CHEMISTRY OF ISOFLAVONE HETEROCYCLIC ANALOGS.

10.* SYNTHESIS OF PYRIMIDINES BY RECYCLIZATION OF ISOFLAVONES AND THEIR HETEROCYCLIC ANALOGS

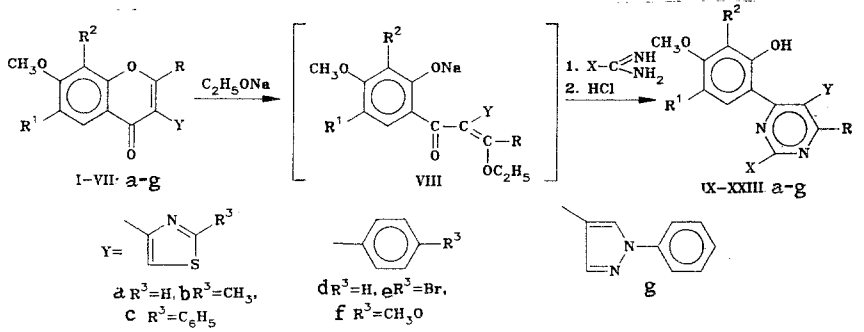
V. P. Khilya, M. Yu. Kornilov,
N. V. Gorbulenko, G. M. Golubushina,
E. N. Kovtun, N. V. Kolotusha,
and G. V. Panasenko

UDC 547.814.1'789.1.07'855.5

Isoflavones and their thiazole and pyrazole analogs are recyclized into the corresponding 4-(2-hydroxyphenyl)-pyrimidine derivatives under the effect of amidines. Their PMR spectra were studied. The effects related to the formation and strength of the intramolecular hydrogen bond were examined.

Natural and synthetic derivatives of chromone exhibit varied physiological activity [2] and are suitable intermediate products for the synthesis of different heterocyclic systems [3-6]. As a result of the reaction of recyclization of thiazole analogs of isoflavones under the effect of hydrazine hydrate and hydroxylamine, the corresponding derivatives of 3-(2-hydroxyphenyl)pyrazole and 3-(2-hydroxyphenyl)isoxazole are obtained [1, 7, 8]. Amidines have been used as other nucleophilic reagents in the reaction with chromones, which permits synthesizing 4-(2-hydroxyphenyl)pyrimidine derivatives [9, 10].

The reaction of isoflavones and their heterocyclic analogs with amidines have not been studied. We investigated the recyclization of isoflavones and their thiazole and pyrazole analogs with formamidine, acetamidine, and guanidine; this reaction takes place as follows



Ia–g, IXa–f, XVId,cXIXb-d, XXIIIg. R=R¹=R²=H; IIa–e, Xa–c, XXIIb R=R²=H, R¹=C₂H₅; IIIb, XIb, XVIIIb XXIb R=R¹=H. R²=CH₃O; IVe XIIe R=CH₃, R¹=C₃H₇, R²=H; Va,b,d,e,gXIIIa,b,d,e,gXVIIb XXb, g R=CF₃, R¹=R²=H; VId, XIVd R=CF₃, R¹=C₂H₅, R²=H; VIIe XVe R=CH₃, R¹=C₆H₁₃, R²=H; IXa–f Xa,b, c XIb, XIIe, XIIIa,b,e,g dXIVd, XVe X=NH₂; XVIb,c XVIIb XVIIIb X=CH₃; XIXb–d,g, XXb, g, XXIb, XXIIb, XXIIIg X=H

The reaction requires prolonged boiling of the corresponding chromone (I-VII) with 2 moles of amidine and 3 moles of sodium ethylate in absolute ethanol. It is convenient to monitor the course of the reaction by TLC. In 5-10 min after the reaction of the starting components begins, the reaction mixture is manifested on the chromatogram as two spots, one corresponding to products IX-XXIII and the other corresponding to intermediate VIII, which produces a color reaction with a solution of iron (III) chloride. The reaction mixture is boiled until the spot for intermediate VIII disappears in the chromatogram.

The prepared derivatives of the pyrimidine series (Table 1) are colorless or light yellow high-melting crystalline substances which are very soluble in polar organic solvents.

*For Communication 9, see [1].

T. G. Shevchenko Kiev State University, Kiev 252017. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1542-1550, November, 1985. Original article submitted November 6, 1984.

0009-3122/85/2111-1273$09.50

TABLE 1. Characteristics of 4-(2-Hydroxyphenyl)-5-heteroaryl(aryl)pyrimidines IX-XIII

