Synthetic Approaches to Novel Di(furocoumarole) Analogues and Some Related Oxygen-Containing Fused Ring Systems of Anticipated Anticoagulant Activity

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Three derivatives of 3,3′-methylene-bis(7,8-diphenyl-4-hydroxy-2*H*-furo[2,3-*g*]-[1]-benzopyran-2-one) were prepared as dicoumarole analogues by condensation of 7,8-diphenyl-4-hydroxy-2*H*-furo[2,3-*g*]-[1]-benzopyran-2-one (*II*) with aliphatic and/or aromatic aldehydes. Cyclization of these products with *o*-hydroxy aldehydes or acetic anhydride afforded the related fused ring systems of two types. Synthesis of additional members of these oxygen-containing ring systems was effected either by oxidative coupling of compound *II* with catechol in the presence of potassium iodate, or by interaction with salicylidenacetone and acyclic or cyclic β-keto esters, respectively. Chemical structure of these products was confirmed on the basis of spectral analyses.

The development of anticoagulant therapy owed its effective start to synthesis and uses of Warfarin and acenocoumarole chemotherapeutics as anticoagulant agents. The presence of a common hydroxycoumarin (2*H*-1-benzopyran-2-one) moiety in such active drugs might lead to the conclusion that the latter moiety could be considered as the basic structural requirement for activity of these products as anticoagulant agents.

Prompted by these findings and the fact that *Benziodarone* drug, a benzofuran analogue, has found use as a coronary vasodilator [1], our interest was stimulated to make use of the parent compound, 7,8-diphenyl-4-hydroxy-2*H*-furo[2,3-*g*]-[1]-benzopyran-2-one (*II*) as an adaptable starting material for synthesis of novel furocoumarole and di(furocoumarole) analogues of types *II* and *IV* (see Scheme 1), that are expected to possess coronary vasodilator and/or anticoagulant activity.

Later on, it was thought noteworthy that fusion of different oxygen-containing heterocyclic fragments of structure *II* to these products might enhance their pharmacological properties. Thus, synthesis of additional members (*VII, X, XII,* and *XIII*) that accomodate these active moieties was investigated *via* oxidative coupling of furo[2,3-*g*]-[1]-benzopyranone derivative (*II*) with catechol in the presence of potassium iodate or by interaction of the former compound *II* with salicylidenacetone and acyclic or cyclic β-keto esters, respectively.

The hitherto prepared compounds might find use as possible chemotherapeutic agents of extended and/or improved activity.

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EXPERIMENTAL

Melting points of the analytical samples were determined using Gallenkamp electric melting point apparatus. Microanalyses for carbon and hydrogen were done on Heraeus elemental analyzer at the microanalytical unit, Mansoura University, Mansoura and at the microanalysis unit, N. R. C., Cairo, Egypt. Infrared spectra were recorded on an SP 2000 Pye—Unicam spectrophotometer using either potassium bromide Waffer technique or Nujol mull technique. The ^{1}H NMR spectra ($CDCl_3$) were measured on a Varian EM 360 NMR spectrometer (60 MHz) with TMS as an internal standard.

7,8-Diphenyl-4-hydroxy-2*H*-furo[2,3-*g*]-[1]-benzopyran-2-one (*II*)

6-Acetyl-2,3-diphenyl-5-methoxybenzofuran (*I*) (3.3 g; 0.01 mol) was dissolved in diethyl carbonate (40 cm^3) with shaking. The solution was cooled and excess metallic sodium (2.5 g) was added and the whole mixture was heated for about 3 h on steam bath and left to cool. The precipitated sodium salt was filtered off, washed with ether, dissolved in water and the resulting solution was extracted with ether. Acidification of the aqueous layer with acetic acid afforded a pale yellow precipitate which was filtered off and recrystallized from ethanol to give cream-coloured product of m.p. = 280 °C in 85 % yield. For $C_{23}H_{14}O_4$ (M_r = 354.34) w_i(calc.): 77.96 % C, 3.98 % H; w_i(found): 77.82 % C, 4.05 % H.

