EFFECTIVE SYNTHESIS OF 7-HYDROXYISOFLAVONE O-GLUCOSIDES

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UDC 547.918:542.954

An effective procedure for condensing acetobromoglucose with 2,4-dihydroxyphenyl benzyl ketones has been developed. The 2-hydroxy-4-(β-D-tetra-O-acetylglucopyranosyloxy)phenyl benzyl ketones synthesized with yields of 47-69% have been converted under the action of ethyl orthoformate in pyridine solution into 7-hydroxyisoflavone O-glucosides and these have also been obtained by the glycosylation of 7-hydroxyisoflavone. The advantages and disadvantages of the alternative pathways of the synthesis of 7-hydroxyisoflavone O-glycosides are discussed.

The majority of flavonoids exist in nature in the form of glycosyloxy derivatives. In comparison with the aglycons, the O-glycosides have increased solubility in water and blood plasma, and their acetates and methyl ethers increased solubility in fats and other weakly polar media. In view of the high and diverse biological activities of the isoflavones [1], considerable interest is presented by a study of the biological action of their glycosyloxy derivatives. It appears unrealistic to perform an investigation with natural glycosides because of the great laboriousness of their isolation from plant raw material in the necessary amounts. It will be more convenient to obtain the desired hydroxyisoflavone O-glycosides synthetically, which will provide the additional possibility of introducing into the isoflavone nucleus fragments that are promising from the point of view of biological activity.

Two approaches to the chemical synthesis of hydroxyisoflavone O-glycosides are known. The first, more common, approach is to obtain a hydroxyisoflavone and then to condense it with an acetobromocarbohydrate [2, 3]. Recently, an isoflavone precursor – 2,4-dihydroxyphenyl benzyl ketone – has been subjected to glycosylation. The glycosylated ketone was then converted in one stage into a hydroxyisoflavone O-glucosides [3-7]. The second approach appears more promising, since the most complex and low-productivity stage – glycosylation – is introduced into it at the beginning of the multistage process. In view of this, we chose this method for obtaining a number of hydroxyisoflavone O-glucosides.

TABLE 1. Conditions for the Synthesis and Yields of 2,4-Dihydroxyphenyl Benzyl Ketone Glucosides

Initial compounds and their amounts								Compound obtained and its yield			
ketone			acetobromoglucose		KOH, 50% solution		acetone, ml	compound	g	%	% according to the literature
compound	g	mmole	g	mmole	ml	mmole					
Ia	45,6	200	41,1	100	14,6	200	30	IIa	38,5	69	37 [3]
Ib	25,8	100	30,8	75	7,3	100	15	IIb	23,8	54	20 [3]
Ic	28,6	100	30,8	75	7,3	100	15	IIc	26,5	58	—
Id	14,3	50	15,6	38	3,7	50	7,0	IId	10,7	47	—
Ie	12,3	50	13,6	33	3,7	50	7,3	IIe	9,5	50	—
If	11,0	45	12,3	30	3,3	45	6,6	IIf	9,0	53	—
Ig	15,4	50	15,6	38	3,7	50	7,0	IIg	10,3	43	—
Ih	23,5	100	20,6	50	7,3	100	15	IIh	16,1	57	27 [7]
Ii	24,9	100	30,8	75	7,3	100	15	IIi	11,7	27	27 [7]

T. G. Shevchenko Kiev State University. Khar'kov State Pharmaceutical Institute. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 511-519, July-August, 1988. Original article submitted September 28, 1987; revision submitted January 29, 1988.