Compound	mp*, °C	PMR spectrum, δ, ppm (DMSO-D_6)								Found, %		Empirical formula	Calculated, %		Yield, %
		protons from phenol part†					protons from pyrimidine part		Protons from thiazole, pyrazole, or p-substituted benzene ring						
		2-OH, s	3-R^2, s	4-OMe, s	5-R^1, dd	6-H, d	2-X, s	6-R, s		N	S(Br)		N	S(Br)	
IXa‡	249—250	9,86	6,58	3,83	6,46	7,14	9,86	8,93	2-H 9,16, d; 5-H 7,25, d	16,4	9,4	$C_{14}H_{12}N_4O_2S\times$ $\times 2\,H_2O$	16,6	9,5	75
IXb	180—181	11,96	6,52	3,88	6,35	7,00	7,19	8,59	2-CH_3 2,77, s; 5-H 7,10, s	17,5		$C_{14}H_{14}N_4O_2S$	17,8		63
IXc	194—195	11,35	6,32	3,62	6,19	6,88	6,96	8,49	2-C_6H_5 *o*-H 7,55, m; *m,p*-H 7,32, m; 5-H 7,10, s	14,3	8,5	$C_{20}H_{16}N_4O_2S$	14,1	8,5	53
IXd	191—192	12,39	6,45	3,73	6,17	6,89	6,09	8,25	2,6-H 7,27, s; 3,5-H 7,27, s; 4-H 7,27, s	14,2		$C_{17}H_{15}N_3O_2$	14,3		51
IXe	238—239	11,76	6,43	3,72	6,27	6,95	7,08	8,23	2,6-H 7,16, d; 3,5-H 7,53, d; 4-Br	11,1	(21,3)	$C_{17}H_{14}N_3BrO_2$	11,1	(21,5)	68
IXf	188—189	9,65	6,13	3,70	6,13	(3,46)	6,70	8,29	2,6-H 7,22, d; 3,5-H 6,90, d; 4-OCH_3 3,70, s	11,5		$C_{19}H_{19}N_3O_4$	11,9		57
Xa	205—206	12,46	6,52	3,86	0,84, t, 2,32, q	6,64, s	7,25	8,46	2-H 9,18, d; 5-H 7,53, d 2-CH_3 2,63, s; 5-H 7,13, s	17,2	9,7	$C_{16}H_{16}N_4O_2S$	17,1	9,8	59
Xb	194—195	12,41	6,36	3,77	0,84, t 2,22, q	6,59, s	7,04	8,25	2-C_6H_5 *o*-H 7,85, m; *m,p*-H 7,44, m; 5-H 7,44, s	16,5	9,2	$C_{17}H_{18}N_4O_2S$	16,4	9,4	52
Xc	196—197	12,24	6,50	3,69	0,77, t, 2,26q	6,82, s	7,22	8,31	2-CH_3 2,74, s; 5-H 6,90, s	13,9	8,1	$C_{22}H_{20}N_4O_2S$	13,9	7,9	68
XIb	184—185	11,58	(3,80)	3,89	6,48	6,80	7,11	8,59	2,6-H 7,14, d; 3,5-H 7,60, d, 4-Br	16,4	9,6	$C_{16}H_{16}N_4O_3S$	16,3	9,3	75
XIIe	179—180	12,90	6,43	3,75	0,67, t, 1,01, m, 2,01, t,	6,39, s	7,07	2,10	2-H 9,00, d, 5-H 7,41, d	9,9	(18,7)	$C_{21}H_{22}BrN_3O_2$	9,8	(18,7)	60
XIIIa	265—267	11,04	6,28	3,64	6,07	6,59	7,50	—	2-CH_3 2,75, s, 5-H 7,32, s	15,2	8,7	$C_{15}H_{11}F_3N_4O_2S$	15,2	8,7	78
XIIIb	199—200	11,49	6,44	3,82	6,23	6,80	7,67	—	2,6-H 7,27, s; 3,5-H 7,27, s; 4-H 7,27, s	14,4	8,4	$C_{16}H_{13}F_3N_4O_2S$	14,6	8,4	60
XIIId	177—178	10,61	6,35	3,70	6,19	6,83	7,46	—	2,6-H 7,13, d; 3,5-H 7,49 d; 4-Br	11,5		$C_{18}H_{14}F_3N_3O_2$	11,6		56
