SYNTHESIS AND STRUCTURE OF 5-METHYL-1-(2-R-PHENYL)-DIHYDRO-2,4(1H,3H)-PYRIMIDINEDIONES AND THEIR 2-THIONO ANALOGS

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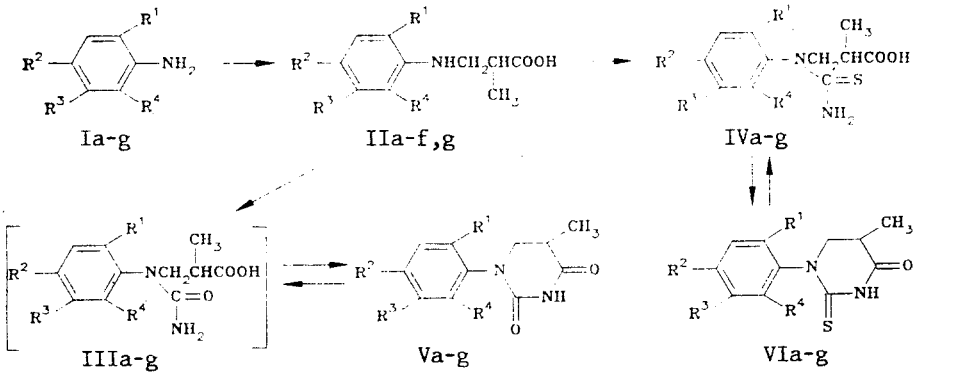
The reaction of o-substituted aromatic amines with methacrylic acid gave N-aryl-α-methyl-β-alanines, which were converted to dihydro-2,4-pyrimidinedione and dihydro-4-pyrimidinone-2-thione derivatives. The alkylation, acylation, and oximation of the dihydro-2,4-pyrimidinediones were accomplished. Conformational analysis of the compounds obtained was carried out by dynamic NMR methods.

We have previously found [3] that 6-methyl-1-(2-R-phenyl)-substituted dihydro-2,4(1H,3H)-pyrimidinediones and their 2-thiono analogs form rotational isomers; this is associated with steric hindrance to rotation of the phenyl group about the $N_{(1)}—C_{(1')}$ bond. Continuing our research on the synthesis and study of 1-aryl-substituted dihydro-2,4(1H,3H)-pyrimidinediones, we synthesized a number of V-X with substituents in the 2 position of the aromatic ring and in the 5 position of the heteroring that are capable, in our opinion, of forming rotational isomers. Compounds Va-g were synthesized from the corresponding N-aryl-α-methyl-β-alanines IIa-g or their hydrochlorides, which, in turn, were obtained by the reaction of aromatic amines Ia-g with methacrylic acid in toluene or without a solvent in the presence of hydroquinone. β-Alanines IIa-d, which are crystallize with difficulty, were isolated in the form of the hydrochlorides. The condensation of N-aryl-α-methyl-β-alanines IIa-g with urea was carried out in glacial acetic acid. The N-aryl-N-carbamoyl-β-alanines IIIa-g formed during the reaction were not isolated in individual form but were cyclized directly to give dihydro-2,4-pyrimidinedione derivatives Va-g under the influence of concentrated hydrochloric acid. 5-Methyl-1-aryldihydro-4(1H,3H)-pyrimidinone-2-thiones VIa-g were synthesized similarly using potassium thiocyanate in place of urea; the cyclization was carried out with 18% hydrochloric acid.



I—VI a $R^1=CH_3$, $R^2=R^3=R^4=H$; b $R^1=R^2=CH_3$, $R^3=R^4=H$; c $R^1=R^3=CH_3$, $R^2=R^4=H$; d $R^1=R^4=CH_3$, $R^2=R^3=H$; e $R^1=OCH_3$; f $R^1=OBz$; g $R^1=Cl$; e–g $R^2=R^3=R^4=H$

To purify V and VIa-g to remove N-substituted ureas they were dissolved in 10% sodium hydroxide solution, thereby converting them to the sodium salts of N-aryl-N-(thio)carbamoyl-β-alanines III and IVa-g. The undissolved substances, particularly the N-substituted (thio)ureas, were removed by filtration, and the filtrate was heated to the boiling point, acidified to pH 1 with hydrochloric acid, and refluxed for 5-10 min.

