CHEMISTRY OF HETEROANALOGS OF ISOFLAVONES

I. SYNTHESIS OF FURAN AND BENZOFURAN ANALOGS OF ISOFLAVONES

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3-Hetaryl-7-methoxychromones were obtained by reaction of α-(5-ethoxycarbonyl-2-furyl)-, α-(2-benzofuryl)-, and α-(2-methoxy-carbonyl-5-benzofuryl)-2-hydroxy-4-methoxyacetophenones with methyl formate or ethyl orthoformate, and 3-hetaryl-4-hydroxy-7-methoxy-coumarins were obtained by reaction of the same compounds with diethyl carbonate. Methods for the synthesis of 3-hetaryl-7-hydroxy-chromones from α-furyl- and α-benzofuryl-substituted, 2,4-dihydroxyacetophenones were investigated.

We have described the reactions of α-furyl- and α-benzofuryl-2,4-dihydroxyacetophenones with some halides and anhydrides of carboxylic acids that lead to the formation of 2-substituted 3-hetarylchromones [1-4]. In a continuation of these investigations we have studied reactions leading to furan and benzofuran analogs of natural isoflavones that do not contain substitutents in the 2 position of the chromone system. With this end in mind, we subjected α-hetaryl-2-hydroxy-4-methoxyacetophenones (Ia-e) to reaction with excess methyl formate in the presence of sodium tert-butoxide at 35-40° C via the Claisen condensation (method A) (a similar reaction of o-hydroxyphenyl benzyl ketones with ethyl formate and sodium is known [6]). Compounds II, which are formed in the first step, were converted to chromones containing 2-hydroxychromanones III by treatment with an acid buffer (pH 0.5-1). 2-Hydroxychromanones III were readily dehydrated to chromones IV by heating the reaction mixture with alcoholic hydrochloric acid. The amounts of contaminating 2-hydroxychromanones were insignificant in the case of the formation of chromones IVa,b. On the other hand, in the closing of acetophenone Id intermediate IIId was present in large amounts. Treatment of α-formylacetophenone IId with 1% hydrochloric acid gave an individual compound, which apparently is the corresponding 2-hydroxychromanone (IIId), inasmuch as chromone IVd was formed as a result of dehydration during its recrystallization from methanol or during the determination of its melting point. In contrast to 2-hydroxy-3-hetarylchromanones, 2-hydroxyisoflavones are more stable and can be obtained in analytically pure form [7].

In the reaction of ketones Ic,e with methyl formate, trans esterification of the ester group occurred along with the formation of a chromone system, as a result of which chromones with melting points identical to the melting points of IVb and IVd were isolated. The fact that acetophenone Ic was converted to chromone IVc on reaction with ethyl formate under similar conditions also served as proof of the observed transesterification. Chromone IVc, like chromone IVb, was obtained from acetophenone Ic and methyl formate, and reacts with ethanolamine to give the same compound (VII).

In order to obtain chromones IVa, b, d we also used another method [8] – acetophenones Ia, b, d were heated in pyridine with ethyl orthoformate in the presence of catalytic amounts of piperidine (method B). (See scheme on following page.)

3-Hetaryl-4-hydroxy-7-methoxycoumarins Va, c, d, the structure of which is confirmed by the UV and IR spectra (Table 1), were obtained as a result of the reaction of ketones Ia, c, d with diethyl carbonate under the conditions of the Claisen condensation with sodium tert-butoxide as the catalyst.