XIIIe	193—195	10,22	6,33	3,67	6,28	6,90	7,41	—	1-C_6H_5 *o*-H 7,77, m; *m,p*-H 7,22, m; 3-H 8,24, s; 5-H 7,49, s	9,4	(18,4)	$C_{18}H_{13}F_3BrN_3O_2$	9,5	(18,2)	59
XIIIg	162—163	10,28	6,35	3,70	6,26	7,03	7,40	—		16,4		$C_{21}H_{16}F_3N_5O_2$	16,4		86
XIVd	181—182	11,39	6,36	3,71	0,75, t, 2,18, q	6,52, s	7,45	—	2,6-H 7,24, s; 3,5-H 7,24, s; 4-H 7,24, s	10,9		$C_{20}H_{18}F_3N_3O_2$	10,8		70
XVe	171—172	12,82	6,47	3,76	0,89, t 1,16, m, 2,08m	6,39, s	6,97	2,10	2,6-H 7,15, d; 3,5-H 7,57, d; 4-Br	9,0	(17,2)	$C_{24}H_{28}BrN_3O_2$	8,9	(17,0)	64
XVIb	130—132	10,48	6,46	3,87	6,53	7,13	2,81	9,01	2-CH_3 2,81, s; 5-H 6,98, s	13,5	10,4	$C_{16}H_{15}N_3O_2S$	13,4	10,2	61
XVIc	190—191	10,20	6,37	3,70	6,37	7,03	2,64	8,98	2-C_6H_5 *o*-H 7,76, m; *m,p*-H 7,39, m; 5-H 7,22, s	11,3	8,6	$C_{21}H_{17}N_3O_2S$	11,1	8,5	39
XVIIb	125—126	10,32	6,40	3,77	6,30	6,93	2,87	—	2-CH_3 2,69, s 5-H 7,32, s	11,2		$C_{17}H_{14}F_3N_3O_2S$	11,0		60
XVIIIb	150—151	9,69	(3,73)	3,91	6,59	6,95	2,76	9,04	2-CH_3 2,76, s, 5-H 6,89, s	12,3	9,5	$C_{17}H_{17}N_3O_2S$	12,2	9,3	44
XIXb	132—133	10,32	6,52	3,89	6,58	7,24	9,21	9,21	2-CH_3 2,81, s; 5-H 7,07, s	14,1	10,9	$C_{15}H_{13}N_3O_2S$	14,0	10,7	64
XIXc	145—146	9,92	6,31	3,65	6,42	7,15	9,14	9,09	2-C_6H_5 *o*-H 7,78, m; *m,p*-H 7,36, m; 5-H 7,25, s	11,8	8,9	$C_{20}H_{15}N_3O_2S$	11,6	8,9	28
XIXd	125—126	10,49	6,35	3,73	6,43	7,14	9,24	8,76	2,6-H 7,33, s; 3,5-H 7,33, s; 4-H 7,33, s	10,3		$C_{17}H_{14}N_2O_2$	10,1		51
XIXg	128—129	9,97	6,57	3,87	6,59	7,29	9,14	9,09	1-C_6H_5 *o*-H 7,87, m; *m,p*-H 7,29, m; 3-H 8,66, s; 5-H 7,43, s	16,2		$C_{20}H_{16}N_4O_2$	16,3		87
XXb	120—122	10,15	6,43	3,77	6,35	6,98	9,44	—	2-CH_3 2,69, s; 5-H 7,36, s	11,4		$C_{16}H_{12}F_3N_3O_2S$	11,4		56
XXg	166—167	9,81	6,35	3,72	6,43	7,17	9,41	—	1-C_6H_5 *o*-H 7,79, m; *m,p*-H 7,31, m 3-H 8,40, s; 5-H 7,56, s	13,5		$C_{21}H_{15}F_3N_4O_2$	13,6		62
XXIb	131—132	9,50	(3,74)	3,91	6,68	7,06	9,23	9,23	2-CH_3 2,78, s; 5-H 7,00, s	12,8	9,8	$C_{16}H_{15}N_3O_3S$	12,8	9,7	46
XXIIb	175—176	(1,95)	6,52	3,76	1,03, t; 2,53, q	6,68	6,74	8,54	2-CH_3 2,63, s; 5-H 7,04, s	14,8	8,6	$C_{19}H_{20}N_4O_3S$	14,6	8,3	68 75
XXIIIg	161—162	(2,05)	6,79	3,85	6,79	7,21	9,15	8,89	1-C_6H_5 *o*-H 7,52, m, *m,p*-H 7,24, m 3-H 7,71, s; 5-H 7,66, s	14,4		$C_{22}H_{18}N_4O_3$	14,5		

