*Chemistry of Natural Compounds, Vol. 34, No. 3, 1998*

# SYNTHETIC ANALOGS OF XANTHOCERCIN

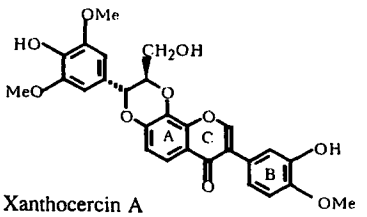
**V. M. Otsalyuk, T. M. Tkachuk, S. P. Bondarenko, V. V. Chkhalo, and V. P. Khilya**

UDC 547.814.5

*Synthetic analogs of xanthocercin in the molecules of which benzodioxole, benzodioxane, or benzodioxepane fragments are annellated to a γ-pyrone ring have been obtained. The structures of the new compounds have been confirmed by analytical and spectral results.*

Natural compounds with 1,4-benzodioxane and 1,3-benzodioxole fragments have been known for a very long time as substances possessing various biological activities [1-4], a hepatoprotector activity being the most clearly expressed [5, 6]. Particularly interesting in this respect are natural heteroanalogs of these compounds, such as flavones and isoflavones [7-9], which are widely distributed in the vegetable kingdom and are being intensively studied [10-12].

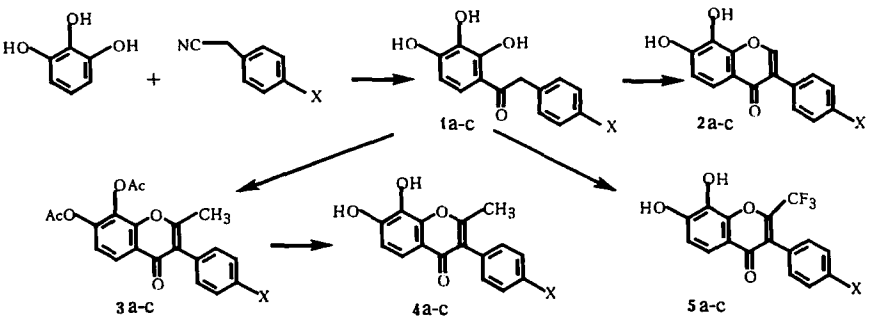
At the end of the 1980s, 2,3-*trans*-3-(4-hydroxy-3,5-dimethoxyphenyl)-8-(3-hydroxy-4-methoxyphenyl)-2-hydroxymethyl-2,3-dihydro-7H-1,4-dioxano[2,3-η]chromen-7-one (xanthocercin A), the first isoflavolignin containing a 1,4-dioxane fragment annellated to ring A of an isoflavone system, was isolated from *Xanthocercis zambesiaca* [13]. The authors concerned have obtained synthetic analogs of xanthocercin A with simpler structures.




Xanthocercin A

As the starting materials for the syntheses of these compounds, they used 7,8-dihydroxyflavones with various substituents in the second (-H, $-CH_3$, $-CF_3$) and third (-Ph, -*p*-F-Ph, -*p*-Cl-Ph) positions of the chromen-4-one system. These substances were obtained with the aid of the Hoesch reaction, in accordance with which the condensation of pyrogallol with the appropriate arylacetonitriles in absolute ether in the presence of freshly calcined $ZnCl_2$ and dry HCl, followed by hydrolysis of the imines formed, led to the intermediate α-aryl-2,3,4-trihydroxyacetophenones (**1a-c**) (Scheme 1). In the PMR spectra, measured in DMSO-$d_6$, of the ketones formed (**1a-c**) the signals of the protons of the OH-2 groups were present in the weak field at 12.4-12.6 ppm because of the participation of this proton in the formation of an intramolecular hydrogen bond of the

Scheme 1




1-5:a(X=H); 1-5:b(X=F); 1-5:c(X=Cl)

Kiev Taras Shevchenko University, ul. Vladimirskaya, 64, Ukraine, tel./fax 225 12 73. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 313-319, May-June, 1998. Original article submitted February 6, 1998.