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TABLE 1. PMR Spectra of Va-d, f, g, VII-IX, and Their 2-Thiono Analogs VIa-g

Compound	Isomer	Chemical shifts, δ, ppm						
		5-CH_3	5*a*	6*a*	6*e*	Ph	NH	R
Va	A	1,12	2,87	3,62	3,48	7,0 . . . 7,5	9,76	2,21 (2′-CH_3)
	B	1,16	2,86	3,45	3,65	7,0 . . . 7,5	9,78	2,19 (2′-CH_3)
Vb	A	1,13	2,90	3,60	3,45	7,0 . . . 7,1	10,18	2,18 (2′-CH_3); 2,28 (4′-CH_3)
	B	1,15	2,90	3,42	3,61	7,0 . . . 7,1	10,19	2,15 (2′-CH_3); 2,28 (4′-CH_3)
Vc	A	1,10	2,92	3,61	3,46	7,0 . . . 7,2	9,78	2,15 (2′-CH_3); 2,27 (5′-CH_3)
	B	1,12	2,90	3,45	3,62		9,80	2,13 (2′-CH_3); 2,27 (5′-CH_3)
Vd	A	1,14	2,92	3,51	3,34	7,0 . . . 7,2	9,76	2,16 (2′-CH_3); 2,20 (6′-CH_3)
	B							
Vf	A	1,05	2,69	3,43	3,55	6,9 . . . 7,5	9,88	3,20 (OCH_2); 6,9 . . . 7,5 (Ph)
	B							
Vg	A	1,11	2,86	3,56	3,51	7,2 . . . 7,6	9,62	
	B	1,15	2,86	3,48	3,67	7,2 . . . 7,6	9,64	
VIa	A	1,12	2,95	3,74	3,64	7,2 . . . 7,4	12,20	2,20 (2′-CH_3)
	B	1,14	3,06	3,65	3,73	7,2 . . . 7,4	12,23	2,18 (2′-CH_3)
VIb	A	1,14	2,96	3,72	3,63	7,0 . . . 7,2	10,18	2,19 (2′-CH_3); 2,28 (4′-CH_3)
	B	1,16	3,06	3,67	3,69	7,0 . . . 7,2	10,20	2,17 (2′-CH_3); 2,28 (4′-CH_3)
VIc	A	1,12	2,96	3,72	3,66	7,0 . . . 7,2	8,86	2,18 (2′-CH_3); 2,28 (5′-CH_3)
	B	1,12	3,04	3,68	3,70	7,0 . . . 7,2	8,90	2,16 (2′-CH_3); 2,28 (5′-CH_3)
VId	A	1,13	3,00	3,74	3,55	7,0 . . . 7,2	9,88	2,17 (2′-CH_3); 2,20 (6′-CH_3)
	B							
VIe	A	1,08	2,84	3,56	3,63	6,9 . . . 7,4	8,88	3,80 (OCH_3)
	B	1,10	2,98	3,54	3,69	6,9 . . . 7,4	8,86	3,79 (OCH_3)
VIf	A	1,06	2,63	3,62	3,69	7,0 . . . 7,5	8,88	3,29 (OCH_2) 7,0 . . . 7,5
	B	1,07	2,95	3,64	3,75	7,0 . . . 7,5	8,88	3,29 (OCH_2) (Ph)
VIg	A	1,13	2,96	3,80	3,68	7,2 . . . 7,7	8,82	
	B	1,16	3,07	3,72	3,74	7,2 . . . 7,7	8,80	
VII	A	1,18	2,88	3,46	3,32	7,0 . . . 7,2	10,08	2,14 (2′-CH_3); 2,24 (5′-CH_3)
	B	1,16	2,89	3,46	3,66	7,0 . . . 7,2	10,00	2,14 (2′-CH_3); 2,24 (5′-CH_3)
VIII	A	1,24	3,00	3,50	3,60	7,0 . . . 7,2	9,92	2,14 (2′-CH_3); 2,28 (5′-CH_3)
	B	1,20	3,00	3,36	3,80	7,0 . . . 7,2	9,92	2,14 (2′-CH_3); 2,08 (5′-CH_3)
IX	A	1,24	3,34	3,94	3,66	7,0 . . . 7,2		2,20 (2′-CH_3); 2,28 (5′-CH_3) 7,5 . . . 7,8 (Ph)
	B	1,24	3,36	3,86	3,76	7,0 . . . 7,2		2,16 (2′-CH_3); 2,28 (5′-CH_3) 7,5 . . . 7,8 (Ph)

TABLE 2. Spin-Spin Coupling Constants of the Protons in the Dihydropyrimidine Ring and Populations (calculated from them) of the Rotations Isomers in 5-Methyl-1-aryldihydro-2,4(1H,3H)-pyrimidinediones Va-g, VII-IX, and Their Thiono Analogs VIa-g

