Chemistry of Natural Compounds, Vol. 33, No. 3, 1997

SYNTHETIC ANALOGS OF NATURAL FLAVOLIGNANS VIII. SYNTHESIS OF 6-CHLORO-1,3-BENZODIOXANE, 1,4-BENZODIOXANE, 1,5-BENZODIOXEPANE, AND 1,6-BENZODIOXOCANE ANALOGS OF 4-THIOFLAVONE

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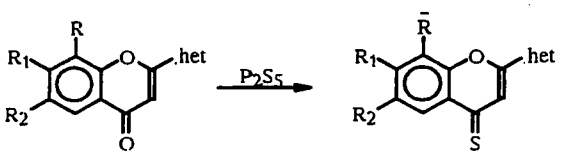
UDC 547.814.5

1,3-Benzodioxane, 1,4-benzodioxane, 1,5-benzodioxepane, and 1,6-benzodioxocane analogs of 4-thioflavone have been synthesized.

The synthesis and study of organic compounds of sulfur is an important direction of modern organic chemistry. The diversity of the properties of organosulfur compounds and the ready availability of the raw material for their production permit their wide use in agriculture and in medicine as drugs, insecticides, various intermediates, etc. [2].

Thanks to their multifunctional nature, flavonoids take part in various reactions, including thionation. A number of chromones modified by nuclei of 1,3-benzodioxane [3], 1,4-benzodioxane [4], 1,5-benzodioxepane [5], and 1,6-benzodioxocane [6] have been converted into the corresponding 4-thiochromones (**5-8**) [7] under the action of phosphorus pentasulfide in absolute toluene.



1-4 **5-8**

a: R=R$_1$=R$_2$=H; b: R=R$_2$=H, R$_1$=Me; c R=R$_2$=H, R$_1$=OMe; d: R=H, R$_1$=R$_2$=Me; e: R=R$_1$=H, R$_2$=Me; f R=R$_1$=H, R$_2$=Cl; g: R=R$_1$=H, R$_2$=F; h R$_1$=H, R=R$_2$=Cl; k: R=R$_1$=H, R$_2$=NO$_2$.
(**5 a-c, e-g, k**): het = 6-chloro-1,3-benzodioxane
(**6 a, d, f-h, k**): het = 1,4-benzodioxane
(**7 f**): het = 1,5-benzodioxepane
(**8 k**): het = 1,6-benzodioxocane

Unlike the initial chromones (**1-4**), the thiochromones (**5-8**) were red or orange substances. Their color is due to the C=S functional group of the 4-thiochromone ring.

TABLE 1. Characteristics of the 4-Thiochromones (**5-8**)

Compound	Yield, %	mp, °C	Empirical formula	Solvent for crystallization
5a	83	220–221	$C_{17}H_{11}ClO_4S$	EtOAc
5b	78	183–184	$C_{18}H_{13}ClO_4S$	EtOAc
5c	79	159–160	$C_{18}H_{13}ClO_4S$	EtOAc
5e	66	162–163	$C_{18}H_{13}ClO_4S$	EtOAc
5f	70	224–225	$C_{17}H_{10}Cl_2O_3S$	EtOAc
5g	73	241–242	$C_{17}H_{10}ClF_3O_3S$	EtOAc
5k	68	191–192	$C_{17}H_{10}ClNO_5S$	EtOAc / heptane
6a	64	169–170	$C_{17}H_{12}O_3S$	abs. EtOH
6d	82	218–219	$C_{19}H_{16}O_3S$	EtOAc
6f	90	185–186	$C_{17}H_{11}ClO_3S$	EtOAc
6g	86	201–202	$C_{17}H_{11}FO_3S$	EtOAc
6h	84	191–192	$C_{17}H_{10}Cl_2O_3S$	EtOAc
7f	91	149–151	$C_{18}H_{13}ClO_3S$	EtOAc
8k	47	197–198	$C_{19}H_{15}NO_5S$	Toluene

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 0009-3130/97/3303-0286$18.00

TABLE 2. Chemical Shifts in the PMR Spectra of the 4-Thiochromones (**5-8**) in $CDCl_3$ (δ, ppm; J, Hz)