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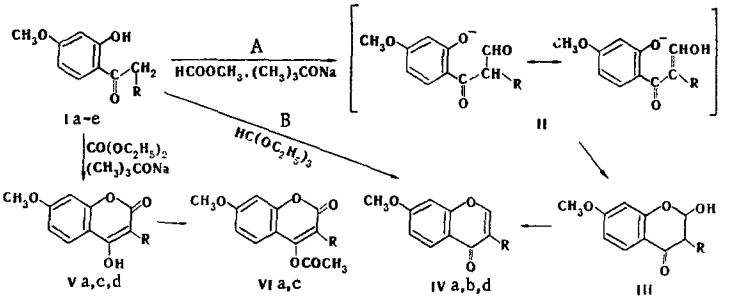
TABLE 1. 3-Hetarylcoumarins V and VI (the formulas are in the text)

Compound	mp, °C (from ethanol)	Empirical formula	Found, % C	Found, % H	Calc., % C	Calc., % H	UV spectrum[a] ε	UV spectrum[a] λ_{max}, nm	IR spectrum, absorption band, cm^{-1}: coumarin C = O	ester C = O	ester C—O	coumarin C = C	furan C = C	furan C—O	out-of-plane CH for the benzene ring	OH	Yield, %
Va	238[b]	$C_{18}H_{12}O_5$	69,4	3,8	70,1	3,9	28000	357	1698 s 1680s 1650 s			1610 s 1600 s 1586 s	1620 m	1258 s 1250 s 1242 s 1280 s	815 m 850 m 805 m 840 m 850 m	3390 m 3370 m 3400 m	96
Vd	220	$C_{20}H_{14}O_7$	64,9	4,3	65,6	3,8	15800	308		1700 s	1203 m						90
Vc	193	$C_{17}H_{14}O_7$	61,2	4,1	61,8	4,3	16800	357	1700 s	1715 s	1200 s	1610 s		1255 s 1295 s	807 s 843 m	3390 s	89
VIa	186	$C_{20}H_{14}O_6$	67,7	3,9	68,5	4,0	29600	363	1722 s	1770 s	1210 s	1610 s	1628 s	1266 m 1288 s	820 s 867 w		80
VIc	202[c]	$C_{19}H_{16}O_8$	61,3	4,4	61,3	4,3	29600	362	1715 s	1730 s 1770 s	1200 s 1219 s	1610 s	1628 m	1280 s	830 m 844 s		95

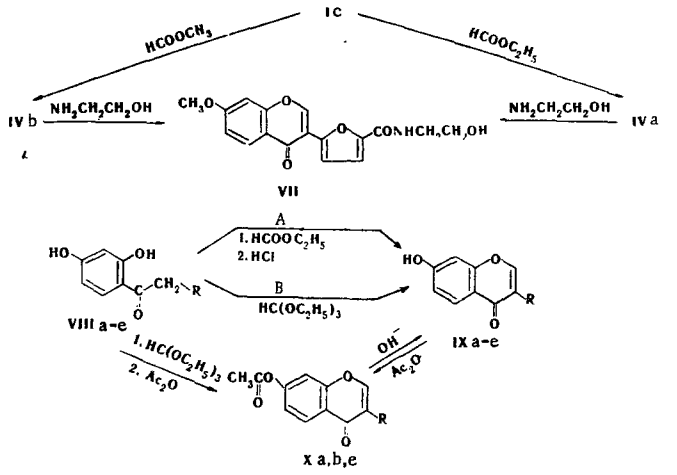
[a] Obtained from $5 \cdot 10^{-5}$ M solutions in dioxane. [b] From toluene. [c] From benzene–hexane (1 : 1).



*Here and subsequently, aR = 2-benzofuryl; bR = 2-methoxycarbonyl-5-furyl; c R = 2-ethoxycarbonyl-5-furyl; d R = 2-methoxycarbonyl-5-benzofuryl; e R = 2-ethoxycarbonyl-5-benzofuryl.

The opinion that only those polyhydroxacetophenones in which all of the hydroxyl groups are protected except the 2-OH group that participates in the formation of the pyrone rings can undergo the Claisen reaction with methyl formate in the presence of sodium metal was propagated in [9]. We have shown that unprotected α-hetaryl-2,4-dihydroxyacetophenones VIIIa and VIIIc [2, 4] undergo the reaction with formic acid esters in the presence of sodium tert-butoxide, and the corresponding 7-hydroxychromones IXa, c (method A) are formed after treatment of the reaction mixture with 1% hydrochloric acid, but the yields of products are somewhat lower than in the case of ketones with a protected 4-hydroxy group.