Compound	Isomer	J, Hz				P_A, %
		5,6a	5,6e	6a,6e	5, CH_3	
Va	A	11,2	5,9	12,1	6,5	51
	B	9,1	5,6	11,7	6,5	49
Vb	A	11,5	5,6	12,2	6,5	58
	B	9,0	5,5	12,0	6,5	42
Vc	A	11,2	6,2	12,0	6,5	56
	B	11,0	6,1	12,0	6,5	44
Vd*		12,0	6,4	12,0	6,7	100
Vf*		11,6	6,1	12,6	7,0	100
Vg	A	11,2	6,0	12,0	6,4	51
	B	10,0	5,6	12,0	6,4	49
VIa	A	11,6	6,5	12,0	6,5	54
	B	11,0	6,5	12,5	6,5	46
VIb	A	11,6	6,0	12,2	6,6	58
	B	10,4	6,0	12,2	6,6	42
VIc	A	11,2	6,3	12,5	5,5	55
	B	10,4	6,3	12,5	5,5	45
VId*		12,3	6,6	13,0	6,6	100
VIe	A	10,0	6,1	12,8	6,6	58
	B	9,8	6,5	12,8	6,6	42
VIf	A	11,0	6,7	12,8	6,5	51
	B	10,6	6,5	13,0	6,5	49
VIg	A	11,0	7,0	12,0	6,5	62
	B	10,4	6,5	12,0	6,5	38
VII	A		7,6	12,0	6,5	59
	B		5,0	12,0	6,5	41
VIII	A	8,5	5,2	12,0	6,5	54
	B	6,0	4,9	12,0	6,5	46
IX	A	11,6	6,1	12,2	6,6	55
	B	11,6	6,0	12,2	6,6	45

*The values for isomers A and B are presented.

Heating 5-methyl-1-(2,5-dimethylphenyl)-5,6-dihydro-2,4(1H,3H)-pyrimidinedione (Vc) with hydroxylamine hydrochloride in a mixture of pyridine and isopropyl alcohol was used to synthesize $N_{(4)}$-hydroximino-5,6-dihydro-2-pyrimidinone VII, which, according to the PMR spectral data, as a ketoxime forms only one isomer, evidently because of the formation of an intramolecular hydrogen bond between a proton of the amido group and the hydroxy group of the C=NOH fragment. This is also confirmed by the acylation of VII, which leads only to one compound (VIII).

In the alkylation and acylation of Vc the $N_{(3)}$ atom of the amide atom of the heteroring undergoes attack to give $N_{(3)}$-methyl- and $N_{(3)}$-benzoyl derivatives IX and X.

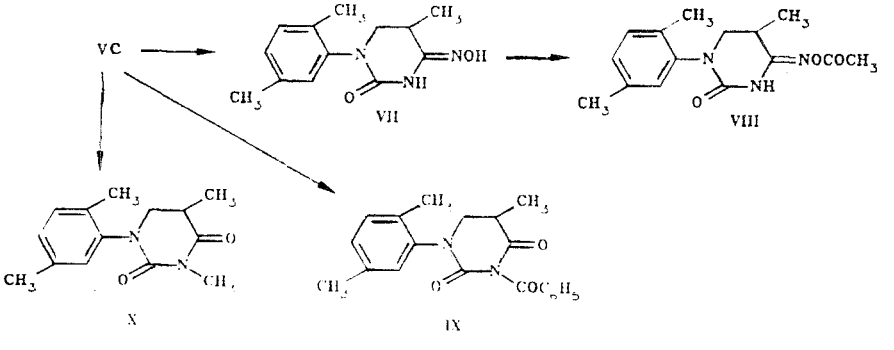

TABLE 3. ^{13}C NMR Spectra of Dihydro-2,4(1H,3H)-pyrimidinediones Va-g, VII-X, and Their 2-Thiono Analogs VIa-g