 0009-3130/98/3403-0284$20.00 

TABLE 1. Characteristics of Compounds (2-14)

| Compound | Yield, % | mp, °C | Empirical formula | Solvent for crystallization |
|---|---|---|---|---|
| 2a | 92 | 215–216 | $C_{15}H_{10}O_4$ | *i*-PrOH:$H_2O$ |
| 2b | 94 | 284 | $C_{15}H_9FO_4$ | *i*-PrOH:$H_2O$ |
| 2c | 86 | 293 | $C_{15}H_9ClO_4$ | EtOH:$H_2O$ |
| 3a | 95 | 103–104 | $C_{20}H_{16}O_6$ | EtOAc |
| 3b | 79.3 | 136–137 | $C_{20}H_{15}FO_6$ | EtOAc |
| 3c | 89 | 144 | $C_{20}H_{15}ClO_6$ | EtOAc |
| 4a | 96 | 220–221 | $C_{16}H_{12}O_4$ | *i*-PrOH:$H_2O$ |
| 4b | 94.5 | 291 dec. | $C_{16}H_{11}FO_4$ | *i*-PrOH:$H_2O$ |
| 4c | 97 | 270–271 | $C_{16}H_{11}ClO_4$ | EtOH:$H_2O$ |
| 5a | 78 | 200 | $C_{16}H_9F_3O_4$ | *i*-PrOH:$H_2O$ |
| 5b | 65 | 255 dec. | $C_{16}H_8F_4O_4$ | *i*-PrOH:$H_2O$ |
| 5c | 67 | 245–246 | $C_{16}H_8ClF_3O_4$ | EtOH:$H_2O$ |
| 6a | 72 | 170–171 | $C_{15}H_{10}O_4$ | *i*-PrOH |
| 6b | 76 | 256 dec. | $C_{16}H_9FO_4$ | *i*-PrOH |
| 6c | 77 | 271–272 | $C_{16}H_9ClO_4$ | EtOH |
| 7a | 75 | 192–193 | $C_{17}H_{12}O_4$ | *i*-PrOH |
| 7b | 77.5 | 276–277 | $C_{17}H_{11}FO_4$ | *i*-PrOH |
| 7c | 80 | 245 | $C_{17}H_{11}ClO_4$ | EtOH |
| 8a | 83 | 230–231 | $C_{17}H_9F_3O_4$ | *i*-PrOH |
| 8b | 76 | 236 | $C_{17}H_8F_4O_4$ | *i*-PrOH |
| 8c | 82 | 211 | $C_{17}H_8ClF_3O_4$ | EtOH |
| 9a | 54 | 167–168 | $C_{17}H_{12}O_4$ | *i*-PrOH |
| 9b | 60.5 | 222 | $C_{17}H_{11}FO_4$ | *i*-PrOH |
| 9c | 51 | 231 | $C_{17}H_{11}ClO_4$ | EtOH |
| 10a | 52 | 202–203 | $C_{18}H_{14}O_4$ | *i*-PrOH |
| 10b | 56.5 | 241 | $C_{18}H_{13}FO_4$ | *i*-PrOH |
| 10c | 53 | 251–252 | $C_{18}H_{13}ClO_4$ | Dioxane |
| 11a | 69 | 224–225 | $C_{18}H_{11}F_3O_4$ | *i*-PrOH |
| 11b | 63 | 216 | $C_{18}H_{10}F_4O_4$ | *i*-PrOH |
| 11c | 64.5 | 222–223 | $C_{18}H_{10}ClF_3O_4$ | EtOH |
| 12a | 38 | 164–165 | $C_{18}H_{12}O_4$ | *i*-PrOH |
| 12b | 32.5 | 256 dec. | $C_{18}H_{13}FO_4$ | *i*-PrOH |
| 12c | 43 | 209–210 | $C_{18}H_{13}ClO_4$ | EtOH |
| 13c | 24.5 | 214 | $C_{19}H_{15}ClO_4$ | EtOH |
| 14a | 31 | 164–165 | $C_{19}H_{13}F_3O_4$ | *i*-PrOH |
| 14b | 27 | 198 | $C_{19}H_{12}F_4O_4$ | *i*-PrOH |
| 14c | 34.5 | 208 | $C_{19}H_{12}ClF_3O_4$ | EtOH |

chelate type with the carbonyl group. The OH-3 and OH-4 groups appeared in the form of singlets at 8.6-8.9 and 9.7-10.2 ppm, respectively. The aromatic protons H-5 and H-6 gave doublets in the 6.4-6.5 and 7.5-7.6 ppm regions with SSCCs of 9.28 Hz.

