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SYNTHESIS OF CAPILLARISINS

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Capillarisins (I), a group of new choleretic substances, have recently been isolated by Komiya et al.[1,2] of these laboratories from the extract of Artemisiae capillaris Herba (Japanese name "Inchinko"), crude drugs prescribed in Chinese medicines as cholagogues. The structures, proposed on the basis of their chemical degradation products and spectroscopic evidence, appeared to be unique in that

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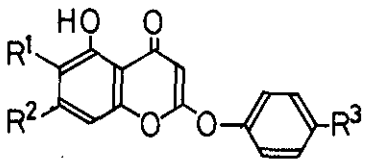
the compounds possessed 4-substituted phenoxy groups at the 2-position of the chromone ring (Table I).



Capillarisins (I)

	R^1	R^2	R^3
Ia:	OCH_3	OH	OH
Ib:	OCH_3	OH	OCH_3
Ic:	OCH_3	OCH_3	OH
Id:	H	OH	OCH_3
Ie:	H	OH	OH

Table I

In order to confirm the structure and to evaluate pharmacological activities of these new class of chromone derivatives, synthesis of 2-phenoxychromones has been attempted. The present paper deals with the synthesis of 2-phenoxychromones (III) and 5,7-dihydroxy-2-(4'-hydroxyphenoxy)chromone (Ie),[2] the latter being a constituent of capillarisins.

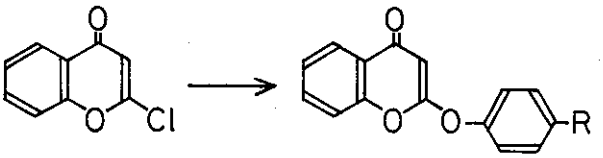
Synthesis of 2-Phenoxychromones (III)

Among chromones which possess a substituent at the 2-position through an oxygen atom, only 2-methoxychromones have been described in the literature,[1,2,3] however, no records have been available with regard to the preparation of 2-phenoxychromones. The present synthesis furnishes III in good yields (Table II) starting from 2-chlorochromone (II).[4]

A mixture of sodium phenoxide (2 mmole) and II (1 mmole) in dry dimethoxyethane (30 ml) was stirred for 15 min at room temperature. To the reaction mixture was added ethyl acetate, then the organic layer

was washed with water and dried over sodium sulfate. After evaporation of the solvent, the residue was purified by silica gel column chromatography (n-hexane-ethyl acetate, 93:7) to afford 2-phenoxychromone (IIIa), mp 83.5-84.5° (from ether-pet. ether).

2-(4'-Methoxyphenoxy)chromone (IIIc) was easily converted into 2-(4'-hydroxyphenoxy)chromone (IIId) by the treatment with boron tribromide in dry dichloromethane at room temperature for 1 hr. The structure of IIIc was confirmed by the direct comparison of the ^{13}C NMR spectrum with that of 2-methoxychromone (VIII)[3,5] (Table III).



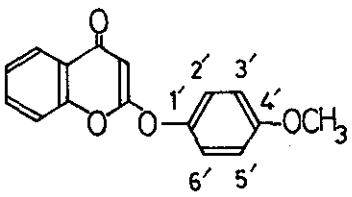
II III

Compd. No.	R	mp (°C)	Yields (%)
IIIa	H	83.5-84.5	67
IIIb	Cl	118.5-120	64
IIIc	OCH_3	119-119.5	78
IIId	OH	185-186.5	82*

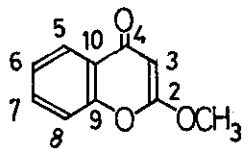
*Yield from IIIc.

Table II

Table III. ^{13}C Chemical Shifts of IIIc and VIII



IIIc



VIII

	2	3	4	5 and 6	7	8
IIIc	167.7	89.8	178.7	125.1 125.5	133.1	117.1
VIII	167.5	87.0	178.7	124.9 125.4	132.9	116.8