Compound	Isomer	Chemical shifts, δ, ppm											Remaining
		$C_{(2)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	5-CH_3	$C_{(1')}$	$C_{(2')}$	$C_{(3')}$	$C_{(4')}$	$C_{(5')}$	$C_{(6')}$	
Va	A	151,78	173,21	35,02	51,00	12,10	140,80	135,36	130,54	127,49	126,65	126,64	17,46 (2′-CH_3)
	B	151,59	173,38	35,02	51,00	12,83	140,80	135,66	130,54	127,25	126,84	127,62	
Vb	A	151,82	173,17	34,98	51,03	12,09	136,44	134,92	131,02	138,22	126,35	127,10	17,33 (2′-CH_3); 20,44 (4′-CH_3)
	B	151,63	173,34	34,98	51,03	12,76	136,73	135,21	131,02	138,22	126,35	127,32	
Vc	A	151,74	173,22	34,99	50,97	12,06	140,54	132,05	130,34	128,12	135,85	126,96	17,00 (2′-CH_3); 20,28 (5′-CH_3)
	B	151,55	173,37	35,01	50,97	12,69	140,59	132,36	130,31	128,02	136,07	127,86	
Vd*		151,43	173,12	34,77	49,41	12,09	139,10	135,73	128,31	128,31	127,57	135,97	16,53; 17,69 (2′,6′-CH_3)
Ve*		152,05	173,46	34,99	50,83	12,38	130,12	154,87	112,42	128,67	120,44	129,04	55,65 (OCH_3)
Vf*		152,08	173,40	35,04	50,92	12,29	130,46	153,86	113,67	129,13	120,75	129,13	69,74 (OCH_2); 136,90 (*i*); 128,38 (*o*); 127,44 (*m*); 127,84 (*n*)
Vg	A	151,70	172,99	34,96	50,63	12,00	138,95	129,81	129,81	129,24	128,03	131,41	
	B	151,70	173,24	34,96	50,63	12,48	139,10	130,16	129,78	129,10	128,14	131,86	
VIa	A	178,21	169,73	34,32	53,67	11,96	143,67	134,63	130,78	128,00	127,00	126,68	17,46 (2′-CH_3)
	B	178,52	169,92	34,13	53,81	12,31	143,67	134,80	130,78	127,30	127,10	127,89	
VIb	A	178,71	169,68	34,28	53,78	11,96	141,13	134,18	131,26	137,23	127,46	126,33	17,33 (2′-CH_3); 20,56 (4′-CH_3)
	B	178,54	169,85	34,09	53,85	12,25	141,20	134,32	131,26	137,09	126,95	127,65	17,41 (2′-CH_3);
VIc	A	178,59	169,75	34,26	53,65	11,92	141,60	131,25	130,58	128,65	136,40	126,82	16,93 (2′-CH_3); 20,32 (5′-CH_3)
	B	178,37	169,95	34,07	53,82	12,11	142,53	131,52	130,58	128,53	136,21	127,52	17,02 (2′-CH_3);
VId*		177,96	169,73	34,10	51,99	11,78	141,97	134,45	128,45	128,48	127,78	134,67	17,46; 17,80 (2′,6′-CH_3)
VIe		179,55	169,92	34,26	53,62	12,13	132,94	153,93	112,78	128,79	120,51	128,96	55,72 (OCH_3)
		179,21	170,02	34,26	53,69	12,16	133,06	154,12	112,69	128,72	120,66	129,23	55,86 (OCH_3)
VIf	A	179,63	169,87	34,29	53,65	11,78	133,26	152,94	114,06	129,16	120,75	129,00	69,80 (OCH_2); 136,82 (*i*)
	B	179,20	170,03	34,29	53,78	12,24	133,42	153,78	113,98	129,16	120,99	129,08	69,96 (OCH_2); 136,76 (*i*); 128,33, 128,38 (*o*); 127,41, 127,65 (*m*), 127,95, 127,76 (*p*)
VIg	A	179,46	169,69	34,35	53,31	11,99	141,67	129,06	130,00	127,44	128,27	130,92	
	B	179,40	169,93	34,19	53,44	12,40	141,73	129,76	129,76	126,98	126,43	131,08	
VII	A	150,20	146,93	29,87	52,55	13,75	141,20	132,16	130,25	130,25	135,83	127,70	17,07 (2′-CH_3); 20,29 (5′-CH_3); 169,70 (CO)
	B	150,20	146,98	29,63	52,55	14,95	141,20	132,35	130,25	130,25	135,91	127,34	17,07 (2′-CH_3); 20,29 (5′-CH_3);
VIII	A	154,61	149,95	29,89	51,71	14,23	140,78	132,23	130,37	128,00	136,04	127,44	17,03 (2′-CH_3); 19,30 (5′-CH_3)
	B	154,51	149,95	29,65	51,71	15,31	140,78	132,23	130,37	128,00	136,04	127,44	17,12 (2′-CH_3); 20,30 (5′-CH_3)
IX	A	150,27	170,26	35,42	50,35	11,18	139,61	131,97	130,53	128,72	136,16	126,99	
	B	150,13	172,40	35,42	50,45	11,57	139,61	132,38	130,00	128,46	136,38	128,14	
X	A	152,22	172,42	35,30	49,84	12,59	141,07	131,99	130,38	128,19	135,65	126,92	17,00 (2′-CH_3); 20,28 (5′-CH_3); 27,38 (N—CH_3)
	B	152,08	172,59	35,25	49,84	13,10	141,12	132,20	130,38	127,98	136,14	127,98	17,00 (2′-CH_3); 20,28 (5′-CH_3); 27,38 (N—CH_3)

*The values for isomers A and B are presented.

