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REACTION OF THIAZOLE ANALOGS OF ISOFLAVOLIGNANS WITH AMIDINES

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Thiazole analogs of isoflavolignans react with amidines to recyclize into pyrimidine derivatives, the PMR spectra of which were examined. Effects connected to the formation and strength of an intramolecular H-bond were studied.

Key words: thiazole analogs of isoflavolignans, recyclization, amidines, pyrimidines.

Natural and synthetic chromone derivatives possess a wide spectrum of biological activity [1]. Furthermore, they are intermediates in the synthesis of various heterocyclic systems [2, 3].

Several reactions of isoflavonoids with bifunctional nucleophiles, in particular, hydrazine and hydroxylamine, have been used to prepare pyrazole and isoxazole derivatives [4, 5]. Other nucleophiles that have been used include amidines. The recyclization of thiazole analogs of isoflavolignans by reaction with formamidine, acetamidine, benzamidine, and guanidine has been studied. The reaction follows the scheme below.

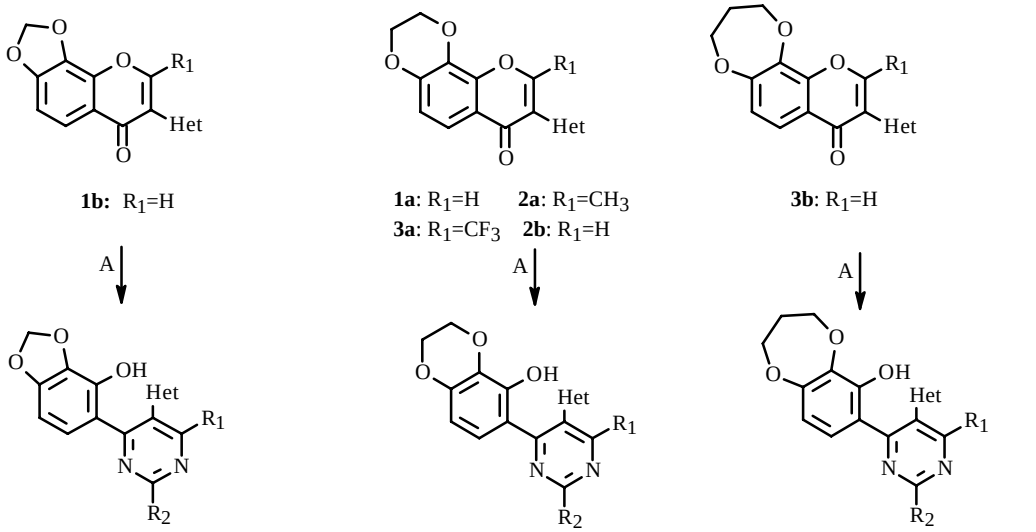

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TABLE 1. Chemical Shifts in PMR Spectra of Pyrimidines in DMSO-d_6, δ, ppm

Compound	Protons						
	phenol part				pyrimdine part		thiazole
	2-OH	O-$(CH_2)_4$-O	5-H, d	6-H, d	R_2, s	6-R_1, s	
4a	11.55	4.25	6.19	6.43	7.04	8.47	2-CH_3 2.62, s; 5-H 6.97, s
5a	12.90	4.21	6.00	6.10	7.05	2.09	2-CH_3 2.70, s; 5-H 7.19, s
6a	10.90	4.23	6.11	6.30	7.44		2-CH_3 2.63, s; 5-H 7.23, s
7a	9.69	4.22	6.22	6.43	2.78		2-CH_3 2.60, s; 5-H 7.30, s
8a	9.30	4.25	6.29	6.56	7.61; 8.42		2-CH_3 2.62, s; 5-H 7.34, s
9a	9.56	4.23	6.25	6.48	9.43		2-CH_3 2.61, s; 5-H 7.35, s
4b	10.00	6.04	6.52	6.67	7.12	8.80	4-CH_3 2.33, s; 5-H 7.07, s
5b	9.63	4.27	6.39	6.56	7.08	8.77	4-CH_3 2.33, s; 5-H 7.06, s
6b	9.30	4.29	6.52	6.75	9.20	9.20	4-CH_3 2.41, s; 5-H 7.29, s
7b	9.21	4.29	6.48	6.71	2.67	9.21	4-CH_3 2.39, s; 5-H 7.23, s
8b	9.05	4.13; 2.14	6.62	6.88	9.33	9.20	4-CH_3 2.40, s; 5-H 7.26, s
9b	9.07	4.09; 2.13	6.53	6.73	7.05	8.85	4-CH_3 2.33, s; 5-H 7.05, s

