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SYNTHETIC AND MODIFIED ISOFLAVONOIDS. X. SYNTHESIS OF 2-ETHYL AND 2-PROPYL HOMOLOGUES OF PSEUDOBAPTIGENIN

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Homologues of pseudobaptigenin containing ethyl and propyl groups in position 2 have been synthesized. The structures of the new compounds have been comfirmed by PMR.

In the development of investigations on the synthesis of various modifications of pseudobaptigenin and the study of the influence on its chemical-biological properties of an expansion of the heterocyclic ring and a lengthening of the hydrocarbon chain of the alkyl substituent in position 2 of benzo-γ-pyrone [1-5] we have obtained ethyl and propyl homologues of pseudobaptigenin with the hetero residues 1,3-benzodioxolane, 1,4-benzodioxane, and 1,5-benzodioxepane.

It is known [6] that 2-methylisoflavones are formed as the result of the interaction of 2-hydroxydeoxybenzoins with acetic anhydride in the presence of organic or inorganic bases. For the synthesis of the 2-ethyl(2-propyl)-substituted analogues of pseudobaptigenin, the ketones (**1**) [2, 4, 5] were heated in a mixture of propionic (butyric) anhydride with triethylamine. The 2-ethyl-7-propionyloxyisoflavones (**2**) so obtained were converted by brief boiling with a 5% solution of alkali in alcohol into the 2-ethyl-7-hydroxyisoflavones (**4**). The 7-butyryloxy-2-propylisoflavones (**3**) formed as intermediates were deacylated to the 7-hydroxyisoflavones (**5**) when the reaction mixture was poured into water. In some cases, a mixture of a 7-butyryloxyflavone (**3**) and the corresponding 7-hydroxyisoflavone (**5**) was isolated. To obtain the individual compound (**5**), the acyl groups in compound **3** were deacylated further.

TABLE 1. Characteristics of Compounds (**2-6**)

Compound	Reaction time, h	Yield, %	mp, °C	Empirical formula	Solvent for crystallization
2a	7	61.1	103—105	$C_{23}H_{22}O_6$	EtOAc
2b	7	58.3	81—82	$C_{24}H_{24}O_6$	EtOAc
2c	8	79	159—160	$C_{22}H_{20}O_6$	EtOAc
2d	7	73	155—156	$C_{24}H_{24}O_6$	EtOAc
2e	7	76.3	130—131	$C_{25}H_{26}O_6$	EtOH
2f	8	48	112—113	$C_{25}H_{26}O_6$	EtOAc
4a		96.1	230—231	$C_{20}H_{18}O_5$	iso-PrOH
4b		99.5	235—236	$C_{21}H_{20}O_5$	iso-PrOH
4c		96.1	239—240	$C_{19}H_{16}O_5$	EtOH:H2O
4f		97.3	258—259	$C_{21}H_{20}O_5$	iso-PrOH
4e		74.7	210—211	$C_{22}H_{22}O_5$	EtOH:H2O
5a	12	37	248—250	$C_{21}H_{20}O_5$	EtOAc
5b	17	44	219—220	$C_{22}H_{22}O_5$	EtOAc
5d	13	63.7	254—255	$C_{22}H_{22}O_5$	EtOAc
5f	18	61	201—203	$C_{23}H_{24}O_5$	EtOAc
6		83.8	229—230	$C_{21}H_{18}O_6$	EtOAc

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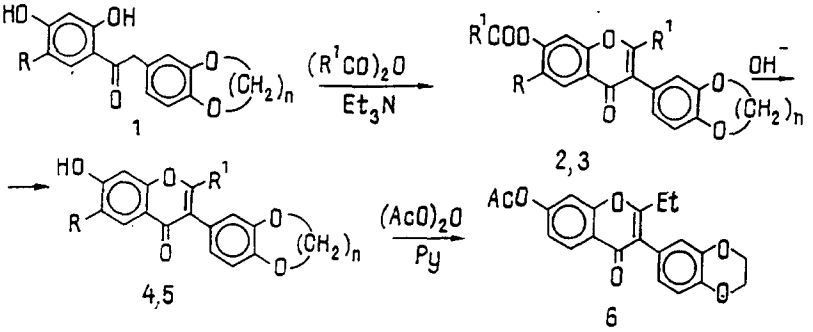
TABLE 2. Chemical Shifts in the PMR Spectra of the 2-Alkyl-substituted Pseudobaptigenin Analogs (**2-6**)

