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Acetylation of 8-Bromo-5-hydroxy-6,7,4'-trimethoxyflavone

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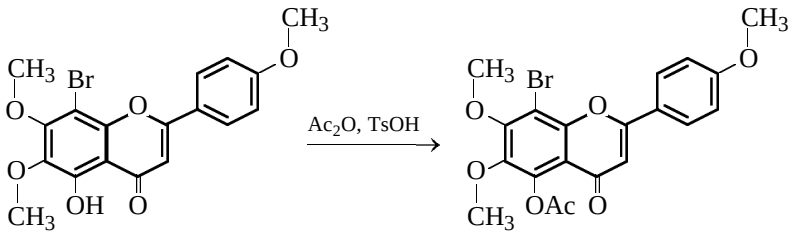
Abstract — 5-Hydroxy-6,7,4'-trimethoxyflavone was isolated from *Centaurea pseudomaculosa* Dobrocz., and its bromo derivative was obtained. The reaction of 8-bromo-5-hydroxy-6,7,4'-trimethoxyflavone with acetic anhydride in the presence of a catalytic amount of *p*-toluenesulfonic acid gave of a 73% 5-acetoxy-8-bromo derivative whose structure was established by X-ray diffraction.

Centaurea is a large genus comprised of about 178 species prevalent in the middle and south Former Soviet Union zone, 27 of which growing in Kazakhstan. Representatives of this genus are promising candidates for study in view of the fact that cornflowers have found wide practical use and contain biologically active compounds of different classes, flavonoids inclusive. Chemical modification of flavonoids offers both theoretical and practical interest, since both the starting materials and their modified derivatives exhibit biological activity. Aiming at searching for new biologically active compounds among methoxylated flavonoids, previously we studied bromination of 5-hydroxy-6,7,4'-trimethoxyflavone (salvigenin) (**I**) and 5-hydroxy-6,7,3',4'-tetramethoxyflavone (**II**), isolated from *Centaurea pseudomaculosa* Dobrocz. Mono- and dibromo derivatives were prepared to find that these flavonoids are brominated into the 3 and 8 positions [1, 2].

Proceeding with the research on synthesis of new derivatives of flavonoids **I** and **II**, we prepared from 8-bromo-5-hydroxy-6,7,4'-trimathoxyflavone (**III**) its acetoxy derivative **IV**.



III **IV**

X-ray diffraction showed that compound **IV** was 5-acetoxy-8-bromo-6,7,4'-tromethoxyflavone. The general view of a molecule of compound **IV** is shown in the figure. The bond lengths (Table 1) and bond angles (Table 2) have almost normal values [3], except for the O^6–C^{14} bond length, on account of the disordered methoxy group. The O^6–C^{14A} and O^6–C^{14B} bond lengths are 1.28 and 1.23 Å, respectively, i.e. these bonds are much shortened compared to ordinary C–O bonds.

The chromene ring is planar within +0.03 Å. The Br^1, O^2, O^5, and O^6 atoms deviate from this plane by –0.11, 0.06, 0.08, and 0.19 Å, respectively. The phenyl ring and O^7 and $C^{7'}$ are coplanar within +0.01 Å. The torsion angle of the phenyl ring with respect to the $C^3C^2C^{1'}C^{6'}$ backbone is 12.6°. The torsion angles between the mean plane of the chromene ring and the plane defined by the acyl group is 88.3°. The $C^8C^7O^6C^{14A}(C^{14B})$ torsion angle is –110.3(+110.6)°.