TABLE 2. Properties of Compounds

Compound	Yield, %	mp, °C	Empirical formula	Solvent for crystallization
4a	68	218	$C_{16}H_{14}N_4O_3S$	EtOH
5a	78	209	$C_{17}H_{16}N_4O_3S$	EtOH
6a	84	194	$C_{17}H_{13}F_3N_4O_3S$	EtOH
7a	79	189	$C_{18}H_{14}F_3N_3O_3S$	MeOH
8a	78	231	$C_{23}H_{16}F_3N_3O_3S$	i-PrOH
9a	77	196	$C_{17}H_{12}F_3N_3O_3S$	EtOH
4b	79	212	$C_{15}H_{11}N_4O_3S$	EtOH
5b	81	202	$C_{16}H_{14}N_4O_3S$	EtOH
6b	62	155	$C_{16}H_{13}N_3O_3S$	EtOH
7b	63	158	$C_{17}H_{15}N_3O_3S$	EtOH
8b	74	188	$C_{17}H_{15}N_3O_3S$	EtOH
9b	78	249	$C_{17}H_{16}N_4O_3S$	EtOH

The reaction occurs if the appropriate flavolignan is boiled in ethanol with two moles of amidine. The course of the reaction is followed using TLC. The reaction mixture is boiled until the spot of the starting material disappears in the chromatogram.

The pyrimidine derivatives that we prepared are yellow crystalline compounds with high melting points. They are readily soluble in polar organic solvents. In contrast with the starting isoflavolignans, they dissolve in aqueous bases. This is consistent with the presence of a phenolic hydroxyl. They give a color reaction (yellow) with an alcoholic solution of $TiCl_4$, which indicates that the recyclization products have an intramolecular H-bond between the phenolic H and the N atom of the pyrimidine ring. A characteristic feature of the ^1H NMR spectra of compounds containing an amine is the separate absorption of the OH and NH_2 protons owing to slow exchange. The slightly broadened 2H singlet of the amine appears at 7.04-7.12 ppm. The signal of the 2-OH hydroxyl is the most sensitive to structural changes in the synthesized derivatives.

An examination of the structural formulas of the compounds indicates that the chemical shift of the hydroxyl proton is determined mainly by the electron-donating properties of the substituents in the pyrimidine ring. Thus, replacing an electron-

accepting (6-CF_3) by an electron-donating (CH_3) substituent shifts the signal of the 2-OH from 10.9 to 12.9 ppm (compounds **6a**, **4a**, and **5a**). This indicates that the H-bond between the 2-OH and the pyrimidine N-3 affects its chemical shift. An electron-donating substituent strengthens this bond whereas an electron-accepting one weakens it. Substituents on the pyrimidine C-2 have an analogous effect. Thus, an NH_2 group shifts the signal of 2-OH to weak field by ~1 ppm compared with the less electron-donating substituents CH or Ph (**6a-8a**). Changing the size of the O-containing heterocycle fused to C-2 and C-3 of the phenol also affects the position of the phenol hydroxyl. Increasing the ring size from benzodioxole to benzodioxane and then to benzodioxepane shifts the 2-OH signal to strong field (**4b**, **5b**, **9b**). This is related to the effect of the ring size on the mutual orientation of the phenol and pyrimidine moieties. Steric hindrance between the benzodioxepane and adjacent thiazole is probably present in that derivative. As a result, the torsion angle between the moieties increases. This weakens the H-bond between 2-OH and pyrimidine N-3.

