SYNTHESIS AND STRUCTURES OF 6-METHYL-1-(2-R-PHENYL)-DIHYDROPYRIMIDINE-2,4-DIONE DERIVATIVES

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N-Aryl-β-methyl-β-alanines were synthesized by the reaction of aromatic amines with crotonic acid. The products were converted to dihydropyrimidine-2,4-dione derivatives. Alkylation, acylation, and oximation of 1-arylpyrimidine-2,4-diones were carried out. Conformational analysis of the compounds obtained was carried out by dynamic NMR methods.

N-Substituted β-amino acids are frequently used for the synthesis of various nitrogen-containing heterocycles, particularly dihydropyrimidine-2,4-dione derivatives. It is known that 5- and 6-methyl-1-(1-naphthyl)dihydropyrimidine-2,4-diones and their 2-thiono analogs form stable conformers because of retarded rotation about the N–C bond and can be isolated in individual form by means of TLC [1, 2]. In the cited research a number of 1-aryl-6-methyldihydropyrimidine-2,4-diones and their 2-thiono analogs having various substituents in the 2 position of the aromatic ring and potentially capable of forming rotational isomers were synthesized and investigated by dynamic NMR methods. The energy characteristics of these processes have not been previously studied.

To synthesize N-substituted β-methyl-β-alanines II, which are the starting compounds for obtaining dihydropyrimidine-2,4-diones, we used the alkylation of aromatic amines by crotonic acid via the Michael reaction. The resulting N-aryl-β-methyl-β-alanines II are difficult-to-crystallize substances, and most of them were therefore isolated in the form of the hydrochlorides.

The dihydropyrimidine-2,4-diones and their 2-thiono analogs were synthesized by refluxing the corresponding N-aryl-β-methyl-β-alanines or their hydrochlorides with urea or alkali metal thiocyanates in glacial acetic acid for 14 h. The N-aryl-, N-carbamoyl-, and N-thiocarbamoyl-β-methyl-β-alanines III and IV formed during the reaction were cyclized, without isolation, to pyrimidinedione derivatives with concentrated hydrochloric acid. The cyclization proceeds with high yields and is virtually complete after refluxing of the reaction mixture for 3-5 min. More prolonged refluxing, as, for example, in the synthesis of Vg and VIg, leads to cleavage of the ester bond and the formation of 1-(2-hydroxyphenyl)dihydropyrimidinedione derivatives. Decyclization and cyclization of the dihydrouracil ring proved to be a convenient method for the purification of V and VI. Compounds V and VI were dissolved by heating in 10% NaOH solution, and the undissolved impurities, particularly the N-substituted ureas, were removed by filtration. The aqueous solution of the sodium salt of the corresponding N-aryl-N-(thio)carbamoyl-β-methyl-β-alanine was acidified to pH 1-2 with concentrated HCl and refluxed for 3-5 min.

3-Methyldihydropyrimidine-2,4-diones VII were isolated in the alkylation of Vb, c with dimethyl sulfate. Acylation of the same compounds with benzoyl chloride also takes place at the amide $N_{(3)}$ atom, and 3-benzoyl derivatives VIIIb, c are formed as a result. The introduction of an alkyl or acyl group into dihydropyrimidinediones V leads to disappearance of the absorption bands of an NH bond at 3195-3230 cm^{-1}, while yet another band of the carbonyl group of an acyl fragment appears in the spectra of VIIIb, c at 1760 cm^{-1}. The presence of two or three clearly expressed absorption bands of carbonyl groups in the spectra of VIIb, c and VIIIb, c excludes the assumption of O-alkylation.

Reactions involving replacement of the oxygen atom of the oxo groups of dihydropyrimidine-2,4-diones by a hydroxyimino group have been heretofore unknown. This can be explained in part by the fact that the dihydropyrimidine ring, under the influence of strong nucleophiles, can undergo recyclization or undergo decomposition to amino acid derivatives such as hydrazides [3]. We synthesized 1-aryl-4-hydroxyimino-6-methyldihydropyrimidinediones IXb, c by heating the corresponding pyrimidine-2,4-diones Vb, c with hydroxylamine hydrochloride in a mixture of pyridine and 2-propanol; the products were obtained in 79-93% yields.

