3-FURYLCHROMONES

V. P. Khilya, L. G. Grishko, and V. Szabo

UDC 547.814.5'722:542.953

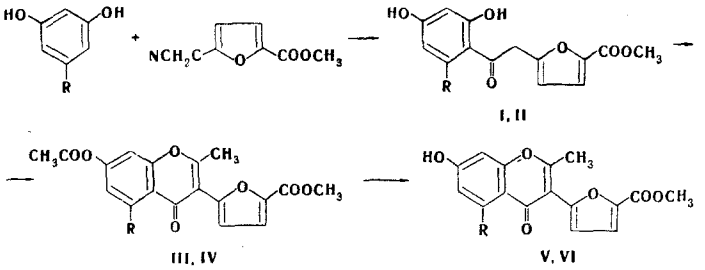
α-[2-(5-Methoxycarbonyl)furyl]-2,4-dihydroxy- and 2,4,6-trihydroxyacetophenones were obtained by the condensation of polyphenols with (2-methoxycarbonyl-5-furyl)acetonitrile. 7-Acetoxy- and 5,7-diacetoxy-2-methyl-3-[2-(5-methoxycarbonyl)furyl]chromones were obtained from them by reaction with acetic anhydride in the presence of triethylamine and were subsequently deacylated to 7-hydroxy and 5,7-dihydroxy compounds. 7-Hydroxy- and 5,7-dihydroxy-2-ethoxycarbonyl-3-[2-(5-methoxycarbonyl)furyl]chromones were obtained from the indicated acetophenones by reaction with ethoxalyl chloride.

There is information available that compounds obtained from 7-hydroxyisoflavone are medicinal preparations [1, 2] with cardiac action. Isoflavone analogs with pyridine rings in the 3 position have a strong physiological action [3]. Those that contain a furan ring condensed with the benzene ring of flavone are encountered among natural flavonoids [4, 5]. In this connection, we undertook an attempt to synthesize new compounds from a 7-hydroxychromone containing a furan ring in the 3 position.

We have worked out conditions for carrying out the Hoesch reaction between 2-methoxycarbonyl-5-furylacetonitrile and polyatomic phenols that make it possible to obtain polyhydroxyacetophenones I and II in 60-70% yields.

An attempt to accomplish the reaction of 2-methoxycarbonyl-5-furylacetonitrile with other phenols (phenol, β-naphthol, and resorcinol dimethyl ether) was unsuccessful in view of the pronounced resinification of the reaction mixture during hydrolysis.

Acetophenones I and II were converted to chromones by heating with acetic anhydride in the presence of triethylamine [6]:



I, II

III, IV

V, VI

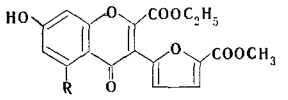
I, III, V R=H; II, VI R=OH; IV R=OCOCH$_3$

Acetyl derivatives III and IV were converted to the corresponding hydroxy compounds (V and VI) by heating with 5% alkali solution.

Acetophenones I and II were also cyclized to chromones by the method in [7] by treating them with ethoxalyl chloride:

T. G. Shevchenko Kiev State University. L. Kossuth Debrecen University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1317-1320, October, 1972. Original article submitted July 28, 1971.

I, II —



VII, VIII

VII R=H; VIII R=OH

Compounds V-VIII were alkylated with alkyl halides and ethyl bromoacetate. Several compounds with ester groups were saponified to compounds with carboxyl groups for convenience in testing for physiological activity. The data on the synthesized compounds are presented in Table 1. The UV spectra in alcohol solution were measured for most of the new compounds obtained. Isoflavones usually have one major absorption maximum at 250-270 nm [8]. As seen from Table 1, the major absorption maximum of the 3-furylchromones is found at 280-295 nm. Thus, replacement of the phenyl ring by a furan ring in 3-chromone is accompanied by a shift in the major absorption maximum to the long-wave region by an average of 20-35 nm.