TABLE 4. Free Energies of Activation of Rotation about the $N_{(1)}$—$C_{(1')}$ Bond of Va-c, g, VII, IX, and X

Compound	Δν, Hz	T_C, K	$\Delta G^{\neq}$,* kcal/mole	Compound	Δν, Hz	T_C, K	$\Delta G^{\neq}$,* kcal/mole
Va**	7,80	320	16,8 (17,2)	VII	9,10	325	17,1 (17,2)
Vb	5,71	319	17,1 (17,4)	IX	7,95	328	17,4 (17,5)
Vc	5,83	317	17,0 (17,5)	X	17,87	335	17,2 (17,5)
Vg	10,54	320	16,8 (17,0)				

*The $\Delta G^{\neq}$ values of the corresponding 6-methyl derivatives [6] are indicated in parentheses.
**For the corresponding thiono analog VIa, $\Delta G^{\neq}$ = 18.7 kcal/mole.

TABLE 5. Physicochemical Characteristics of IIa-f, Va-g, VIa-g, and VII-X

Compound	Empirical formula	mp, °C (ethanol)	Yield, %	Compound	Empirical formula	mp, °C (ethanol)	Yield, %
IIa	$C_{11}H_{15}NO_2 \cdot HCl$	163...164	45,3	Vg	$C_{11}H_{11}ClN_2O_2$	158...159	8,0
IIb	$C_{12}H_{17}NO_2 \cdot HCl$	188...190*	47,0	VIa	$C_{12}H_{14}N_2OS$	155...157	65,8
IIc	$C_{12}H_{17}NO_2 \cdot HCl$	188...190*	29,7	VIb	$C_{13}H_{16}N_2OS$	150...151	74,1
IId	$C_{12}H_{17}NO_2 \cdot HCl$	224...225*	17,1	VIc	$C_{13}H_{16}N_2OS$	189...191	98,7
IIe	$C_{11}H_{15}NO_3$	90...91	47,0	VId	$C_{13}H_{16}N_2OS$	203...204	40,3
IIf	$C_{17}H_{19}NO_3$	61...62**	39,3	VIe	$C_{12}H_{14}N_2O_2S$	171...172	77,3
Va	$C_{12}H_{14}N_2O_2$	153...155	42,2	VIf	$C_{18}H_{18}N_2O_2S$	184...185	82,8
Vb	$C_{13}H_{16}N_2O_2$	147...149	80,1	VIg	$C_{11}H_{11}ClN_2O$	164...165	13,0
Vc	$C_{13}H_{16}N_2O_2$	179...181	87,1	VII	$C_{13}H_{17}N_3O_2$	225...226***	79,3
Vd	$C_{13}H_{16}N_2O_2$	193...194	61,2	VIII	$C_{15}H_{19}N_3O_3$	222...224*	83,3
Ve	$C_{12}H_{14}N_2O_3$	173...175	57,0	IX	$C_{20}H_{20}N_2O_3$	128...130	65,5
Vf	$C_{18}H_{18}N_2O_3$	185...186	42,9	X	$C_{11}H_{18}N_2O_2$	86...88	97,6

*From CH_3COOH.
**From hexane.
***From dioxane.

Compounds V-X, like 6-methyl-1-(2-R-phenyl)dihydropyrimidine-2,4-diones [1-3], exist in the form of rotational isomers because of hindrance to rotation of the N-phenyl group about the $N_{(1)}$—$C_{(1')}$ bond. In their PMR and ^{13}C NMR spectra these compounds give two sets of signals with different intensities (Tables 1-3). The assignment of the lines in the spectra to a definite rotamer was made using their different populations. The assignment of the signals in the aromatic region in the ^{13}C NMR spectra was confirmed by means of the 2D-exchange spectra (Fig. 1). To determine the energy parameters of rotation of the substituted phenyl group about the $N_{(1)}$—$C_{(1')}$ bond we studied the temperature dependence of the PMR spectra. With an increase in the temperature the peaks that correspond to the CH_3 group in the 5 position of the dihydropyrimidine ring undergo broadening for both rotational isomers and then merge together. Depending on the substituent in the phenyl ring, the coalescence point is reached over the temperature range 317-345°K. The free energies of activation calculated from the Eyring equation [4] are presented in Table 4. The introduction of substituents into the phenyl ring and into the 3 and 4 positions of the dihydropyrimidine ring does not have a substantial effect on the $\Delta G^{\neq}$ values; this constitutes evidence for the steric nature of the measured energy barrier.