The starting thiazole analogs of isoflavolignans (**1b-3b** and **1a-3a**) that are required to synthesize the pyrimidines were obtained by cyclization of thiazolylacetophenones with subsequent annelation by dioxole, dioxane, and dioxepane moieties [6]. Then, ketones were prepared via condensation of pyrogallol with thiazolylacetonitriles under Hesch conditions [6].

Thus, PMR spectra of recyclization products of thiazole analogs of isoflavolignans confirm their structure and are consistent with the presence of an intramolecular H-bond between the phenolic hydroxyl and the pyrimidine N atom.

EXPERIMENTAL

The purity of the prepared compounds was monitored by TLC on Silufol UV-254 plates using benzene—ethanol (9:1) and $CHCl_3$—C_2H_5OH (9:1). PMR spectra were measured on a Bruker WP-100SY spectrometer in DMSO-d_6 with TMS (internal standard). Elemental analyses corresponded to those calculated.

2-Amino-4-(2-hydroxy-3,4-ethylenedioxyphenyl)-5-(4-methyl-2-thiazolyl)-pyrimidine (5b). A solution of **2b** (3.01 g, 10 mmole) in alcohol (50 mL) was treated with guanidinium carbonate (1.8 g, 10 mmole) and boiled for 8 h. The solvent was removed under vacuum. The dry solid was dissolved in water (100 mL) and acidified with acetic acid. The precipitated pyrimidine was filtered off and dried. Yield 2.8 g (82%) of yellow needles (from alcohol). Compounds **4a-6a**, **4b**, and **9b** were prepared analogously from chromones **1a-3a**, **1b**, and **3b**.

2-Methyl-4-(2-hydroxy-3,4-ethylenedioxyphenyl)-5-(4-methyl-2-thiazolyl)-pyrimidine (7b). A solution of **2b** (3.01 g, 10 mmole) in alcohol (50 mL) was treated with acetamidine chloride (1.89 g, 20 mmole) and potash (1.38 g, 10 mmole). The reaction mixture was boiled until the starting material disappeared. The solvent was removed under vacuum. The dry solid was dissolved in water (100 mL) and acidified with acetic acid. The precipitated pyrimidine was filtered off and dried. Light yellow crystals were obtained from alcohol. Compound **7a** was obtained analogously from **3a**.

4-(2-Hydroxy-3,4-ethylenedioxyphenyl)-5-(4-methyl-2-thiazolyl)-pyrimidine (6b). A solution of 3-(4-methyl-2-thiazolyl)-7,8-ethylenedioxychromone (3.01 g, 10 mmole) in the minimal amount of alcohol was treated with formamidine acetate (2.08 g, 20 mmole) and potash (1.38 g, 10 mmole). The reaction mixture was boiled until the starting material disappeared. The alcohol was removed under vacuum. The solid was dissolved in water and precipitated with acetic acid. The precipitated pyrimidine was filtered off and dried. Yellow plates were obtained from aqueous alcohol. Compounds **9a** and **8b** were obtained analogously from **3a** and **3b**.

2-Phenyl-4-(2-hydroxy-3,4-ethylenedioxyphenyl)-5-(2-methyl-4-thiazolyl)-6-trifluoromethylpyrimidine (8a). A solution of 2-trifluoromethyl-3-(2-methyl-4-thiazolyl)-7,8-ethylenedioxychromone (3.69 g, 10 mmole) in the minimal amount of alcohol was treated with benzamidine chloride (3.13 g, 20 mmole) and potash (1.38 g, 10 mmole). The reaction mixture was boiled until the starting material disappeared. The solvent was removed under vacuum. The solid was dissolved in water and precipitated with acetic acid. The solid was filtered off and dried. Yellow needles were obtained from isopropanol.

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