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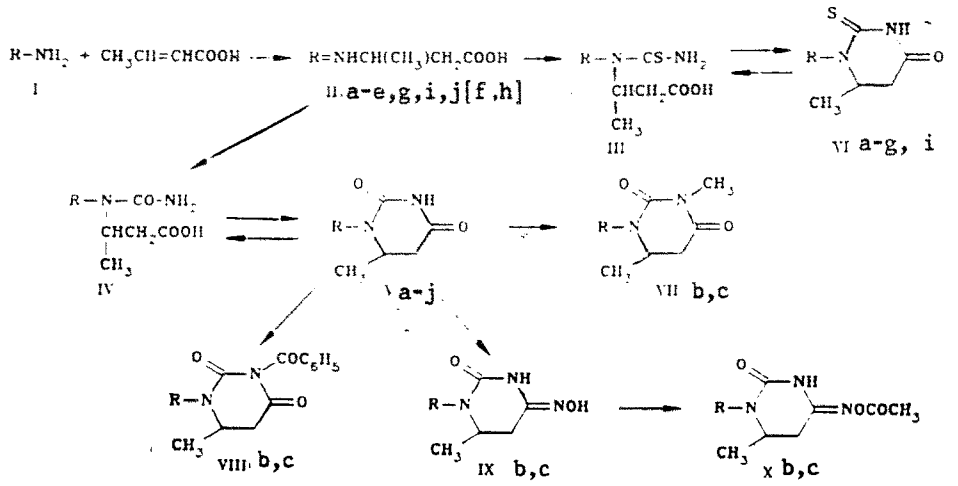
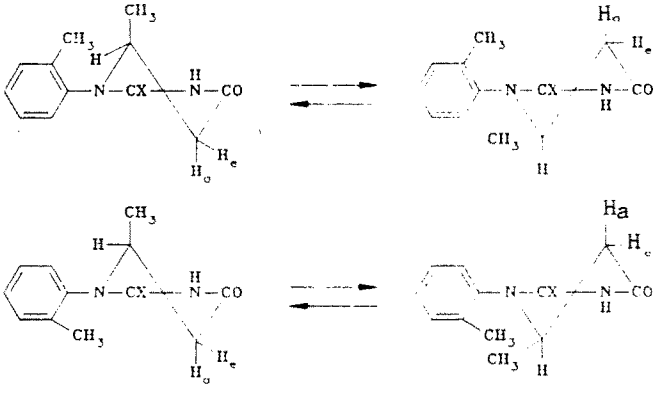


a R=2-$CH_3C_6H_4$; b R=2,4-$(CH_3)_2C_6H_3$; c R=2,5-$(CH_3)_2C_6H_3$; d R=2-$CH_3OC_6H_4$; e R=
=2-$C_2H_5OC_6H_4$; f R=2-$(CH_3)_2CHOC_6H_4$; g R=2-$C_6H_5CH_2OC_6H_4$; h R=2-$C_6H_5NHC_6H_4$;
i R=2-ClC_6H_4; j R=2-BrC_6H_4

Replacement of the oxygen atom attached to the heteroring $C_{(4)}$ atom is evidently due to the lower electron density on the oxygen atom of the 4-C=O group [4] than on the oxygen atom of the 2-C=O group, which promotes attack by a nucleophilic reagent. It is known that ketoximes can form syn and anti isomers as a consequence of retarded rotation about the double bond. An analysis of the PMR spectra shows that only one substance is formed in this reaction. The chemical shifts (CS) in the ^{13}C NMR spectra on passing from the ketone (Va) to the oxime (IXb, c) provide evidence for a strong-field shift of the signal corresponding to the $C_{(5)}$ atom of ~8 ppm. A comparison of the NMR data that we obtained with the data obtained for model compounds [5] provides evidence that the characteristic shift for the anti isomer is a shift on the order of 9 ppm. Thus, isomers of IXb, c with an anti orientation of the OH group (relative to the $C_{(5)}$ atom) are formed as a result of the oximation of Va-j. The formation of a single isomer can be explained by the probability of the formation of an intramolecular hydrogen bond (IMHB) between the proton of the amido group and the hydroxy group of the C=NOH fragment, which is also confirmed by the acylation of IXb, c.

