SYNTHESIS OF α-ARYLOXY-2,4-DIHYDROXYACETOPHENONE 4-O-β-D-GLUCOPYRANOSIDES AND THEIR CONVERSION INTO 3-ARYLOXY-7-GLUCOSYLOXYCHROMONES

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A convenient route to the synthesis of 3-aryloxy-7-β-D-glucopyranosyloxychromones has been developed which consists in the condensation of α-aryloxy-2,4-dihydroxyacetophenones with acetobromoglucose and the conversion of the α-hydroxy-2,4-dihydroxyacetophenone 4-O-glucosides so obtained into the desired 3-aryloxy-7-glucosyloxychromones. Conditions for the effective performance of the latter transformation have been found.

Isoflavones and their glycosides are known as biologically active substances with a broad spectrum of pharmacological action [1]; in particular, ononin (7-β-D-glucopyranosyloxy-4'-methoxyisoflavone) possesses a hypoglycemic action [2].

In order to find new highly effective hypoglycemic drugs among aryloxychromones – structural analogs of the isoflavones – we have synthesized the 7-glucosyloxy-3-phenoxychromones (Va, b) (see scheme). One of them, 7-β-D-glucopyranosyloxy-3-(4-methoxyphenoxy)chromone (its acetate being Va) is a structural analog of ononin.

The initial compounds for this synthesis were resorcinol and the 4'-substituted aryloxyacetonitriles (Ia, b). Under the conditions of the Hoesch synthesis they were converted into the corresponding ketimine hydrochlorides which, without isolation in the pure form, were hydrolyzed to the α-aryloxy-2,4-dihydroxyacetophenones (IIa, b). Compounds (IIa, b) give a brown coloration with an ethanolic solution of iron(III) chloride because of the formation of a chelate complex. Their PMR spectra (in acetone or DMSO) each contains a narrow singlet at 11.5-11.9 ppm, corresponding to the proton of the 2-OH hydroxyl bond by an intramolecular

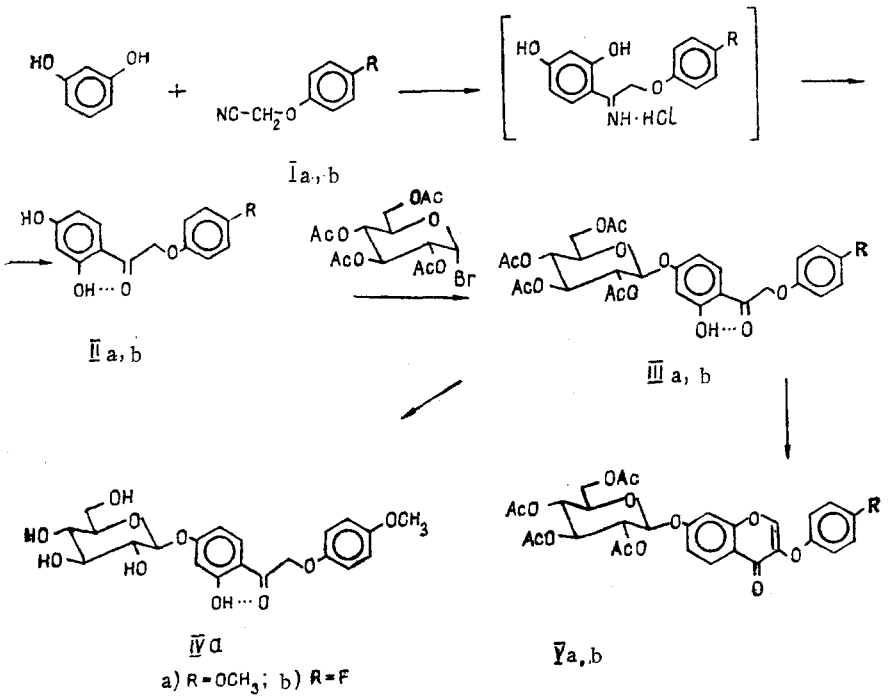

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TABLE 1. Physicochemical Characteristics of Compound (IIa, b)-(Va, b)*

