4. The majority of phenolic components isolated showed a high antiradical and antioxidant activity.

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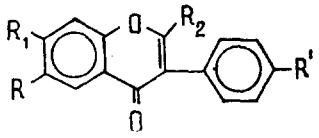
SYNTHESIS OF ANALOGS OF NATURAL ISOFLAVONES FROM 2,4-DIHYDROXYDEOXYBENZOINS

M. S. Luk'yanchikov, V. P. Khilya,
and A. L. Kazakov

UDC: 547.814.5

A number of analogs of natural isoflavones have been synthesized. The starting materials were 2,4-dihydroxydeoxybenzoins obtained under modified conditions of the Houben–Hoesch reaction. The yields of the isoflavones synthesized were 63-69%. All the analogs of natural flavones possess a pronounced hypolipidemic action.

In order to expand the arsenal of biologically active compounds possessing a hypolipidemic action, we have continued [1, 2] the synthesis of compounds close in structure to the natural isoflavonoids. In the present paper we consider the synthesis of a number of isoflavones containing electron-donating and electron-accepting substituents in positions 2, 6, 7, and 4'.



As the prototype of the synthetic isoflavones we used the chemical structure of the natural isoflavone formononetin isolated from clovers and sainfoins [3, 4]. In the planned structures of the synthetic analogs, we also took into account the results of mathematical structure-activity model [5].

The starting materials for the synthesis of the isoflavones were the 2,4-dihydroxydeoxybenzoins (I-VIII), which were obtained under the conditions of the Houben–Hoesch reaction [6], as modified by ourselves. In place of the absolute ether and zinc chloride of the classical variant, we used boron trifluoride ethereate in the presence of dry hydrogen chloride,

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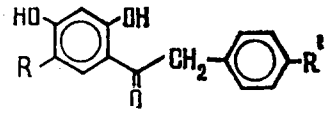
TABLE 1. 2,4-Dihydroxydeoxybenzoins



Compound	R	R'	Yield, %	mp, °C	Formula	Element	Found	Calc.
							%	
I	C_2H_5	H	96	100—102	$C_{16}H_{16}O_3$	C	74,60	75,02
						H	6,22	6,30
II	C_3H_7	H	88	92—93	$C_{17}H_{18}O_3$	C	75,40	75,53
						H	6,20	6,15
III	C_4H_9	H	92	79—80	$C_{18}H_{20}O_3$	C	76,50	76,03
						H	7,02	7,08
IV	C_5H_{11}	H	81	94—95	$C_{19}H_{22}O_3$	C	76,73	76,50
						H	7,60	7,43
V	C_6H_{13}	H	83	83—84	$C_{20}H_{24}O_3$	C	76,80	76,90
						H	7,80	7,74
VI	H	Br	90	176—177	$C_{14}H_{11}BrO_3$	Br	26,01	26,03
VII	C_2H_5	Br	80	124—125	$C_{16}H_{15}BrO_3$	Br	23,70	23,90
VIII	C_2H_5	Cl	80	130—131	$C_{16}H_{15}ClO_3$	Cl	12,30	12,25

this simultaneously fulfilling the functions of solvent and catalyst in the reaction. In the modified method, the condensation of resorcinol derivatives with phenylacetonitriles was preformed in a homogeneous system, which enabled the yield of 2,4-dihydroxydeoxybenzoin to be raised to 80-96% in place of the 50-75% by the classical variant.

The 2,4-dihydroxydeoxybenzoins obtained (Table 1) were colorless or yellowish crystalline substances soluble in methanol and ethanol and insoluble in water.

The synthesis of the isoflavones was performed in several variants with yields of 63-96%.

To synthesize the 7-hydroxyisoflavones (IX-XIII, XV, and XVI), we heated a mixture of 2,4-dihydroxydeoxybenzoins with ethyl orthoformate in pyridine in the presence of catalytic amounts of piperidine. The 2-trifluoromethylisoflavones (XIV, XVII, and XVIII) and the 2-ethoxycarbonylisoflavone (XIX) were obtained by the action on 2,4-dihydroxydeoxybenzoins of trifluoroacetic anhydride and ethoxalyl chloride, resectively, in pyridine. The reactions of the 7-hydroxyisoflavones with dimethyl sulfate in the presence of potassium carbonate or with acetic anhydride in absolute pyridine were completed by the formation of the 7-methoxy- and 7-acetoxyisoflavones (XX-XXIV).