The most commonly used approach to the synthesis of natural and synthetic isoflavones consists in C-formylation at the methylene groups of α-aryl-2-hydroxyacetophenones, followed by cyclization. This principle has been made the basis of numerous methods of obtaining isoflavones using various formulating and acylating agents.

To obtain natural analogs of the 7,8-dihydroxyisoflavones (**2a-c**) unsubstituted in position 2 of the chromone ring, ketones (**1a-c**) were heated with triethyl orthoformate in pyridine at 125°C in the presence of a catalytic amount of piperidine.

There is definite interest in obtaining isoflavones containing alkyl substituents in position 2 of the isoflavone system. Thus, the heating of ketones (**1a-c**) with acetic anhydride and triethylamine at 120°C formed the 7,8-diacetoxy-2-methylisoflavones (**3a-c**), which, on brief heating with 5% sodium hydroxide, gave the corresponding 7,8-dihydroxy-2-methylisoflavones (**4a-c**). When trifluoroacetic anhydride was used as the acylating agent in pyridine at room temperature, the 7,8-dihydroxy-2-trifluoromethylisoflavones (**5a-c**) were formed.

In the PMR spectrum of each of the isoflavones (**2-5a-c**) (Table 2), the H-2 proton of the chromone ring appeared in the form of a narrow singlet at 7.95-8.44 ppm, while $CH_3$-2 gave a singlet at 2.2-2.4 ppm. Acetyl groups appeared in the spectrum in the form of singlets in the 2.3-2.5 ppm region, and the hydroxylic protons of OH-7 and OH-8 absorbed in the intervals of 10.3-10.7 and 9.4-9.6 ppm, respectively. Doublets of the aromatic protons H-5 and H-6 in compounds (**2-5a-c**) appeared in the 7.4-7.89 and 6.93-7.1 ppm regions with a SSCC of 8 Hz.

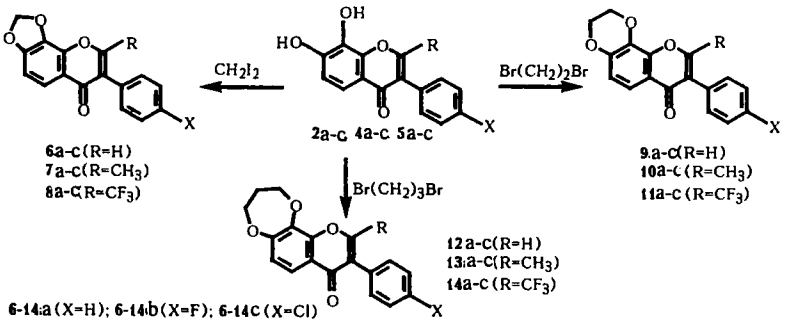
To obtain synthetic analogs of xanthocercin, we used the alkylation of 7,8-dihydroxyisoflavones with dihaloalkanes (methylene iodide, 1,2-dibromoethane, and 1,3-dibromopropane) in the presence of catalytic amounts of freshly calcined potash.

TABLE 2. Chemical Shifts in the PMR Spectra of Isoflavones (**2-5**)