 0009-3130/88/2404-0432 $12.50

TABLE 2. Properties of Glucosides (IIa-i, IIIa, b, h, and Va-j)

Compound	Yield, %	mp, °C	$[\alpha]_D^{23}$, deg	c, vol. %	Solvent	Empirical formula	Solvent for crystallization
IIa	69	161	—27	1	Chlf	$C_{28}H_{30}O_{12}$	Isopropanol
IIb	54	153	—27	0,5	Chlf	$C_{29}H_{32}O_{13}$	Isopropanol
IIc	58	153	—28	0,6	Chlf	$C_{30}H_{32}O_{14}$	
IId	47	130	—30	0,5	Chlf	$C_{31}H_{36}O_{13}$	
IIe	50	123	—29	0,7	Chlf	$C_{28}H_{29}FO_{12}$	
IIf	53	162	—28	0,7	Chlf	$C_{28}H_{29}FO_{12}$	
IIg	43	160	—29	0,5	Chlf	$C_{28}H_{29}BrO_{12}$	
IIh	57	153	—30	1	Chlf	$C_{25}H_{27}NO_{12}S$	
IIi	27	135	—28	1	Chlf	$C_{26}H_{29}NO_{12}S$	
IIIa	95	185	—45	1	DMSO	$C_{20}H_{22}O_8$	Methanol
IIIb	89	178	—40	1	DMSO	$C_{21}H_{24}O_9$	Methanol
IIIh	75	203	—42	1	DMSO	$C_{17}H_{19}NO_8S$	Aqueous methanol
IIIi	98	229	—44	1	DMSO	$C_{18}H_{21}NO_8S$	Methanol
Va	56	155	—22	1	Chlf	$C_{29}H_{28}O_{12}$	
Vb	71	187	—27	1	Chlf	$C_{30}H_{30}O_{13}$	
Vc	67	169	—25	0,7	Chlf	$C_{31}H_{30}O_{14}$	
Vd	51	132	—28	0,5	DMSO	$C_{32}H_{34}O_{13}$	
Ve	61	196	—31	0,5	Chlf	$C_{29}H_{27}FO_{12}$	
Vf	88	169	—27	0,7	Chlf	$C_{29}H_{27}FO_{12}$	
Vg	82	220	—25	0,5	Chlf	$C_{29}H_{27}BrO_{12}$	
Vh	88	224	—31	1	Chlf	$C_{26}H_{25}NO_{12}S$	
Vi	64	205	—30	1	Chlf	$C_{27}H_{27}NO_{12}S$	
Vj	32	211	—29	0,5	DMSO	$C_{29}H_{27}ClO_{13}$	

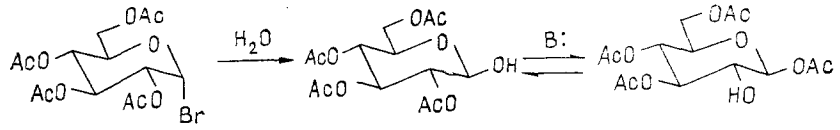
Note. The analytical results for (IIc-Vj) corresponded to the calculated figures.

The most common method of glycosylating phenolic compounds is the condensation of the sodium or potassium salt of the corresponding phenol with an acetobromocarbohydrate in dilute aqueous acetone solution [8]. After the elimination of by-products the desired hydroxyisoflavone O-glycosides are obtained with yields of 15-30% [2-7].

In the present paper we give the results of a search for the optimum conditions of synthesizing hydroxyisoflavone O-glycosides and their precursors — 2-hydroxyphenyl benzyl ketone glycosides.

It is known that acetobromocarbohydrates and, in particular, acetobromoglucose, dissociate comparatively readily with the formation of an acyloxonium cation because of which they react with nucleophiles by a mechanism close to monomolecular nucleophilic substitution [9]. On this basis, the main side reaction in the interaction of acetobromoglucose with salts of phenols in dilute aqueous acetone solution may be considered to be the hydrolysis of glucopyranosyl bromide (Scheme 1). It is possible to eliminate this reaction by performing the

Scheme 1



B: — base (ArO^-, OH^- etc.).

glycosylation of phenols in an anhydrous medium. However, as experiments have shown, under anhydrous conditions the yield of glycoside remains practically unchanged. For example, on the condensation of acetobromoglucose with the sodium salt of 2,4-dihydroxyphenyl 4-methoxybenzyl ketone in dry dimethylformamide the yield of the corresponding glucoside amounted to 18%, while on the interaction of acetobromoglucose with the sodium salt of 2,4-dihydroxy-α-(thiazol-4-yl)acetophenone in dry acetone the glucoside was isolated with a yield of 25% (see Experimental). In all probability, when reactions are carried out in anhydrous aprotic solvents (acetone, dimethylformamide, etc.) a different side reaction takes place — the elimination of hydrogen bromide from the acetobromoglucose with the formation of 2-acetoxyglucal

