SYNTHESIS OF NATURAL ISOFLAVONES AND THEIR STRUCTURAL ANALOGS

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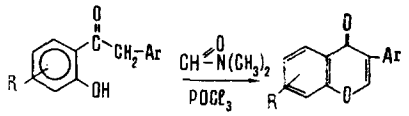
We have previously attempted to synthesize isoflavones but their yields did not exceed 25-35%. In the present paper we give the results of the choice of the optimum conditions for the synthesis of these substances with higher yields by methods A and B.

The proposed method A consists in the reaction of the corresponding o-hydroxydeoxybenzoin with ethyl orthoformate with the addition to their mixture of an equimolar amount of 70% perchloric acid. The 4-ethoxyisoflavylium perchlorates so obtained, which separated out a few minutes after the components have been mixed, are suitable for further transformations without recrystallization. Their hydrolysis to isoflavones takes place quantitatively.

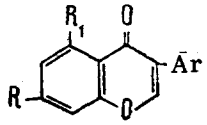
Method B was proposed by S. A. Kagal et al. [2] and modified by us. In this method, isoflavones are obtained in one stage by the formylation of o-hydroxydeoxybenzoins with the aid of the Vilsmeier reagent.



These authors performed this reaction by heating o-hydroxydeoxybenzoin with the Vilsmeier complex (DMFA + $POCl_3$) for several hours. It was impossible to synthesize isoflavones from phloroglucinol derivatives by this method.

In our variant, the synthesis of isoflavones is performed by keeping o-hydroxydeoxybenzoin in an excess of DMFA and phosphorus oxychloride for a short time. The isoflavone separates out in the solid form when the reaction mixture is poured into water. In this way, 5,7-dihydroxy-3',4'-dimethoxyisoflavone has been obtained from phloroglucinol derivatives. The excess of phosphorus oxychloride apparently gives unstable esters at the free hydroxy groups of the deoxybenzoin which are readily split off when the mixture is poured into water. No special protection of the free hydroxy groups is required, which, together with the simplicity of operation, makes this method more acceptable than others.

The yields and some constants of the isoflavones synthesized



are given in Table 1.

The structures of the isoflavones obtained were confirmed by UV spectroscopy with ionizing and complex-forming additives.

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TABLE 1

R	R_1	Ar	Yield of isoflavone (%) by method A	Yield of isoflavone (%) by method B	Mp, °C, according to us	Mp, °C, according to the literature	$\lambda_{max}^{C_2H_5OH}$ (log ε)	Isoflavone derivative
OH	H	C_6H_5	72,0	93,5	206 – 207	205—206 [1]	247 (4,33), 300 (3,56)	—
OCH_3	H	C_6H_5	76,0	100,0	154 — 155	—	249 (4,45), 297 (4,05)	Formononetin
OH	H	p—$C_6H_4OCH_3$	68,0	93,5	254 – 255	255—260 [4]	250 (4,47), 302 (4,06)	Daidzein
OH	H	p—C_6H_4OH	—	85,0	319—320	320 [4]	249 (4,22), 302 (3,90)	Cladrin
OH	H	3′,4′—$(OCH_3)_2$—C_6H_3	—	94,0	256 — 257	257—258 [3]	250 (4,28)	Cabreuvin
OCH_3	H	3′,4′—$(OCH_3)_2$—C_6H_3	—	92,0	162—163	164—165 [3]	262 (4,23)	—
OH	OH	3′,4′—$(OCH_3)_2$—C_6H_3	—	70,0	189—191	—	263 (4,39), 332 (3,95)	—

EXPERIMENTAL

Method A. 4-Ethoxy-7-methoxyisoflavylium Perchlorate. A solution of 1.2 g (0.005 mole) of benzyl 2-hydroxy-4-methoxyphenyl ketone in 20 ml of freshly-distilled ethyl orthoformate was treated with 0.5 ml (0.005 mole) of 70% perchloric acid. After 3-5 h, the precipitate of 4-ethoxy-7-methoxyisoflavylium perchlorate that had deposited was filtered off and was washed with ether. Yield 1.5 g (78.9%), mp 127-129°C, $C_{18}H_{17}ClO_7$ (the results of the analysis here and below corresponded to the calculated figures).

4-Ethoxy-7-hydroxyisoflavylium and 4-ethoxy-7-hydroxy-4'-methoxyisoflavylium perchlorates were obtained similarly with yields of 75 and 70%, mp 136-139°C and 170°C, respectively.

7-Methoxyisoflavone. A mixture of 3.8 g (0.01 mole) of 4-ethoxy-7-methoxyisoflavylium perchlorate, 10 ml of water, and 10 ml of ethanol was gently warmed and stirred. After 10-15 min, the precipitate was filtered off, washed with water, and dried. Yield 2.4 g (96%), mp 154-155°C (from ethanol), $C_{16}H_{12}O_3$.

In the same way we obtained 7-hydroxyisoflavone and 7-hydroxy-4'-methoxyisoflavone with yields of 96 and 97%, respectively (see Table 1).

Method B. 7-Hydroxyisoflavone. A solution of 4.56 g (0.02 mole) of 2,4-dihydroxydeoxybenzoin in 20 ml of dimethylformamide (DMFA) was added with stirring to 12 ml of $POCl_3$ at such a rate that the temperature of the mixture did not exceed 90-100°C. After 30 min, the solution was poured into 200 ml of water. The isoflavone that deposited was filtered off, washed with water, and dried. Yield 4.45 g (93.5%), mp 206-207°C (from methanol).

All the other isoflavones were obtained similarly (see Table 1). The isoflavones described can also be synthesized by keeping at room temperature (25°C) for 10-12 h a mixture of dimethylformamide, phosphorus oxychloride, and the appropriate deoxybenzoin. The reactants are taken in the same proportions as described above.

CONCLUSIONS

A number of natural isoflavones and their structural analogs have been synthesized by improved ethyl orthoformate and dimethylformamide methods. It has been possible to use the dimethylformamide method for the first time for the synthesis of 5,7-dihydroxyisoflavones. Two new isoflavones have been synthesized: 7-methoxyisoflavone and 5,7-dihydroxy-3',4'-dimethoxyisoflavone.

LITERATURE CITED

1. V. V. Mezheritskii and G. N. Dorofeenko, Zh. Obshch. Khim., 40, 2459 (1970).
2. S. A. Kagal et al., Tetrahedron Lett., 14, 593 (1962).
3. V. A. Bandyukova, Rast. Res., 8, No. 2, 283 (1972).
4. F. M. Dean, Naturally Occurring Oxygen Ring Compounds, Butterworth's Scientific Publications, London (1963), p. 366.