| Compound | PMR spectra*, δ, ppm | | | | | |
|---|---|---|---|---|---|---|
| | Chromone protons | | | | | Aryl protons |
| | H-2 or Me-2, s | H-5, d, J=8.7 Hz | H-6, d, J=8.7 Hz | AcO-7 or HO-7 | AcO-8 or HO-8 | H-2',3',4',5',6' m or H-2',6' d, H-3',5' d., J=8 Hz |
| 2a | 8.44 | 7.6 | 6.99 | 10.38 | 9.55 | 7.47 |
| 2b | 8.44 | 7.49 | 6.97 | 10.36 | 9.59 | 7.51 |
| 2c | 8.48 | 7.48 | 6.98 | 10.35 | 9.45 | 7.48, 7.63 |
| 3a | 2.22 | 7.83 | 7.12 | 2.42 | 2.39 | 7.38 |
| 3b | 2.26 | 7.91 | 7.17 | 2.42 | 2.36 | 7.32 |
| 3c | 2.30 | 8.11 | 7.21 | 2.43 | 2.37 | 7.21, 7.43 |
| 4a | 2.27 | 7.38 | 6.93 | 10.28 | 9.43 | 7.38 |
| 4b | 2.27 | 7.37 | 6.9 | 10.24 | 9.38 | 7.31 |
| 4c | 2.27 | 7.48 | 6.91 | 10.23 | 9.37 | 7.3, 7.48 |
| 5a | | 7.4 | 7.02 | 10.7 | 9.6 | 7.4 |
| 5b | | 7.43 | 7.03 | 10.68 | 9.72 | 7.26 |
| 5c | | 7.42 | 7.05 | 10.67 | 9.7 | 7.31, 7.53 |

*The PMR spectra of compounds (**3a-c**) were measured in DMSO-$d_6$, and all the others in $CDCl_3$.

Scheme 2




When the given components were heated in dioxane, the reaction time amounted to more than 20 h, which cannot but affect the yield of desired products. In order to shorten the reaction time and raise the product yield, dioxane has been successfully replaced by DMFA. With vigorous stirring of the components dissolved in the minimum amount of DMFA with a magnetic stirrer at 80-90°C, the reaction time shortened to 1.5-3 h and the yield of products increased.

In the PMR spectra (Table 3) of the isoflavones obtained (**6-14a-c**), the signals of the methylene groups of the dioxane and dioxolane rings were singlets in the 6.0-6.2 and 4.2-4.4 ppm regions, respectively, while the protons of the dioxepane ring were observed in the form of two triplets at 4.2-4.4 ppm and a quintet at 2.1-3.2 ppm. The signals of the remaining protons had scarcely changed their positions as compared with the initial 7,8-dihydroxyisoflavones.

The synthetic analogs of xanthocercin that had been obtained were colorless crystalline substances with high melting points, readily soluble in the majority of organic solvents and insoluble in water. The results of the biological screening of these compounds will be communicated in subsequent publications.

## EXPERIMENTAL

The purity of the compounds obtained was checked by TLC on Silufol UV-254 plates, using benzene–ethanol and chloroform–methanol (9:1) systems. The PMR spectra of compounds (**1-14a-c**) were measured on a Bruker WP-100SU instrument in $CDCl_3$ and DMSO-$d_6$ relative to TMS (internal standard). The elementary analyses of all the compounds corresponded to the calculated values. Compounds (**1-4a**) had been obtained previously by other methods [14-16].

TABLE 3. Chemical Shifts in the PMR Spectra of the Xanthocercin Analogs (6-14)

