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SYNTHETIC AND MODIFIED ISOFLAVONOIDS
XIX. SYNTHESIS OF 8-METHYL-SUBSTITUTED ANALOGS OF PSEUDOBAPTIGENIN

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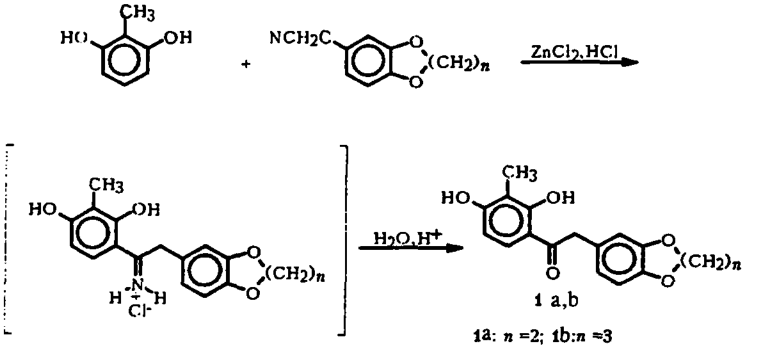
New 8-methyl-substituted chromones with 1,4-benzodioxane and 1,5-benzodioxepane nuclei in position 3 have been synthesized. Their structures have been confirmed by chemical transformations and PMR spectra.

Continuing work on the synthesis of analogs and derivatives of peudobaptigenin [1], in the present paper we give the results of the preparation of 8-methyl-substituted isoflavones.

The starting materials for the synthesis of the 8-methylisoflavones were the α-hetaryl-2,4-dihydroxy-3-methylacetophenones (**1 a,b**) containing 1,4-benzodioxane and 1,5-benzodioxepane nuclei, respectively, which were obtained by condensing 6-cyanomethyl-1,4-benzodioxane and 7-cyanomethylbenzodioxepane with 2-methylresorcinol.



1 a,b

1a: $n = 2$; 1b: $n = 3$

The structures of the ketones obtained (**1 a,b**) were confirmed by the results of elementary analysis, a qualitative reaction with an alcoholic solution of iron(III) chloride, and PMR spectra.

In the PMR spectra of ketones (**1 a,b**) measured in deuterated DMSO, the aromatic protons appeared in the form of doublets with a spin-spin coupling constant (SSCC) of 8.8 Hz in the 6.46-7.81 region, the other signals being singlets.

Separate absorption was observed for the protons of the 2-OH and 4-OH hydoxy groups in the molecules of ketones (**1 a,b**). The proton of the 2-OH hydroxy group takes part in the formation of an intramolecular hydrogen bond with the carbonyl oxygen atom and gives a weak-field signal (12.99 ppm), while the 4-OH hydroxyl, forming an intermolecular hydrogen bond, absorbs in a stronger field (10.6 ppm).

As a result of the interaction of (**1 a,b**) with dimethylformamide in the presence of boron trifluoride etherate and phosphorus pentachloride at 70°C, the 7-hydroxy-8-methylisoflavones (**2 a,b**) were formed in high yields, while the interaction of the latter with acetic anhydride in triethylamine gave the 7-acetoxy-2,8-dimethylisoflavones (**3 a,b**). Isoflavone (**2a**) was readily acetylated at the phenolic hydroxyl under the action of acetic anhydride in absolute pyridine at room temperature, forming the isoflavone (**4a**). Under the influence of 5% caustic soda solution, the 7-acetoxy-2-methylisoflavone (**3a**) was transformed quantitatively into the free 7-hydroxyisoflavone (**5a**). The latter, on alkylation with diethyl sulfate in the presence of potash in boiling acetone formed compound (**6a**), ethylated at the 7-OH group. On alkylation with diethyl sulfate, isoflavone (**2b**) formed the 7-ethoxyisoflavone (**7b**).

