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SYNTHETIC AND MODIFIED ISOFLAVONOIDS. XI. SYNTHESIS OF ANALOGUES OF MAXIMA ISOFLAVONE A AND XANTHOCERCIN

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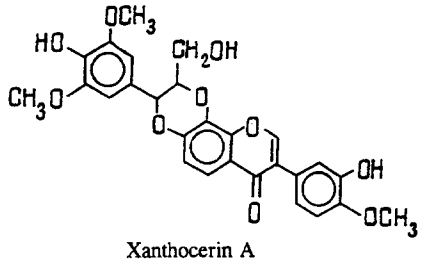
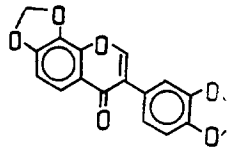
Analogues of maxima isoflavone A and of xanthocercin containing benzodioxolane, benzodioxane, and benzodioxepane fragments in rings A and B of isoflavone have been synthesized. The structures of the compounds obtained have been confirmed by analytical and spectral characteristics.

The heterocyclic systems of benzodioxane and, particularly, benzodioxolane are widely distributed in the vegetable kingdom. They are components of many flavonoids and other natural compounds isolated from plants.

It is known that maxima isoflavone A, isolated from the roots of *Tephrosia maxima* Aers has a 7,8:3′,4′-bismethylenedioxyisoflavone structure [2] and xanthocercin [2,3-*trans*-3-(4-hydroxy-3,5-dimethoxyphenyl)-8-(3-hydroxy-4-methoxyphenyl)-2-hydroxymethyl-2,3-dihydro-7H-1,4-dioxano[2,3-*h*]-chromene-7-one – an isoflavolignan isolated from *Xanthocercis zambesiaca* – contains a 1,4-benzodioxane fragment in ring A of the isoflavone moiety [3].



Xanthocerin A



Maxima isohavone A

Natural 1,3-benzodioxolane and 1,4-benzodioxane analogues of the flavonoids possess various biological activities [4, 5]. In this connection, synthetic analogues of maxima isoflavone A and xanthocercin are of interest.

The initial compounds for obtaining the above-mentioned analogues were the α-heteryl-2,3,4-trihydroxyacetophenones (**1a-c**) containing 1,3-benzodioxolane, 1,4-benzodioxane, and 1,5-benzodioxepane nuclei. To obtain them we made use of a modified Hoesch reaction [6] in which boron trifluoride etherate was used simultaneously as the solvent and the catalyst of the process. The reaction was performed at 40-45°C.

The alkylation of ketone (**1a**) with dibromoethane in the presence of potash in acetone gave the the 3,4-ethylenedioxyketone (**2**) with a yield of 19.3%. As can be seen from the yield, the synthesis of analogues of maxima isoflavone A and xanthocercin via ketone (**2**) is irrational. For this reason, we have proposed the synthesis of the above-mentioned compounds from the 7,8-dihydroxychromones (**4**).

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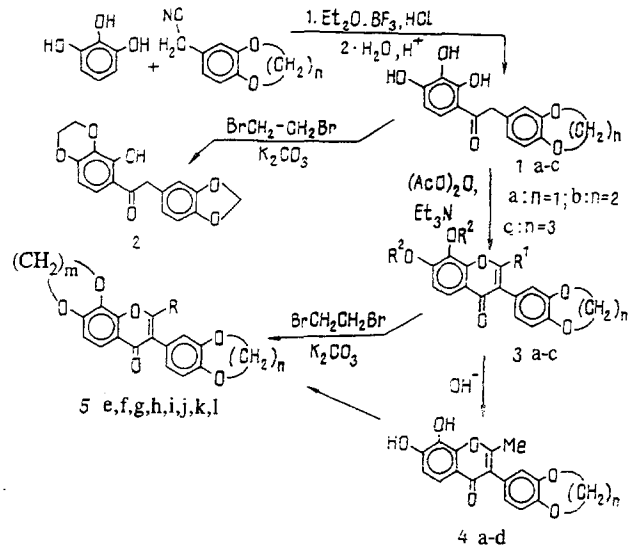

3,4 a: n=1, R^1=Me, R^2=Ac; b: n=2, R^1=Me, R^2=Ac; c: n=3, R^1=Me, R^2=Ac; d: n=3,R^1=H, R^2=H; 5 e: n=1, m=2, R=Me; f: n=2, m=1, R=Me; g: n=m=2, R=Me; h: n=2, m=3, R=Me; i: n=3, m=1, R=Me; j: n=3, m=2, R=Me; k n=3, m=2, R=H; m: n=m=3, R=Me

The structures obtained were confirmed their analytical characteristics and also their PMR spectra.