The analogs of the natural isoflavones that were obtained were colorless crystalline substances readily soluble in organic solvents. The structures of the compounds synthesized were established on the basis of elementary analysis, physical constants (Table 2), and UV, IR, and PMR spectroscopy. The UV spectra had distinctive absorption maxima in the 240-260 nm region and less distinctive ones at 305-330 nm, which is characteristic for the isoflavone structure. The IR spectra were characterized by the presence of strong bands specific for the acetoxy group (1170 cm^{-1}), the hydroxy group (3150-3220 cm^{-1}), the carbonyl group (1625-1635 cm^{-1}), and the ethoxycarbonyl group (1735 cm^{-1}), and also for an aromatic ring (1580-1630 cm^{-1}). The PMR spectra clearly showed the signals of protons in the form of doublets in the 7.8-8.2 ppm region that form a characteristic feature of the chromone ring.

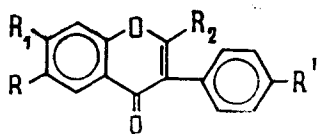
The individuality of the isoflavones was confirmed by thin-layer chromatography on Silufol plates. The eluent was a mixture of benzene and ethanol (9:1).

Biological trials showed that the isoflavones obtained possessed a pronounced hypolipidemic action 1.5 times greater than the level of activity of the officinal drugs cetamiphen and polisponin.

EXPERIMENTAL

2,4-Dihydroxy-6-R-deoxybenzoins (I-VIII). With stirring, a rapid current of dry halogen chloride was passed into a mixture of 0.1 mole of the appropriate phenylacetonitrile and 4-R-resorcinol (0.11 mole) in 80 ml of boron trifluoride ethereate for 8-10 h, and then the mixture was left at room temperature for 10 h. After this, it was added to 300 ml of hot water and the

TABLE 2. Physicochemical Properties of the Synthetic Isoflavones



Compound	R	R_1	R_2	R'	Yield, %	mp, °C	Formula	Element	Found	Calc.
									%	
IX	C_2H_5	OH	H	H	96	227–228	$C_{17}H_{14}O_3$	C	76,61	76,67
								H	5,40	5,30
X	C_3H_7	OH	H	H	71	215–216	$C_{18}H_{16}O_3$	C	77,21	77,12
								H	5,95	5,80
XI	C_4H_9	OH	H	H	63	192–193	$C_{19}H_{18}O_3$	C	77,70	77,55
								H	6,32	6,10
XII	C_5H_{11}	OH	H	H	72	167–169	$C_{20}H_{20}O_3$	C	77,93	77,90
								H	6,41	6,53
XIII	C_6H_{13}	OH	H	H	95	159–160	$C_{21}H_{22}O_3$	C	78,50	78,23
								H	7,10	6,90
XIV	C_2H_5	OH	CF_3	H	92	252–253	$C_{18}H_{13}F_3O_3$	F	17,15	17,05
XV	C_2H_5	OH	H	Cl	91	262–263	$C_{17}H_{13}ClO_3$	Cl	11,91	11,80
XVI	H	OH	H	Br	93	270–271	$C_{15}H_9BrO_3$	Br	25,50	25,20
XVII	H	OH	CF_3	Br	89	253–254	$C_{16}H_8BrF_3O_3$	Br	20,80	20,80
XVIII	C_2H_5	OH	CF_3	Br	95	303–304	$C_{18}H_{12}BrF_3O_3$	Br	19,40	19,34
XIX	H	OH	$OCOC_2H_5$	Br	91	204–205	$C_{18}H_{13}BrO_5$	Br	20,52	20,56
XX	C_2H_5	OCH_3	H	H	89	118–120	$C_{18}H_{16}O_3$	C	77,52	77,15
								H	5,30	5,67
XXI	C_2H_5	OCH_3	CF_3	H	87	162–163	$C_{19}H_{15}F_3O_3$	F	17,0	16,35
XXII	C_2H_5	OCH_3	H	Cl	91	211–212	$C_{18}H_{15}ClO_3$	Cl	11,21	11,30
XXIII	C_2H_5	$OCOCH_3$	H	H	96	113–114	$C_{19}H_{16}O_4$	C	74,00	74,00
								H	5,60	5,20
XXIV	C_2H_5	$OCOCH_3$	H	Cl	95	173–174	$C_{19}H_{15}ClO_4$	Cl	10,36	10,34

resulting mixture was kept at 90°C, pH 1.0, for 30-60 min. The precipitate was filtered off from the hot solution and washed with water to neutrality. The ketones (I-V) were crystallized from hexane, (VI) and (VII) from ethanol, and (VIII) from carbon tetrachloride.