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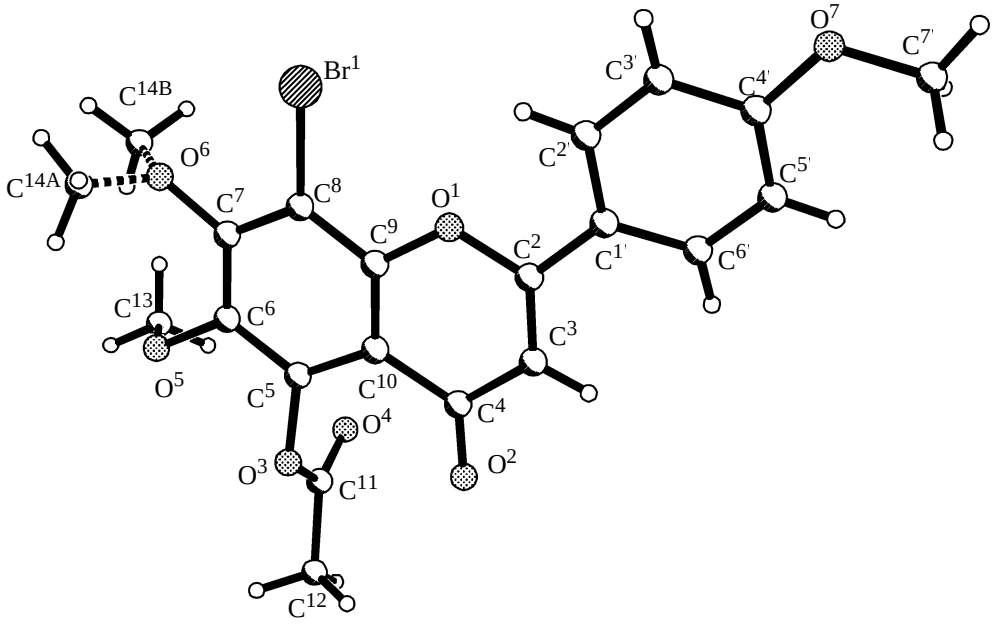

Molecular structure of compound **IV**.

EXPERIMENTAL

X-ray diffraction analysis of compound IV. The unit cell parameters and the intensities of 3141 unique reflections were measured on a Bruker P-4 diffractometer (MoK. radiation, graphite monochromator, $\theta/2\theta$ scanning, $2\theta \leq 50°$). Triclinic crystals, *a* 5.522(2), *b* 11.900(3), *c* 14.564(4) Å; α 81.05(2), β 84.95(3), γ 87.35(3)°; *V* 941.2(5) Å^3, d_{calc} 1.585 g cm^{-3}, *Z* 2 ($C_{20}H_{17}O_7Br$), space group *P*1. The structure was solved by the direct method and refined by full-matrix least squares for non-hydrogen atoms. The C^{14} atom is statistically disordered and was revealed in two positions with different weights (C^{14A}

Table 1. Bond lengths (*d*, Å) in **IV**

Bond	*d*	Bond	*d*
Br^1–C^8	1.883(6)	C^3–C^4	1.439(9)
O^1–C^9	1.363(7)	C^4–C^{10}	1.483(8)
O^1–C^2	1.363(6)	C^5–C^{10}	1.394(8)
O^2–C^4	1.234(7)	C^5–C^6	1.395(9)
O^3–C^{11}	1.349(7)	C^6–C^7	1.390(9)
O^3–C^5	1.402(7)	C^7–C^8	1.380(9)
O^4–C^{11}	1.195(7)	C^8–C^9	1.390(8)
O^5–C^6	1.368(8)	C^9–C^{10}	1.383(8)
O^5–C^{13}	1.399(14)	C^{11}–C^{12}	1.470(9)
O^6–C^{14B}	1.230(30)	$C^{1'}$–$C^{2'}$	1.381(9)
O^6–C^{14A}	1.281(14)	$C^{1'}$–$C^{6'}$	1.381(8)
O^6–C^7	1.361(7)	$C^{2'}$–$C^{3'}$	1.360(10)
O^7–$C^{4'}$	1.367(8)	$C^{3'}$–$C^{4'}$	1.381(9)
O^7–$C^{7'}$	1.419(9)	$C^{4'}$–$C^{5'}$	1.358(10)
C^2–C^3	1.346(8)	$C^{5'}$–$C^{6'}$	1.369(10)
C^2–$C^{1'}$	1.461(8)		