Table 1. Characterization Data for Compounds *IVa—IVc*, *Va—Vc*, and *VIa*, *VIb*

Compound	R	R′	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	M.p./°C Solvent[a]
IVa	H	–	$C_{47}H_{28}O_8$ 720.69	78.32 78.01	3.92 3.95	> 300 E
IVb	*p*-C_6H_4Br	–	$C_{53}H_{31}BrO_8$ 875.69	72.69 72.53	3.57 3.60	251—255 E
IVc	*p*-$C_6H_4NO_2$	–	$C_{53}H_{31}NO_{10}$ 841.79	75.62 75.23	3.71 3.96	244—245 E
Va	H	H	$C_{53}H_{30}O_8$ 794.77	80.09 80.41	3.80 3.66	172—174 M
Vb	OCH_3	H	$C_{54}H_{32}O_9$ 824.80	78.63 78.28	3.91 3.94	254 M
Vc	OCH_3	NO_2	$C_{54}H_{31}NO_{11}$ 869.80	74.56 74.85	3.59 3.25	267—269 A
VIa	*p*-C_6H_4Br	–	$C_{53}H_{29}BrO_7$ 857.67	74.22 74.50	3.41 3.24	> 300 A
VIb	*p*-$C_6H_4NO_2$	–	$C_{53}H_{29}NO_9$ 823.77	77.27 77.13	3.55 3.61	> 300 A

a) A = acetic acid, E = ethanol, M = methanol.

3,3′-Methylene-bis(7,8-diphenyl-4-hydroxy-2*H*-furo[2,3-*g*]-[1]-benzopyran-2-one) Derivatives *IVa—IVc*

To the benzopyran derivative (*II*) (0.7 g; 0.002 mol) suspended in ethanol (15 cm^3) aliphatic or aromatic aldehyde (0.001 mol in each case) was added and the whole mixture was refluxed on steam bath for 1 h and left to cool. The separated product was filtered off, washed with water and recrystallized as yellowish crystals in an average good yield. Characterization data for these dicoumaroles are given in Table 1.

9,10-Diphenyl-5*H*,6*H*-5-(7′,8′-diphenyl-4′-hydroxy-2′-oxo-2′*H*-furo[2′,3′-*g*]-[1]-benzopyran-3′-yl)-1-benzopyrano[3,2-*c*]furo[2,3-*g*]-[1]-benzopyran-6-one Derivatives *Va—Vc*

To a solution of *II* (1.77 g; 0.005 mol) in ethanol (30 cm^3) the *o*-hydroxy aldehyde derivative (0.0025 mol in each case) was added and the whole mixture was refluxed for 2 h. Distillation of excess solvent under reduced pressure afforded a semisolid product which was boiled for 1 h with the benzene—ethyl acetate mixture (φ_r = 3 : 1). Concentration of the latter solution to one third of its original volume followed by overnight keeping in a refrigerator afforded a granular solid that was filtered off and recrystallized in an average 70—85 % yield. Physical properties of these products are listed in Table 1.

7-Aryl-2,3,11,12-tetraphenyl-6*H*,7*H*,8*H*-difuro[2,3-*g*:2′,3′-*g*′]pyrano[3,2-*c*:5,6-*c*′]-bis-1-benzopyran-6,8-dione Derivatives *VIa* and *VIb*

To a suspension of the dicoumarole derivative *IVb* or *IVc* (0.001 mol in each case) in acetic anhydride (25 cm^3) anhydrous pyridine (5 cm^3) was added. The resulting clear solution was kept at ambient temperature for 24 h where a solid product was precipitated. Filtration of the latter solid followed by recrystallization afforded the required products as yellow crystals in an average 70 % and 73 % yield, respectively. Physical constants for these products are given in Table 1.

2,3-Dihydroxy-8,9-diphenyl-5*H*-benzofuro[3,2-*c*]-furo[2,3-*g*]-[1]-benzopyran-5-one (*VII*)

To a well stirred mixture of the furobenzopyran derivative (*II*) (2.1 g; 0.006 mol), catechol (0.1 g), and sodium acetate (4 g) in acetone—water mixed solvent (50 cm^3, φ_r = 1 : 1) a solution of potassium iodate (1 g) and sodium acetate (2 g) in water (10 cm^3) was added slowly and the whole mixture was left to stand for 1 h. The so formed precipitate was

Table 2. Characterization Data for Compounds *VII*, *X*, *XII*, and *XIII*

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	M.p./°C Solvent[a]
VII	$C_{29}H_{16}O_6$ 460.42	75.65 75.92	3.50 3.32	> 300 E
X	$C_{33}H_{22}O_5$ 498.51	79.50 79.33	4.45 4.51	259—261 A
XII	$C_{27}H_{16}O_5$ 420.40	77.13 77.25	3.84 3.93	135—137 A
XIII	$C_{42}H_{26}O_5$ 610.63	82.61 82.44	4.29 4.24	210—212 A

a) A = acetic acid, E = ethanol.