The coalescence temperatures of the signals could not be reached for the 2-thiono analogs. In addition, the 2D spectra of the latter do not contain exchange cross peaks. As in the case of the 6-CH_3 derivatives [3], all of this provides evidence for a very high barrier to rotation.

To evaluate the contribution caused by the CH_3 group in the pyrimidine ring on the barrier to rotation about the $N_{(1)}$—$C_{(1')}$ bond we compared the barriers in 6-CH_3- and 5-CH_3-1-(2-R-phenyl)dihydropyrimidine-2,4-diones (see Table 4) and some of their derivatives. It is apparent that the distance of the CH_3 groups from the bond undergoing rotation has virtually no effect on the barrier to rotation. This is extremely unexpected and makes it possible to conclude that the height of the energy barrier is determined not by the presence or absence of a CH_3 group in the 6 position of the pyrimidine ring but rather by interaction between the 2-CO group and the 2-R substituent in the phenyl ring. The observed pronounced increase in the barrier both on passing from the 2-methyl

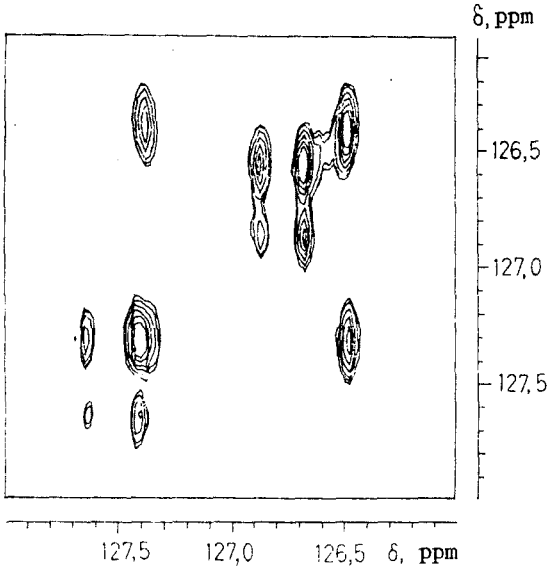

Fig. 1. Aromatic region of the ^{13}C 2D-exchange spectrum for Va.

derivative (Va) to the 2,6-dimethyl derivative (Vd) and on passing from the 2-oxo derivative to the 2-thiono derivative is in agreement with this conclusion. These results cast doubt on the currently prevailing opinion that the nature of the barrier in N-acyl-o-toluidines is determined by rotation about the amide bond [5, 6], since, in our case, the latter is excluded because in view of inclusion of the amide bond in the pyrimidine ring.

An analysis of the spin-spin coupling constants (SSCC) of the protons in the dihydropyrimidine ring of V-X (see Table 2) provides evidence for the preferred distorted half-chair conformation with a pseudoequatorial substituent in the 5 position of the dihydropyrimidine ring. The nature of the substituents in the $N_{(1)}$-aryl ring, as well as in the 3 and 4 positions of the dihydropyrimidine ring, causes no significant shift whatsoever in the conformational equilibrium in the dihydropyrimidine ring. An analysis of the chemical shifts (CS) and SSCC in the spectra of these compounds provides evidence for this. In the case of 6-methyl-(2-R-phenyl)dihydropyrimidine-2,4-diones changes of this sort are more significant [3]. The percentages of the conformers with a pseudoequatorial substituent in the 5 position of the dihydropyrimidine ring calculated in accordance with [4] also do not differ for the two rotational isomers (see Table 2). This fact can be explained by a decrease in the steric repulsion between substituent R in the phenyl ring and the CH_3 group in the 5 position as compared with the repulsion involved in interaction of substituent R with the 6-CH_3 group in 6-methyl-1-(2-R-phenyl)dihydropyrimidine-2,4-diones.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra of solutions of the compounds in d_6-DMSO were recorded with a Bruker WM-360 spectrometer with tetramethylsilane (TMS) as the internal standard. The progress of the reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates with development in UV light or with iodine.

The physicochemical characteristics of the compounds obtained are presented in Table 5. The results of elementary analysis for C, H, N, and Cl were in agreement with the calculated values.

N-Substituted α-Methyl-β-alanine IIa-d Hydrochlorides. A 0.2-mole sample of the corresponding aromatic amine Ia-d, 25.8 g (0.3 mole) of methacrylic acid, and 1 g of hydroquinone was heated for 20 h at 70°C, after which 10% sodium hydroxide solution was added until the mixture was alkaline, and the residual amine was extracted with diethyl ether (4 × 50 ml). The resulting alkaline solution was acidified to pH 6 with acetic acid, and the liberated oily mass of the β-alanine was extracted with 150 ml of diethyl ether. A stream of dry HCl was passed through the ether solution, and the resulting precipitate was removed by filtration and washed with acetone and ether.