*Compounds IXb-f, Xa, b, c, XIb, XIIe, XIIIb, d, e, g, XIVd, XVe, XIXd, g, and XXIIb were crystallized from alcohol; IXa and XIIb were crystallized from aqueous alcohol; XIIIa, XVIc, and XXg were crystallized from n-propanol; XVIb and XIXb, c were crystallized from aqueous acetone; XVIIb and XVIIIb were crystallized from carbon tetrachloride; XXIIIg was crystallized from benzene.

†The values of the chemical shifts of the CH_3O group (for compounds IXf, XIb, XVIIIb, and XXIb) and the $OCOCH_3$ group (for XXIIb and XXIIIg) are reported in parentheses.

‡The spectrum was recorded while heating.

In contrast to the starting compounds, they are also soluble in aqueous alkalis, indicating the presence of a phenol hydroxyl, and produce a color reaction (yellow coloring) with an alcohol solution of titanium(IV) chloride which can serve as a sign of the presence of an intramolecular hydrogen bond (IMHB) involving the hydrogen atom in the phenol hydroxyl and the nitrogen atom in the pyrimidine ring in the products of recyclization.

To confirm the structure of the prepared compounds, their PMR spectrum in DMSO-D_6 were recorded; the results of the measurements are reported in Table 1. A distinctive feature of compounds IX-XV which contain an amino group is the separate absorption of protons from the OH and NH_2 groups due to slow proton exchange. A two-proton slightly broadened singlet of the amino group in compounds IXa-f, Xa-c, XIb, XIIe, XIIIa, b, d, e, g, XIVd, XVe, and XXIIb appears in the 6.96-7.67 ppm region and quickly disappears on addition of deuterium oxide. The signals from the NH_2 group in pyrimidines XIIIa, b, d, e, g and XIVd fall into the weaker field (7.40-7.67 ppm) due to the effect of the CF_3 substituent. The chemical shift of the phenol hydroxyl proton is essentially dependent on the nature of the substituents in the pyrimidine part of the molecules of these compounds. In derivatives XIVb, c, XVIIb, XVIIIb, XIX-b-d, g, XXb, g, and XXIb, which contain no amino group, the proton of the hydroxyl group absorbs in the region of 9.50-10.48 ppm. The more basic compounds with an amino group in position 2 of the pyrimidine ring* (IXb-e, Xa-c, XIb, XIIe, XIIIa, b, d, e, g, XIVd, XVe) produce a signal from the OH group which is usually shifted to the weaker field (10.22-12.90 ppm). This confirms the formation of a stable IMHB (compare with [7]) due to the hydrogen atom of the phenol hydroxyl and the nitrogen atom in position 3 of the pyrimidine ring. This property is more characteristic of compounds with an amino group and is not only dependent on the nature of the substituents in the immediate vicinity of the groups forming the hydrogen bond but also those at a greater distance from them. Substitution of the phenyl substituent in position 5 of the pyrimidine nucleus (compound IXd) by a thiazole residue (compounds IXb, c) thus results in a diamagnetic shift of the signal of the OH group by 0.5-1 ppm. A similar effect is observed in the series of compounds Xa-c, XIIe, and XVe. Introduction of an alkyl substituent (C_2H_5, C_3H_7) in position 5 of the phenol part of the molecule (compounds Xa-c, XIIe) causes a marked paramagnetic shift of the signal of the OH group in comparison to compounds with a free position 5 (IXb-e). The effect of the more remote substituents can be followed in pairs of compounds IXd and IXe (introduction of bromine in the phenyl substituent in position 5), IXb and XIIIb, IXd and XIIId, and IXe and XIIIe (introduction of a CF_3 group in position 6 of the pyrimidine ring).

These effects can be explained by studying stereochemical models of the molecules of these compounds, which suggests that the aromatic nuclei are noncoplanar and the substituent in position 5 goes out of the plane of the pyrimidine ring to a greater degree. The phenol ring occupies a more or less fixed position with respect to the pyrimidine ring due to the formation of IMHB. In compound IXf, the formation of this bond is impossible for steric reasons, and the signal of the phenol hydroxyl proton thus falls into the same region as for the other compounds which form a weak IMHB or do not form this bond due to the low basicity of the pyrimidine ring (compounds XVIb, c, XVIIb, XVIIIb, XIXb-d, g, XXb, g, XXIb with no NH_2 group in position 2). At the same time, methoxy derivative XIb, which is an isomer of compound IXf, produces a phenol hydroxyl proton signal at 11.58 ppm, indicating the insignificant weakening of the IMHB by the methoxy group in position 3 (compare with IXb).

The change in the mutual position of the aromatic rings can also be judged by the shift in the signal of the 6-H proton caused by the introduction of different substituents in the phenol part of the molecule and in the heterocyclic nuclei. There is no paramagnetic shielding of the 6-H phenol proton by the $N_{(3)}$ atom in the pyrimidine ring closest to it in any of the compounds studied. The signal of this proton is observed in the region of 6.39-7.29 ppm, i.e., it is shifted to the strong field (compare with data in [12]). This is due to the fact that the introduction of a bulky CH_3 or CF_3 group in position 6 of the pyrimidine ring (XIIe, XIIIa, b, d, e, g, XIVd, XVe, XVIIb, XXb, g) forces the aryl (heteroaryl) nucleus into a position almost at a right angle to the plane of the pyrimidine ring. Due to this, the 6-H proton in the phenol part of the molecule falls into the region of diamagnetic shielding by the ring currents of the π electrons of the aromatic ring near it (phenyl, thiazole, pyrazole), and the signal of this proton is shifted to the strong field. In the case of thiazole derivatives (XIIIa, b, XVIIb, XXb), the effect of the CF_3 group on the chemical shift of the 5-H thiazole proton, whose signal undergoes a 0.3-0.4 ppm paramagnetic shift in comparison to compounds containing no CF_3 groups (IXa, b, XVIb, XIXb), is marked.

*The introduction of an amino group in position 2 of the pyrimidine ring results in an increase in the pKa by more than two units [11].