In the PMR spectra of ketones (**1**) measured in DMSO-d_6, the signal of the proton of the OH-2 group was present in the weak field at 12.5-12.7 ppm because of the participation of this proton in the formation of an intramolecular hydrogen bond with the carbonyl group. The OH-3 and the OH-4 groups gave signals in the form of singlets at 8.6-8.9 ppm and 9.7-10.2 ppm, respectively. The H-5 and H-6 aromatic protons gave doublets in the 6.4-6.5 and 7.5-7.6 ppm regions. In the spectrum of the ketone (**2**), in place of the signals of the protons of the OH-3 and OH-4 groups a four-proton singlet of the ethylenedioxy fragment appeared at 4.29 ppm.

On the interaction of ketone (**1c**) with the Vilsmeier reagent in the presence of boron trifluoride etherate at 70°C, the 7,8-dihydroxyisoflavone (**3d**) was formed.

The conversion of the ketone (**1**) into the isoflavones (**3a-c**) containing a methyl group in position 2 was achieved by heating (**1a-c**) with acetic anhydride and triethylamine. The resulting 7,8-diacetoxy-2-methylisoflavones (**3a-c**) were converted into the corresponding 7,8-dihydroxy-2-methylisoflavones (**4a-c**) by brief heating with a 5% solution of alcoholic alkali. The alkylation of the 7,8-dihydroxyisoflavones (**3d, 4a-c**) with methylene iodide, dibromoethane, or dibromopropane in DMFA or dioxane in the presence of potash led to the corresponding analogues of maxima isoflavone A and xanthocercin (**5e-*l***) (Table 1).

In the PMR spectra of compounds (**3-4**) (see Tables 2 and 3), an H-2 proton of the pyrone ring was shown in the form of a narrow singlet, The H-2 proton of compound (**3d**) gave a peak at 8.4 ppm. For compound (**5k**), the signal of the same proton was shifted downfield and appeared at 7.96 ppm. Acetyl groups were represented by singlets in the 2.3-2.4 region, while the hydroxylic protons of OH-7 and OH-8 absorbed in the interval of 9.4-10.3 ppm. The doublets of the aromatic protons H-5 and H-6 in the isoflavones (**3-5**) scarcely changed their position on passing from compound to compound. The signals of the methylene groups of the dioxolane (6.0-6.2 ppm) and dioxane (4.2-4.4 ppm) rings appeared in the form of singlets, while the analogous protons of the dioxepane ring were revealed in the form of a triplet (4.2-4.4 ppm) and a quintet (2.1-3.2 ppm) (see Tables 2 and 3).

The isoflavones obtained were colorless crystalline substances with high melting points readily soluble in the majority of organic solvents and insoluble in water.

Thus, cyclization of 1,3-benzodioxolane, 1,4-benzodioxane, and 1,5-benzodioxepane derivatives of 2,3,4-trihydroxyacetophenone under the action of acetic anhydride or the Vilsmeier reagent in the modified variant [7] takes place readily and leads with good yields to 7,8-substituted isoflavones. The performance of alkylation simultaneously at two phenolic hydroxyls

TABLE 1. Characteristics of Compounds (3-5)