N-(2-Methoxyphenyl)-α-methyl-β-alanine (IIe). A mixture of 24.6 g (0.2 mole) of o-anisidine, 25.8 g (0.3 mole) of methacrylic acid, 1 g of hydroquinone, and 100 ml of toluene was refluxed for 5 h, after which 10% sodium hydroxide solution was added until the mixture was alkaline, and the residual amine was extracted with toluene (4 × 50 ml). The alkaline solution was acidified to pH 6 with acetic acid, and the liberated oily mass was washed with water. The mass began to crystallize after standing at 4°C, and the IIe crystals were removed by filtration, washed with water, and dried.

N-(2-Benzyloxyphenyl)-α-methyl-β-alanine (IIf). A 19.9-g (0.1 mole) sample of 2-benzyloxyaniline, 12.9 g (0.15 mole) of methacrylic acid, 0.5 g of hydroquinone, and 50 ml of toluene was refluxed for 6 h, after which it was cooled and made alkaline by the addition of 10% sodium hydroxide solution. The unchanged amine was extracted with diethyl ether (4 × 50 ml). The alkaline solution was acidified to pH 6 with acetic acid, and the liberated β-alanine IIf, obtained in the form of an oily mass, was washed with water. Compound IIf crystallized out after standing at 20°C and was removed by filtration, washed with water, and dried.

1-Aryl-5-methyldihydro-2,4(1H,3H)-pyrimidinediones Va-f. A mixture of 0.05 mole of the corresponding α-methyl-β-alanine II, 4.2 g (0.07 mole) of urea, and 20 ml of acetic acid was refluxed for 14 h, after which 10 ml of concentrated HCl was added, and the mixture was refluxed for another 10 min (5 min for Vf). The mixture was then diluted with 50 ml of water, and the V crystals liberated upon standing were removed by filtration and washed with water. To purify V to remove the N-substituted ureas the crystals were dissolved in 30 ml of 10% sodium hydroxide solution, and the solution was cooled and filtered. The filtrate was heated to the boiling point, 10 ml of HCl was added, and the mixture was refluxed for 10 min (5 min for Vf). It was then cooled, and the precipitated V was removed by filtration and washed with water.

5-Methyl-1-(2-chlorophenyl)dihydro-2,4(1H,3H)-pyrimidinedione (Vg). A mixture of 31.8 g (0.25 mole) of methacrylic acid, 1 g of hydroquinone, and 100 ml of toluene was refluxed for 5 h, after which the mixture was cooled and treated with 10% sodium hydroxide solution until the mixture was alkaline, and the unchanged amine was extracted with toluene (4 × 50 ml). The alkaline solution was acidified to pH 6 with acetic acid, and the liberated β-alanine, in the form of oily mass, was washed with water and dissolved in 30 ml of acetic acid. The acetic acid solution was treated with 12 g (0.2 mole) of urea, and the mixture was refluxed for 20 h. It was then treated with 25 ml of concentrated HCl and refluxed for another 20 min. The resulting mixture was diluted with 50 ml of water, and the liberated oily mass was separated, washed with water, and dissolved by heating in 30 ml of 10% sodium hydroxide solution. This mixture was then cooled, and the undissolved substance was removed by filtration. The filtrate was heated to the boiling point and treated with 15 ml of concentrated HCl. This mixture was then refluxed for 20 min, after which it was cooled, and the Vg crystals were removed by filtration and washed with water.

1-Aryl-5-methyldihydro-4(1H,3H)-pyrimidinone-2-thiones VIa-f. A mixture of 0.05 mole of the corresponding β-alanine or its II hydrochloride, 5.8 g (0.06 mole) of potassium thiocyanate, and 20 ml of acetic acid was refluxed for 14 h, after which 20 ml of 18% HCl was added, and the mixture was refluxed for another 10 min (5 min for VIf). The mixture was then diluted with 30 ml of water, and the liberated VI crystals were removed by filtration, washed with water, and purified in analogy to V.

5-Methyl-1-(2-chlorophenyl)dihydro-4(1H,3H)-pyrimidinone-2-thione (VIg). This compound was obtained from 31.8 g (0.25 mole) of o-chloroaniline as in the synthesis of Vg using potassium thiocyanate in place of urea.