TABLE 2. Characteristics of Ketones XXIVa, c–e and XXV–4–XXVIIIe

Compound	mp.*, °C	PMR spectrum, δ, ppm (DMSO-D_6)							Found, Br(S), %	Empirical formula	Calc., Br(S), %	Yield, %
		protons of phenol part					$COCH_2Ar$ (Het) protons					
		2-OH,s	3-H,s	4-OH,s	5-R^1	6-H,s	CH_2,s	Ar(Het)				
XXIVa	157—158	12,24	6,27	10,59	1,05, t; 2,45, q	7,68	4,42	8,91, d; 7,43, d	(12,1)	$C_{13}H_{13}NO_3S$	(12,2)	58
XXIVc	189—190	12,30	6,36	10,62	1,09, t; 2,51, q	7,74	4,46	2-C_6H_5, *o*-H 7,74, m; *m,p*-H 7,34, m; 5-H 7,38, s	(9,5)	$C_{19}H_{17}NO_3S$	(9,4)	71
XXIVd	100—102	12,47	6,45	10,72	1,21,t; 2,69, q	7,83	4,42	7,30, s		$C_{16}H_{16}O_3$ †		95
XXIVe	176—177	12,25	6,30	10,71	6,99, s	7,66, e	4,31	7,37, d; 7,63, d	26,0	$C_{14}H_{11}BrO_3$	26,0	83
XXVe	105—106	12,22	6,41	10,62	0,94, t, 1,59, m; 2,52, m	7,74	4,40	7,25, d; 7,52, d	23,0	$C_{17}H_{17}BrO_3$	22,9	40
XXVIe	107—108	12,30	6,39	10,59		7,73	4,36	7,26, d; 7,52, d	20,8	$C_{20}H_{23}BrO_3$	20,5	55
XXVIIe	100—101	12,52	6,40	3,85‡	0,92, t; 1,61, m; 2,56, m	7,49	4,22	7,13, d; 7,48, d	22,1	$C_{18}H_{19}BrO_3$	22,0	96
XXVIIIe	75—76	12,64	6,39	3,85‡	0,92, t, 1,37, m; 2,54, m	7,51	4,17	7,10, d; 7,48, d	20,0	$C_{21}H_{25}BrO_3$	19,9	98

*Compounds XXIVd and XXVIIe were crystallized from hexane, and XXIVa, c, e, XXVe, XXVIe, and XXVIIIe were crystallized from alcohol.

†Found: C 74.6; H 6.2%. Calculated: C 75.0; H 6.3%.

‡Chemical shift of the CH_3O group.

TABLE 3. Characteristics of 3-Aryl- and 3-Heteroarylchromones Ie, IIa, c, IVe, Ve, VId, VIIe, XXIXd, e, and XXXa, c, e

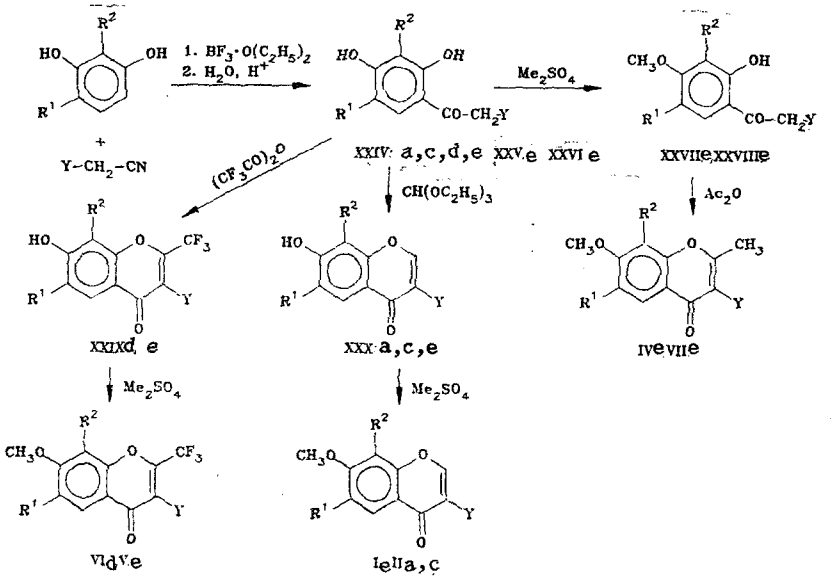
Compound	mp *, °C	PMR spectrum, δ, ppm† ($CDCl_3$)						Found, %			Empirical formula	Calc., %			Yield, %
		chromone ring protons					thiazole or p-substituted benzene ring protons	C(S)	H(N)	Br(F)		C(S)	H(N)	Br(F)	
		2-H, s or 2-Me, s	5-H,s	6-R^1	7-OH,s or 7-OMes	8-H,s									
Ie	212—213	7,93	8,20, d	7,04, dd	3,96	6,88	7,51, s			24,5	$C_{16}H_{11}BrO_3$			24,2	80
IIa	194—195	8,88	7,99	1,25, t 2,72, q	3,92	6,78	2-H 8,71, d; 5-H 8,55, d	(11,2)	(5,2)		$C_{15}H_{13}NO_3S$	(11,1)	(4,9)		88
IIc	184—185	8,94	7,98	1,23, t, 2,66, q	3,81	6,68	2-C_6H_5 *o*-H 7,92, m; *m,p*-H 7,34, m; 5-H 8,52, s	(9,0)			$C_{21}H_{17}NO_3S$	(8,8)			96
IVe	192—193	2,34	7,89	0,98, t; 1,68, m; 2,72, m	3,96	6,77	7,13, d; 7,52, d			20,9	$C_{20}H_{19}BrO_3$			20,7	89
Ve	153—154	—	8,11, d	7,01, dd	4,00	6,95	7,15, d; 7,58, d			19,9	$C_{17}H_{10}BrF_3O_3$			20,0	78
VId	162—163	—	7,92	1,24, t; 2,74, q	3,95	6,87	7,35, s	65,6	4,6	(16,4)	$C_{19}H_{15}F_3O_3$	65,5	4,3	(16,3)	87
VIIe	167—168	2,28	7,89	0,88, t; 1,33, m, 2,68, m	3,92	6,76	7,15, d; 7,53, d			19,2	$C_{23}H_{25}BrO_3$			18,7	98
XXIXd	255—256	—	7,88	1,24, t; 2,74, q	11,20	7,06	7,51, s	64,8	4,1	(17,2)	$C_{18}H_{13}F_3O_3$	64,7	3,9	(17,1)	98
XXIXe	253—254	—	7,97, d	7,02, dd	11,20	6,99	7,28, d; 7,71, d			20,8	$C_{16}H_8BrF_3O_3$			20,8	89
XXXa	237—238	9,03	7,91	1,23, t; 2,70, q	10,93	6,98	2-H 9,22, d; 5-H 8,61, d	(12,1)	(5,2)		$C_{14}H_{11}NO_3S$	(11,7)	(5,1)		97
XXXc	270—271	9,01	8,17	1,47, t 3,01, q		7,28	2-C_6H_5 *o*-H 8,07, m; *m,p*-H 7,78, m; 5-H 8,28, s	(9,1)			$C_{20}H_{15}NO_3S$	(9,1)			85
XXXe	270—271	8,44	8,07, d	7,04, dd	10,91	6,94	7,59, s			25,5	$C_{15}H_9BrO_3$			25,2	93