Compound	Yield, %	mp, °C.	Empirical formula	Solvent for crystallization.
3b	86.1	173—174	$C_{22}H_{18}O_8$	EtOH
3c	73	134—135	$C_{23}H_{20}O_8$	EtOAc
3d	98	230—231	$C_{18}H_{14}O_6$	MeCOMe
4a	95	252—253	$C_{17}H_{12}O_6$	EtOH:H2O
4b	93	>305	$C_{18}H_{14}O_6$	Dioxane H2O
4c	73	231—233	$C_{19}H_{16}O_6$	EtOH
5e	46.3	234—235	$C_{19}H_{14}O_6$	EtOH
5f	83.5	264—265	$C_{19}H_{14}O_6$	C_6H_6
5g	82.2	236—237	$C_{20}H_{16}O_6$	EtOAc
5h	25.6	174—176	$C_{21}H_{18}O_6$	C_6H_6
5i	33	147—148	$C_{20}H_{16}O_6$	EtOA hexane
5j	46	230—231	$C_{21}H_{18}O_6$	EtOH
5k	68	182—183	$C_{20}H_{16}O_6$	EtOH
5l	20	150—151	$C_{22}H_{22}O_6$	EtOH

enables new synthetic analogues of maxima isoflavone A and xanthocercin to be obtained. The time necessary for performing the latter reactions rises in proportion to the size of the ring formed.

EXPERIMENTAL

The conditions for chromatography and for recording the spectra have been described in [1].

α-Hetaryl-2,3,4-trihydroxyacetophenones (1a-c). A mixture of 12.6 g (10 mmoles) of sublimed pyrogallol and 10 mmoles of the corresponding heterylacetonitrile in 80 ml of boron trifluoride etherate was stirred in a current of dry hydrogen chloride at 40-45°C for 5-8 h, and the reaction mixture was left overnight at room temperature. Then it was poured into 400 ml of water, and the mixture was boiled for 3-4 h and was made alkaline to pH 3 with ammonia. The resulting precipitate was filtered off and crystallized from a suitable solvent. Compound **(1a)**, yield 33% (ethanol); lit. [8]: yield 22%, mp 185°C (ethyl acetate–petroleum ether). Empirical formula $C_{15}H_{12}O_6$, (DMSO-d_6, δ, ppm): 4.25 (s, 2H, $COCH_2$), 12.70 (s, 1H, OH-2), 8.75 (s, 1H, OH-3), 10.25 (s, 1H, OH-4), 6.46 (d, 1H, J = 9.28 Hz, H-5), 7.60 (d, 1H, J = 9.28 Hz, H-6); benzodioxolane protons: 6.90 (d, 1H, J = 1.95 Hz, H-4), 6.80 (d.d, 1H, J = 7.81 Hz; 1.95 Hz, H-6), 6.90 (d, 1H, J = 7.81 Hz, H-7), 6.05 (s, 2H, OCH_2O).

Compound (1b), yield 43% (ethyl acetate), mp 151-152°C. Empirical formula $C_{16}H_{14}O_6$. PMR spectrum (DMSO-d_6, δ, ppm): 4.13 (s, 2H, $COCH_2$), 12.52 (s, 1H, OH-2), 8.60 (s, 1H, OH-3), 10.10 (s, 1H, OH-4), 6.42 (d, 1H, J = 9.28 Hz, H-5) 7.48 (d, J = 9.28 Hz, H-6); benzodioxane protons: 6.76 (m, 3H, H-5, H-7, H-8), 4.20 (s, 4H, OCH_2CH_2O).

Compound (1c), yield 68% (ethanol), mp 172–173°C. empirical formula $C_{17}H_{14}O_6$. PMR spectarum (DMSO-d_6, δ, ppm): 4.16 (s, 2H, $CO-CH_2$), 12.48 (s, 1H, OH-2), 8.89 (s, 1H, OH-3), 9.75 (s, 1H, OH-4), 6.42 (d, 1H, J = 9.28 Hz, H-5), 7.48 (d, J = 9.28 Hz, H-6); benzodioxepane protons: 6.87 (m, 3H, H-6, H-8, H-9), 4.09 (t, 2H, 2-CH_2 and CH_2-4), 2.08 (q, 2H, 3-CH_2).