The IR spectra of I-XX contain absorption bands [9-11] at 1650 cm^{-1} (chromone $\nu_{C=O}$), 1580, 1600-1610 cm^{-1} (chromone $\nu_{C=C}$), 3200-3290 cm^{-1} (ν_{OH}), 1725-1745 cm^{-1} (ester $\nu_{C=O}$), 1150, 1300-1310 cm^{-1} (ester ν_{C-O}), 1260 cm^{-1} (phenol ν_{C-O}), 1220 cm^{-1} (furan ν_{C-O}), 1630 cm^{-1} (furan $\nu_{C=C}$), 1445, 1370 cm^{-1} ($\delta_{as,s}$ CH_3), 2960, 2850 cm^{-1} ($\nu_{as,s}$ CH_3), 860, 900 cm^{-1} (out-of-plane δ_{C-H} for a 1,2,4-trisubstituted benzene ring with two adjacent and one isolated hydrogen atoms) [9-11].

EXPERIMENTAL

The purity of the individual compounds and the course of the reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel G with elution by dichloroethane–methanol (95 : 5 or 90 : 10). Most of the compounds obtained have blue fluorescence on irradiation with UV light.

The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrophotometer.

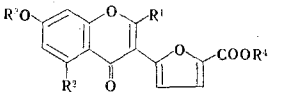
α-(5-Methoxycarbonyl-2-furyl)-2,4-dihydroxyacetophenone (I). A rapid stream of dry hydrogen chloride was bubbled with stirring and cooling to 0° into a solution of 2 g (12.1 mmole) of 2-methoxycarbonyl-5-furylacetonitrile [12] in 25 ml of benzene for 30 min, after which a solution of 1.6 g (14.5 mmole) of sublimed resorcinol and 0.8 g (6 mmole) of fused zinc chloride in 15 ml of absolute ether was added in portions in the course of 5-7 min. Stirring and bubbling-in of hydrogen chloride were continued for another 20 min, and when intensive oil formation commenced, stirring was discontinued; hydrogen chloride was bubbled into the mixture for another 30-60 min. The resulting mobile, rose oil gradually solidified. The reaction mixture was allowed to stand for 3-5 h at 0°, and the solvent was decanted from the precipitate, which was washed and triturated twice with dry ether. It was then added to 100 ml of hot water, and the mixture was allowed to stand for 10 min at 80-90°. The resulting light-yellow powder was removed from the hot solution by filtration and washed on the filter with hot water to give 2-2.4 g (60-70%) of needles with mp 186° (from aqueous acetone). Found: C 60.6; H 4.4%. $C_{14}H_{12}O_6$. Calculated: C 60.9; H 4.4%.

α-(5-Methoxycarbonyl-2-furyl)-2,4,6-trihydroxyacetophenone (II). A mixture of 4.5 g (36 mmole) of phloroglucinol, 6 g (36 mmole) of 2-methoxycarbonyl-5-furylacetonitrile, and 3.5 g (24 mmole) of anhydrous zinc chloride in 130 ml of absolute ether was saturated with dry hydrogen chloride at 0°. After a certain excess HCl pressure had been created, the mixture was allowed to stand overnight in a refrigerator. The ether was decanted, and the residual oil was triturated twice with dry ether, 180 ml of hot water was added, and the mixture was refluxed for 1 h to give 7.5 g of yellow crystals with mp 239-240° (dec.). Crystallization from aqueous alcohol or aqueous acetone gave a product with mp 242° (dec.). Found: C 57.6; H 4.1%. $C_{14}H_{12}O_7$. Calculated: C 57.5; H 4.1%.

2-Methyl-3-(5-methoxycarbonyl-2-furyl)-7-acetoxychromone (III). A mixture of 2 g (7.25 mmole) of I, 4.3 ml (45 mmole) of acetic anhydride, and 5.7 ml (35 mmole) of triethylamine was heated at 150-160° for 5 h. It was then poured into 70 ml of water containing 7 mole of hydrochloric acid per mole of acetophenone used. The resulting oil soon began to solidify, and the solid was washed repeatedly with water until the odor of acetic anhydride and triethylamine was absent. The yield of colorless needles was 2.5 g.

2-Methyl-3-(5-methoxycarbonyl-2-furyl)-5,7-diacetoxychromone (IV). This compound was similarly obtained.

