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SYNTHETIC AND MODIFIED ISOFLAVONOIDS XVIII. SYNTHESIS OF 7-ISOPROPOXY-SUBSTITUTED ANALOGS OF PSEUDOBAPTIGENIN

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7-Isopropoxy derivatives of isoflavones have been synthesized from 1,3-benzodioxole, 1,4-benzodioxane, and 1,4-benzodioxepane analogs of pseudobaptigenin. Their structures have been confirmed by PMR.

The majority of isoflavone derivatives are ethers of hydroxyisoflavones. For example, maxima isoflavone B is the 7-dimethylallyl ether of pseudobaptigenin, and maxima isoflavone A, isolated from the roots of *Tephrosia maxima* Aers, has a 3′,4′,7,8-bismethylenedioxy structure. It is known that the 7-isopropoxyisoflavones and their derivatives possess anabolic activity and are used as drugs for curing ischemic disease of the heart [2].

In order to obtain alkyl ethers at a hydroxy group in position 7, we have studied the alkylation of 7-hydroxyisoflavones with isopropyl iodide. We made an attempt to synthesize the corresponding 7-isopropoxy derivatives in a series of isoflavones with 1,3-benzodioxole, 1,4-benzodioxane, and 1,5-benzodioxepane nuclei. The starting materials for the syntheses were the 7-hydroxyisoflavones (**1-3**), which have been described in [3-7].

TABLE 1. Characteristics of Compounds (**4-6**)

Compound	Yield, %	mp, °C	Empirical formula	Solvent for crystallization
4d	85	158–159	$C_{22}H_{20}O_5$	EtOH
4e	97	136–137	$C_{22}H_{22}O_5$	EtOH / H_2O
4g	95	134–135	$C_{22}H_{19}F_3O_5$	EtOH
4h	98	122–123	$C_{22}H_{22}O_5$	iso-PrOH
4i	71	149–150	$C_{23}H_{24}O_5$	iso-PrOH
4j	97	114–115	$C_{23}H_{21}F_3O_5$	EtOH · H_2O
4l	97	135–136	$C_{23}H_{24}O_5$	iso-PrOH
4m	52	08–109	$C_{24}H_{26}O_5$	EtOH
4o	90	97–98	$C_{25}H_{28}O_5$	EtOH
5a	96	121–122	$C_{20}H_{18}O_5$	EtOH
5b	93	167–168	$C_{21}H_{20}O_5$	EtOH
5c	84	173–174	$C_{21}H_{17}F_3O_5$	EtOH
5d	89	73–74	$C_{22}H_{22}O_5$	EtOH · H_2O
5e	84	144–145	$C_{23}H_{24}O_5$	MeOH · H_2O
5g	74	141	$C_{23}H_{21}F_3O_5$	EtOH
5h	87	88–89	$C_{23}H_{24}O_5$	EtOH / H_2O
5i	81	156–157	$C_{24}H_{26}O_5$	EtOH
5j	81	128–129	$C_{24}H_{23}F_3O_5$	EtOH
5k	80	96	$C_{22}H_{22}O_5$	EtOH
5l	99.8	118–120	$C_{24}H_{26}O_5$	EtOH
5m	88.5	111–112	$C_{25}H_{28}O_5$	EtOH
5n	74	211–212	$C_{25}H_{28}O_5$	EtOH
6b	94	141–142	$C_{22}H_{22}O_5$	EtOH
6n	41	128–129	$C_{26}H_{30}O_5$	EtOH

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TABLE 2. Chemical Shifts in the PMR Spectra of the 7-Isopropoxyisoflavones (**4-6**) in $CDCl_3$