Compound	Yield, %	mp, °C	$[\alpha]_D^{25}$ deg	c, vol. %	Solvent	Empirical formula	IR spectra, cm^{-1}		Solvent for crystallization
							$\nu_{C=O}$ of a ketone	$\nu_{C=O}$ of an acyl group (ν_{OH})	
IIa	63	179	—	—	—	$C_{15}H_{14}O_5$	1630	(3300)	Isopropanol–water
IIb	63	165	—	—	—	$C_{14}H_{11}FO_4$	1630	(3300)	Isopropanol
IIIa	45	180	—27	1	Chlf	$C_{29}H_{32}O_{14}$	1660	1750	"
IIIb	34	174	—28	1	Chlf	$C_{28}H_{29}FO_{13}$	1645	1750	"
IVa	93	144	—38	0,7	DMSO	$C_{21}H_{24}O_{10}$	1650	(3350)	Water–methanol
Va	85	143	—24	0,5	DMSO	$C_{30}H_{30}O_{14}$	1650	1750	Isopropanol
Vb	80	145	—23	0,5	DMSO	$C_{29}H_{27}FO_{13}$	1650	1750	"

*The results of the elementary analyses of the compounds corresponded to the calculated figures.

hydrogen bond to the keto group, and a broadened singlet at 10.7 ppm belonging to the proton of the 4-OH hydroxyl. The protons of the methylene unit give a singlet in the 5.4-ppm region. The aromatic protons of the phenolic moiety and of the phenoxyl fragment are revealed in the form of doublets or multiplets with the corresponding ortho and meta spin-spin coupling constants.

The condensation of the potassium salts of the 2,4-dihydroxyacetophenones (IIa, b) with acetobromoglucose in concentrated aqueous acetone solution (as we recommended previously [3]) could not be carried out because of the poor solubility of the salts mentioned. To increase the solubility of the reactants we used as the medium a mixture of water, acetone, and dimethylformamide and performed the reaction not at 0 but at 20°C. Under these conditions glucosides (IIIa, b) were obtained with yields of 45 and 34%, respectively. They gave a brown coloration with an ethanolic solution of iron chloride which showed the presence of 2-OH hydroxy groups and, consequently, the location of the carbohydrate residue in position 4 of the ketone. The PMR spectrum confirmed this assignment completely (Table 2). The chemical shifts and spin-spin coupling constants of the anomeric proton (5.15 ppm and 7.6 Hz, respectively) and also the negative values of the angles of specific rotation (Table 1) showed the β-configuration of the anomeric centers of glucosides (IIIa, b).

The free glucoside (IVa) was obtained from the acetate (IIIa) by the action on a methanolic solution of the latter of an excess of a 2 N solution of sodium hydroxide in water. The results of elementary analysis polarimetry, and IR spectroscopy confirmed the structure proposed for glucoside (IVa) (Table 1).

Our attempt to convert the ketones (IIIa, b) into the chromones (Va, b) with the aid of ethyl orthoformate [3] proved unsuccessful. A chromatographic analysis of the reaction mixture showed that the desired glucosyloxychromone was formed only in insignificant amounts. The predominating process was the decomposition of the initial compound. Consequently, the ethyl orthoformate method is unsuitable for the synthesis of 3-aryloxyglycosyloxychromones.

Bass's method [4] has well recommended itself in the preparation of 3-aryloxychromones; it consists in the action on corresponding 2-hydroxyacetophenones of a complex of the reagents boron trifluoride etherate, dimethylformamide, and methanesulfonyl chloride and the subsequent prolonged boiling of the reaction mixture with a 10% aqueous solution of sulfuric acid. The comparatively severe conditions of Bass's method threw doubt on the success of its use in the synthesis of 3-aryloxy-7-glycopyranosyloxychromones. It was not known whether, under the conditions of the reaction mentioned, the β-glucosidic bond would withstand the possibility of anomerization and, in general, whether this bond would be retained if both processes [5] took place under such conditions. With a positive answer to this question, for the successful preparation of 3-aryloxyglucosyloxychromones it would be necessary to solve the problem of the hydrolysis of the reaction mixture, since the hydrolysis with an aqueous solution of sulfuric acid used in this procedure would be inapplicable for glycosyloxychromones.