TABLE 1



Compound	R^1	R^2	R^3	R^4	mp, °C	λ_{max}, nm	Empirical formula	Found, %		Calc., %		Yield, %
								C	H	C	H	
III	CH_3	H	$COCH_3$	CH_3	137	280	$C_{18}H_{14}O_7$	63,3	4,1	63,2	4,1	98
IV	CH_3	$OCOCH_3$	$COCH_3$	CH_3	141,5	280	$C_{20}H_{16}O_9$	59,7	4,1	60,0	4,0	94
V	CH_3	H	H	CH_3	219	—	$C_{16}H_{12}O_6$	63,8	4,0	64,0	4,0	~100
VI	CH_3	OH	H	CH_3	268 †	—	$C_{16}H_{12}O_7$	61,0	4,0	60,8	3,8	~100
VII	$COOC_2H_5$	H	H	CH_3	196,5	290	$C_{18}H_{14}O_8$	60,3	3,9	60,3	4,0	~100
VIII	$COOC_2H_5$	OH	H	CH_3	197	—	$C_{18}H_{14}O_9$	56,6	4,0	57,8	3,8	95
IX*	CH_3	H	CH_3	CH_3	164	287	$C_{17}H_{14}O_6$	65,0	4,5	65,0	4,5	94
X	CH_3	H	C_2H_5	CH_3	146	—	$C_{18}H_{16}O_6$	65,9	5,2	65,8	4,9	~100
XI	CH_3	H	C_3H_7	CH_3	127,5	—	$C_{19}H_{18}O_6$	67,0	5,4	66,7	5,3	82
XII	$COOC_2H_5$	H	CH_3	CH_3	178	285	$C_{19}H_{16}O_8$	61,3	4,5	61,3	4,3	~100
XIII	$COOC_2H_5$	H	C_2H_5	CH_3	167	285	$C_{20}H_{18}O_8$	62,4	4,9	62,2	4,7	~100
XIV	$COOC_2H_5$	H	C_3H_7	CH_3	127,5	—	$C_{21}H_{20}O_8$	63,2	5,3	63,0	5,0	~100
XV	$COOC_2H_5$	H	C_4H_9	CH_3	134	285	$C_{22}H_{22}O_8$	63,6	5,3	63,8	5,4	50
XVI	CH_3	H	$CH_2COOC_2H_5$	CH_3	153	285	$C_{20}H_{18}O_8$	61,9	4,8	62,2	4,7	78
XVII	$COOC_2H_5$	H	$CH_2COOC_2H_5$	CH_3	150	—	$C_{22}H_{20}O_{10}$	59,5	4,5	59,5	4,5	85
XVIII	CH_3	H	$CH_2C_6H_5$	CH_3	156,5	—	$C_{23}H_{18}O_6$	70,3	4,6	70,7	4,6	19
XIX	CH_3	H	$CH_2C_6H_5$	H	230	—	$C_{22}H_{16}O_6$	70,3	4,3	70,2	4,2	40
XX	CH_3	H	H	H	228	290	$C_{15}H_{10}O_6$	62,6	4,0	62,7	3,5	97

* Compounds IX–XVIII were crystallized from alcohol.

† With decomposition.

2-Methyl-3-(5-methoxycarbonyl-2-furyl)-7-hydroxychromone (V). A total of 4.2 ml of 5% sodium hydroxide solution was added dropwise to a hot solution of 1.8 g (5.3 mmole) of III in 30 ml of ethanol, and the mixture was boiled for a few seconds. Water (22 ml) was then added, and the mixture was heated to the boiling point and refluxed for a few minutes. The solution was neutralized to pH 4-5 with dilute hydrochloric acid, and the resulting white powder was crystallized from aqueous alcohol to give 1.57 g of needles.

2-Methyl-3-(5-methoxycarbonyl-2-furyl)-5,7-dihydroxychromone (VI). This compound was similarly obtained.