α-(1,3-Benzodioxolan-5-yl)-2-hydroxy-3,4-ethylenedioxyacetophenone (2). To a hot solution of 5.96 (20 mmoles) of ketone **(1a)** in 100 ml of dry benzene were added 16.6 g (120 mmoles) of freshly calcined potash and 1.98 ml (22 mmole) of 1,2-dibromoethane, and the mixture was boiled for 1 h. Then the inorganic deposit was filtered off, the filtrate was acidified with 3-4 drops of acetic acid, and the benzene was distilled off in water-pump vacuum. The residue was crystallized from alcohol. Yield 1.2 g (19.3%), mp 131-133°C (ethanol). Empirical formula $C_{17}H_{14}O_6$ PMR spectrum (DMSO-d_6, δ, ppm): 4.24 (s, 2H, $COCH_2$), 12.49 (s, 1H, OH-2), 4.29 (s, 4H, OCH_2CH_2O-3, 4), 6.48 (d, 1H, J = 8.29 Hz, H-5), 7.59 (d, 1H, J = 8.29 Hz, H-6); benzodioxolane protons: 6.85 (d, 1H, J = 1.95 Hz, H-4), 6.72 (d.d, 1H, J = 7.81 Hz; 1.95 Hz, H-6), 6.85 (d, 1H, J = 7.81 Hz, H-7), 5.97 (s, 2H, OCH_2O).

3-Hetaryl-7,8-Diacetoxy-2-methylchromones (3a-c). A mixture of 20 mmoles of the appropriate ketone **(1a-c)**, 27.6 ml (300 mmoles) of acetic anhydride, and 33.6 ml (240 mmoles) of triethylamine was heated at 120-130°C for 8-12 h. Then the mixture was poured into cold water containing 5.1 ml of hydrochloric acid. The precipitate that deposited was filtered off, carefully washed with water, and crystallized from a suitable solvent.

TABLE 2. Chemical Shifts in the PMR Spectra of the Isoflavones (**3-4**)

Compound	PMR spectrum*, δ, ppm								
	Chromone protons					Protons of the hetero residue			
	H-2 or Me-2	H-5, or J=8.79 Hz	H-6, d J=8.79 Hz	7-OAc or 7-OH, s	8-OAc or 8-OH, s	H-4 (H-5) or H-6,d J=2 Hz	H-6 (H-7) or H-8, d.d J=8.0; 2.0 Hz	H-7 (H-8) or H-9, d J=8 Hz	O(CH2)nO t,q
3 b	2.30	8.11	7.20	2.40	2.34	6.76	6.72	6.92	4.27 c
3 c	2.30	8.11	7.20	2.41	2.36	6.88	6.82	7.02	4.25; 2.02
3 d	8.41	7.47	6.96	10.34	9.47	7.18	6.99	7.22	4.16, 2.41
4a	2.27	7.36	6.91	10.24	9.36	6.82	6.71	6.95	6.05 c
4 b	2.27	7.37	6.90	9.70	9.70	6.77	6.68	6.87	4.26 c
4 c	2.27	7 37	6.91	10.17	9.42	6.86	6.83	6.99	4.16; 2.11

*The PMR spectra of compounds (**3b,c**) were measured in $CDCl_3$ and those of the other compounds in DMSO-d_6.

TABLE 3. Chemical Shifts in the PMR Spectra of the Analogues of Maxima Isoflavone A and of Xanthocercin (**5d-*l***) (in $CDCl_3$)

Compound	PMR spectrum, ppm							
	Chromone proton, ppm				Protons of the hetero residue.			
	H-2 or Me-2, s	H-5, d J=9.28 Hz	H-6, d J=9.28 Hz	O(CH2)nO t,q	H-4 (H-5) or H-6, d J=2 Hz	H-6 (H-7) or H-8, d.d J=8; 2 Hz	H-7 (H-8) or H-9, d J=8 Hz	O(CH2)nO t,q
5 e	2.35	7.71	6.90	4.41 s	6.75	6.72	6.87	6.00 s
5 f	2.31	7.79	6.91	6.18 s	6.77	6.72	6.91	4.28 s
5 g	2.35	7.70	6.90	4.40 s	6.78	6.72	6.91	4.28 s
5 h	2.35	7.76	6.94	4.42; 2.32	6.78	6.73	6.92	4.28 s
5 i	2.30	7.78	6.93	6.18 s	7.05	6.99	7.09	4.24; 2.20
5 k	2.34	7.69	6.90	4.40 s	6.88	6.85	7.02	4.24; 3.19
5 *l*	7.96	7.78	6.95	4.41 s	7.15	7.01	7.18	4.25; 2.12
5 m	2.35	7.76	6.94	4.44; 2.26	6.89	6.83	7.03	4.25; 2.21

