

## AMINOMETHYLATION OF FORMONONETIN AND CLADRIN BY PRIMARY AMINES

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*The reaction of natural isoflavones formononetin and cladrin with primary amines and formalin in the presence of a base catalyst was studied. Several novel substituted 9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-ones containing alkyl, benzyl, or heterylalkyl substituents in the N-9 position were synthesized.*

**Key words:** isoflavone, formononetin, cladrin, electrophilic substitution, 9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-one.

Flavonoids, some representatives of which are present in practically all plant species, are the most widely distributed natural compounds of plant origin [1].

Isolation of the natural isoflavone formononetin (4'-methoxy-7-hydroxyisoflavone) from leaves of *Genista* [2] and cladrin (3',4'-dimethoxy-7-hydroxyisoflavone) from *Cladrastis lutea* [3] has been reported.

Isoflavonoids containing a methoxy group in the *p*-position of ring B are used as natural anti-oxidants [4] and for treatment of cardiovascular diseases [5] and breast [6] and prostate [7] cancers. Formononetin exhibits hypolipidemic activity [8] and lowers the level of cholesterol and triglycerides in blood, phospholipids, and  $\beta$ -lipoproteins [9, 10]. Considering these factors, modification of the natural isoflavones formononetin and cladrin seemed interesting from both chemical and biological points of view.

We have previously studied the reaction of natural isoflavones and their analogs with amination reagents and prepared a series of 8-aminomethyl derivatives containing secondary amines [11, 12].

Mannich reaction conditions with the appropriate ratio of substrate, amine, and formaldehyde in the presence of a base catalyst [KOH, *N,N*-dimethylaminopyridine (DMAP)] is known to produce through electrophilic substitution derivatives of 3,4-dihydro-1,3-benzooxazines [13-17]. Annelation of an oxazine ring to the coumarin core by reaction of 7-hydroxycoumarins and synthesized beforehand *N,N*-bis(hydroxymethyl)amines in the presence of DMAP forms derivatives of 9,10-dihydro-2H,8H-chromeno[8,7-e][1,3]oxazin-2-one [18] whereas isomeric derivatives of 9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-one are formed by condensation of isoflavone derivatives with esters of  $\alpha$ -amino acids and an excess of formalin [19].

In continuation of research on the synthesis and reactivity of isoflavonoids, we studied the reaction of formononetin and cladrin with primary aliphatic amines and formalin and obtained new derivatives of these natural isoflavones that may exhibit biological activity.

As it turned out, heating 7-hydroxyisoflavones **1** and **2** with equivalent amounts of primary amines and a two-fold excess of formalin in propan-2-ol in the presence of a catalytic amount of DMAP formed derivatives of 9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-one in satisfactory yields without preliminary preparation of the *N,N*-bis(hydroxymethyl)amines. Thus, simultaneous C- and O-aminomethylation of the benzopyran-4-one core produced derivatives of 9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-ones **3-16** containing alkyl, benzyl, or heterylalkyl substituents in the 9-position.

It was shown earlier that the 3,4-dihydro-1,3-oxazine ring is smoothly annelated to a benzopyran-2-one ring by using *N,N*-bis(hydroxymethyl)amines that were synthesized beforehand from aliphatic amines, benzylamines, and *p*-substituted anilines. The 9,10-dihydro-2H,8H-chromeno[8,7-e][1,3]oxazin-2-ones were not formed if anilines containing strong electron-accepting or bulky substituents in the *o*-position to the amine were used [18].

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