TABLE 3. PMR Spectra of Glucosides (IIa-i, IIIa, b, h, i) (solvent – deuterochloroform)

Compound	Chemical shifts of the protons of the carbohydrate moiety						Protons of the acetyl or hydroxy groups	Chemical shifts of the protons of the phenolic moiety					Chemical shifts of the protons of the benzyl residue
	1-H (J, Hz)	2-H	3-H	4-H	5-H	6-CH_2		2-OH	3-H	5-H	6-H	CH_2	
IIa*	5,74 (8,0)	5,10	5,42	5,02	4,40—4,10		2,02; 1,98	11,87	6,58	6,59	8,07	4,37	7,30 (2, 3, 4, 5, 6-H)
IIb	5,15 (6,0)	5,23—5,39		5,15	3,89	4,24; 4,16	2,09; 2,06	12,61	6,52	6,59	7,78	4,14	7,19 (2, 6-H); 6,88 (3, 5-H); 3,79 (CH_3)
IIc	5,16 (7,9)	5,23—5,36		5,15	3,91	4,30; 4,17	2,09; 2,05; 2,04; 2,03	12,57	6,52	6,48	7,75	4,09	4,22 (CH_2-CH_2); 6,76 (5-H); 6,71 (7-H); 6,82 (8-H)
IId*	5,72 (7,7)	5,12	5,39	5,05	4,27	4,12	2,01	12,43	6,56	6,56	8,06	4,27	7,19 (2, 6-H); 6,84 (3, 5-H); 4,55; 1,24 (i-Pr)
IIe	5,16 (7,0)	5,23—5,37		5,16	3,91	4,27; 4,18	2,09; 2,07; 2,05; 2,04	12,51	6,54	6,51	7,76	4,21	7,03 (2, 6-H); 7,24 (3, 5-H);
IIf	5,17 (8,0)	5,24—5,34		5,16	3,91	4,27; 4,19	2,09; 2,05	12,42	6,55	6,52	7,81	4,27	7,28 (3-H); 7,14 (4-H); 7,06 (5-H); 7,23 (6-H)
IIg	5,72 (7,6)	5,12	5,40	5,04	4,35	4,13	2,04; 2,00	12,26	6,58	6,59	8,05	4,38	7,53 (3, 5-H); 7,24 (2,6-H)
Ih**	5,10 (8,0)	5,17—5,30		5,09	3,85	4,20; 4,10	2,09; 1,99; 1,98; 1,97	12,37	6,47	6,43	7,80	4,41	8,73 (2-H); 7,19 (5-H)
Ii**	5,10 (8,0)	5,17—5,28		5,09	3,85	4,20; 4,11	2,03; 1,99; 1,98; 1,97	12,38	6,46	6,41	7,77	4,31	2,64 (CH_3); 6,92 (5-H)
IIIa*	5,06 (6,0)	3,80—3,10			3,80—3,10		5,37; 5,13; 5,02; 4,57	12,39	6,58	6,61	8,06	4,36	7,30 (2, 3, 4, 5, 6-H)
IIIb*	5,06 (4,5)	3,80—3,10			3,80—3,10		5,36; 5,13; 5,02; 4,58	12,43	6,57	6,61	8,04	4,27	7,22 (2, 6-H); 6,88 (3, 5-H); 3,72 (CH_3)
IIIh*	4,99 (***)	3,90—3,10			3,90—3,10		5,32; 4,99; 4,47	12,05	6,51	6,55	7,94	4,47	8,94 (2-H); 7,47 (5-H)
IIIi*	4,86 (***)	3,70—3,20			3,70—3,20		4,86	12,27	6,56	6,54	7,98	4,46	2,60 (CH_3); 7,30 (5-H)

*Spectrum measured in DMSO-d_6 on an instrument with a working frequency of 100 MHz.
**Internal standard HMDS.
***Could not be determined.

