SYNTHESIS OF KHELLIN DERIVATIVES

G. N. Dorofeenko, V. V. Tkachenko,
and V. V. Mezheritskii

UDC 547.814.5'722.07

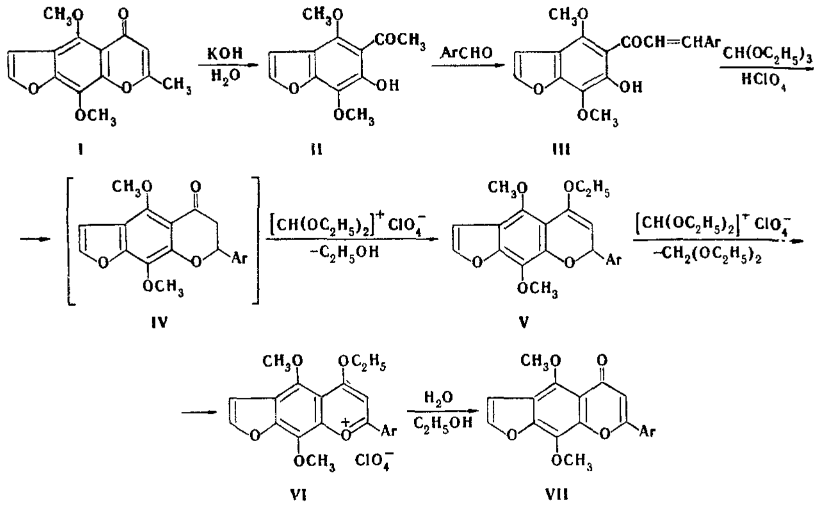
The reaction of orthoformic ester with o-hydroxychalcones in the presence of perchloric acid has yielded 4-ethoxy-5,9-dimethoxy-6,7-fluroflavylium salts which have been converted by treatment with aqueous ethanol into 5,9-dimethoxy-6,7-furoflavones.

It is known that khellin dilates the vessels of the cardiac muscle, and flavones possess a vitamin-P (capillary-strengthening) activity [1]. In view of this, it appeared of interest to obtain furoflavones with aromatic substituents in the position 2. Compounds of this type are difficultly accessible: previously, only the simplest furoflavones possessing vitamin-P activity [3] have been obtained by Baker's method [2].

Continuing our investigations on the synthesis of 4-ethoxyflavylium salts, in the present work this method has been used to synthesize previously unknown furoflavylium salts from the corresponding o-hydroxychalcones (III), ethyl orthoformate, and 70% perchloric acid [4]. The chalcones (III) (Table 1) were obtained by the alkaline condensation of khellinone (II), obtained by the action of alkali on khellin (I) with aromatic aldehydes [3].

Intermediate products are the 4-ethoxy-5,9-dimethoxy-6,7-furoflavylium salts (VI) (Table 2), which were obtained with yields of 30-40% when a mixture of (III) with a perchloric acid in an excess of ethyl orthoformate was heated (70-90°C) for 50-60 min.

The IR spectra of the pyrylium salts (VI) each have an absorption band at 1610-1620 cm^{-1} (stretching vibrations of a pyrylium cation [5]) which, in a number of cases, overlaps the band (1600 cm^{-1}) of the absorption of the aromatic ring. Absorption in the 1240-1280-cm^{-1} region corresponds to methoxy groups.



III, VI, VII a) Ar=C_6H_5; b) Ar=4-$CH_3OC_6H_4$, c) Ar=3,4-$(CH_3O)_2C_6H_3$; d) Ar=
=3,4-$CH_2\genfrac{}{}{0pt}{}{O}{O}C_6H_3$, e) Ar=4-$OHC_6H_4$, f) Ar= α-thienyl

---

Rostov State University. Scientific-Research Institute of Physical and Organic Chemistry, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1020-1023, August, 1973. Original article submitted July 12, 1972.