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TABLE 1. Characteristics of Compounds (2-7)

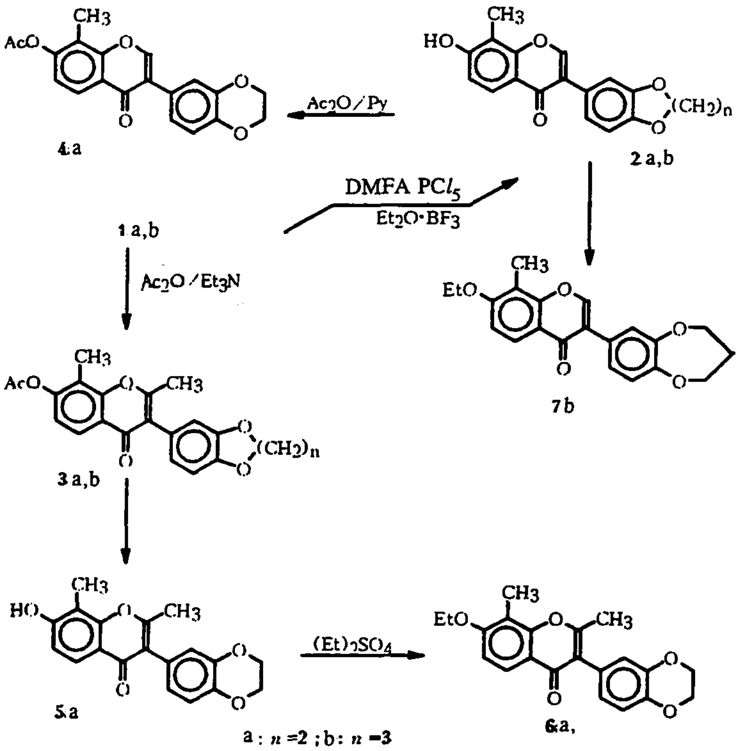
Compound	Yield, %	mp, °C	Empirical formula
2a	98	271–272	$C_{18}H_{14}O_5$
2b	78	253–254	$C_{19}H_{16}O_5$
3a	72	208–209	$C_{21}H_{18}O_6$
3b	69	198–199	$C_{22}H_{20}O_6$
4a	75	181–182	$C_{19}H_{14}O_6$
5a	83	310	$C_{19}H_{16}O_5$
6a	73	180–181	$C_{21}H_{20}O_5$
7b	77	189–190	$C_{21}H_{20}O_5$

The characteristics of isoflavones (2-7) are given in Table 1, and details of their PMR spectra in Table 2.

In the spectrum of each of the isoflavones (2 **a,b**), the H-2 proton of the pyrone ring appeared in the form of a narrow singlet at 8.4 ppm, since it experienced the influence of the unshared electron pair of the oxygen atom of the pyrone ring and the descreening action of the carbonyl group of the same ring. In each of compounds (2-7) the aromatic protons of the chromone ring, H-5 and H-6, were detected in the form of doublets, each with an SSCC of 8.8 Hz. The 7-OH group took part in an intermolecular hydrogen bond with another isoflavone molecule and appeared at 10.5-10.6 ppm.

In the PMR spectra of the 2-methylflavones (**3a, b**), in each case the two-proton singlet of the methylene group and the weak-field peak of the 2-OH group of the initial ketone had disappeared and in their place the three-proton signal of a methyl group had arisen at 2.4 ppm. The 7-ethoxy group gave a three-proton triplet and a two proton quartet. The methylene protons of the 3′,4′-propylenedioxy ring gave a triplet and a quintet at 4.24 and 2.2 ppm, respectively.

In a study of the biological activity of the new analogs of natural isoflavones it was found that some of them possess a pronounced anabolic activity.



EXPERIMENTAL

The course of the reactions and the purity of the compounds obtained were monitored on Silufol-254 (UV) plates in the benzene–ethanol (9:1) system. UV light was used for detection. PMR spectra were obtained on a Bruker WP100SY in-

TABLE 2. Chemical Shifts in the PMR Spectra of the 3-Hetaryl-8-methylchromones (2-7) (δ, ppm)

Compound	Chromone protons					Protons of the hetero residue			
	H-2 or Me-2, s	H-5, d, J=8.8 Hz	H-6, d, J=8.8 Hz	OH-7 or OAc-7, or OEt-7	Me-8, s	H-5 or H-6, d (2.0)	H-7 or H-8, dd (8.0; 2.0)	H-8 or H-9, d (8.0)	$O(CH_2)_nO$, s
2a*	8.37	7.52	6.99	10.59	2.22	7.11	7.06	6.87	4.26
2b*	8.43	7.81	7.01	10.67	2.23	7.16	7.16	7.09	1.16t; 2.22qn
3a	2.36	8.09	7.07	2.38	2.31	6.79	6.74	6.92	4.28
3b	2.35	8.07	7.08	2.38	2.30	6.89	6.84	7.04	4.24t; 2.21qn
4a	8.53	8.0	7.26	2.37	2.25	7.12	7.08	6.89	4.26
5a*	2.27	7.72	6.84	10.48	2.23	6.74	6.69	6.88	4.27
6a	2.32	8.03	6.91	4.16q 1.47t	2.32	6.79	6.74	6.83	4.28
7b	7.97	8.13	6.97	1.48t, 4.16q	2.32	7.21	7.15	7.0	4.24t; 2.20qn

