH₃), 3.3 (dd, 2H, pyrazolinyl H-4), 4.8–4.9 (t, 1H, pyrazolinyl H-5), 6.3 (s, 1H, H-2), 7.5 (m, 16H, Ar-H, NH, OH), 12.2 (s, 1H, OH). EI mass spectrum, m/z (Iᵣ/%): 536 (100, [M⁺]).

4,6-Dihydroxy-2-methoxy-3-[4,5-diphenylimidazol-2-yl]acetophenone Oxime (XV)

A mixture of XI (2.0 g; 5 mmol), hydroxylammonium chloride (0.35 g; 5 mmol), and few drops of pyridine in absolute ethanol (30 cm³) was refluxed for 5 h. The precipitate that formed was filtered off, dried and crystallized from ethanol to give XV, m.p. = 242°C; yield = 91 %. For C₂₄H₂₃O₄N₃ (Mᵣ = 415.45) w₁(found): 69.55 % C, 5.00 % H; w₁(calc.): 69.39 % C, 5.09 % H. IR spectrum: ν(C≡N)/cm⁻¹: 1620, ν(NH, OH)/cm⁻¹: 3300–3450. EI mass spectrum, m/z (Iᵣ/%): 415 (87.9, [M⁺]).

Phenylhydrazone Derivative XVI

A mixture of XI (2.0 g; 5 mmol) and phenylhydrazine (0.54 cm³, 5 mmol) in absolute ethanol (30 cm³) was refluxed for 2 h. The precipitate that formed was filtered off and crystallized from chloroform to give XVI, m.p. = 275–276°C; yield = 90 %. For C₃₀H₂₉O₄N₄ (Mᵣ = 490.56) w₁(found): 73.00 % C, 5.1 % H; w₁(calc.): 73.45 % C, 5.34 % H. IR spectrum:

ν(C≡N)/cm⁻¹: 1620, ν(NH, OH)/cm⁻¹: 3300–3500. EI mass spectrum, m/z (Iᵣ/%): 490 (21.3, [M⁺]).

REFERENCES