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SYNTHETIC AND MODIFIED ISOFLAVONOIDS XVII. INTERACTION OF SYNTHETIC ANALOGS OF ISOFLAVONES WITH GUANIDINE

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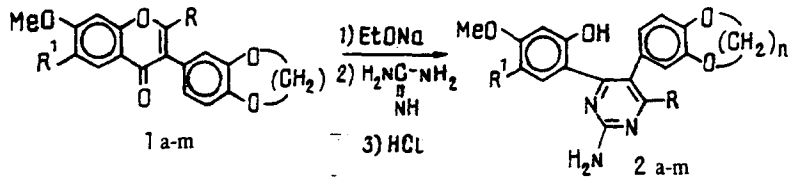
Under the influence of guanidine, 1,3-benzodioxolane, 1,4-benzodioxane, and 1,5-benzodioxepane analogs of isoflavone are converted into 2-aminopyrimidine derivatives

2-Aminopyridine derivatives possess various biological activities. Among them there are substances possessing antifungicidal and antibacterial properties.

It has been established [3, 4] that, under the influence of amidines, isoflavones recyclize into the corresponding derivatives of 4-(2-hydroxyphenyl)pyrimidine. We have studied the recyclization of benzodioxolane, benzodioxane, and benzodioxepane analogs of isoflavone with guanidine. Thus when the 7-methoxyisoflavones (1a-m*) [5-8] were heated with guanidine in the presence of sodium ethanolate in absolute ethanol, the pyrone ring opened and the resulting intermediate products then cyclized to the corresponding pyrimidines (2a-i).



a: R=H, R^1=Et, *n*=1; b: R=H, R^1=Pr, *n*=1; c: R=Me, R^1=Pr, *n*=1; d: R=R^1=H, *n*=2; e: R=H, R^1=Et, *n*=2; g: R=H, R^1=Pr, *n*=2; h: R=Me, R^1=H, *n*=2; i: R=Me, R^1=Et, *n*=2; j: R=Me, R^1=Pr, *n*=2; k: R=R^1=H, *n*=3; *l*: R=H, R^1=Pr, *n*=3; m: R=Me, R^1=Pr, *n*=3

The reaction required prolonged boiling of the isoflavone with 2 moles of guanidine and 3 moles of sodium ethanolate in absolute ethanol. It was convenient to monitor the course of the reaction by the TLC method. At first the reaction mixture appeared on the chromatogram in the form of two spots, one of which corresponded to the pyrimidine (2) and the other to the intermediate product, giving the well-known reaction with an alcoholic solution of ferric chloride. The reaction mixture was boiled until the spot of the intermediate had disappeared from the chromatogram.

The derivatives of the pyrimidine series (2) that we had obtained were colorless or light yellow crystalline substances readily soluble in polar organic solvents (Table 1). In contrast to the initial compounds, they also dissolved readily in aqueous alkalis, which showed the presence of a phenolic hydroxyl, and they gave a color reaction (yellow coloration with an alcoholic solution of titanium(IV) chloride) that indicated the presence in the recyclization products of an intramolecular hydrogen bond with the participation of the phenolic hydroxyl and the nitrogen atom of the pyrimidine nucleus.

*No compounds (1f) and (2f) are mentioned in this paper — Translator.

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TABLE 1. Characteristics of the 4-(2-Hydroxyphenyl)-5-hetarylpyrimidines (2)

Compound	Yield, %	mp, °C	Empirical formula	IR spectrum, ν cm^{-1}		
				ν NH_2	ν C=N	ν OH
2a	76	235—236	$C_{20}H_{19}N_3O_4$	3220, 3080	1670	
2b	48	218—220	$C_{21}H_{21}N_3O_4$			
2c	32	190—191	$C_{22}H_{23}N_3O_4$	3400, 3280	1630	3140
2d	71	187—188	$C_{19}H_{17}N_3O_4$	3370, 3300	1635	3160
2e	65	203—205	$C_{21}H_{21}N_3O_4$			
2g	88	187—188	$C_{22}H_{23}N_3O_4$			
2h	66	179—180	$C_{20}H_{19}N_3O_4$	3418, 3280	1610	3160
2i	37	201—203	$C_{22}H_{23}N_3O_4$	3414, 3283	1617	3156
2j	32	177—178	$C_{23}H_{25}N_3O_4$	3410, 3288	1630	3130
2k	68	215—216	$C_{20}H_{19}N_3O_4$			
2l	66	165—166	$C_{23}H_{25}N_3O_4$	3390, 3280	1630	3150
2m	53	206—207	$C_{24}H_{27}N_3O_4$			

*Compound 2a, d crystallized from isopropyl alcohol, 2b — from benzene, 2h — from a mixture of benzene and petroleum ether, 2i, j — from aqueous alcohol, 2c, e, g, j, k, *l*, m — from alcohol.

To confirm the structures of the pyrimidines we measured their PMR and DMSO-d_6 spectra (Table 2). A characteristic feature of the pyrimidines (2) is the separate positions of the absorption of the protons of the OH and the NH_2 groups because of slow proton exchange. A two-proton, slightly broadened, singlet of the amino group in compounds 2a-m appeared in the 6.8-11.4 ppm region and rapidly disappeared on the addition of heavy water.