2-Ethoxycarbonyl-3-(5-methoxycarbonyl-2-furyl)-7-hydroxychromone (VII). A 1.7-g (12 mmole) sample of ethoxalyl chloride was added slowly to a cooled (0°) solution of 1.9 g (6.8 mmole) of I in 6 ml of absolute pyridine, and the mixture was allowed to stand at room temperature for 48 h, after which it was poured into ice water. The resulting yellow oil crystallized on standing. The solid was washed repeatedly with water until the odor of pyridine was completely absent to give 2.5 g of product.

2-Ethoxycarbonyl-3-(5-methoxycarbonyl-2-furyl)-5,7-dihydroxychromone (VIII). This compound was similarly obtained and was crystallized successively from aqueous acetone, ethyl acetate, and heptane.

2-Methyl-3-(5-methoxycarbonyl-2-furyl)-7-methoxychromone (IX). A mixture of 0.5 g (1.6 mmole) of chromone V, 1.36 g (9.6 mmole) of methyl iodide, and 0.41 g (3 mmole) of calcined potassium carbonate in 120 ml of absolute acetone was stirred and refluxed for 4-5 h. The hot solution was filtered, the acetone was removed by distillation, and the residual crystals were removed by filtration and washed with ether to give 0.49 g of product.

Compounds X-XV, XVII, and XVIII were similarly obtained, during which the reaction time varied from 3 to 8 h (it was 14 h in the case of XVIII). In the synthesis of XVIII, XIX was also isolated: the hot-acetone-insoluble residue was diluted with water, and the precipitated potassium salt of acid XIX was removed by filtration. Dilute hydrochloric acid was added to a suspension of this salt in alcohol until it dissolved on heating. Dilution with water precipitated XIX.

2-Methyl-3-(5-methoxycarbonyl-2-furyl)-7-(ethoxycarbonylmethoxy)chromone (XVI). A mixture of 0.5 g (1.6 mmole) of V, 1.07 g (6.4 mmole) of ethyl bromoacetate, and 0.77 g (5.6 mmole) of calcined potassium carbonate in 110 ml of absolute acetone was stirred and refluxed for 5-6 h, and the hot solution was filtered. The acetone was removed by distillation, a small amount of water was added to the residue, and the colorless crystals that precipitated immediately were removed by filtration to give 0.65 g of product.

2-Methyl-3-(5-carboxy-2-furyl)-7-hydroxychromone (XX). A total of 6.92 ml of 5% sodium hydroxide solution was added dropwise to a hot solution of 1.3 g (4.35 mmole) of V in 100 ml of acetone. The mixture was diluted with water to twice its original volume and refluxed for a few minutes. It was then neutralized with dilute hydrochloric acid to pH 2-3 to precipitate (from the hot solution) 1.2 g of white needles.

LITERATURE CITED

1. Ferrari-Casagrande, J. Med. Chem., 9, 979 (1966).
2. S. A. Siphar, Belgian Patent No. 666,541 (1965); Chem. Abstr., 65, 3846 (1966).
3. Belgian Patent No. 633,436 (1963); Chem. Abstr., 61, 1840 (1964).
4. R. Aneja, S. K. Mukerjee, and T. R. Seshadri, Tetrahedron, 4, 256 (1958).
5. S. K. Pavanaram and L. R. Row, Austral. J. Chem., 9, 132 (1956).
6. G. Zemplen, L. Farkas, and V. Schuller, Acta Chim. Acad. Sci. Hung., 19, 277 (1959).
7. W. Baker, J. Chadderton, J. B. Harborne, and W. D. Ollis, J. Chem. Soc., 1852 (1953).
8. T. A. Geissman, The Chemistry of Flavonoid Compounds, Oxford–London–New York–Paris (1962), p. 147.
9. L. Bellamy, Infra-Red Spectra of Molecules, Methuen (1958).
10. K. Nakanishi, Infrared Spectra and the Structure of Organic Compounds [Russian translation], Mir, Moscow (1965), p. 64.
11. L. H. Briggs and L. D. Colebrook, J. Chem. Soc., 2458 (1960).
12. Synthesis of Heterocyclic Compounds [in Russian], Vol. 2, Erevan (1957), p. 50.