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SYNTHETIC AND MODIFIED ISOFLAVONOIDS. XIII. SYNTHESIS OF ANALOGUES OF FUJIKININ

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Analogues of a natural isoflavone glycoside – fujikinin – have been synthesized. Their structures have been confirmed by their PMR spectra.

Carbohydrate derivatives of flavonoids, like those of other phenolic compounds, are widely distributed in nature. The O-glycosides of these compounds are found most frequently. The O-glycosides of isoflavones are promising in connection with pharmacological research since they exhibit a more effective action on the cardiovascular system than the aglycons themselves. Furthermore, isoflavone glycosides are more soluble in water and in blood plasma, and their acetates and alkyl ethers are more soluble in fats and other media of low polarity, which facilitates the introduction of these compounds into the system of a living organism.

Isoflavones glycosylated in the seventh position are found most frequently in nature. They include pseudobaptisin [7-hydroxy-3′,4′-methylenedioxy)isoflavone 7-O-(6-O-α-L-rhamnopyranosyl-β-D-glucopyranoside)], isolated from the roots of wild indigo (*Baptisia tinctoria* L.) [2, 3], dalpantin (7-hydroxy-5′,8-dimethoxy-3′,4′-methylenedioxyisoflavone β-D-glucopyranoside), isolated from *Dalbergia paniculata* [4], and fujikinin (7-hydroxy-8-methoxy-3′,4′-methylenedioxyisoflavone β-D-glucopyranoside) [5], isolated from the bark of *Cladrastis platycarpa*. As can be seen from the structures of the isoflavone-glycosides isolated from plants, they contain a 1,3-benzodioxolane fragment in the molecule. In view of the useful properties of isoflavone glycosides, it was of interest to synthesize new analogs of fujikinin and to study their chemical and biological properties.

The initial substances for the synthesis of the desired compounds were α-hetaryl-2-hydroxy-4-O-(tetraacetyl-β-D-glucopyranosyl) derivatives (**2**), obtained, in their turn, by the interaction of the potassium salts of the ketones (**1**) with α-acetobromoglucose by a modified Michael method [9]. Information on them is given in Table 1.

The synthesis of the tetraacetylglucosides (**3**) containing no substituents in position 2 of the chromone nucleus was carried out by the action on the initial ketones (**2**) of the Vilsmeier reagent in the presence of boron trifluoride etherate. The formation of the chromone system took place in 0.5 h at 70°C. The acetylated glycosides of 2-methylisoflavones (**4**) were obtained by the interaction of the ketones (**2**) with acetic anhydride in the presence of triethylamine at 120-130°C. The interaction of ketone (**2b**) with trifluoroacetic anhydride in pyridine took place at 40-50°C in 30 min, as the result of which the 2-trifluoromethyl-7-O-tetraacetylglycosyl analog of fujikinin was formed. The glucopyranosides (**6-8**) were obtained by the deacetylation of the corresponding acetates (**3-5**) under the action of catalytic amounts of sodium methanolate in absolute methanol.

The physicochemical characteristics, including the PMR spectra of the analogs (**6-8**) and derivatives (**3-5**) of fujikinin are given in Tables 1 and 2. The PMR spectra of compounds (**2-5**), recorded from solutions of the samples in deuterated benzene, gave complete information on the structures of the compounds synthesized. In particular, in the spectra of compounds (**2a, c**) the signal of the proton of the OH-2 hydroxy group was present in the 13.1-13.2 ppm region, which shows the