3-(1,5-Benzodioxepan-7-yl)-7,8-dihydroxychromone (3d). With stirring, 11 ml (90 mmoles) of boron trifluoride etherate was added dropwise to a solution of 4.74 g (15 mmoles) of ketone (**1c**) in 24 ml (300 mmole) of dimethylformamide. Then 3.44 g (16.5 mmoles) of phosphorus pentachloride was added at such a rate that the temperature of the reaction mixture did not rise above 60-70°C. After the end of the reaction, the reaction mixture was poured into 200-250 ml of water and the resulting mixture was kept at 70°C for 1 h. The precipitate that had deposited was then filtered off and crystallized from acetone.

3-Hetaryl-7,8-dihydroxy-2-methylchromones (4a-c). A hot solution of 20 mmole of one of the isoflavones (**3a-c**) in 100 ml of alcohol was treated with 25.9 ml of 5% caustic soda solution, and the mixture was boiled for 10 min. Then it was neutralized with dilute hydrochloric acid and the resulting precipitate was filtered off and crystallized from a suitable solvent.

3-(1,3-Benzodioxolan-5-yl)-2-methyl-7,8-ethylenedioxychromone (5e). A hot solution of 3.12 g (10 mmoles) of the isoflavone (**4a**) in 70 ml of absolute dioxane or DMFA was treated with 1.4 g (10.5 mmoles) of freshly calcined potash and 0.99 ml (11 mmoles) of 1,2-dibromoethane, and the mixture was boiled with constant stirring for 18 h. Then it was poured into 100 ml of water and the resulting precipitate was filtered off and crystallized from ethanol.

3-(1,4-Benzodioxan-6-yl)-2-methyl-7,8-methylenedioxychromone (5f) was obtained in a similar way to compound (**5e**) from 3.26 g (10 mmoles) of the isoflavone (**4b**) and 1.05 ml (13 mmoles) of diiodomethane, with boiling for 15 h.

3-(1,4-Benzodioxan-6-yl)-2-methyl-7,8-ethylenedioxychromone (5g) was obtained in a similar way to compound (**5b**) from 3.26 g (10 mmoles) of isoflavone (**4b**) and 0.99 ml (11 mmoles) of 1,2-dibromoethane by boiling for 19 h.

3-(1,4-Benzodioxan-6-yl)-2-methyl-7,8-propylenedioxychromone (5h) was obtained in a similar way to compound (**5e**) from 3.26 g (10 mmoles) of isoflavone (**4b**) and 1.23 ml of (12 mmoles) of 1,3-dibromopropane by boiling for 22 h.

3-(1,5-Benzodioxepan-7-yl)-2-methyl-7,8-methylenedioxychromone (5i) was obtained in a similar way to compound (**5e**) from 3.4 g (10 mmoles) of isoflavone (**4c**) and 1.05 ml (13 mmoles) of diazomethane by boiling for 15 h.

3-(1,5-Benzodioxepan-7-yl)-2-methyl-7,8-ethylenedioxychromone (5j) was obtained in a similar way to compound (**5e**) from 3.4 g (10 mmoles) of isoflavone (**4c**) and 0.99 ml (11 mmoles) of 1,2-dibromoethane by boiling for 20 h.

3-(1,5-Benzodioxepan-7-yl)-7,8-ethylenedioxychromone (5k) was obtained in a similar way to compound (**5e**) from 3.26 g (10 mmoles) of isoflavone (**3d**) and 0.99 ml (11 mmoles) of 1,2-dibromoethane by boiling for 18 h.

3-(1,5-Benzodioxepan-7-yl)-2-methyl-7,8-propylenedioxychromone (5*l*) was obtained in a similar way to compound (5e) from 3.4 g (10 mmoles) of isoflavone (4c) and 1.23 ml (12 mmoles) of 1,3-dibromopropane by boiling for 22 h.

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