TABLE 4. Details of the PMR Spectra of the Chromone Glycosides (Va-j) (solvent – deuterochloroform)

Compound	Chemical shifts of the protons of the carbohydrate moiety						Protons of the acetyl groups	Chemical shifts of the chromone protons				Chemical shifts of the protons of the aryl substituent
	1-H (J, Hz)	2-H	3-H	4-H	5-H	6-CH_2		2-H	5-H	6-H	8-H	
Va*	5,83 (7,5)	5,18	5,41	5,09	4,37	4,20	2,04; 2,00	8,51	8,12	7,15	7,28	7,66 — 7,37 (2, 3, 4, 5, 6-H)
Vb*	5,84 (7,5)	5,18	5,41	5,10	4,39	4,17	2,04	8,46	8,12	7,15	7,27	7,55 (2, 6-H); 7,02 (3,5-H); 3,80 (CH_3)
Vc	5,23 (7,5)	5,33	5,36	5,19	3,97	4,29 ;4,22	2,11—2,07	7,93	8,23	7,03	7,02	4,28 (CH_2-CH_2); 7,10 (5-H); 7,03 (7-H); 6,92 (8-H)
Vd*	5,81 (7,5)	5,19	5,41	5,10	4,38	4,36	2,04; 2,00	8,46	8,10	7,14	7,26	7,51 (2, 6-H); 6,98 (3, 5-H); 4,66; 1,29 (i-Pr)
Ve	5,25 (7,5)	5,33	5,36	5,19	3,98	4,29; 4,23	2,10—2,04	7,96	8,24	7,06	7,05	7,54 (2, 6-H); 7,13 (3, 5-H);
Vg**	5,39 (7,5)	5,22	5,32	5,10	4,10	4,22; 4,14	2,00—1,94	8,05	8,11	7,04	7,08	7,50 (2, 6-H); 7,44 (3, 5-H)
Vf*	5,86 (7,6)	5,18	5,41	5,09	4,40	4,17	2,04; 2,00	8,49	8,09	7,18	7,31	7,60 — 7,25 (3, 4, 5, 6-H)
Vh	5,24 (8,0)	5,33	5,35	5,18	3,98	4,31; 4,25	2,11—2,06	9,01	8,26	7,07	7,09	8,82 (2-H); 8,61 (5-H)
Vi	5,23 (7,8)	5,33	5,35	5,17	3,98	4,30; 4,25	2,11—2,06	8,95	8,23	7,06	7,07	2,74 (CH_3); 8,34 (5-H)
Vj	5,10 (6,2)	5,20—5,31		5,09	3,83	4,22—4,14	2,05—1,99	7,84	12,63+	6,37	6,43	7,41 (2, 6-H); 7,36 (3, 5-H)