In the synthesis of 7-hydroxychromones IXa-e by method B it was found to be convenient in some cases (IXa, b) to immediately acylate the crude reaction products and to subsequently deacylate their individual acetyl derivatives (Xa, b) to 7-hydroxy compounds. Chromone IXa was also obtained by heating the appropriate 7-methoxy compound IVa or chromone XI, which we obtained in [2], with pyridine hydrochloride by the method in [10].



Attempts to demethylate 7-methoxy derivatives IVb, d or to remove the 2-ethoxycarbonyl group in 3-(5-ethoxycarbonyl-2-furyl)- or 3-(2-ethoxy-carbonyl-5-benzofuryl)-7-hydroxychromones [1, 3] were unsuccessful in view of the pronounced resinification of the reaction products when the reaction mixtures were heated.

The structures of the chromones obtained are confirmed by the UV and IR spectra (Tables 2 and 3).

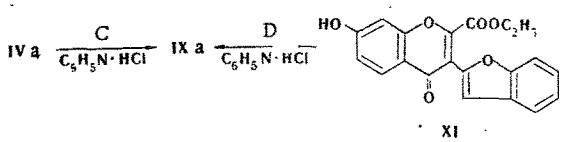
TABLE 2. Furan and Benzofuran Analogs of Isoflavones (see the formulas in the text)

Compound	mp, °C	λ_{max}, nm ($\varepsilon \cdot 10^{-4}$)[a]	Empirical formula	Found, % C	Found, % H	Calc., % C	Calc., % H	Yield, % A	Yield, % B
IV a	204 b	284 (3,88), 295 (3,44), 308 (2,84)	$C_{18}H_{12}O_4$	73,8	4,1	73,9	4,1	91	73
IV b	225 c	289 (3,60)	$C_{16}H_{12}O_6$	64,3	4,4	64,0	4,0	90	58
IV d	244 c	272 (3,60), 283 (3.10), 305 (1,90)	$C_{20}H_{14}O_6$	68,8	4,1	68,6	4,0	89	85
IV c	161 d	289 (3,36)	$C_{17}H_{14}O_6$	65,0	4,6	65,0	4,5	70	
X a	201 e	275 (5,50), 300 (4,01), 313 (3,92)	$C_{19}H_{12}O_5$	71,0	4,0	71,2	3,8		54
X b	202 e	280 (3,40), 305 (3,18)	$C_{17}H_{12}O_7$	62,0	4,0	62,2	3,7		72
X e	238 e	275 (2,85), 305 (1,50)	$C_{22}H_{16}O_7$	67,1	3,9	67,3	4,1		68
IX a	308 f	284 (3,70), 295 (3,52), 307 (3,00)	$C_{17}H_{10}O_4$	73,3	4,0	73,4	3,6	83	95g
IX c	231 d	295 (3,25)	$C_{16}H_{12}O_6$	63,8	4,1	64,0	4,0	56	77
IX b	245 d	298 (5,45)	$C_{15}H_{10}O_6$	62,8	3,9	62,9	3,6		92g
IX d	304 h		$C_{19}H_{12}O_6$	67,6	3,8	67,9	3,6		86
IX e	256 b	260 (4,20), 300 (2,50)	$C_{20}H_{14}O_6$	68,5	3,9	68,6	4,0		85

[a] The UV spectra of Xa, b, e and IXc, b, e were obtained from $2.5 \cdot 10^{-5}$ M solutions in ethanol, those of IVa-c and Xb were obtained from solutions in ethanol-dioxane (40 : 1), and that of IVd was obtained from a dioxane solution. [b] From propanol. [c] From dioxane. [d] From ethanol. [e] From benzene. [f] From butanol. [g] The yield was based on the acetyl derivative. [h] From dimethylformamide.