4-Hydroximino-5-methyl-1-(2,5-dimethylphenyl)-5,6-dihydro-2-pyrimidinone (VII). A mixture of 5.8 g (25 mmole) of dihydro-2,4-pyrimidinone Vc and 2.1 g (0.03 mole) of hydroxylamine hydrochloride in a mixture of 10 ml of pyridine and 5 ml of isopropyl alcohol was refluxed for 5 h, after which the mixture was diluted with water (1:4). The VII that precipitated on standing was removed by filtration and washed with water and ethanol.

4-Acetoximino-5-methyl-1-(2,5-dimethylphenyl)-5,6-dihydro-2-pyrimidinone (VIII). A mixture of 2.45 g (0.01 mmole) of VII and 20 ml of acetic anhydride was refluxed for 0.5 h, after which the liquid fractions were removed by distillation in vacuo with a rotary evaporator, and the residue was treated with 5 ml of water. The precipitated VIII was removed by filtration and washed with water and ethanol.

3-Benzoyl-1-(2,5-dimethylphenyl)-5-methyldihydro-2,4(1H,3H)-pyrimidinone (IX). A mixture of 2.3 g (0.01 mole) of Vc, 2.8 g (0.02 mole) of benzoyl chloride, and 5 ml of pyridine was refluxed for 3 h, after which the mixture was diluted with water (1:4). The liberated oily IX was diluted with water and crystallized from 15 ml of ethanol.

3,5-Dimethyl-1-(2,5-dimethylphenyl)dihydro-2,4(1H,3H)-pyrimidinedione (X). A mixture of 5.8 g (25 mmole) of Vc, 10.3 g (75 mmole) of potassium carbonate, and 9.4 g (75 mmole) of dimethyl sulfate was refluxed for 5 h, after which it was cooled and filtered, and the solvent was removed by distillation in vacuo. The residue was washed with water, and the X crystals that formed on standing were removed by filtration and washed with water.

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STEREOSELECTIVE 1,3-DIPOLAR CYCLOADDITION OF UNSATURATED NITRILES TO ISOQUINOLINIUM YLIDS. MOLECULAR AND CRYSTAL STRUCTURE OF 1,2-trans-3,3-DICYANO-1-CARBAMOYL-2-(3-PYRIDYL)-1,2,3,4-TETRAHYDROBENZO[f]INDOLIZINE

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The reactions of isoquinolinium ylids with arylmethylenemalononitriles proceed highly stereoselectively via a pathway involving synchronous 1,3-dipolar cycloaddition to give 1,2-trans-2-aryl-3,3-dicyano-1-carbamoyl(benzoyl)-1,2,3,4-tetrahydrobenzo[f]indolizines. The regiospecificity and stereospecificity of these reactions were confirmed by the results of PMR spectroscopy and x-ray diffraction analysis.

Reactions involving 1,3-dipolar cycloaddition of pyridinium, quinolinium, and isoquinolinium ylids to unsaturated compounds are finding extensive application in precise organic synthesis, particularly the synthesis of indolizines and related heterocyclic compounds [1-6]. Thus the reactions of azinium ylids with acetylenes have been quite thoroughly studied [1, 6]. The behavior of ethylenes in these transformations has not been adequately studied [2-6], and the determination of their regiospecificity and stereoselectivity is extremely urgent. Evidence for this is provided by the data in [2-5], which were devoted to the determination of the stereospecificity of reactions involving 1,3-dipolar addition of isoquinolinium ylids to acenaphthylene, norbornene, styrene, and some other ethylene derivatives. However, the NMR spectroscopic method used in this case does not make it possible to draw definitive conclusions regarding the stereochemistry of the process, since in the NMR spectra of the resulting tetrahydroindolizines and related cyclic azines the ^3J constants of spin-spin coupling (SSCC) between the hydrogen atoms of the hydrogenated pyrrole fragment have an intermediate value of 4-8 Hz for the cis and trans configurations; it also seems virtually impossible to form a judgment regarding the spatial orientation of the substituents bonded to the pyrrole ring of the condensed azines formed.

Considering what we have stated above, in the present research we studied the reactions of isoquinolinium ylids with arylmethylenemalononitriles and, on the basis of the results of PMR spectroscopy and x-ray diffraction analysis, established their regioselectivity and stereoselectivity. The selection of the subjects of our investigation is explained by the fact that the molecules of the starting compounds are, with respect to the electron-density distribution, highly asymmetrical and have relatively high dipole moments [7, 8]. In this connection, if the reaction in the investigated series were to proceed regio- and stereoselectively, as expected, the reaction should be preceded by, first, an intermolecular reaction (regioelectronic control), which predetermines the regiospecificity of the transformation, and, second, by steric interactions of the substituents in the starting molecules (stereo control), which determine the stereospecificity of the reactions under consideration.

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