*Compounds IIa, c, IVe, VId, VIIe, XXIXd, and XXXc, e were crystallized from alcohol, Ie was crystallized from dioxane, and Ve was crystallized from acetone.

†The PMR spectra of compounds XXIXdd, e–XXXa, e were made in DMSO-D_6 and the spectrum of XXXc was made in CF_3COOH.

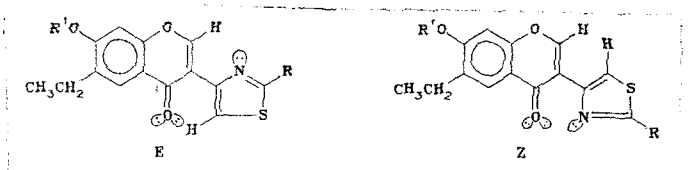
The reaction of pyrimidines Xb and XIXg with acetic anhydride results in the formation of monoacetyl derivatives XXIIb and XXIIIg. The position of the $COCH_3$ group in their molecules was established from the PMR spectra in $CDCl_3$: the signal of the phenol hydroxyl proton is absent, and the signal of the NH_2 group (6.74 ppm) remains in the same region of the spectrum as in the initial compounds (7.04 ppm).

The initial 3-aryl- and 3-hetero-7-methoxychromones I-VIIa-g, required for the synthesis of pyrimidines IX-XXIIIa-g, like the known 3-(4-thiazolyl)-7-methoxychromones (Ia-c, IIb, Va, b) [13, 14], 7-methoxyisoflavones (Id, f) [15], 2-trifluoromethyl-7-methoxyisoflavone (Vd) [16], 3-(1-phenyl-4-pyrazolyl)-7-methoxychromones (Ig, Vg) [17, 18], 3-(2-methyl-4-thiazolyl)-7,8-dimethoxychromone (IIIb) [19], and the new 7-methoxy- and 6-alkyl-7-methoxyisoflavones Ie, IVe, Ve, VId, VIIe, and 3-(4-thiazolyl)-6-ethyl-7-methoxychromones IIa, c, were prepared by cyclization of ketones XXIVa, c, d, e, XXVe-XXVIIIe to 3-aryl- and 3-heteroaryl-7-hydroxychromones XXIXd, e, and XXXa, c, e with their subsequent methylation. Ketones XXIVa, c, d, e, XXVe, and XXVIe are in turn formed with good yields as a result of condensation of the derivatives of resorcin with aryl- and heteroarylacetonitriles (see scheme).



XXIVa,c, XXIVd[20], XXIXd, XXXa,c $R^1=C_2H_5$, $R^2=H$; XXIVe, XXIXe, XXXe $R^1=R^2=H$; XXVe, XXVIIe $R^1=n\text{-}C_3C_7$, $R^2=H$; XXVIe, XXVIIIe $R^1=n\text{-}C_6H_{13}$, $R^2=H$

The physical constants, analytic, and spectral data for compounds Ie, IIa, c, IVe, Ve, VId, VIIe, XXIVa-e, XXVe-XXVIIIe, XXIXd, e, and XXXa, c, e are reported in Tables 2 and 3. The structure of these ketones and chromones was confirmed by the PMR spectra. The hydrogen atom in the hydroxyl group in position 2, which participates in the formation of an IMHB of the chelate type, absorbs in the narrow interval of 12.24-12.64 ppm. The hydrogen atom of the phenol hydroxyl in position 4 forms an intermolecular hydrogen bond with the solvent and absorbs at 10.59-10.72 ppm. In contrast to the starting ketones, there is no signal of the phenol hydroxyl in position 2 but instead a singlet of the 2-CH_3 methyl group or the 2-H proton of the pyrone nucleus in the PMR spectra of the chromones. As a result of methylation of chromones XXIXd, e and XXXa, c, e by dimethyl sulfate, 7-methoxychromone Ie, IIa, c, Ve, and VId are formed, and their PMR spectra contains no signal of the 7-OH phenol hydroxyl proton; it is instead replaced by the three-proton singlet of the methyl group in the 3.8-4.0 ppm region.