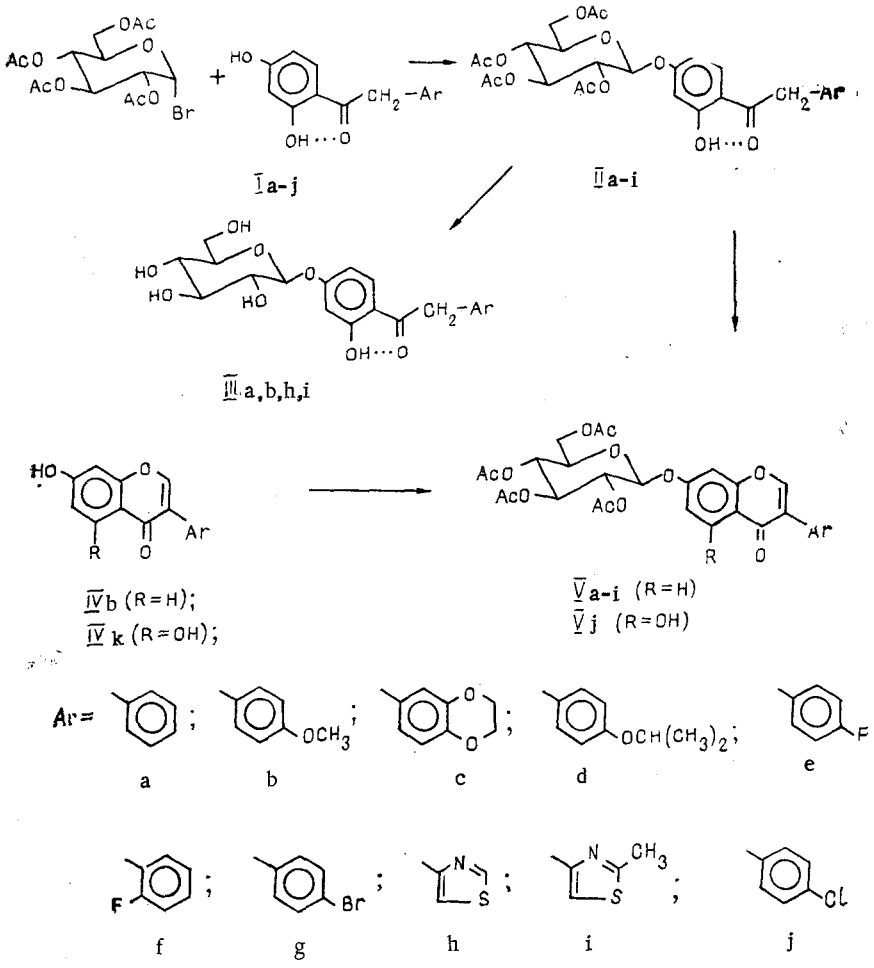
*Spectrum measured in DMSO-d_6 on an instrument with a working frequency of 100 MHz.
**In a mixture of dichloromethane-d_4 and acetone-d_6.
+Chemical shift of the 5-OH proton.

(Scheme 2) [10]. Summarizing what has been said, it may be assumed that both the protonic (water) and the aprotic components of the solvent have an adverse effect on the yield of aryl O-glycosides in the reaction under consideration, and it is probably possible to achieve an advantageous effect by using the minimum amounts of solvent.

Scheme 2

We have performed the condensation of acetobromoglucose with the potassium salts of the 2,4-dihydroxyphenyl benzyl ketones (Ia-i) present in aqueous acetone solution (Scheme 3). To prepare highly concentrated solutions of these salts we used an equivalent amount of a 50% (13.5 M) aqueous solution of potassium hydroxide and double (relative to the volume of alkali) amounts of acetone. Under such conditions, glycosides (IIa-h) were obtained with yields of 47-69% (Table 1), which are 2-2.5 times greater than the yields of the compounds mentioned under standard conditions [3, 7].

Scheme 3



It must be mentioned that the proposed glycosylation conditions are not suitable for all polyhydroxy compounds. An obvious bar to the occurrence of the reaction is an unsatisfactory solubility of the phenol salts in aqueous acetone. During the experiments, we were therefore forced to replace the sodium salts of the phenols (Ia-i) by the more soluble potassium salts. For this reason it was not possible to achieve significant results in the glycosylation of the 2,4-dihydroxyphenyl ketones (Ii, j) and of 7-hydroxyisoflavone (formononetin) (IVb).

The condensation of 2,4,6-trihydroxyphenyl-4-methoxybenzyl ketone with acetobromoglucose under the proposed conditions led to complications at the stage of isolating the reaction products. As the results of TLC showed, during the reaction two compounds (R_f ~ 0.50 and 0.55) were formed in approximately equal amounts, and also another compound (R_f ~ 0.8) in somewhat smaller amounts. They all, including the initial ketone (R_f ~ 0.4), gave a brown coloration with an ethanolic solution of iron(III) chloride. In this case, probably, the two hydroxy groups of the ketone not bound by an intramolecular hydrogen bond (2-OH and 4-OH) underwent glycosylation and, accordingly, two monoglucosides and one diglucoside were formed. This assumption is in harmony with information in the literature [2].