Compound	Chromone protons					Protons of the hetero residue			
	H-3, s	H-5	H-6 or R_2-6	R_1-7	R-8	H-5(6) or H-7,d(2.0)	H-7(8) or H-9,dd (8.0;2.0)	H-8(9) or H-10,d (8.0)	CH_2-2s,CH_2-4 s, or $O(CH_2)_nO$
5a	8.09	8.57 m	7.43 m	7.75 m	7.54 m	7.11(2.5)	7.85(2.5)	–	5.38; 4.94
5b	8.06	8.46(8.5)	7.25 (8.5; 2.5)	2.50 s	7.37 d (2.5)	7.11(2.5)	7.84(2.5)	–	5.35; 4.94
5c	7.99	8.48(8.0)	7.0 (8;2)	3.95 s	6.93 d (2.0)	7.09(2.5)	7.81(2.5)	–	5.37; 4.93
5e	8.12	8.35(2)	2.48	7.55 dd (8; 2)	7.10 d (8)	7.10(2.5)	7.83(2.5)	–	5.38; 4.94
5f	8.08	8.52 d (2.5)	–	7.66 dd (8.5; 2.5)	7.5 d (8.5)	7.12(2.5)	7.82(2.5)	–	5.38; 4.94
5g	8.09	8.22 d (2.5)	–	7.41 dd (8.5;2.5)	7.58 d (8.5)	7.12(2.5)	7.83(2.5)	–	5.38; 4.94
5k	7.81	9.07 d (2.5)	–	9.13 dd (8.5;2.5)	7.90 d (8.5)	7.15(2.5)	7.95(2.5)	–	5.39; 4.95
6a	4.67	8.57	7.38 m	7.68 m	7.46 m	7.49	7.51	6.95	4.32 s
6d	7.66	8.33 s	2.38 s	2.38 s	7.32 s	7.53	7.49	6.97	4.33 s
6f	7.66	8.52 d (2.0)	–	7.62 dd (8.0;2.0)	7.45 d (8.0)	7.49	7.45	6.96	4.33 s
6g	7.70	8.26 d	–	7.49 dd	7.49 d	7.53	7.49	6.98	4.33 s
6a	7.69	8.44 d	–	7.71 dd	–	7.57	7.51	7.45	4.33 s
7f	7.65	8.50 d (2.0)	–	7.64 dd	7.03 d(8.09)	7.57	7.51	7.45	4.33 t; 2.2 q
8k	7.25	9.36 d(2.93)	–	8.49 dd (9.3;2.93)	7.53–7.70 m	7.53	7.7 m	7.05	4.58 t; 4.33 t 1.97 s

The structures of the 4-thiochromones (**5-8**) obtained were confirmed by elementary analysis and PMR spectra (Tables 1 and 2).

The PMR spectra of the 4-thiochromones (**5-8**), obtained included signals corresponding to the protons of the chromone ring and of the hetero residue. The most characteristic were the signals of the H-3 and H-5 protons of the chromone nucleus. On passing from the chromones to the thiochromones, the signals of the H-3 and H-5 protons shifted downfield by 0.8-1.0 and 0.3-0.5 ppm, respectively, as a result of the greater descreening of these protons by sulfur than by oxygen.

The signals of the protons of the methylene groups of the 1,3-benzodioxane ring appeared in the 5.3 ppm (CH_2-2) and 4.94 ppm (CH_2-4) regions, while the 1,4-benzodioxane ring gave a peak in the form of a singlet at 4.3 ppm, the benzodioxepane ring appeared in the form of a triplet and a quintet at 4.3 and 2.3 ppm, and the butylenedioxy group in the form of two triplets (4.58 and 4.33 ppm) and a singlet (1.97 ppm).

Thus, it is desirable to use thionation for the introduction of sulfur-containing functional groups into the molecules of natural and modified flavonoids. Trials of biological activity have shown that among the 4-thioflavone analogs there are substances with a high hepatoprotective activity.

EXPERIMENTAL

For thin-layer chromatography we used Silufol UV-254 plates and the benzene–ethanol (9:1) system. PMR spectra were recorded on a Bruker spectrometer in $CDCl_3$ with TMS as internal standard. The elementary analyses of compounds (**5-8**) corresponded to the calculated figures.

The 2-Hetaryl-4-thiochromones (5-8). A well-ground mixture of 1 mmole of the appropriate chromone and 0.148 g (0.66 mmole) of phosphorus pentasulfide in 5 ml of absolute toluene was boiled for 45 min. The hot solvent was decanted off, and the oily residue was extracted with toluene (4 × 10 ml). The toluene solutions were combined and evaporated to dryness. The residue was crystallized from a suitable solvent.

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