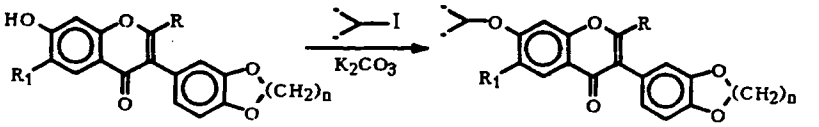
Compound	δ, ppm (J, Hz)						
	protons of the chromone ring					protons of the hetero residue	$-O(CH_2)_nO-$
	R-2	H-5	R-6	Me_2CH-7, d; sep	H-8		
4d	7.8	7.98s	2.68q; 1.20t	4.59; 1.36	6.70s	7.04(d.HH,J 2Hz, H-4); 6.76(d.d.HH, J=8; 2.0 Hz H-6); 6.81(d.HH,J=8Hz, H-7)	5.86s
4e	2.26s	7.89s	2.67q; 1.21t	4.64; 1.39	6.72s	6.72(m, H-4, H-6, H-7)	5.94s
4g	–	7.95s	2.70q; 1.22t	4.69; 1.45	6.82s	6.76(m, H-4, H-6, H-7)	5.99s
4h	7.76s	7.92s	2.67t, 1.67m, 0.91t	4.60; 1.37	6.70s	6.95(m, H-4, H-6, H-7)	5.90s
4i	2.26s	7.91s	2.65t; 1.68m 0.93t	4.65; 1.39	6.71s	6.71(m, H-4, H-6, H-7)	5.91s
4j	–	7.96s	2.68t; 1.66m, 0.95t	4.70; 1.41	6.87s	6.80(m, H-4, H-6, H-7)	6.01s
4l*	2.54q; 1.17t	7.75s	2.54q; 1.17t	4.83; 1.35	7.14s	6.81(d, HH, J 2 Hz, H-4), 6.69(d.d, HH, J 8; 2.0 Hz, H-6) 6.97(d, HH, J=8 Hz, H-7)	6.07s
4m*	2.60q; 1.19t	7.72	2.60t; 1.58m, 0.88t	4.84; 1.32	7.14s	6.79(d, HH, J=2Hz, H-4), 6.69(d.d, HH, J 8; 2Hz, H-6); 6.96(d, HH, J=8Hz, H-7)	6.07s
4o*	2.56t; 1.61m 0.86t	7.73s	2.56t; 1.61m, 0.86t	4.84;1.34	7.12s	6.78(d, HH, J=2Hz, H-4); 6.67(d.d, HH, J=8; 2.0Hz, H-6) 6.97(d, HH, J=8Hz, H-7)	6.07s
5a	7.81s	8.14d (8.5)	6.86d.d (8.5; 2.5)	4.66; 1.39	6.79d(2.5)	7.06(d, HH, J=2Hz, H-5); 6.93(m, H-7, H-8)	4.27s
5b	2.30s	8.09d(8.5)	6.9d.d (8.5; 2.5)	4.67; 1.43	6.8d(2.5)	6.8(m, H-5, H-7, H-8)	4.28s
5c	–	8.08d(8.5)	6.95d.d(8.5; 2.5)	4.68; 1.41	6.89d (2.5)	6.82(m, H-5, H-7, H-8)	4.30s
5d	7.85s	8.03s	2.66q; 1.22t	4.62; 1.41	6.77s	7.04(m, H-5, H-7, H-8)	4.28s
5e	2.28s	7.92s	2.68q; 1.20t	4.65; 1.42	6.72s	6.79(m, H-5, H-7, H-8)	4.29s
5g	–	8.01s	2.78q; 1.26t	4.79; 1.49	6.90s	6.88(m, H-5, H-7, H-8)	4.33s
5h	7.81s	7.96s	2.65t; 1.64m, 0.95t	4.60; 1.41	6.74s	7.01(m, H-5, H-7, H-8)	4.28s
5i	2.30s	7.90s	2.64t; 1.62m, 0.93t	4.64; 1.42	6.75s	6.81(m, H-5, H-7, H-8)	4.29s
5j	–	7.92s	2.66t; 1.62m, 0.95t	4.69; 1.45	6.82s	6.86(m, H-5, H-7, H-8)	4.30s
5k*	2.53q; 1.18t	7.88d (8.5)	7.00d.d(8.5; 2.5)	4.83; 1.31	7.11d (2.5)	6.73(d, HH, J=2Hz, H-5); 6.88(d.d, HH, J=8; 2.0 Hz, H-7);	4.28s

TABLE 2 (continued)