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*PMR spectra taken in DMSO-d_6.

strument in DMSO-d_6 or $CDCl_3$ with TMS as internal standard. The analyses of the compounds synthesized corresponded to the calculated figures.

The α-hetaryl-2,4-dihydroxy-3-methylacetophenones (1 a,b) were synthesized by the procedure of [2]. The precipitates were crystallized from isopropyl alcohol. Compound **(1a)**, yield 50%, mp 166-167°C, empirical formula $C_{17}H_{16}O_5$. PMR spectrum (DMSO-d_6, δ, ppm): protons of the phenolic moiety — 12.99 (s, 1H, OH-2); 1.93 (s, 3H, Me-3); 10.59 (s, 1H, OH-4); 6.46 (d, 1H, J=8.8 Hz, H-5); 7.81 (d, 1H, J=8.8 Hz, H-6); 4.13 (s, 2H, CH_2); benzodioxane protons — 6.76 (d, 1H, H-5); 6.76 (m, 1H, H-7); 6.76 (m, 1H, H-8); 4.20 (s, 4H, OCH_2CH_2O).

Compound **(1b)** was crystallized from alcohol; yield 75%, mp 165-166°C, empirical formula $C_{18}H_{15}O_5$. PMR spectrum (DMSO-d_6, ppm): protons of the phenolic moiety — 12.97 (s, 1H, OH-2); 1.95 (s, 3H, Me-3); 10.6 (s, 1H, OH-4); 6.46 (d, 1H, J=8.8 Hz, H-5); 7.84 (d, 1H, J=8.8 Hz, H-6); 4.16 (s, 2H, CH_2); — 6.88 (s, 1H, H-7); 6.88 (s, 1H, H-8); 6.88 (s, 1H, H-9); 4.08; 2.06 (tq, 6H, $O(CH_2)_3O$).

The 3-hetaryl-7-hydroxy-8-methylchromones (2a, b) were synthesized by the procedure of [2]. The precipitate that deposited was filtered off and crystallized from isopropanol.

The 3-Hetaryl-7-acetoxy-2,8-dimethylchromones (3a, b). A mixture of 20 mmole of a ketone **(1a, b)**, 9.2 ml (100 mmole) of acetic anhydride, and 11.2 mmole (80 mmole) of triethylamine was heated at 120-130°C for 4.5-5 h. The mixture was poured into cold water containing 1.7 ml of hydrochloric acid. The precipitate that deposited was filtered off and was carefully washed with water. The desired compounds **(3a, b)** were purified by crystallization from ethyl acetate.

7-Acetyl-3-(1,4-benzodioxan-6-yl)-8-methylchromone (4a). A hot solution of 6.2 g (20 mmole) of the 7-hydroxy-isoflavone **(2a)** in 5 ml of pyridine was treated with 9.2 ml (100 mmole) of acetic anhydride, and the reaction mixture was left at room temperature for 12 h. The acetate that deposited on cooling was filtered off, washed with cold alcohol, and crystallized from isopropanol.

3-(1,4-Benzodioxan-6-yl)-7-ethoxy-2,8-dimethylchromone (6a) and 3-(1,5-Benzodioxepan-7-yl)-7-ethoxy-8-methylchromone (7b). To each of hot solutions of 15 mmole of the isoflavones **(5a)** and **(2b)**, respectively, was added 15 mole of diethyl sulfate and 6.5 g (45 mmole) of freshly calcined potash, and the mixtures were boiled for 3-4 h. The inorganic deposits were filtered from the hot solutions, and each filtrate was acidified with 2-3 drops of acetic acid. The solvent was distilled off in water-pump vacuum, and the residues were crystallized from ethyl acetate.

REFERENCES

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