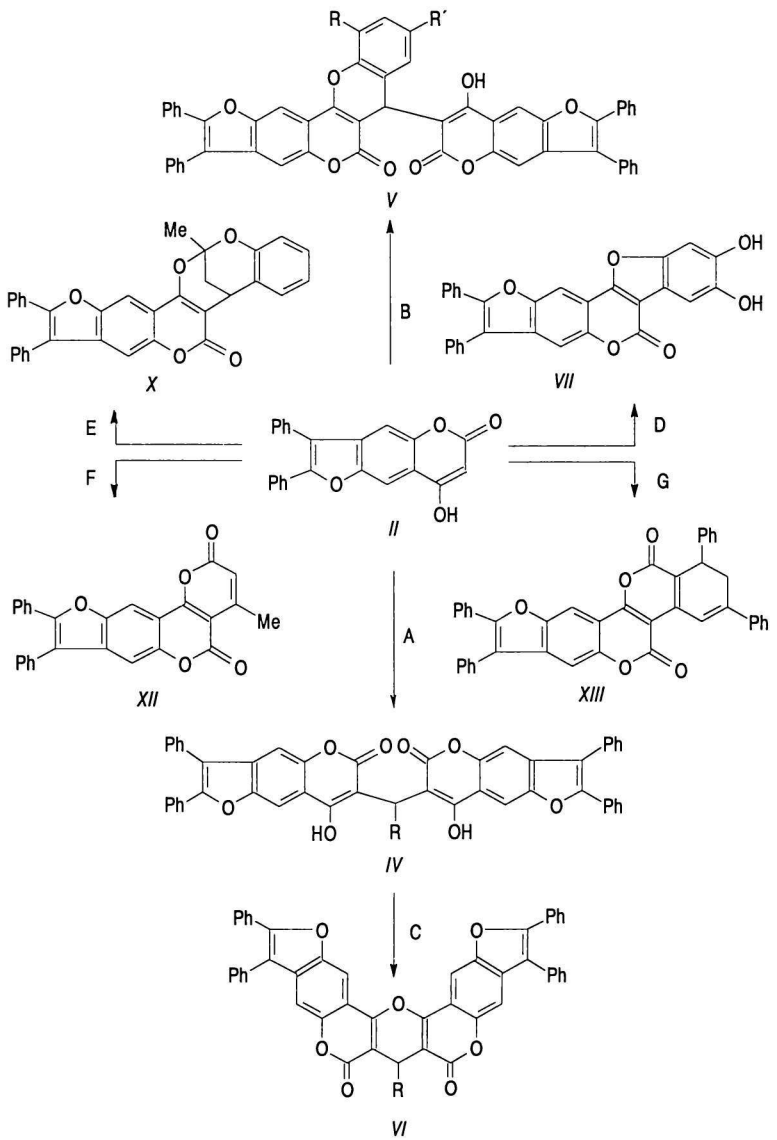
filtered off, washed with water and recrystallized to give a pure crystalline pale yellow solid in 70 % yield (*cf.* Table 2).

9,10-Diphenyl-14-methyl-5,14-methano-5*H*,6*H*-furo[2,3-*g*]-[1]-benzopyrano[4,3-*d*]-[1,3]-benzodioxocin-6-one (*X*)

To a solution of salicylidenacetone (0.2 g; 0.01 mol) in anhydrous pyridine (10 cm^3) the hydroxyfurobenzopyran derivative *II* (3.5 g; 0.01 mol) was added. The mixture was refluxed for 1 h, left to cool and then poured into excess water. Acidification to pH 1, using 5 M hydrochloric acid, and subsequent stirring for 30 min afforded a dark product which was filtered off, washed with 70 % aqueous ethanol, dried and recrystallized to give compound *X* as brown crystals in 85 % yield (*cf.* Table 2).

8,9-Diphenyl-4-methyl-2*H*, 5*H*-furo[2,3-*g*]pyrano-[3,2-*c*]-[1]-benzopyran-2,5-dione (*XII*) and 1,3,8,9-Tetraphenyl-1*H*,2*H*,5*H*,13*H*-furo[2,3-*g*]-[2]-benzopyrano[4,3-*c*]-[1]-benzopyran-5,13-dione (*XIII*)

A mixture of *II* (3.5 g; 0.01 mol), acyclic or cyclic β-keto ester (0.01 mol in each case), and ammonium acetate (3.85 g; 0.05 mol) was fused for 1 h in an oil bath at 200 °C where ethanol and ammonia were liberated during the first 30 min. The obtained solid product was broken up and the unreacted starting



A ≡ condensation with aldehydes
B ≡ condensation with *o*-hydroxyaldehydes
C ≡ acetic anhydride and pyridine
D ≡ oxidative coupling with catechol
E ≡ salicylidenacetone
F ≡ acyclic β-keto esters
G ≡ cyclic β-keto esters

Scheme 1

materials were removed by overnight stirring with sodium carbonate solution (w = 4 %; $\overline{V}$ = 150 cm^3). The residual material was collected by filtration and recrystallized to give yellow and orange crystals of the desired products *XII* and *XIII*, respectively (*cf.* Table 2).