TABLE 2. Details of the PMR Spectra of Compounds (IIa, b)-(Va, b)*

Compound	Chemical shifts of the protons in the aglycon										
	2-OH	2-H	3-H	4-OH	5-H	6-H	8-H	α-CH_2	2'-, 6'-H	3'-, '-H	4'-OMe
IIa	11,90	—	6,45	10,75	6,50	7,86	—	5,42	6,91	6,91	3,75
IIb	11,56	—	6,38	10,79	6,43	7,76	—	5,43	7,03	7,03	—
IIIa	12,20	—	6,56	—	6,54	7,46	—	5,17	6,84	6,89	3,77
IIIb	12,20	—	6,52	—	6,49	6,68	—	5,15	6,82	6,93	—
Va	—	7,88	—	—	8,21	7,05	7,05	—	6,84	6,88	3,78
Vb	—	7,94	—	—	8,09	6,99	7,02	—	6,88	6,91	—

Compound	Chemical shifts of the protons of the carbohydrate moiety						
	1-H (J, Hz)	2-H	3-H	4-H	5-H	6-CH_2	acetyl CH_3 groups
IIa	—	—	—	—	—	—	—
IIb	—	—	—	—	—	—	—
IIIa	5,17 (7,6)	5,25	5,33	5,16	3,92	4,27; 4,17	2,11—2,05
IIIb	5,15 (—)	—	5,31	5,06	3,88	4,19; 4,10	2,00—1,94
Va	5,23 (8,0)	5,31	5,34	5,17	3,97	4,29; 4,22	2,09—2,05
Vb	5,14 (8,5)	5,26	5,29	5,11	3,96	4,23; 4,16	2,09—1,98

*The spectra were measured in the following deuterated solvents: (IIa) in acetone, (IIb) in DMSO, (IIIa) in chloroform, (IIIb) in dichloromethane (internal standard: HMDS), (Va) in chloroform (internal standard: HMDS), (Vb) in chloroform.

In the first experiment, it was found that on heterocyclization under Bass's conditions [4], no anomerization or cleavage of the β-glucosidic bond took place. Thus, under the action of the dimethylformamide—methanesulfonyl chloride complex on glucoside (IIIa) in the presence of boron trifluoride we obtained the glucoside (Va). The specific rotation of the compound obtained (−24°) was close to that for the initial substance (−27°), which indicated the retention of the configuration of the glycosidic bond in compound (Va).

In the preparation of the 3-aryloxyglucosyloxychromones (Va, b), the hydrolysis of the reaction mixture was carried out at room temperature without the use of sulfuric acid. The high yields of glucosides (Va, b) (85 and 80%, respectively; Table 1) indicated only a slight intensity of the side reactions under the conditions selected.

The results of elementary analysis and of IR and PMR spectroscopy of compounds (Va, b) confirmed the structures proposed for them (Tables 1 and 2). In the PMR spectrum of each of them, the 2-H proton of the chromone ring gave a signal in the 7.9-8.2 ppm region. The signals of the 5-H, 2'-H, and 6'-H protons of the chromone nucleus were shifted downfield in comparison with those for the initial ketones (IIIa, b). Unlike the initial compounds, glucosides (Va, b) did not give a coloration with an ethanolic solution of ferric chloride. These facts indicate the presence of a chromone system in the compounds obtained. Thus, the 3-aryloxy-7-(tetra-O-acetyl-β-D-glucopyranosyloxy)chromones that we have synthesized will serve as a basis for obtaining new substances with given properties.

EXPERIMENTAL

The course of the reaction and the purity of the compounds obtained were monitored by the TLC method on Silufol UV-254 plates with dimensions of 25 × 75 mm. Chloroform—methanol (9:1 or 85:15) was used as eluent. Specific rotations were measured on a Polamat A polarimeter. PMR spectra were taken on a Bruker CXP-200 instrument (for the glucosides) or a ZKR-60 instrument (for the initial ketones), using TMS as internal standard. IR spectra were recorded on a Specord IR-71 spectrometer in potassium bromide tablets. Melting points were measured on a PTP instrument.