In the IR spectra (Table 1) of pyrimidines (2) in potassium bromide tablets, the amino group appears in the form of two absorption bands at 3080-3418 cm^{-1} (ν_{NH_2}), while a band of medium intensity at 1610-1670 cm^{-1}corresponds to the stretching vibrations of the C=N bond.

The OH-2 group in the pyrimidines obtained absorbed in the weak field (11.4-14.0 ppm), which serves as an indication of the formation of a more or less strong intramolecular hydrogen bond.

In the molecules of compounds (2) the aromatic nuclei are noncoplanar, as follows both from a consideration of Stuart-Briegleb models and from the PMR spectra. The heterocyclic nucleus departs from the plane of the pyrimidine ring to a greater degree. The phenol ring occupies a more or less fixed position relative to the pyrimidine ring in view of the formation of an intramolecular hydrogen bond. As well as from the information on the chemical shifts of the OH group given above, this also follows from the fact that in all the compounds studied there was no paramagnetic screening of the phenolic H-6 proton by the nitrogen atom of the pyrimidine ring closest to it: the signal of this proton was observed in the 6.5-6.9 region. The introduction of an alkyl substituent (Et, Pr) into position 5 of the phenol moiety and an increase in the number of methylene groups in the hetaryl substituent in (2c, j, m) caused an appreciable paramagnetic shift of the signals of the OH group in comparison with compounds having a free position 5 (2d, h).

Thus, the interaction of benzodioxolane, benzodioxane, and benzodioxepane analogs of isoflavones with guanidine leads to the corresponding 1-amino-4-(2-hydroxyphenyl)-5-hetarylpyrimidine derivatives. A study of the biological activities of the new compounds has shown that some of them exhibit neuroleptic activity.

EXPERIMENTAL

The course of the reactions and the purity of the substances obtained were monitored by TLC on Silufol UV-254 plates in benzene—ethanol (9:1). PMR spectra were measured on a Bruker WP-100 SU instrument in DMSO-d_6 with TMS as internal standard. The analyses of the compounds synthesized corresponded to the calculated figures.

TABLE 2. Chemical Shifts in the PMR Spectrum (δ, ppm, J, Hz) of the 4-(2-Hydroxyphenyl)-5-hetarylpyrimidines (2) (DMSO-d_6)

Compund	Protons of the phenol moiety					Pyrimidine protons		Protons of the hetero residue	
	OH-2, s	H-3, s	OMe-4, s	R^1-5	H-6, s	NH_2-2, s	R-6, s	H-4(5) or (6), H-6(7) or (8), H-7(8) or (9)	$-O(CH_2)_nO-$ n=1, 2, 3,
2a	11.37	6.57	3.79	2.37 q; 0.92 t	6.92	11.37	8.59	6.81 m	6.06 s
2b	9.09	6.52	3.79	2.32 t; 1.32 t; 1.34 m; 0.74 t	6.81	9.09	8.49	6.76 m	6.00 s
2c	13.16	6.30	3.71	2.05 t; 1.14 m; 0.68 t	6.52	6.83	2.11	6.61 m	5.95 s
2d	12.38	6.41 d, (2.0)	3.78	6.17 d.d, (8.0; 2.0)	6.92 d, (8.0)	7.05	8.10	6.71 m	4.28 s
2g	8.07	6.51	3.81	2.31 q; 0.86	6.83	8.07	8.46	6.75 m	4.25 s
2h	12.94	6.43 d, (2.0)	3.77	6.11 d.d, (8.0; 2.0)	6.95 d, (8.0)	7.01	2.15	6.73 m	4.35 s
2i	7.05	6.47	3.84	2.21 q; 0.80 t	6.93	7.05	2.17	6.71 m	4.36 s
2k	13.48	6.41	3.77	2.12 t; 1.11 m; 0.77 t	6.87	6.99	2.15	6.66 m	4.31 s
2l	12.75	6.39	3.77	2.13 t; 1.14 m; 0.73 t	6.64	7.00	8.09	6.81 m	4.11 t, 2.13 q
2m	14.1	6.41	3.76	2.12 t; 1.15 m; 0.74 t	6.67	6.96	2.12	6.78 m	4.17 t, 2.12 q

4-(2-Hydroxyphenyl)-5-hetarylpyrimidines (2a-m). To a solution of 0.92 g (40 mmole) of sodium in 50 ml of absolute alcohopl was added 1.91 g (20 mmole) of guanidine hydrochloride, and the resulting precipitate of sodium chloride was filtered off. The filtrate so obtained was treated with 10 mmole of the appropriate 7-methoxyisoflavone (1a-m), and the reaction mixture was boiled for 18-40 h. After evaporation of the alcohol in vacuum, the dry residue was dissolved in water and the solution was acidified to pH 6 with dilute hydrochloric acid. The product that precipitated was filtered off and dried. The compounds obtained were crystallized from suitable solvents.

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