| Compound | PMR spectra*, δ, ppm | | | | |
|---|---|---|---|---|---|
| | Chromone protons | | | | Aryl protons |
| | H-2 or Me-2, s | H-5, d, J=9.28 | H-6, d, J=9.28 | O-$(CH_2)_n$-O | H-2',3',5',6' m or H-2',6' d, H-3',5' d J=8 Hz |
| 6a | 7.92 | 7.89 | 6.95 | 6.2 s | 7.5 |
| 6b | 7.88 | 7.50 | 6.98 | 6.22 s | 7.15 |
| 6c | 8.45 | 7.71 | 7.15 | 6.31 s | 7.48, 7.53 |
| 7a | 2.31 | 7.8 | 6.93 | 6.2 s | 7.4 |
| 7b | 2.31 | 7.8 | 6.92 | 6.2 s | 7.18 |
| 7c | 2.31 | 7.79 | 6.94 | 6.2 s | 7.21, 7.41 |
| 8a | | 7.83 | 7.01 | 6.26 s | 7.4 |
| 8b | | 7.81 | 7.01 | 6.25 s | 7.21 |
| 8c | | 7.81 | 7.04 | 6.26 s | 7.19, 7.42 |
| 9a | 8.00 | 7.76 | 6.93 | 4.39 s | 7.5 |
| 9b | 7.98 | 7.78 | 6.97 | 4.43 s | 7.16 |
| 9c | 8.00 | 7.72 | 6.96 | 4.43 s | 7.41, 7.54 |
| 10a | 2.35 | 7.71 | 6.93 | 4.42 s | 7.39 |
| 10b | 2.35 | 7.7 | 6.92 | 4.42 s | 7.15 |
| 10c | 2.28 | 7.69 | 6.98 | 4.43 s | 7.31, 7.49 |
| 11a | | 7.71 | 6.98 | 4.43 s | 7.4 |
| 11b | | 7.7 | 7.01 | 4.44 s | 7.22 |
| 11c | | 7.71 | 7.00 | 4.44 s | 7.2, 7.43 |
| 12a | 8.02 | 7.85 | 7.01 | 2.32 q, 4.45 t | 7.5 |
| 12b | 7.91 | 7.85 | 7.00 | 2.33 q, 4.42 t | 7.3 |
| 12c | 8.01 | 7.81 | 7.00 | 2.33 q, 4.44 t | 7.4, 7.53 |
| 13c | 2.34 | 7.75 | 6.95 | 2.34 q, 4.42 t | 7.22, 7.42 |
| 14a | | 7.77 | 7.03 | 2.35 q, 4.47 t | 7.41 |
| 14b | | 7.75 | 7.06 | 2.36 q, 4.48 t | 7.21 |
| 14c | | 7.76 | 7.03 | 2.36 q, 4.47 t | 7.18, 7.41 |

*The PMR spectra of compounds (**6-14**) were measured in $CDCl_3$.

**α-Phenyl-2,3,4-trihydroxyacetophenone (1a).** With stirring at room temperature, a solution of 11.7 g (0.1 mole) of phenylacetonitrile in 40 ml of absolute ether was saturated with a current of dry hydrogen chloride for 30-40 min. Then 14 g (0.1 mole) of freshly calcined zinc chloride and 12.6 g (0.1 mole) of pyrogallol in 40 ml of absolute ether were added. Saturation with hydrogen chloride was continued for 6 h, after which the mixture was left for 12 h, and it was then hydrolyzed in 300 ml of water at 95-100°C for 1-1.5 h. After a day, the precipitate was filtered off and was well washed with cold water. Yield 13.4 g (55%). mp 143-145°C (from toluene); lit. [14]: yield 43%, mp 144°C (from alcohol). Empirical formula $C_{14}H_{12}O_4$. PMR spectrum (DMSO-$d_6$, ppm, J, Hz): 4.25 (2H, s, $COCH_2$), 12.7 (1H, s, OH-2), 8.75 (1H, s, OH-3), 10.25 (1H, s, OH-4), 6.46 (1H, d, J = 9.28, H-5), 7.6 (1H, d, J = 9.28, H-6), 7.3 (5H, m, Ph).

Compound (**1b**), yield 15.1 g (58%), mp 159°C (from toluene). Empirical formula $C_{14}H_{11}FO_4$. PMR spectrum (DMSO-$d_6$, δ, ppm, J, Hz): 4.31 (2H, s, $COCH_2$), 12.44 (1H, s, OH-2), 8.64 (1H, s, OH-3), 10.11 (1H, s, OH-4), 6.43 (1H, d, J = 9.28, H-5), 7.49 (1H, d, J = 9.28, H-6), 7.22 (4H, m, Ph).

Compound (**1c**), yield 17.1 g (62%), mp 145°C (from alcohol). Empirical formula $C_{14}H_{11}ClO_4$. PMR spectrum (DMSO-$d_6$, ppm, J, Hz): 4.33 (2H, s, $COCH_2$), 12.41 (1H, s, OH-2), 8.68 (1H, s, OH-3), 10.16 (1H, s, OH-4) 6.44 (1H, d, J = 9.28, H-5), 7.49 (1H, d, J = 9.28, H-6), 7.35 (4H, m, Ph).