The initial phenoxyacetonitriles (Ia, b) were synthesized by a known method [6]. All the reagents used in the work were of khch [chemically pure] grade.

2,4-Dihydroxy-α-(4-methoxyphenoxy)acetophenone (IIa). A current of dry hydrogen chloride was passed into a solution of 41 g (0.25 mole) of 4-methoxyphenoxyacetonitrile in 190 ml of dry benzene for 15 min, after which a solution of 17.03 g (0.125 mole) of anhydrous zinc chloride and 33 g (0.30 mole) of resorcinol in 125 ml of dry ether was added. While the temperature of the reaction mixture was kept between 0 and 5°C, with vigorous stirring

a current of dry hydrogen chloride was passed in to saturation. After a day, the reaction mixture was poured into 1 liter of hot water, and the mixture was boiled for 3 h and was cooled. The precipitate was filtered off and recrystallized from isopropanol containing 10-15% of water. This gave 49.8 g (72.5%) of compound (IIa). Colorless prisms. The physicochemical characteristics of the compounds synthesized are given in Tables 1 and 2.

α-(4-Fluorophenoxy)-2,4-dihydroxyacetophenone (IIb) was obtained in a similar way to ketone (IIa) from 37.6 g (0.25 mole) of 4-fluorophenoxyacetonitrile (IIb), 33 g (0.30 mole) of resorcinol, and 17.03 g (0.125 mole) of zinc chloride with a yield of 41 g (63%). Colorless prisms.

2-Hydroxy-α-(4-methoxyphenoxy)-4-(tetra-O-acetyl-β-D-glucopyranosyloxy)acetophenone (IIIa). With stirring and the passage of a current of nitrogen into the reactor, 11 ml (0.15 mole) of a 50% aqueous solution of potassium hydroxide was added dropwise to a mixture of 27.4 g (0.1 mole) of compound (IIa), 8 ml of dimethylformamide, and 16 ml of acetone. The mixture was cooled to 20°C , 27.4 g (0.067 mole) of acetobromoglucose was added in 0.5 g portions, and the resulting mixture was stirred for 5 h and was left for a day at room temperature. The viscous mass was dissolved in 250 ml of chloroform, the solution was filtered, and the filtrate was cooled to 0°C and was washed successively with 34 ml of 2 N sodium hydroxide solution and 200 ml of water. The organic layer was dried over sodium sulfate, and the solvent was evaporated off under reduced pressure. The oily residue was recrystallized from isopropanol, as a result of which 18 g (45%) of the glucoside (IIIa) was obtained in the form of colorless needles.

α-(4-Fluorophenoxy)-2-hydroxy-4-(tetra-O-acetyl-β-D-glucopyranosyloxy)acetophenone (IIIb) was obtained in a similar way to compound (IIIa) from 26.2 g (0.1 mole) of the ketone (IIb) in 21 ml of dimethylformamide, 7.28 ml (0.1 mole) of a 50% aqueous solution of potassium hydroxide, and 27.5 g (0.067 mole) of acetobromoglucose, with a yield of 13.5 g (34%). Colorless needles.

4-β-D-Glucopyranosyloxy-2-hydroxy-α-(4-methoxyphenoxy)acetophenone (IVa). To a boiling suspension of 4.0 g (6.7 mmole) of the acetate (IIIa) in 20 ml of methanol was gradually added 25 ml of a 2 N aqueous solution of sodium hydroxide. After 0.5 h, the hot solution was neutralized with acetic acid. The precipitate that deposited was filtered off and was washed with 10 ml of 50% methanol. This gave 2.7 g (93%) of chromatographically homogeneous substance (IVa) in the form of a microgranular powder.

3-(4-Methoxyphenoxy)-7-(tetra-O-acetyl-β-D-glucopyranosyloxy)chromone (Va). With stirring, and in portions, first 11 ml (12.4 g, 90 mmole) of boron trifluoride etherate and then a mixture of 9 ml of dimethylformamide and 2.57 ml (3.8 g, 33 mmole) of methanesulfonyl chloride were added to a mixture of 9.06 g (15 mmole) of compound (IIIa) and 15 ml of dimethylformamide. The solution formed was kept at 70°C for 30 min and was then cooled and was poured into 200 ml of ice water. The suspension so formed was neutralized with 10% aqueous ammonium hydroxide solution and the resulting precipitate was filtered off and recrystallized from methanol. This gave 7.75 g (85%) of compound (Va) in the form of colorless prisms.