The free glucosides (IIIa, b, h, i) were also obtained from the acetates (IIa, b, h, i) by treating methanolic solutions of the latter with equivalent amounts of 2 N aqueous sodium hydroxide solution [7].

The construction of the chromone nucleus in compounds (IIa-i) was also performed by Venkataraman's method [1, 7]. The yields of the 7-hydroxyisoflavone O-glucosides (Va-i) (50-88%) were comparable with those for the corresponding isoflavones synthesized by the same method [1]. This confirms once again the advantages of the method of synthesizing 7-hydroxyisoflavone O-glycosides that we selected in comparison with the variant usually employed, since, as shown in the present work, the precursors of the 7-hydroxyisoflavones undergo glycosylation considerably more effectively than the isoflavones themselves.

In the case of the 5,7-dihydroxyisoflavones the situation was somewhat different. The glycosylation of their precursors – 2,4,6-trihydroxyphenyl benzyl ketones containing two hydroxy groups of equivalent acidity led to a mixture of isomeric glycosides. It is possible to avoid such difficulties by the direct glycosylation of 5,7-dihydroxyisoflavones where the hydroxy groups are not equivalent because of an intramolecular hydrogen bond of one of them with the carbonyl group. In actual fact, in contrast to 2,4,6-trihydroxyphenyl 4-methoxybenzyl ketone, the glycosylation of 4'-chloro-5,7-dihydroxyisoflavone led to the corresponding 7-O-glucoside (Vj) with a yield of 32% (Table 2). As was shown by TLC analysis of the reaction mixture, the isomeric 5-O-glucoside was not formed.

All the compounds obtained consisted of microcrystalline colorless substances. Ketones (IIa-i, IIIa, b, h, i), and also the isoflavone (Vj) gave brown colorations with an ethanolic solution of iron(III) chloride because of the formation of a chelate complex, which showed the absence of a substituent at the 2-OH group of the ketone. This was also shown by the PMR spectra of these compounds, which contained a singlet at 12 ppm relating to the 2-OH proton of the ketone (Table 3). Consequently, the 4-OH group of the initial ketone had undergone glycosylation. All the compounds obtained had the β-configuration of the anomeric center, since they were all characterized by negative values of the angles of specific rotation (see Table 2). An additional confirmation of what has been said is provided by the chemical shift and the form of the signal of the anomeric proton in the PMR spectrum of each of the compounds mentioned (5.25-5.05 ppm, J = 6-8 Hz, Tables 3 and 4). The fact that compounds (Va-j) were isoflavones was also shown by the presence in the PMR spectrum of each of them of a singlet at 7.9-9.0 ppm relating to the 2-H proton of an isoflavone, and also by the substantial downfield shift of the signals of the 5-H, 2'-H, and 6'-H protons of the isoflavone nucleus as compared with the positions of the signals in the PMR spectra of the precursors (IIa-i) of the isoflavone O-glycosides (see Tables 3 and 4). The melting points and specific rotations for compounds (IIa, b, h, i) and (Va, b, h, i) corresponded to those given in the literature [3, 7]. Thus, we had synthesized 7-hydroxyisoflavone O-β-D-glucopyranosides.

EXPERIMENTAL

The course of the reactions and the purity of the compounds obtained were monitored by the TLC method on Silufol UV-254, 25 × 75 mm, plates in the chloroform–methanol (9:1) system [or (85:15) for the deacetylated glucosides]. Specific rotations were measured on a Polamat A polarimeter. PMR spectra were recorded on a Bruker CXP-200 instrument. Melting points were determined on a PTP instrument. Elementary analysis was performed for carbon and hydrogen, or for sulfur or halogen. The values found corresponded to the calculated figures.

The initial dihydroxyphenyl benzyl ketones (Ia-j) were synthesized from resorcinol and the appropriate arylacetonitriles under the standard or modified conditions of the Hoesch reaction [1, 11]. The isoflavones (IVb, j) were synthesized from the corresponding hydroxyphenyl benzyl ketones with the use of acetoformic anhydride as cyclizing agent [12].