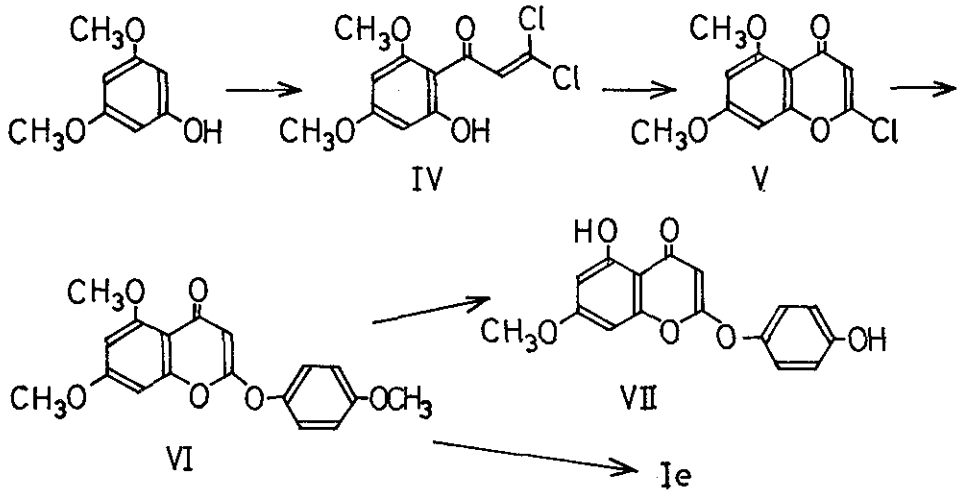
	9	10	1' and 4'	2' and 6'	3' and 5'	OCH_3
IIIc	153.4	122.7	144.5 157.8	121.5	115.0	55.5
VIII	153.2	122.5	—	—	—	56.1

Chemical shifts were recorded in ppm downfield from internal standard TMS in $CDCl_3$.

Synthesis of 5,7-Dihydroxy-2-(4'-Hydroxyphenoxy)chromone (Ie)

The starting material, 2-chloro-5,7-dimethoxychromone (V), was prepared by the following procedure, and in the present reactions, it seems to be noteworthy that 3,3-dichloroacrylonitrile[6] underwent the "normal" Hoesch reaction.[7] Substitution of 3,5-dimethoxyphenol with 3,3-dichloroacrylonitrile in benzene in the presence of boron trifluoride etherate at 80° for 5 hr, followed by hydrolysis with ethanolic 1N hydrochloric acid under *refluxing for 1 hr* gave 2-(3,3-dichloroacryloyl)-3,5-dimethoxyphenol (IV), mp 221-222.5° (from methanol), in

25% yield. Cyclization of IV with 0.01N sodium hydroxide was effected by leaving the reaction mixture to stand overnight[4] to afford V in 90% yield, mp 166-167° (from ethanol).



Scheme 1

Treatment of V with sodium phenoxide according to the aforementioned procedure yielded 5,7-dimethoxy-2-(4'-methoxyphenoxy)chromone (VI), mp 185.5-188° (from methanol-ethyl acetate), in 84% yield. When VI was treated with boron tribromide in dry dichloromethane at room temperature for 15 min, there was obtained the corresponding monomethoxychromone (VII), mp 242-244° (from methanol) (lit.[2] mp 212-218°),[8] in 78% yield, while under refluxing for 1 hr VI gave Ie, mp 240-244° (from methanol) (lit.[2] mp 237-242°), identical in all respects with the natural product, in 80% yield.

References and Notes

(1) T. Komiya, M. Tsukui, and H. Oshio, Chem. Pharm. Bull., (Tokyo), 23, 1387 (1975); Yakugaku Zasshi, 96, 841 (1976).

(2) T. Komiya, M. Tsukui, and H. Oshio, Yakugaku Zasshi, 96, 855 (1976).

(3) F. Arndt, L. Loewe, R. Ün, and E. Ayça, Chem. Ber., 84, 319 (1951); S. Janiszewska-Drabarek, Chem. Abstr., 49, 3175 (1955).

(4) M. Levas, E. Levas, and M. Delépine, Compt. rend., 250, 2919 (1960).

(5) 2-Methoxychromones[1,2,3] have been obtained only as mixtures of two isomeric products, 2-methoxychromones as minor components and 4-methoxycoumarins as major ones, from 2-hydroxychromones (4-hydroxycoumarins). By the present procedure VIII was prepared in 54% yield as a sole product by the treatment of II with sodium methoxide.

(6) N. Hashimoto, Y. Kawano, and K. Morita, J. Org. Chem., 34, 828 (1970).

(7) P. E. Spoerri and A. S. DuBois, Organic Reactions, 5, 389 (1949).

(8) Both the monomethoxychromones (VII), derived from the natural product[2] and obtained in the present case, were identical by the direct comparison of their IR spectra.