RESULTS AND DISCUSSION

Synthesis of the hitherto prepared compounds was accomplished in accordance with the sequence of reactions that are given in Scheme 1.

The parent 7,8-diphenyl-4-hydroxy-2*H*-furo[2,3-*g*]-[1]-benzopyran-2-one (*II*) was synthesized by treatment of 6-acetyl-2,3-diphenyl-5-methoxybenzofuran (*I*) [2] with diethyl carbonate in the presence of powdered sodium. The formation of *II* may be effected through ethoxycarbonylation of *I* and subsequent cyclization of the resulting intermediate, β-keto ester *III* as illustrated in Scheme 2. Compound *II* was found to be identical in all aspects (melting point and mixed melting point) with an authentic sample prepared by an alternative synthetic route [3].

The IR spectra of this compound showed an intense absorption band at $\tilde{\nu}$ = 1660 cm^{-1} that was assigned, in accordance to an earlier report [4], to the lactonyl CO function of hydroxy-1-benzopyran moiety.

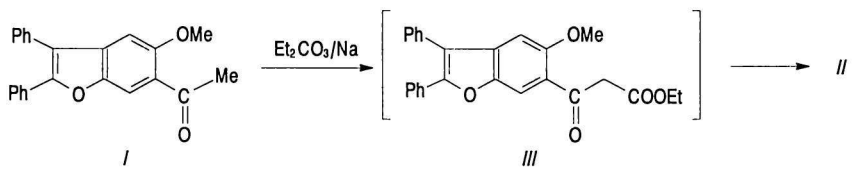
Synthesis of di(furocoumarole) analogues *IVa—IVc* was effected by condensation of *II* with some selected aliphatic and/or aromatic aldehydes. Supporting evidence for the structure of these dicoumarole analogues was inferred from spectral data. IR spectra of these products displayed characteristic absorption band near $\tilde{\nu}$ = 1660 cm^{-1} that might be attributed to the lactonyl CO group of benzopyran moiety. Besides the appearance of a singlet signal for the two hydroxy protons at δ = 7.80 (exchangeable with D_2O), ^{1}H NMR spectrum of compound *IVa* revealed additional signals at δ = 1.4 and 6.80—7.70 for aromatic and methylene protons, respectively.

On the other hand, when compound *II* was allowed to react with 2-hydroxybenzaldehydes, namely 2-hydroxy-, 2-hydroxy-3-methoxy-, and 2-hydroxy-3-methoxy-5-nitrobenzaldehyde, the corresponding 5-(furo[2′,3′-*g*]-[1]-benzopyran-3′-yl)-[1]-benzopyrano[3,2-*c*]furo[2,3-*g*]-[1]-benzopyran-6-one derivatives *Va—Vc* were formed in a good yield.

Structures *Va—Vc* were supported by spectral data. IR spectrum of *Va* exhibited characteristic absorption bands at $\tilde{\nu}$ = 1660 cm^{-1} and 1720 cm^{-1} corresponding to the two δ-lactone moieties. ^{1}H NMR spectrum of *Vc* displayed three signals at δ = 6.80—7.80 (br, m, H_{arom}, O<u>H</u>), 3.9 (s, C<u>H</u>$_3$O), and 1.45 (s, C<u>H</u> proton).

Dehydration of dicoumaroles (*IVa, IVb*) using acetic anhydride in the presence of anhydrous pyridine furnished a third group of di(furocoumarole) analogues (*VIa, VIb*). IR spectra of these products revealed one type of carbonyl absorptions nearby $\tilde{\nu}$ = 1730 cm^{-1} assignable to lactonyl CO function in these molecules.

Incorporation of both benzofuran and furo[2,3-*g*]-[1]-benzopyran moieties in one structure was achieved *via* oxidative coupling of catechol with *II* in the presence of potassium iodate. Besides correct elemental analysis, structure of *VII* was confirmed from its spectral behaviour. Its IR spectra revealed intense absorptions at $\tilde{\nu}$ = 3350 cm^{-1} and 1730 cm^{-1} that might be assigned to the OH and lactonyl CO functions, respectively. ^{1}H NMR spectrum of this product showed a broad multiplet at δ = 6.30—7.60 corresponding to the aromatic and hydroxy protons.