**7,8-Dihydroxyisoflavones (2a-c).** A mixture of 20 mmole of the appropriate ketone (**1a-c**), 20 ml of ethyl orthoformate, 20 ml of dry pyridine, and 2.5 ml of piperidine was heated at 125°C for 5 h. The reaction mixture was poured onto ice and the precipitate that deposited was filtered off and washed well with cold water on the filter. It was crystallized from aqueous alcohol.

**7,8-Diacetoxy-2-methylisoflavones (3a-c).** A mixture of 20 mmole of the appropriate ketone (**1a-c**), 13.6 ml (140 mmole) of acetic anhydride, and 21 ml (100 mmole) of triethylamine was heated at 110-120°C for 5-6 h and was then poured into 300 ml of cold water. The resulting precipitate was washed repeatedly with water on the filter and was crystallized from ethyl acetate–hexane (1:1).

**7,8-Dihydroxy-2-methylisoflavones (4a-c).** A hot solution of 20 mmole of the appropriate isoflavone (**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. It was then neutral-

ized with dilute hydrochloric acid and the resulting precipitate was filtered off and crystallized from a suitable solvent (see Table 1).

**7,8-Dihydroxy-2-trifluoromethylisoflavones (5a-c).** In drops, 7.2 ml (60 mmole) of trifluoroacetic anhydride was added to a solution of 20 ml of the appropriate ketone (**1a-c**) in 24 ml of dry pyridine cooled to 0°C. The reaction mixture was shaken for 10-15 min with ice cooling and was left at room temperature for 12 h. It was then heated to 50-60°C and was again left at room temperature for 12 h, after which it was poured into cold water, and the precipitate was filtered off. The desired product was crystallized from aqueous alcohol.

**7,8-Methylenedioxyisoflavone (6a).** A hot solution of 2.54 g (10 mmole) of the isoflavone (**2a**) in 25 ml of absolute DMFA was treated with 3.45 g (25 mmole) of freshly calcined potash and 0.9 ml (11 mmole) of diodomethane, and, with vigorous stirring by a magnetic stirrer, the mixture was heated at 80-90°C for 1-1.5 h. Then it was added to 40-50 ml of cold water, and the resulting precipitate was filtered off and crystallized from alcohol.

Compounds (**6b**, **6c**, **7a-c**, and **8a-c**) were obtained analogously to compound (**6a**) from the corresponding isoflavones (**2b**, **2c**, **4a-c**, and **5a-c**).

**2-Methyl-4'-fluoro-7,8-ethylenedioxyisoflavone (10b).** A hot solution of 2.86 g (10 mmole) of isoflavone (**4b**) in 25 ml of absolute DMFA was treated with 3.45 g (25 mmole) of freshly calcined potash and 0.92 ml (11 mmole) of 1,2-dibromoethane, and, with vigorous stirring on a magnetic stirrer, the mixture was heated at 80-90°C for 1.5 h. Then it was added to 40-50 ml of cold water, and the resulting precipitate was filtered off and crystallized from alcohol.

Compounds (**9a-c**, **10a**, **10c**, and **11a-c**) were obtained analogously to (**10b**) from the corresponding isoflavones (**2a-c**, **4a**, **4c**, and **5a-c**).

**7,8-Propylenedioxy-2-trifluoromethyl-4'-chloroisoflavone (14c).** A hot solution of 3.56 g (10 mmole) of the isoflavone (**5c**) in 20 ml of absolute DMFA was treated with 3.45 g (25 mmole) of freshly calcined potash and 1.11 g (11 mmole) of 1,3-dibromopropane, and, with vigorous stirring on a magnetic stirrer, the reaction mixture was heated at 80-90°C for 2 h. Then it was poured into 40-50 ml of cold water, and the resulting precipitate was filtered off and crystallized from alcohol.

Compounds (**12a-c**, **13c**, **14a**, and **14b**) were obtained analogously to (**14c**) from the corresponding isoflavones (**2a-c**, **4a-c**, **5a**, and **5b**).

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