TABLE 3. IR Spectra of Furan and Benzofuran Analogs of Isoflavones

Compound	ν or δ, cm^{-1}: chromone C=O	ester C=O	chromone C=C	furan C=C	furan C–O	phenolic C–O	out-of-plane CH for the benzene ring		OH
IVa	1636 s		1598 s	1620 s	1228 m 1250 s	1260 s	860 s	896 w	
IVb	1645 s	1722 s	1598 s	1620 s	1210 s	1255 s	825 s	850 s	
IVd	1635 s	1730 s	1598 s	1625 s	1238 m	1261 s	820 m	860 m	
Xa	1660 s	1770 s	1590 w	1625 m	1230 s	1253 m 1263 w	830 s	875 m	
Xb	1670 s	1768 s 1740 w	1589 w	1630 m	1231 s	1275 w	812 s	865 m	
IXa	1631 s		1595 s		1210 s 1290 s	1260 s	820 m	875 m	3100 w
IXc	1665 s	1710 s	1590 w 1610 s	1635 s	1235 s	1268 s	815 m	847 m 865 m	3395 s
IXd	1640 s	1722 s	1580 m 1610 m		1238 m	1255 m	840 m		3320 s



XI

EXPERIMENTAL

The UV spectra were recorded with Unicam SP-800 and SF-4A spectophotometers. The IR spectra of KBr pellets of the compounds were recorded with UR-10 and Unicam SP-200G spectrometers.

α-(5-Methoxycarbonyl-2-furyl)-2-hydroxy-4-methoxyacetophenone (Ib). A 1.14-ml (12 mmole) sample of dimethyl sulfate and 4.95 g (36 mmole) of freshly calcined potassium carbonate were added to a hot solution of 3.3 g (12 mmole) of α-(5-methoxycarbonyl-2-furyl)-2,4-dihydroxyacetophenone [1] in 240 ml of absolute benzene, after which the mixture was refluxed for 6 h. The inorganic precipitate was then removed by filtration, the filtrate was acidified with three to four drops of glacial acetic acid, and the solution was vacuum evaporated (with a water aspirator). The residue was crystallized from methanol to give 2.9 g (83 %) of colorless needles with mp 97°. Found: C 61.8; H 5.1 %. $C_{15}H_{14}O_6$. Calculated: C 62.1, H 4.9%.

α-(2-Ethoxycarbonyl-5-benzofuryl)-2-hydroxy-4-methoxyacetophenone (Ie). This compound was similarly obtained from 2.6 g (7.65 mmole) of α-(2-ethoxycarbonyl-5-benzofuryl)-2,4-dihydroxyacetophenone [3] in 120 ml of acetone, 0.8 ml (8.4 mmole) of dimethyl sulfate, and 3.17 g (23 mmole) of potassium carbonate. The yield of colorless needles with mp 135° (from alcohol) was 2.2 g (82%). Found: C 67.4; H 5.3%. $C_{20}H_{18}O_6$. Calculated: C 67.7; H 5.1%.

3-Hetaryl-7-methoxychromones (IVa, b, d). Method A. A 10-mmole sample of sodium tert-butoxide was added with stirring in an atmosphere of an inert gas to a cooled (to 0-3°) solution of 1 mmole of acetophenone Ia-e in absolute methyl or ethyl formate. After 10-15 min, the mixture was heated to 35-40°, and stirring was continued for 4-8 h. The solvent was then evaporated, and the calculated amount of an acid buffer [concentrated hydrochloric acid–glacial acetic acid (1 : 1)] and 1-2 ml of water were added to the dry residue. When this is done, the pH of the reaction mixture should be 0.5-1. The initially formed oil solidified completely on standing. A solution or suspension of the reaction product in alcohol was refluxed for 30 min with hydrochloric acid (0.5 ml of concentrated hydrochloric acid per gram of the compound), after which the solution was cooled, and the resulting precipitate was removed by filtration and washed to free it of acid.