II, XXX a R=H, c R=C_6H_5; IIa,c $R^1=CH_3$; XXXa,c $R^1=H$

Based on the PMR spectra of the thiazole analogs of isoflavones IIa, c and XXXa, c, it is possible to determine in which of the two possible coplanar conformations (E and Z) these compounds are found. Conformation E is preferred, since the nitrogen and oxygen atoms of like charge are farthest from each other, and the thiazole 5-H and chromone ring 2-H hydro-

gen atoms are subject to a strong free interaction with the carbonyl oxygen atom and the thiazole nucleus nitrogen atom as a result. This interaction causes a marked paramagnetic shift in the signals of these protons by an average of 1.1-1.3 ppm.

The PMR spectra of the compounds in this series thus permit confirming the structure of the isoflavones, their heterocyclic analogs, and the products of their recyclization and determining the degree of perturbation of the coplanarity of the aromatic nuclei, the presence and strength of the IMHB, and the structure of the preferred conformer.

EXPERIMENTAL

The individuality of the prepared compounds and the course of the reactions were controlled by TLC on Silufol UV-254 plates in a benzene–ethanol system, 9:1. The PMR spectra were made on a ZKR-60 spectrometer (60 MHz) with TMS as the internal standard.

The constants and yields of the compounds are reported in Tables 1-3.

2-Amino-4-(2-hydroxy-4-methoxyphenyl)-5-(2-methyl-4-thiazolyl)pyrimidine (IXb). Here 1.91 g (0.02 mole) of guanidine hydrochloride was added to a solution of 0.92 g (0.04 mole) of sodium in 50 ml of absolute alcohol and filtered sodium chloride sediment after 5 min. Then 2.73 g (0.01 mole) of 3-(2-methyl-4-thiazolyl)-7-methoxychromone was added to the filtrate [14] and the reaction mixture was boiled for 20 h. The dry residue after vacuum evaporation of the alcohol was dissolved in 100 ml of cold water and acidified with dilute hydrochloric acid to pH 6. The precipitated product was filtered off and dried. Yield of 2.65 g (84%). After crystallization from alcohol, 2 g of a product in the form of large yellow prisms were obtained.

Compounds IXa, c-e, Xa-c, XIb, XIIe, XIIIa, b, d, e, g, XIV, and XVe were prepared in a similar manner. In the preparation of pyrimidines XVIb, c, XVIIb, and XVIIIb, acetamidine was used instead of guanidine, and formamidine was used in the preparation of compounds XIXb, c, g, XXb, g, XXIb, XXIIb, and XXIIIg.

2,4-Dihydroxy-5R-deoxybenzoins (XXIVd, e, XXVe, XXVIe). A fast current of dry hydrogen chloride was passed through a mixture of 0.1 mole of the corresponding phenylacetonitrile and 4-alkylresorcinol (0.11 mole) in 80 ml of boron trichloride etherate while stirring over 8-10 h, and the mixture was left at room temperature overnight. The reaction mixture was then placed in 300 ml of hot water and held at 90°C and pH 1 for 0.5-1 h. The sediment was filtered from the boiling solution and carefully washed with water to a neutral reaction.

α-(4-Thiazolyl)-2,4-dihyroxy-5-ethylacetophenone (XXIVa) and α-(2-phenyl-4-thiazolyl)-2,4-dihydroxy-5-ethylacetophenone (XXIVc) were prepared according to [19], and 2-hydroxy-4-methoxy-5-propyl-4'-bromodeoxybenzoin (XXVIIe) and 2-hydroxy-4-methoxy-5-hexyl-4'-bromodeoxybenzoin (XXVIIIe) were prepared according to [17].

7-Hydroxychromones XXXa, c, e. A mixture of 20 moles of the corresponding ketone XXIVa, c, e, 20 ml of ethyl o-formate, 20 ml of pyridine, and 40 drops of piperidine was heated for 4-10 h at 120-130°C. The reaction mixture was diluted with 300 ml of water, and the precipitated sediment was filtered off and washed with water. It was crystallized from alcohol.

2-Methyl-6-propyl-7-methoxy-4'-bromoisoflavone (IVe), 2-methyl-6-hexyl-7-methoxy-4'-bromoisoflavone (VIIe), 2-trifluoromethyl-6-ethyl-7-hydroxyisoflavone (XXIXd), and 2-trifluoromethyl-7-hydroxy-4'-bromoisoflavone (XXIXe) were prepared according to [18], and 7-methoxy-4'-bromoisoflavone (Ie), 3-(4-thiazolyl)-6-ethyl-7-methoxychromone (IIa), 3-(2-phenyl-4-thiazolyl)-6-ethyl-7-methoxychromone (IIc), and 2-trifluoromethyl-7-methoxy-4'-bromoisoflavone (Ve) and 2-trifluoromethyl-6-ethylisoflavone (VId) were prepared according to [14].