3-(4-Fluorophenoxy)-7-(tetra-O-acetyl-β-D-glucopyranosyloxy)chromone (Vb) was obtained in a similar way to glucoside (Va) from 0.60 (1 mmole) of compound (IIIb) in 1.5 ml of dimethylformamide, 0.74 ml (6 mmole) of boron trifluoride etherate, 0.4 ml (5 mmole) of dimethylformamide, and 0.17 ml (2.2 mmole) of methanesulfonyl chloride with a yield of 0.48 g (80%). Colorless crystals.

CONCLUSIONS

A convenient method of synthesizing 3-aryloxy-7-β-D-glucopyranosyloxychromones has been developed which consists in the condensation of α-aryloxy-2,4-dihydroxyacetophenones with acetobromoglucose and the conversion of the α-aryloxy-4-glucosyloxy-2-hydroxyacetophenones so obtained into the desired 3-aryloxy-7-glucosyloxychromones. Conditions have been found for the effective performance of the latter conversion.

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HYDROCARBONS AND CAROTENOIDS OF THE MEDICINAL MUD OF LAKE KARACHI

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The composition of the hydrocarbons and carotenoids of the lipids of a typical ooze-like sulfide mud from Lake Karachi has been studied. The presence of carcinogenic 3,4-benzopyrene in the hexane fraction of the liquid has been established. A high antioxidant activity has been found in the chloroform fraction, which also possesses a pronounced hepatoprotective action.

Experimental pharmacological investigations have shown the high therapeutic efficacy of the lipids of the medicinal mud from Lake Karachi in toxic hepatitis, myocarditis, and acute and chronic arthritis [1-3]. The curative action of the lipids is connected with the presence in them of unsaturated fatty acids, phospholipids, and prostaglandins [4]. The aim of the present investigation was a detailed study of the chemical composition of the lipids of a typical ooze-like sulfide mud from Lake Karachi and the determination of the biologically active and ballast substances and possible toxic substances. The results are given of an investigation of the composition of two classes of compounds – hydrocarbons (HCs) and carotenoids. Biological activity was tested on the model of acute toxic hepatitis caused by CCl_4. In the organism, CCl_4 undergoes enzymatic homolytic breakdown with the formation of the free radicals $CCl_3^{\cdot}$ which induce the peroxide oxidation of the lipids in the membrane of the liver. Consequently, for a preliminary estimate of the hepatoprotective action we also determined the antioxidant activity of fractions of the lipids of the medicinal mud.

The medicinal mud of Lake Karachi accumulated under the conditions of pronounced hydrogen sulfide contamination from residues of planktonic organisms (Microcystis salina, Artemia salina) transformed by the bottom microflora. The mineral fraction is represented by clays, carbonates, and salts (NaCl, Na_2SO_4, $CaSO_4$, $MgSO_4$).

A lipid extract of the medicinal mud from Lake Karachi consists of a resinous substance of dark-brown color with a specific balsamic odor, soluble in chloroform and ethanol and partially soluble in hexane and petroleum ether. This property of the lipids was used for their separation in two fractions – a hexane (nonpolar) and a chloroform (polar) fraction. According to the experimental results, the yield of the polar fraction of lipids was 59% and that of the nonpolar fraction 41%.

The antioxidants in the hexane fraction consisted of one type of weakly active inhibitors and those in the chloroform fraction of two types of inhibitors possessing a pronounced antioxidant action. The characteristics of the antioxidant properties of the lipid fractions of the medicinal mud of Lake Karachi are given below:

Function	$k_{7_1} \cdot 10^{-4}$, liter/mole·sec	$k_{7_2} \cdot 10^{-4}$, liter/mole·sec	Concentration of inhibitors, mole/kg
Hexane	–	1.40	0.23
Chloroform	7.10	0.96	0.28
Ionol	2.40	–	–

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