Method B. A 1-mmole sample of acetophenone and 6 mmole of orthoformate ester were heated in 1 ml of absolute pyridine with two drops of piperidine at 120-130° for 1-4 h [the end of the reaction was determined from a negative test of a sample of the reaction mixture with an alcohol solution of ferric chloride or by means of thin-layer chromatography (TLC) on Merck silica gel G in benzene–ethanol (90 : 10 or 95 : 5)]. The mixture was cooled, and the resulting precipitate was removed by filtration and washed successively on the filter with a small amount of pyridine, alcohol, and ether.

3-[5-N-(2-Hydroxyethylcarbamido)-2-furyl]-7-methoxychromone (VII). A solution of 0.18 g (0.57 mmole) of chromone IVc and 0.18 ml (2.86 mmole) of ethanolamine in 1.6 ml of absolute alcohol was refluxed for 3 h, after which the mixture was cooled, and the resulting precipitate was removed by filtration to give 0.16 g (85%) of colorless needles with mp 192-5° (from methanol). Found: N 4.7%. $C_{17}H_{15}NO_6$. Calculated: N 4.3%. Compound VII was similarly obtained from chromone IVb in 35% yield (dioxane was used as the solvent).

3-Hetaryl-4-hydroxy-7-methoxycoumarins (Va, c, d). A 10-mmole sample of sodium tert-butoxide was added with stirring in an inert gas atmosphere at room temperature to a solution of 1 mmole of acetophenone Ia, c, d in absolute diethyl carbonate, and the mixture was stirred at 120-130° for 4 h. The solvent was then evaporated, and the dry residue was transferred to 40-50 ml of water. The mixture was acidified with dilute hydrochloric acid to pH 2-3, and the resulting precipitate was removed by filtration.

3-Hetaryl-4-acetoxy-7-methoxycoumarins (VIa, c). A solution of 1 mmole of coumarin Va, c in 6 ml of absolute acetic anhydride was refluxed for 10 min, after which the mixture was allowed to stand at room temperature for 24 h. It was then added to ice water, and the resulting precipitate was removed by filtration and washed thoroughly with water.

3-Hetaryl-7-hydroxychromones. Method A. The method used to prepare chromones IV was used to obtain IXa, c from α-hetaryl-2,4-dihydroxyacetophenones VIIIa, c and ethyl formate. After removal of the ethyl formate, the reaction mixture was treated with the calculated amount of 1% hydrochloric acid. When the intermediate 2-hydroxychromanone (of the III type) was present, the mixture was refluxed for ~30 min in alcohol containing hydrochloric acid.

Method B. As in the preparation of chromones IV, IXa-e were obtained from acetophenones VIIIa-e and orthoformate ester in pyridine in the presence of a few drops of piperidine. Chromones IXc-e precipitated at the end of the reaction, whereas chromones IXa, b were isolated by treatment of the reaction mixtures with water, and the IXa, b were immediately converted to acetyl derivatives Xa, b by treatment with acetic anhydride in pyridine at room temperature (4 moles of acetic anhydride per mole of chromone). After 24 h, the resulting precipitate was removed by filtration and washed on the filter with ether. A 0.6-ml sample of 5% sodium hydroxide solution was added to a hot acetone solution or suspension of 1 mmole of 7-acetoxy derivative Xa, b, the solution was diluted to twice its volume with water, and the mixture was refluxed for 5 min. It was then acidified with dilute hydrochloric acid, and the resulting precipitate was removed by filtration from the cold solution.

3-(2-Benzofuryl)-7-hydroxychromone (IXa). Method C. A mixture of 0.58 g (2 mmole) of IVa and 2.08 g (18 mmole) of pyridine hydrochloride was heated at 170-180° for 8 h, after which it was added to 50 ml of water. The resulting precipitate was removed by filtration and washed thoroughly with water to give 0.31 g (56%) of IXa.

Method D. A mixture of 1.05 g (3 mmole) of chromone XI and 3.12 g (27 mmole) of pyridine hydrochloride was heated at 160-170° for 10 h, after which it was added to 70 ml of water, and the resulting precipitate was removed by filtration to give 0.5 g (60%) of IXa.

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