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SYNTHETIC AND MODIFIED ISOFLAVONOIDS
V. SYNTHESIS OF 2-TRIFLUOROMETHYL-SUBSTITUTED ANALOGUES OF PSEUDOBAPTIGENIN

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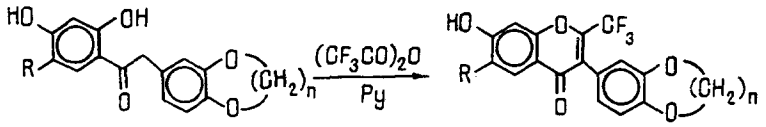
New two-trifluoromethylchromones with 1,3-benzodioxole and 1,4-benzodioxane nuclei in position 3 have been synthesized.

Continuing a study of new pseudobaptigenin derivatives [1-4], we have undertaken the synthesis of its 2-trifluoromethyl analogues. The latter are of interest in connection with the elucidation of the influence of this group on the chemical and biological properties of pseudobaptigenin analogues.

The starting materials for the synthesis of these compounds were the α-hetaryl-2,4-dihydroxyacetophenones (I) and (II) [2, 4]. As is known fron literature sources [5], the interaction of α-azahetaryl-2-hydroxyacetophenones with trifluoroacetic anhydride in pyridine under mild conditions leads to the formation of 2-trifluoromethyl-3-hetarylchromones with high yields. The application of this acylating reagent to ketones (I) and (II) with the aim of their conversion into 2-trifluoromethyl analogues of pseudobaptigenin did not take place so smoothly. The desired 2-trifluoromethylisoflavones (III,IV) were formed only when the mixture of reagents was kept at 40-50°C.



I a,b; II a-c

a: R=Et; b: R=Pr; c: R=H

III a,b; IV a-c

I, III: n=1; II, IV: n=2

The new isoflavones (III, IV) were colorless crystalline substances readily soluble in organic solvents and aqueous solutions of alkalis. Unlike the initial ketones, they did not give a positive reaction with an alcoholic solution of ferric chloride, which showed the absence from their molecules of hydroxyls capable of forming chelates.

The characteristics and PMR spectra of the pseudobaptigenin analogues (III) and (IV) are given in Tables 1 and 2.

Thus, both in the series of α-hetarylacetophenones (I, II) and in the corresponding chromones (III, IV) the positions of the signals of the aromatic protons of the benzene nucleus depend little on the structure of the hetero residues and are due above all to the nature and position of the substituents in the benzene ring of the chromone and also to the nature of the substituents in position 2 of the benzo-γ-pyrone moiety. The 2-CF_3 electron-accepting group exerts an influence on the chemical shifts of the aromatic protons in the annelated benzene ring and in the 1,3-benzodioxole and 1,4-benzodioxane nuclei. The voluminous 2-CF_3 group disturbs the coplanar structure of the 3-heterylchromone system, as a result of which the aromatic protons of the hetero residues, H-4(5) and H-6(7), fall under the influence of the ring currents of the chromone ring and give a diamagnetic shift of 0.1-0.4 ppm as compared with the corresponding pseudobaptigenin analogue [2, 4]. The OH-7 phenolic protons also experience the action of the electron-accepting CF_3 group and absorb in a weaker field by 0.3-0.4 ppm than pseudobaptigenin analogues unsubstituted in position 2.

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TABLE 1. Characteristics of Compounds (III, IV)

Compound	Yield, %	mp, °C	Empirical formula
IIIa	84	247—248	$C_{19}H_{13}F_3O_5$
IIIb	88	279—280	$C_{20}H_{15}F_3O_5$
IVa	96	230—231	$C_{20}H_{15}F_3O_5$
IVb	66	279—280	$C_{21}H_{17}F_3O_5$
IVc	93	255—256	$C_{18}H_{11}F_3O_5$

TABLE 2. Chemical Shifts in the PMR Spectra of the 2-CF_3-Substituted Pseudobaptigenin Analogues (III-IV) (in DMSO-d_6, δ, ppm)

Compound	Chromone protons				Protons of the hetero residue			
	H-5, s	R	OH-7, s	H-8, s	H-4(5), d J=2 Hz	H-6(7), dd J=8 Hz; J=2 Hz	H-7(8), d J=8 Hz	$-O(CH_2)_nO-$ n=1, 2, s
IIIa	7.74	2.62 q; 1.15 t	11.14	6.90	6.81	6.68	6.94	6.06
IIIb	7.75	2.62 t; 1.57 m; 0.90 t	11.15	6.94	6.84	6.71	6.97	6.08
IVa	7.73	2.61 q; 1.14 t	11.15	6.89	6.89	6.65	6.78	4.25
IVb	7.74	2.60 t; 1.57 m; 0.90 t	11.1	6.93	6.74	6.70	6.82	4.28
IVc	7.91d J=8 Hz	6.98 dd, J=8 Hz; J=2 Hz	11.12	6.94 d J=2 Hz	6.94	6.69	6.97	4.28

Thus, the cyclization of α-hetaryl-2,4-dihydroxyacetophenones under the action of trifluoroacetic anhydride in pyridine takes place under more severe conditions than those given in [5]. Nevertheless, the trifluoromethyl analogues of pseudobaptigenin were obtained with good yields. Some of them have exhibited a well-defined hypolipidemic activity in experiments on animals.

EXPERIMENTAL

PMR spectra were measured on a Bruker WP-100 SU instrument in DMSO-d_6 relative to TMS (internal standard). The purity of the compounds was checked by the TLC method on Silufol UV-254 plates in the benzene–ethanol (9:1) system. The analyses of all the compounds corresponded to the calculated figures.

The 3-Hetaryl-7-hydroxy-2-trifluoromethylchromones (IIIa, b; IVa, b, c). In drops, 1.42 ml (10 mmole) of trifluoroacetic anhydride was added to a solution of 5 mmole of a ketone (Ia, b; IIa-c) in 5-7 ml of dry pyridine cooled to 0°C. The reaction mixture was shaken, with ice cooling, for 10-15 min and was left overnight. On the following day, it was heated to 40-50°C for 10-15 min and was again left at room temperature for 12 h. Then it was poured into 50-70 ml of cold water, and the precipitate was filtered off. Compounds (IIIa, b; IVb) were crystallized from aqueous alcohol, and compounds (IVa, c) from alcohol.

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