LITERATURE CITED

1. V. P. Khilya, I. P. Kupchevskaya, A. L. Kazakov, T. M. Tkachuk, and G. M. Golubushina, Khim. Geterotsikl. Soedin., No. 3, 321 (1982).
2. T. V. Ramwell, D. S. A. Sherrat, and V. E. Leonard, in: Biochemistry of Phenolic Compounds, J. Harborne, ed., Academic Press (1964).
3. W. Baker, G. G. Clarke, and J. B. Harborne, J. Chem. Soc., No. 3, 998 (1954).
4. C. Morin and R. Beugelmans, Tetrahedron, 33, 3183 (1977).
5. W. Basinski and Z. Jerzmanowska, Roczn. Chem., 48, 989 (1974).
6. V. Szabo, J. Borda, and L. Losonczi, Acta Chim. Acad. Sci. Hung., 97, 69 (1978).
7. V. P. Khilya, M. Yu. Kornilov, I. P. Kupchevskaya, and V. F. Vakulenko, Ukr. Khim. Zh., 44, 265 (1978).

8. V. P. Khilya, V. F. Vakulenko, and I. P. Kupchevskaya, Khim. Geterotsikl. Soedin., No. 1, 25 (1979).
9. K. Takagi and M. Hubert-Habart, Bull. Soc. Chim. Fr., 369 (1977).
10. W. Löwe, Ann. Chem., No. 6, 1050 (1977).
11. A. Albert, R. Goldacre, and J. N. Phillips, J. Chem. Soc., No. 12, 2240 (1948).
12. V. P. Krivolapov and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 7, 987 (1979).
13. V. P. Khilya, A. L. Kazakov, G. M. Golubushina, V. N. Mel'nik, and T. M. Tkachuk, Khim.-Farm. Zh., 15, 40 (1981).
14. V. P. Khilya, V. Sabo, L. G. Grishko, D. V. Vikhman, F. S. Babichev, and V. A. Dymovich, Khim. Geterotsikl. Soedin., No. 8, 1030 (1975).
15. L. Farkas, Chem. Ind., No. 36, 1212 (1957).
16. V. Szabó and Sz. Borbély, Acta Univ. Debrecen, Ser. Phys. Chem., 261 (1972/1973).
17. V. P. Khilya, L. G. Grishko, and T. I. Zhul', Khim. Geterotsikl. Soedin., No. 8, 1108 (1976).
18. V. P. Khilya, L. G. Grishko, T. N. Sokolova, and B. Sabo, Zh. Org. Khim., 9, 2572 (1973).
19. V. P. Khilya, N. A. Yasnikova, A. L. Kazakov, and G. M. Golubushina, Ukr. Khim. Zh., 48, 765 (1982).
20. J. Murai, Sci. Rep. Saitama Univ., 1A, 139 (1954); Chem. Abstr., 50, 981 (1956).

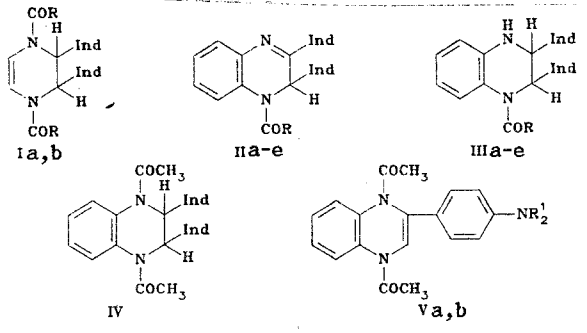
DUAL REACTIVITY OF 1,2-DISUBSTITUTED DIHYDRO-N-HETEROAROMATIC SYSTEMS. 9.* ALKALINE HYDROLYSIS AND AROMATIZATION OF N-ACTYL PARTIALLY HYDROGENATED DERIVATIVES OF PYRAZINE AND QUINOXALINE

Kh. Ya. Lopatinskaya, N. A. Klyuev, and A. K. Sheinkman

UDC 547.861.3'863.1.04:543.422

The aromatization with splitting of the N-actyl groups of 2,3-disubstituted N-acyl- and N,N'-diacyl-1,2-dihydro-, and 1,2,3,4-tetrahydropyrazines and quinoxalines under the effect of alcohol alkali was studied. A new reaction of recyclization of 1,4-diacyl-1,2,3,4-tetrahydroquinoxaline was discovered.

Aromatization of N-substituted 1,2-dihydrobenzopyridines is essentially dependent on the nature of the substituent on the ring nitrogen atom: the greater the electron-acceptor properties it has, the more difficult the reaction is [2]. N-acyl derivatives of dihydro-N-heteroaromatic compounds are most difficult to aromatize [2], especially the mono- and diacyl derivatives of dihydro- and tetrahydro-1,4-diazines [1]. It could be hypothesized that



Ia,b IIa-e IIIa-e IV Va,b

Ind=3-indolyl I—III a R=CH_3, b R=C_6H_5, c R=C_6H_4—Cl-*n*, d R=C_6H_4—NO_2-*n*, e R=C_6H_4—CH_3-*o*; V a R^1=CH_3; b R^1=C_2H_5

*Cf. [1] for Communication 8.

Dnepropetrovsk Construction Engineering Institute, Dnepropetrovsk 320300. Institute of Physical Organic Chemistry and Carbon Chemistry, Academy of Sciences of the Ukrainian SSR, Donetsk 340114. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1551-1556, November, 1985. Original article submitted June 5, 1984; revision submitted February 12, 1985.

0009-3122/85/2111-1279$09.50