Compound	δ, ppm (J, Hz)						
	protons of the chromone ring					protons of the hetero residue	$-O(CH_2)_nO-$
	R-2	H-5	R-6	Me_2CH-7d. sept.	H-8		
5l*	2.54q; 1.16t	7.75s	2.54q; 1.16t	4.84;1.34	7.12 s	6.9(d, 1H, J=8Hz, H-8) 6.72(d, 1H, J=2 Hz H-5); 6.67(dd, 1H, J=8; 2.0 Hz H-7);	4.28 s
5m*	2.55q; 1.18 t	7.71s	2.55t; 1.57m 0.87t	4.83; 1.32	7.12s	6.89(d, 1H, J=8 Hz H-8) 6.72(d, 1H, J=2 Hz H-5); 6.66(dd, 1H, J=8, 2.0Hz, H-7)	4.28 s
5n*	2.54t; 1.66m 0.86 t	7.74 s	2.54q; 1.16 t	4.85; 1.35	7.12 s	6.88(d, 1H, J=8Hz, H-8) 6.72(d, 1H, J=2 Hz, H-5); 6.66(dd, 1H, J=8; 2.0Hz, H-7);	4.28 s
6b	2.28 s	8.11d (8.5)	6.87–7.0m	4.66; 1.39	6.80 d (2.4)	6.90(d, 1H, J=8 Hz, H-8) 6.85–7.0(H-6, H-8); 7.03(d, 1H, J=8 Hz, H-9)	4.24 t 2.20qn
6n*	2.59t; 1.66m 0.85t	7.725 s	2.59q; 1.16t	4.85; 1.34	7.13s	6.83(d, 1H, J=2 Hz, H-6); 6.78(dd, 1H, J=8; 2.0 Hz H-8) 7.02(d, 1H, J=8 Hz, H-9)	4.17 t 2.14qn

*Spectra taken in DMSO-d_6.

The alkylation of the 3-(1,3-benzodioxol-5-yl)-7-hydroxychromones (**1 d,e,g-j,l,m,o**) with isopropyl iodide formed compounds (**4 d,e,g-j,l,m,o**)



a: R=R$_1$=H; b: R=Me, R$_1$=H; c: R=CF$_3$, R$_1$=H; d: R=H, R$_1$=Et; e: R=Me, R$_1$=Et; g: R=CF$_3$, R$_1$=Et; h: R=H, R$_1$=Pr; i: R=Me, R$_1$=Pr; j: R=CF$_3$, R$_1$=Pr; k: R=Et, R$_1$=H; l: R=Et, R$_1$=Et; m: R=Et, R$_1$=Pr; n: R=Pr, R$_1$=Et; o: R=R$_1$=Pr;

4: n=1; **5**: n=2; **6**: n=3

1,4: d,e,g-j,l,m,o; **2,5**: a-e,g-n ; **3,6**: b, n.

The analogous isopropylation of the 3-(1,4-benzodioxan-6-yl)-7-hydroxychromones (**2 a-e,g-n**) and the 3-(1,5-benzodioxepan-7-yl)-7-hydroxychromones (**3 b,n**) led to compounds (**5 a-e,g-n**) and (**6 b,n**) respectively.

The physical constants, analytical results, yields, and PMR spectra of the 7-isopropoxy derivatives (**4-6**) are given in Tables 1 and 2. The PMR spectra confirmed the structures of these compounds.

The PMR spectra of compounds (**4−6**), measured in $CDCl_3$, contained the signals of protons relating to the chromone and the heterocyclic fragments of the molecules. The protons of the isopropyl group appeared in the form of a doublet and a septet in each case.

Thus, the alkylation of 7-hydroxyisoflavones with isopropyl iodide enables new compounds with a 7-isopropxy group to be obtained. In a study of the biological activity of the new pseudobaptigenin analogs it was found that some of them possess a pronounced hypolipidemic activity.

EXPERIMENTAL

The course of the reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates in benzene−ethanol (9:1). PMR spectra were taken on a Bruker WP-100 SY instrument in $CDCl_3$ relative to TMS (internal standard). The analyses of all the compounds corresponded to the calculated figures.

The 3-Hetaryl-7-isopropoxychromones (4-6 a-e, g-o). A hot solution of 10 mmole of the appropriate 7-hydroxyisoflavone in 200 ml of dry acetone was treated with 4.14 g (30 mmole) of freshly calcined potash and 1 ml (10 mmole) of isopropyl iodide, and the mixture was boiled for 15-25 h. The end of the reaction was determined by TLC. Then the inorganic residue was filtered off and was washed on the filter several times with hot acetone. The acetone was distilled off under water-pump vacuum, and the residue was crystallized from a suitable solvent.

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