The 7-Hydroxyisoflavones (IX-XII, XV, XVI). A mixture of 0.02 mole of the corresponding deoxybenzoin, 20 ml of ethyl orthoformate, 20 ml of pyridine, and 40 drops of piperidine was heated at 120-130°C for 4-10 h. Then the reaction mixture was diluted with 200 ml of water and the resulting precipitates was filtered off and washed with water. It was crystallized from ethanol.

6-Ethyl-7-hydroxy-2-trifluoromethylisoflavone (XIV) and 6-R-4'-Bromo-7-hydroxy-2-trifluoromethylisoflavones (XVII and XVIII). In drops, 4.2 g (0.02 mole) of trifluoroacetic anhydride was added to solution of 0.01 mole of the ketone (I), (VI), or (VII) in 10 ml of pyridine cooled to 0°C. Then the reaction mixture was poured into cold water. The precipitate that deposited was filtered off, washed with water until it was free from odor, and crystallized from acetone.

4'-Bromo-2-ethoxycarbonyl-7-hydroxyisoflavone (XIX). In drops, 4.3 g (0.04 mole) of ethoxalyl chloride was added to a solution of 6.14 g (0.02 mole) of ketone (VI) in 15 ml of pyridine cooled to 0°C, and the mixture was kept at room temperature for 24 h. Then it was poured into 50 ml of cold water containing 3-5 ml of 1 N hydrochloric acid. The oil that separated out rapidly solidified. It was crystallized from aqueous ethanol.

The 7-Alkoxyisoflavones (XX-XXII). An acetone solution of 0.001 mole of a 7-hydroxyisoflavone (IX, XIV, or XV) and 0.004-0.005 mole of an alkyl halide or 0.001 mole of dimethyl sulfate was stirred at 50-60°C with 0.003 mole of freshly calcined potassium carbonate for 3-5 h, after which the hot solution was filtered. The filtrate was acidified with two drops of glacial acetic acid and the residue after the acetone had been distilled off was crystallized from ethanol.

The 7-Acetoxyisoflavones (XXIII, XXIV). To a hot solution of 0.001 mole of a 7-hydroxyisoflavone (IX or XV) containing 0.5 ml of pyridine was added 0.005 mole of acetic anhydride and the reaction mixture was left at room temperature for 24 h. The reaction product was filtered off and crystallized from ethanol.

SUMMARY

A series of analogs of natural isoflavones has been synthesized from 2,4-dihydroxydeoxybenzoins. The yields amounted to 63-96%.

All the isoflavones synthesized possess a pronounced hypolipidemic activity.

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DYNAMICS OF THE ACCUMULATION OF THE MONOTERPENOIDS OF *Citrus limon*

N. A. Kekelidze, M. I. Dzhanikashvili,
L. V. Rusadze, and A. P. Kachurina

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The amounts and compositions of the essential oils in the leaves and fruit of Meyer's lemon in the various vegetation periods have been studied. It has been established that as the fruit ripens the amount of essential oils and of monoterpene hydrocarbons in its peel and in the leaves increases.

We have studied the amount and composition of the essential oils of the leaves and fruit of Meyer's lemon [*Citrus limon*] in the various vegetation periods. The leaves and fruit were collected from normally developed fruit-bearing plants from the middle, with respect to height, parts of the crown from all sides in the morning in dry weather on experimental-production plots of the Sukhumi Zonal Experimental Station of Essential-Oil Crops and the Sukhumi Experimental Station of Subtropical Crops of the All-Union Institute of Plant-Growing.

The leaves were collected every month for a year, beginning with the flowering period. The collection of the fruit was begun in July when its size had reached 5-7 mm. The essential oils were isolated by the steam distillation method 30-40 min after the material under investigation had been gathered. The oils were isolated from the distillate by extraction with methylene chloride and were analyzed by gas-liquid chromatography.

Results on the amount of essential oils are shown in Fig. 1. The biosynthesis of the essential oil in the peel of the fruit intensified as the fruit ripened and reached a maximum in the period of full ripeness. The amount of essential oil in the leaves increased from the flowering period up to September. In October, i.e, at the beginning of the ripening of the fruit, the biosynthesis weakened considerably, and then, in the period of full ripeness of the fruit, the process of oil-formation intensified and reached a maximum. In winter, in the period of forced dormancy, the amount of essential oils scarcely changed. From the beginning of the growth of the shoots to the flowering period, the amount of oil in the leaves increased.

Analysis of the results on the change in the monoterpenoids in the leaves during the year (Table 1) shows that from the flowering period to September there is an intensive bio-

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