2,4-Dihydroxyphenyl 3,4-Ethylenedioxybenzyl Ketone (Ic). A solution of 39.6 g (0.36 mole) of resorcinol and 20.4 g (0.15 mole) of anhydrous zinc chloride in 150 ml of dry ether was added to a solution of 52.5 g (0.3 mole) of 3,4-ethylenedioxyphenylacetonitrile in 220 ml of dry benzene. With stirring, a current of dry hydrogen chloride was passed through at 0°C until the reaction mixture was completely saturated with it. After a day, the reaction mixture was poured into 1 liter of water and the resulting mixture was boiled for 1 h. Then it was cooled to room temperature, and the precipitate was filtered off and was recrystallized from aqueous ethanol. Yield 71.2 g (83%). Colorless prisms with mp 131°C. Found, %: C 67.0, H 5.2. $C_{16}H_{14}O_5$. Calculated, %: C 67.1, H 4.9. PMR spectrum (60 MHz, in DMSO-d_6, internal standard TMS): 4.24 s, 2H (CH_2 of a benzyl residue); 6.34 s 1H (H-3); 6.43 d, 1H (H-5), 6.63 m, 3H (2'-, 5'-, 6'-H), 7.96 d, 1H (H-6), 10.94 s, 1H (4-OH), 12.58 s, 1H (OH-2).

2,4-Dihydroxyphenyl 2-fluorobenzyl ketone (If) was obtained in a similar manner to ketone (Ic) from 13.4 g (0.1 mole) of 2-fluorophenylacetonitrile in 75 ml of dry benzene, 13.2 g (0.12 mole) of resorcinol, and 6.8 g of zinc chloride in 50 ml of dry ether, with a yield of 20.7 g (84.1%). Colorless needles (from isopropanol) with mp 138°C. Found, %: F 7.8. $C_{14}H_{11}FO_3$. Calculated, %: F 7.7. PMR spectrum (60 MHz, in DMSO-d_6; internal standard TMS): 4.41 s, 2H (CH_2), 6.37 s, 1H (H-3), 6.46 d, 1H, (H-5), 7.86 d, 1H (H-6), 7.17 m, 4H (H-3'—6'); 10.63 s, 1H (OH-4), 12.20 s, 1H (OH-2).

Synthesis of the O-Glycosides in Anhydrous Aprotic Solvents. a) With stirring, 1 g (12 mmole) of sodium isopropanolate was added to a solution of 2.35 g (10 mmole) of 2,4-dihydroxy-α-(thiazol-4-yl)acetophenone (Ih) in 50 ml of dry acetone. With continued stirring, after 10 min 3.9 g (9.5 mmole) of acetobromoglucose was added to the mixture in portions. After 10 h, the mixture was poured into 200 ml of water, the aqueous layer was decanted off, the residue was dissolved in 50 ml of chloroform, and the solution was dried over sodium sulfate and evaporated under reduced pressure. The oily residue was recrystallized from isopropanol. The yield of glucoside (IIh) was 1.34 g (25%).

b) A solution of 2.58 g (10 mmole) of 2,4-dihydroxyphenyl 4-methoxybenzyl ketone (Ib) in 30 ml of dimethylformamide was treated with 0.73 ml (10 mmole) of a 50% aqueous solution of potassium hydroxide. After 10 ml of the solvent had been distilled off under water-pump vacuum, the solution was cooled to 0°C and, with stirring, 3.9 g (9.5 mmole) of acetobromoglucose was added. After 5 h, the mixture was poured into 200 ml of water, the aqueous layer was decanted off, and the oily precipitate that had deposited was dissolved in 50 ml of chloroform. This solution was washed with 40 ml of 0.2 N aqueous sodium hydroxide, dried over sodium sulfate, and evaporated to dryness under reduced pressure. The oily residue was recyrstallized from isopropanol. This gave 1 g (18%) of the glucoside (IIb).

The two products gave no depression of the melting point in admixture with samples of compounds (IIb) and (IIh) obtained under other conditions.