TABLE 1. Substituted 2-Hydroxy-3,6-dimethoxy-4,5-furochalcones (III)

Comp.	Ar	mp, °C[a]	Empirical formula	Found, %		Calc., %		IR spectrum, ν, cm^{-1}	Yield, %
				C	H	C	H		
IIIa	C_6H_5	127[b]	$C_{19}H_{16}O_5$					1620, 1550	82
IIIb	4-$CH_3OC_6H_4$	137[c]	$C_{20}H_{18}O_6$					1625, 1600, 1560	77
IIIc	3,4-$(CH_3O)_2C_6H_3$	155	$C_{21}H_{20}O_7$	65,4	5,1	65,6	5,2	1625, 1600	85
IIId	3,4-$CH_2<{}^{O}_{O}>C_6H_3$	154[c]	$C_{20}H_{16}O_7$					1625, 1605, 1550	80
IIIe	4-HOC_6H_4	172	$C_{19}H_{16}O_6$	66,8	4,9	67,1	4,7	3250, 1625, 1605, 1545	75
IIIf	α-Thienyl	125	$C_{17}H_{14}O_5S$[d]	61,5	4,0	61,8	4,2	1620, 1560	85

[a]From ethanol (the chalcone IIIe from aqueous ethanol).

[b]Corresponds to the literature [7].

[c]Corresponds to the literature [3].

[d]Found: S 9.4%; Calculated: S 9.7%.

TABLE 2. 4-Ethoxy-5,9-dimethoxy-6,7-furoflavylium Perchlorates (VI)

Comp.	Ar	mp, °C[a]	Empirical formula	Found, %			Calc., %			IR spectrum, ν, cm^{-1}	Yield, %
				C	H	Cl	C	H	Cl		
VIb	4-$CH_3OC_6H_4$	187	$C_{22}H_{21}ClO_{10}$	54,6	4,5	7,0	54,9	4,3	7,3	1620, 1600, 1550, 1525, 1250, 1100	40
VIc	3,4-$(CH_3O)_2C_6H_3$	196	$C_{23}H_{23}ClO_{11}$	53,8	4,6	6,7	54,1	4,5	6,9	1615, 1540, 1520, 1240, 1280, 1100	40
VId	3,4-$CH_2<{}^{O}_{O}>C_6H_3$	203—204	$C_{22}H_{19}ClO_{11}$	53,5	4,1	6,6	53,4	4,0	7,2	1620, 1560, 1515, 1260, 1090	35
VIe	4-HOC_6H_4	220	$C_{21}H_{19}ClO_{10}$	54,6	4,1	7,6	54,1	4,1	7,6	1610, 1550, 1520, 1255, 1060, 3270	35

[a]From glacial acetic acid.

TABLE 3. 5,9-Dimethoxy-6,7-furoflavones (VII)

Comp.	Ar	mp, °C[a]	Empirical formula	Found, %		Calc. %		IR spectrum, ν, cm^{-1}	Yield, %
				C	H	C	H		
VIIa	C_6H_5	176[b]						1635, 1620	Traces
VIIb	4-$CH_3OC_6H_4$	175—176	$C_{20}H_{16}O_6$	68,3	4,7	68,2	4,5	1640, 1600, 1510, 1250—1270	70
VIIc	3,4-$(CH_3O)_2C_6H_3$	183	$C_{21}H_{18}O_7$	66,2	4,6	65,9	4,7	1635, 1610, 1520, 1270	75
VIId	3,4-$CH_2<{}^{O}_{O}>C_6H_3$	216	$C_{20}H_{14}O_7$	65,8	3,6	65,6	3,8	1650, 1620, 1550, 1230—1280	70
VIIe	4-HOC_6H_4	250	$C_{19}H_{14}O_6$	67,8	4,3	67,5	4,1	1635, 1600, 1580, 1260, 3380	70

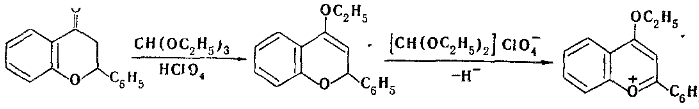
[a]From ethanol.

[b]According to the literature [3], mp 176-177°C.

There is also an intense band in the 1070-1100-cm^{-1} region, which is characteristic for the ClO_4^- anion. In the IR spectra of the flavones (VII) (Table 3) an absorption band of the C =O of a pyrone ring [6] is found in the 1635-1650-cm^{-1} region.

The mechanism of the dehydrogenation of the flavanone system is confirmed indirectly by the production of the 4-ethoxybenzopyrylium salts (IX) from the flavanone (VIII), ethyl orthoformate, and perchloric acid.

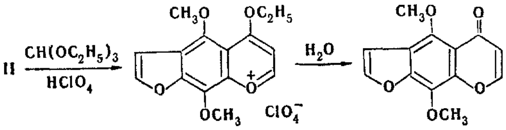
In the case of the chalcones (IIIa,f), the corresponding pyrylium salts could not be isolated in the pure state; nevertheless, when the reaction product (IIIa) was hydrolyzed, the known [3] furoflavone (VIIa) was obtained in low yield.