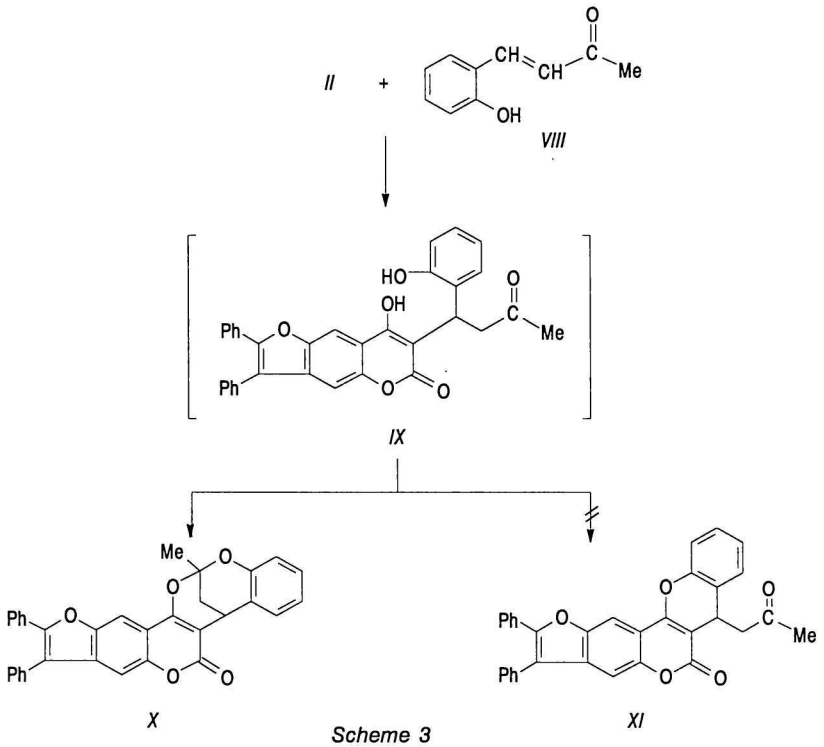


Scheme 2

This kind of oxidative coupling reactions finds support from the previously reported work of *Wanzlick et al.* [5] for the synthesis of Welelactone analogues.

Michael condensation of benzopyran-2-one derivatives with benzalacetone and *p*-nitrobenzalacetone afforded the corresponding Warfarin [6] and acenocoumarole [7], anticoagulant agents, respectively. The importance of the former drug as anticoagulant agent especially as a rat poison, through intensive increase in bleeding of these animals till death, prompted us to try the synthesis of new Warfarin analogues starting from the already available furo[2,3-*g*]benzopyran derivative *II*. Treatment of *II* with salicylidenacetone (*VIII*) in anhydrous pyridine furnished the furo[2,3-*g*]-[1]-benzopyrano[4,3-*d*]-[1,3]-benzodioxocine derivative *X* rather than the Warfarin analogue *XI*. The formation of *X* might be reconciled on the basis of cyclization of the intermediate structure *IX* (*cf.* Scheme 3).

Preference of structure *X* rather than *XI* was supported by spectral analyses. IR spectrum of this product revealed the absence of any absorption for acetyl CO group and the appearance of an intense absorp-



Scheme 3

tion band at $\tilde{\nu}$ = 1720 cm^{-1} that might be assigned to the lactonyl CO function. Besides a multiplet signal for aromatic protons, ^{1}H NMR spectrum revealed three signals at δ = 2.00, 2.20, and 4.15 corresponding to the methyl, methano, and benzylic protons, respectively.

Recently, Pechmann reaction has found extensive application [8] in the field of preparation of a lot of naturally occurring coumarin analogues. New modification for this reaction was introduced by *Kappe et al.* [9—11], who used β-enamino esters in an interaction with electron-rich phenols to afford the desired coumarin derivatives in an excellent yield. On these bases, compound *II* was allowed to react with acyclic or cyclic β-keto esters in the presence of ammonium acetate as a source of ammonia, to give the corresponding pyrano[3,2-*c*]- and -[2]-benzopyrano[4,3-*c*]furo[2,3-*q*]benzopyranone derivatives *XII* and *XIII*, respectively. IR spectra of each of these products exhibited two absorption bands nearby $\tilde{\nu}$ = 1770 cm^{-1} and 1730 cm^{-1} for the two lactonyl CO groupings.

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