2-Hydroxy-4-(β-D-tetra-O-acetylglucopyranosyloxy)phenyl 4-Methoxybenzyl Ketone (IIb). With stirring, 7.28 ml (0.1 mole) of a 50% aqueous solution of potassium hydroxide was added to a mixture of 25.8 g (0.1 mole) of ketone (Ib) and 15 ml of acetone present in a reactor in an atmosphere of nitrogen. After the reactor had been cooled to 5-20°C, 30.8 g (0.75 mole) of acetobromoglucose was added to it in 0.5-g portions. The resulting mixture was stirred at room temperature for 4 h and was left overnight. The viscous mass that had formed 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 aqueous sodium hydroxide solution and 200 ml of water. The aqueous extracts, after neutralization with acetic acid, yielded 10 g of the initial compound (IIb). The organic layer was dried over sodium sulfate and the solvent was evaporated under reduced pressure. The oily residue was recrystallized from isopropanol. This gave 31.8 g (54%) of the glucoside (IIb). Glucosides (IIa, c-i) were obtained under the conditions given in Table 1.

4-Methoxy-7-(tetra-O-acetyl-β-D-glucopyranosyloxy)isoflavone (Vb). With stirring, 1.46 ml (20 mmole) of a 50% aqueous potassium hydroxide solution was added dropwise to a mixture of 5.36 g (20 mmole) of 7-hydroxy-4'-methoxyisoflavone (IVb) and 30 ml of acetone. After 0.5 h, 5.75 g (14 mmole) of acetobromoglucose was added in portions. The reaction mixture was stirred for 10 h and was then diluted with 100 ml of chloroform and filtered. The filtrate was evaporated under reduced pressure. The oily residue was recrystallized from methanol. This gave 2.3 g (27%) of compound (Vb).

4'-Chloro-5-hydroxy-7-(tetra-O-acetyl-β-D-glucopyranosyloxy)isoflavone (Vk) was obtained in a similar manner to compound (Vb) from 2.89 g (10 mmole) of the isoflavone (IVk), 5 ml of acetone, 0.75 ml (10 mmole) of 50% potassium hydroxide solution, and 3.08 g (7.5 mmole) of acetobromoglucose with a yield of 1.48 g (32.4%).

The 4-(β-D-Glucopyranosyloxy)-2-hydroxyphenylbenzyl ketones (IIIa, b, h, i) were obtained by a general procedure. A mixture of 1 mmole of one of the acetates (IIa, b, h, i), 5 ml of a 2 N aqueous sodium hydroxide solution, and 10 ml of methanol was boiled for 10 min and was neutralized with acetic acid. The precipitate that deposited was filtered off and recrystallized from methanol. The yields and physicochemical characteristics of compounds (IIIa, b, h, i) are given in Table 2.

7-(Tetra-O-acetyl-β-D-glucopyranosyloxy)isoflavone (Va). A mixture of 11.2 g (20 mmole) of compound (IIa), 60 ml (361 mmole) of ethyl orthoformate, 40 ml of pyridine, and 1 ml of piperidine was boiled for 16 h, and the ethanol formed was distilled off. The solution was cooled, and 10 ml of acetic anhydride was added. After 0.5 h the mixture was poured into 0.5 liter of cold water. The precipitate that formed was filtered off and was recrystallized from methanol. The yield of compound (Va) was 6.34 g (56%). Glucosides (Vb-i) were obtained in a similar way to compound (Va). Their yields and physicochemical characteristics are given in Table 2.

CONCLUSIONS

Conditions have been developed for the effective glycosylation of 2,4-dihydroxyphenylbenzyl ketones. The 2-hydroxy-4-(tetra-O-acetyl-β-D-glucopyranosyloxy)phenylbenzyl ketones synthesized have been converted under the action of ethyl orthoformate into 7-hydroxyisoflavone glucosides, which have also been obtained by the condensation of isoflavones with acetobromoglucose. The advantages and disadvantages of the alternative methods of synthesizing 7-hydroxyisoflavone glycosides have been discussed.

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