VIII

IX

The reaction of ethyl orthoformate with khellin in the presence of 70% perchloric acid gave 4-ethoxy-5,9-dimethoxy-6,7-furochromylium perchlorate (X) which, on being boiled with water, was converted quantitatively into 5,9-dimethoxy-6,7-furochromone (XI).



X XI

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrophotometer in paraffin oil.

o-Hydroxychalcones. 2'-Hydroxy-3',4,6'-trimethoxy-5',4'-furochalcone (IIIb). To a hot solution of 0.5 g of khellinone and 0.25 g of anisaldehyde in 10 ml of ethanol was added 2 ml of 50% caustic soda. The reaction mixture was left overnight at room temperature, and the precipitate that had formed was filtered off, washed with dilute hydrochloric acid, and then crystallized from ethanol to give yellow-brown crystals with mp 137°C. The chalcones (IIIa,c,f) (Table 1) were obtained similarly.

The chalcones (IIId,e) were obtained in the same way, except that the reaction mixture was heated in the water bath until a dark red precipitate had been formed (1 h 30 min to 2 h) and was then left at room temperature for 10-12 h.

4-Ethoxy-3',4',5,9-tetramethoxy-6,7-furoflavylium Perchlorate (VIc). A mixture of 0.9 g (2.5 mmoles) of the chalcone (IIIc), 11 ml of freshly distilled orthoformic ester, and 0.8 ml (8 mmoles) of 70% $HClO_4$ was heated at 80-90°C under reflux for 1 h. The cooled mixture was treated with 11 ml of orthoformic ester and was heated for another 5-7 min at 60-70°C. After cooling, the solution was diluted with ether and was left in the refrigerator for 5-10 h. The brown crystals (0.5 g, 40%) that deposited were filtered off and were washed with ether. After precipitation with ether from hot glacial acetic acid, they were recrystallized (Table 2).

The Furoflavones (VII). Boiling 1 g (2 mmoles) of the perchlorate (VIc) in aqueous ethanolic solution gave a 70-80% yield of 3',4',5,9-tetramethoxy-6,7-furoflavone, mp 183°C. The other furoflavones (VIIb,d,e) were obtained similarly (Table 3).

4-Ethoxy-5,9-dimethoxy-6,7-furochromylium Perchlorate (X). To a solution of 4.8 g (0.02 mole) of khellinone and 60 ml (0.4 mole) of freshly distilled orthoformic ester was added 4 ml (0.04 mole) of 70% perchloric acid. After 60-80 min, the mixture was diluted with ether and the red crystals that deposited (5.0 g, 70%) were filtered off; mp 136°C (from glacial acetic acid). IR spectrum, cm^{-1}: 1635, 1610, 1585, 1530, 1100. Found, %: C 47.7; H 3.8; Cl 10.0. $C_{15}H_{15}ClO_9$. Calculated,%: C 48.1; H 4.0; Cl 9.5.

5,9-Dimethoxy-6,7-furochromone (XI). A mixture of 0.38 g of the salt (X) and 40-50 ml of water was boiled for 3-5 min. The colorless precipitate that deposited was filtered off and dried. Yield 0.24 g (quantitative), mp 182°C [3].

Dehydrogenation of the Flavanone. To 0.22 g (1 mmole) of flavone were added 1.1 ml of freshly distilled orthoformic ester and 0.1 ml of 70% $HClO_4$. The mixture was heated at 60-70°C for 3-4 min and was diluted with ether. The colorless crystals of the salt (IX) that deposited (.14 g, 40%) were filtered off and recrystallized from acetic acid, mp 185°C. According to the literature [4], mp 184°C.

LITERATURE CITED

1. G. Dyson and P. May, Chemistry of Synthetic Drugs, 5th Edition, Longmans (1959).
2. W. Baker, J. Chem. Soc., 1381 (1933).
3. A. Schonberg and A. Sina, J. Amer. Chem. Soc., 72, 1611 (1950).
4. G. N. Dorofeenko and V. V. Tkachenko, Zh. Organ. Khim., 7, 2633 (1971).
5. A. D. Semenov, G. N. Dorofeenko, and V. I. Dulenko, Zh. Organ. Khim., 2, 1492 (1966).
6. R. H. Wiley and J. Cs. Esterle, J. Org. Chem., 22, 1257 (1957).
7. A. Shonberg, N. Badran, and N. A. Starkowsky, J. Amer. Chem. Soc., 75, 4992 (1953).