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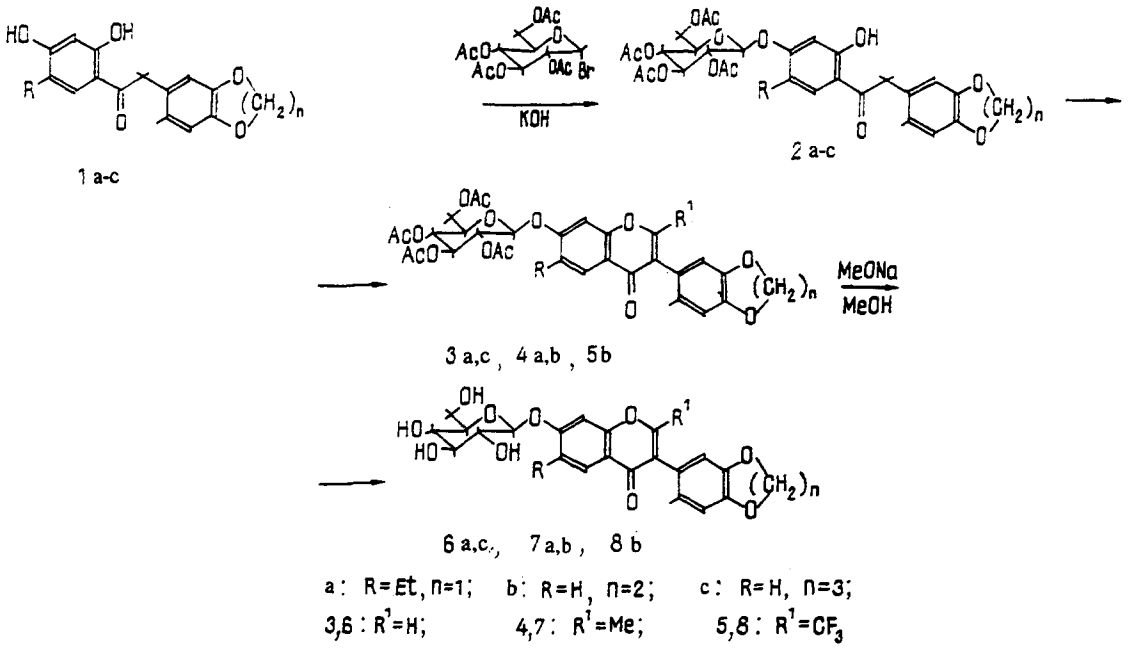

formation of an intramolecular hydrogen bond with the keto group and, simultaneously, the fact that the OH-4 hydroxy group had undergone glycosylation, since the signal of its proton was absent from the spectrum. The anomeric proton of the carbohydrate residue was shown in the form of a doublet (J = 7.3-7.5 Hz) at 4.7 ppm. The position of its signal and the spin–spin coupling constant indicated the β-configuration of the glycosidic bond formed. The signals of the anomeric protons occupied approximately the same position in the PMR spectra of the acetylated chromone glycosides (**3a, c, 5b**) (J = 7.5-7.8 Hz). Consequently, during the formation of the chromome system the configuration of the glycosidic bond was retained. The PMR spectra of the free glucosides (**6a, c, 8b**) contained the signals of the H-2 or the CH_3-2 protons of the aglycon (8.43 and 2.27 ppm, respectively). The positions of the signals of the protons of the benzodioxane nucleus of the trifluoromethyl derivative (**8b**) coincided with the positions of the signals of these protons in the spectrum of compound (**7b**). These facts show that the pyrone rings of these compounds were not destroyed during deacetylation.

Thus, by the glycosylation of α-hetaryl-2,4-dihydroxyacetophenones we have synthesized the corresponding O-(tetra-O-acetyl-α-D-glucopyranosides), which ave been converted by the closure of the chromone ring into tetraacetylglycosides of 7-hydroxyisoflavones containing in the molecule a benzodioxolane, benzodioxane, or benzodioxypane nucleus. As a result of deacylation, these compounds yielded synthetic analogs of the natural glycoside fujikinin. The structures of the compounds synthesized were shown with the aid of PMR spectroscopy.

EXPERIMENTAL

The conditions for chromatography and for recording the spectra have been described in [6].