Table 2. Bond angles (ω, deg) in **IV**

Angle	ω	Angle	ω
$C^9O^1C^2$	120.0(4)	$C^7C^8C^9$	119.8(5)
$C^{11}O^3C^5$	118.1(5)	$C^7C^8Br^1$	120.3(4)
$C^6O^5C^{13}$	113.7(8)	$C^9C^8Br^1$	119.9(4)
$C^{14B}O^6C^7$	131.7(18)	$O^1C^9C^{10}$	122.8(5)
$C^{14A}O^6C^7$	121.9(9)	$O^1C^9C^8$	114.9(5)
$C^{4'}O^7C^{7'}$	117.3(6)	$C^{10}C^9C^8$	122.3(5)
$C^3C^2O^1$	120.9(5)	$C^9C^{10}C^5$	116.5(5)
$C^3C^2C^{1'}$	128.8(5)	$C^9C^{10}C^4$	118.7(5)
$O^1C^2C^{1'}$	110.3(5)	$C^5C^{10}C^4$	124.8(5)
$C^2C^3C^4$	123.5(5)	$O^4C^{11}O^3$	122.5(6)
$O^2C^4C^3$	122.9(5)	$O^4C^{11}C^{12}$	127.3(6)
$O^2C^4C^{10}$	123.1(6)	$O^3C^{11}C^{12}$	110.2(5)
$C^3C^4C^{10}$	114.0(5)	$C^{2'}C^{1'}C^{6'}$	116.2(6)
$C^{10}C^5C^6$	122.5(6)	$C^{2'}C^{1'}C^2$	121.4(5)
$C^{10}C^5O^3$	119.9(5)	$C^{6'}C^{1'}C^2$	122.3(5)
$C^6C^5O^3$	117.4(5)	$C^{3'}C^{2'}C^{1'}$	122.1(6)
$O^5C^6C^7$	120.9(6)	$C^{2'}C^{3'}C^{4'}$	120.5(7)
$O^5C^6C^5$	119.9(6)	$C^{5'}C^{4'}O^7$	125.4(6)
$C^7C^6C^5$	118.8(6)	$C^{5'}C^{4'}C^{3'}$	118.2(6)
$O^6C^7C^8$	119.6(6)	$O^1C^{4'}C^{3'}$	116.3(6)
$O^6C^7C^6$	120.5(6)	$C^{4'}C^{5'}C^{6'}$	121.0(6)
$C^8C^7C^6$	119.8(6)	$C^{5'}C^{6'}C^{1'}$	121.8(6)

Table 3. Coordinates ($\times 10^3$) of non-hydrogen atoms in **IV**

Atom	*x*	*y*	*z*
Br^1	7738(1)	1060(1)	9682(1)
O^1	7420(7)	429(3)	7831(2)
O^2	2939(9)	1444(4)	5759(3)
O^3	271(7)	2685(3)	6964(3)
O^4	2279(9)	4087(4)	6060(3)
O^5	458(11)	3710(5)	8503(4)
O^6	4008(11)	3012(5)	9741(4)
O^7	15590(10)	–3190(5)	7208(4)
C^2	7714(11)	–19(5)	7020(4)
C^3	6232(11)	310(5)	6335(4)
C^4	4260(11)	1136(5)	6398(4)
C^5	2243(11)	2417(5)	7512(4)
C^6	2238(12)	2920(5)	8316(4)
C^7	3914(12)	2524(5)	8960(4)
C^8	5566(11)	1660(5)	8788(4)
C^9	5627(10)	1232(4)	7951(4)
C^{10}	3997(10)	1601(4)	7290(4)
C^{11}	543(11)	3504(5)	6213(4)
C^{12}	–1559(12)	3550(6)	5654(5)
C^{13}	1190(30)	4835(9)	8263(9)
C^{14A}	2360(30)	2865(17)	10419(10)
C^{14B}	4590(70)	3960(30)	9850(20)
$C^{1'}$	9742(11)	–854(5)	7048(4)
$C^{2'}$	10883(14)	–1205(6)	7855(5)
$C^{3'}$	12746(16)	–1996(7)	7896(5)
$C^{4'}$	13662(13)	–2431(5)	7106(5)
$C^{5'}$	12618(13)	–2069(6)	6297(5)
$C^{6'}$	10718(13)	–1286(6)	6263(5)
$C^{7'}$	16548(16)	–3655(8)	6406(7)

0.67 and C^{14B} 0.33). The C^{13} atom is, too, slightly disordered [U_{eq} 0.195(8) Å^2], but it could not be located. All hydrogen atoms were calculated geometrically and located in the rider model. The calculations included 2406 reflections with $I > 2\sigma(I)$. Final divergence factors: R 0.073 and R_W 0.188. The structure was solved by the SHELXS-86 program and refined by the SHELXL-97 program. The coordinates of non-hydrogen atoms are listed in Table 3.

5-Acetoxy-8-bromo-6,7,4'-trimethoxyflavone. Acetic anhydride, 4 ml, was added dropwise to 200 mg of compound **III**. When the latter had dissolved completely, a catalytic amount of *p*-toluenesulfonic acid was added. The reaction mixture was treated with $NaHCO_3$ to a weakly basic reaction, diluted with 20 ml of ethyl acetate, washed with water, and dried over $MgSO_4$. The solvent was distilled off, and the residue was subjected to chromatography on silica gel of KSK brand, eluents petroleum ether, petroleum ether–ethyl acetate, and ethyl acetate. Recrystallization from ethanol gave compound **IV** as white needles, yield 73%, mp 171–172°C (from ethanol), $[M]^+$ 400.

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