Compound	PMR spectrum*, δ, ppm, J, Hz)								
	Chromone protons					Protons of the hetero residue			
	CH_3CH_2-2 or $CH_3CH_2CH_2$-2 (J=7.0 Hz)	H-5, s	R-6 t,m,t, (7.0)	OH-7, OOCEt-7 or OAc-7 q,t (7.0)	H-8, s	H-4 (5) or H-6,d (2.0)	H-6 (7) or H-8 d.d (8.0:2.0)	H-7 (8) or H-9,d (8.0)	$O(CH_2)O$ t,q (5.4)
2a	2.58 q; 1.19 t	7.94	2.58 q; 1.19 t	2.67; 1.19	7.51	6.83	6.71	6.98	6.08 s
2b	2.62 q; 1.18 t	7.93	2.62; 1.56; 0.88	2.62; 1.18	7.50	6.82	6.71	6.98	6.07 s
2c	2.62 q; 1.20 t	8.22 d (8.5)	7.11 d.d (8.5; 2.5)	2.62; 1.29	7.27 d (2.5)	6.77	6.72	6.91	4.28 s
2d	2.62 q; 1.16 t	7.94	2.62 q; 1.16 t	2.62; 1.16	7.50	6.77	6.70	6.92	4.29 s
2e	2.63 q; 1.23 t	8.07	2.63; 1.64; 0.95	2.63; 1.33	7.22	6.76	6.70	6.94	4.29 s
2f	2.70 q; 1.19 t	7.94	2.70 q; 1.19 t	2.70; 1.19	7.50	6.88	6.83	7.03	4.18;2.14
4a	2.58 q; 1.16 t	7.72	2.58 q; 1.16 t	10.74 s	6.86	6.79	6.67	6.95	6.06 s
4b	2.55 q; 1.16 t	7.70	2.55; 1.59; 0.90	10.68 s	6.87	6.80	6.67	6.96	6.07 s
4c	2.49 q; 1.15 t	7.86 d (8.5)	6.89 d.d (8.5; 2.5)	10.69 s	6.84 d (2.5)	6.72	6.67	6.74	4.26 s
4d	2.53 q; 1.16 t	7.71	2.53 q; 1.16 t	10.72 s	6.87	6.71	6.66	6.89	4.28 s
4e	2.50 q; 1.13 t	7.67	2.50; 1.55; 0.87	10.64 s	6.83	6.69	6.62	6.85	4.25 s
5a	2.58 t; 1.64 m; 0.83 t	7.72	2.64 q; 1.16 t	10.74 s	6.86	6.77	6.66	6.95	6.06 s
5b	2.52 t; 1.61 m; 0.83 t	7.70	2.52; 1.61; 0.90	10.72 s	6.86	6.77	6.66	6.95	6.06 s
5d	2.50 t; 1.67 m; 0.84 t	7.71	2.62 q; 1.17 t	10.72 s	6.86	6.70	6.64	6.89	4.28 s
5f	2.51 t; 1.64 m; 0.83 t	7.72	2.52 q; 1.17 t	10.77 s	6.85	6.81	6.76	7.00	4.16; 2.12
6	2.59 q; 1.24 t	8.24 d (8.5)	7.10 d.d (8.5; 2.5)	2.35 s	7.28 d (2.5)	6.76	6.72	6.91	4.28 s

*The PMR spectra of compounds (**2c, e**) and (**6**) were measured in $CDCl_3$, and those of the other compounds in DMSO-d_6.



a: R=Et, n=1; b: R=Pr, n=1; c: R=H, n=2; d: R=Et, n=2; e: R=Pr, n=2; f: R=Et, n=3; 2, 4: R^1=Et; 3, 5: R^1=Pr

The action of acetic anhydride on a pyridine solution of the 7-hydroxyisoflavone (**4c**) at room temperature led to the formation of the 7-acetoxyisoflavone (**6**). The 2-alkylisoflavones obtained, (**2-6**), were colorless crystalline substances readily soluble in organic solvents. The characteristics and details of the NMR spectra of the 2-alkyl-substituted derivatives and homologues of pseudobaptigenin, (**2-6**), are given in Tables 1 and 2.

A comparison of the conditions of the experiment for the synthesis of 2-alkylisoflavones in the present and preceding investigations showed that a lengthening of the hydrocarbon chain of the carboxylic acid anhydride has a substantial effect on the time of the heterocyclization process. However, an expansion of the dioxolane ring has no appreciable influence on the course of cyclization.

EXPERIMENTAL

Conditions for chromatography and for recording the spectra have been given in [1].

2-Ethyl-3-hetaryl-7-propionyloxychromones (2a-f) and 2-Propyl-3-hetaryl-7-hydroxychromones (5a, b, d, f). A mixture of 20 mmoles of one of the ketones (**1a-f**), 100 ml of propionic (or butyric) anhydride, and 11.2 ml (80 mmoles) of triethylamine was heated at 120-130°C for 7-18 h. Then the reaction mixture was poured into cold water containing 1 ml of hydrochloric acid. The precipitate that deposited was filtered off, washed with water, dried, and crystallized from a suitable solvent.

2-Ethyl-3-hetaryl-7-hydroxychromones (4a-e). A hot solution of 30 mmoles of a 2-ethyl-7-propionyloxyisoflavone (**2a-e**) in 150 ml of alcohol was treated with 24 ml (30 mmoles) of a 5% solution of caustic soda, and the mixture was boiled for 10 min and was then neutralized with dilute hydrochloric acid to pH 7. The precipitate that deposited was filtered off and crystallized from a suitable solvent.

7-Acetoxy-(1,4-benzodioxan-6-yl)-2-ethylchromone (6). A hot solution of 3.24 g (10 mmoles) of the 7-hydroxyisoflavone (**4c**) in 5 ml of pyridine was treated with 4.6 ml (50 mmoles) of acetic anhydride, and the reaction mixture was left overnight at room temperature. It was then poured into cold water. The precipitate that deposited was filtered off, washed with water, dried, and crystallized from ethyl acetate.

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