α-Hetaryl-4-(tetra-O-acetyl-β-D-glucopyranosyloxy)-2-hydroxyacetophenones (2a-c). A 100-ml flask was charged with 100 mmoles of the appropriate ketone (**Ia-c**), the air was eliminated, and 7.28 ml of 50% caustic potash and 15 ml of acetone were added in a current of nitrogen. On stirring, the whole of the ketone dissolved. Then the mixture was cooled to 0°C, 30 g (75 mmoles) of acetobromoglucose was added, with stirring, over 30 min. The mixture was stirred at 0°C for 4 h, and at room temperature for 2 h and was left for 48 h. The reaction mixture was dissolved with heating in 400 ml of chloroform, and the solution was washed with 80 ml of 0.1 N caustic soda. The chloroform layer was dried over sodium sulfate and evaporated to dryness. The oily residue was recrystallized from isopropanol. Ketone (**1b**) has been described previously [10].

3-Hetaryl-7-(tetra-O-acetyl-β-D-glucopyranosyloxy)chromones (3a, c). With stirring, 3.7 ml (30 mmoles) of boron trifluoride etherate was added to a solution of 5 moles of a ketone (**2a, c**) in 7.5 ml (100 mmoles) of dimethylformamide. Then 1.1 g (5.5 mmoles) of phosphorus pentachloride was added at such a rate that the temperature of the reaction mixture

TABLE 1. Characteristics of Compounds (2-8)

Compound	Yield, %	mp, °C	Empirical formula	Solvent for crystallization.
2a	44	159—160	$C_{31}H_{34}O_{14}$	*i*-PrOH
2c	39	164—165	$C_{31}H_{36}O_{14}$	*i*-PrOH
3a	82.4	186—187	$C_{32}H_{32}O_{14}$	*i*-PrOH
3c	70.4	165—166	$C_{32}H_{32}O_{14}$	*i*-PrOH
4a	60	179—180	$C_{33}H_{34}O_{14}$	MeOH
4b	68.3	227—228	$C_{32}H_{32}O_{14}$	EtOAc
5b	89.7	116—117	$C_{32}H_{29}F_3O_{14}$	*i*-PrOH
6a	98.4	141—142	$C_{24}H_{24}O_{10}$	aq. EtOH
6c	79.5	131—132	$C_{24}H_{24}O_{10}$	EtOH
7a	96.4	160—161	$C_{25}H_{26}O_{10}$	EtOH
7b	71.5	158—159	$C_{24}H_{24}O_{10}$	EtOH
8b	25	261—262	$C_{24}H_{21}F_3O_{10}$	EtOH

TABLE 2. Details of the PMR Spectra of Compounds (2a, c-8b)*

Compound	Chemical shifts of the protons of the aglycon (δ, ppm)										
	OH-2 s	H-2, s	H-3, d	R-5, m	R-6, m	H-8, d	CH_2-a, s	H-2', d	H-5', d	H-6', d.d	—O(CH2)nO— m
2a	13.12	-	6.66	1.11; 2.51	7.31c	-	3.67	6.71	6.60	6.48	5.26s
2c	13.22	-	7.02	6.33	7.25	-	3.61	6.62	7.02	6.64	3.75; 1.71
3a	-	8.27	-	7.32s	1.07; 2.55	6.91s	-	7.16	6.75	6.97	5.34s
3c	-	7.27	-	8.31d	6.76	7.54	-	6.84	7.16	7.16	3.85; 1.59
4a	-	1.88	-	8.27s	1.10; 2.54	7.02s	-	6.92	7.80	6.69	5.43s
4b	-	1.83	-	8.37d	6.85	6.73	-	6.82	7.05	6.90	3.56s
5b	-	-	-	8.08d	7.12	6.76	-	6.67	7.02	6.76	3.50s
6a	-	8.43	-	7.88s	1.19; 2.73	7.24s	-	7.15	6.96	7.09	6.05s
6c	-	8.47	-	8.04d	7.12	7.24	-	7.16	7.00	7.12	4.16; 2.11
7a	-	2.27	-	7.77s	1.18; 2.70	7.21s	-	6.84	6.97	6.71	6.06s
7b	-	2.26	-	7.93d	7.09	7.19	-	6.76	6.90	6.71	4.26s
8b	-	-	-	8.00d	7.19	7.35	-	6.80	6.90	6.71	4.28s

Compound	Chemical shifts of the protons of the carbohydrate moiety (δ, ppm)						
	H-1, d (J, Hz)	H-2, m	H-3, m	H-4, t	H-5, m	CH_2-6, m	Acetyl CH_3 (OH)
2a	4.68 (7.3)	5.52	5.44	5.11	3.12	4.00	1.65; 1.70; 1.73; 1.82
2c	4.76 (7.5)	5.49	5.43	5.15	3.16	4.02	1.66; 1.70; 1.70; 1.78
3a	4.76 (7.3)	5.50	5.43	5.20	3.28	4.12	1.70; 1.71; 1.74; 1.75
3c	4.86 (7.8)	5.50	5.50	5.24	3.28	4.09	1.69; 1.69; 1.74; 1.74
4a	4.91 (7.8)	5.56	5.50	5.24	3.39	4.14	1.71; 1.73; 1.76; 1.80
4b	4.82 (7.5)	5.51	5.46	5.21	3.21	4.06	1.67; 1.71; 1.71; 1.71
5b	4.78 (7.8)	5.51	5.47	5.16	3.21	4.06	1.68; 1.72; 1.72; 1.79
6a	5.07 (7.0)	3.15 — 3.81 m			3.15 — 3.81 m		(4.35)
6c	5.14 (—)	3.15 — 3.81 m			3.15 — 3.81 m		(5.45; 5.14; 5.14; 4.61)
7a	5.08 (7.0)	3.15 — 3.81 m			3.15 — 3.81 m		(3.90 — 4.90)
7b	5.11 (—)	3.15 — 3.81 m			3.15 — 3.81 m		(5.45; 5.14; 5.14; 4.61)
8b	5.16 (—)	3.15 — 3.81 m			3.15 — 3.81 m		(5.45; 5.14; 5.14; 4.61)

*The spectra were measured in the following deuterated solvents: (2a-c and 5b, c), benzene; (6a-c and 8b, c), dimethyl sulfoxide.

did not rise above 60-70°C. After the reaction mixture had been kept for 1 h, it was poured into 200-250 ml of water and the resulting mixture was heated to 70°C for about 1 h. The precipitate that deposited was filtered off and crystallized from isopropanol.

3-Hetaryl-2-methyl-7-(tetra-O-acetyl-β-D-glucopyranosyloxy)chromones (4a, b). A mixture of 40 mmoles of a ketone (**2a, b**), 44.8 ml (480 mmoles) of acetic anhydride, and 49.6 ml (480 mmoles) of triethylamine was heated at 120-130°C for 6-8 h. After this, the reaction mixture was poured into water containing 2.5 ml of hydrochloric acid. The precipitate that deposited was filtered off and washed with water. The desired compounds (**4a, b**) were crystallized from suitable solvents.

3-(1,4-Benzodioxan-6-yl)-2-trifluoromethyl-7-(tetra-O-acetyl-β-D-glucopyranosyloxy)chromone (5b). In drops, 2.84 ml (20 mmoles) of trifluoroacetic anhydride was added to a solution of 10 mmoles of ketone (**2b**) in 10 ml of dry pyridine. The reaction mixture was shaken, with ice cooling, and was left overnight. On the following day it was heated to 40-50°C for 30 min and was again left at room temperature, for 10 h. Then it was poured into 150 ml of cold water and the resulting precipitate was filtered off.

3-Hetaryl-7-β-D-glucopyranosyloxychromones (6a, c, 7a, b, 8b). In the presence of catalytic amounts of sodium methanolate, a solution of 5 mmole of a compound (**3a, c, 4a, 5b**) in 50 ml of absolute methanol was boiled for 2-3 min. The solvent was distilled off in water-pump vacuum, and the residue was washed with water and was crystallized from a suitable solvent.

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