According to the data in [2-7], rotation about the $N_{(1)}$–$C_{(1')}$ bond is hindered in 1-aryl-substituted dihydropyrimidines. This shows up in the NMR spectra in the form of two sets of signals from both the 1-aryl substituent and from the dihydropyrimidine ring. However, the energy characteristics of this process have not yet been studied. In conformity with this, two sets of signals with different intensities, which are related to the protons in the 5 and 6 positions of the dihydropyrimidine ring, as well as the protons of the 6-CH_3 and NH groups, are observed in the PMR spectra of Va-c, VIa-i, IXb, c, and Xb, c recorded in d_6-DMSO. This constitutes evidence for the presence of two rotational isomers that are associated with sterically hindered rotation of the substituted phenyl group about the $N_{(1)}$–$C_{(1')}$ bond. Since the atropo isomers are present in the spectra in different ratios, no difficulties are encountered in assigning the signals to definite isomers (the ^1H and ^{13}C NMR spectra are presented in Tables 1 and 2).



It is known [1, 8, 9] that the dihydropyrimidine ring exists in a distorted half-chair conformation, and we therefore adopted the same conformation in the case of the investigated I-X. For the assignment of the signals to syn or anti isomers we used nuclear Overhauser effect (NOE) 2D spectroscopy. For Va the presence of a distinct cross peak in the NOESY spectrum (Fig. 1), which corresponds to the $C_{(6\text{-}H)}$–$ArCH_3$ distance for the isomer with a higher population, constitutes evidence that an anti orientation of the substituent in the phenyl ring and the 6-CH_3 group is characteristic for the latter.

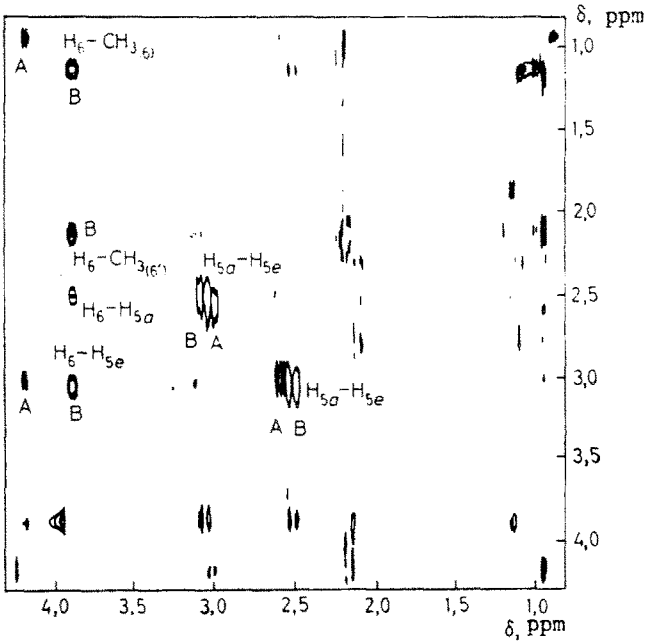


Fig. 1. Part of the NOESY spectrum of a 1-aryl-6-methyldihydropyrimidine-2,4-dione (τ_m = 0.35 sec).

Cross peaks due to an NOE between 6-H and the methyl group of the phenyl ring are not observed for the second isomer with a lower population. In addition to this, in the NOESY spectrum the intensities of the cross peaks corresponding to interaction between the protons in the 6 and 5 positions of the dihydropyrimidine ring differ substantially for the two isomers. Thus, the cross peaks corresponding to the 5e–6 and 5*a*–6 distances for anti isomers have virtually equal intensities, while for the syn isomer the 5e–6 cross peak is substantially more intense than for the pair of 5*a*–6 protons. These observations show that primarily the conformations of the dihydropyrimidine ring in the two isomers differ; this is confirmed by an analysis of the constants of spin-spin coupling (SSC) between the protons in the 5 and 6 positions of the heteroring in the two isomers.

It is apparent from the scheme that the amount of the conformer with a pseudoaxial orientation of the 6-CH_3 group can be determined using the $^3J_{(6-5a)}$ SSCC

$$^3J^{\text{obs}}_{(6-5a)} = pJ_{(aa)} + (1-p)J_{(ae)}, \quad (1)$$

where p is the fraction of the conformer with an axially oriented 6-CH_3 group, and $J_{(aa)}$ and $J_{(ae)}$ are "model" SSCC for axially-axially and axially-equatorially oriented protons of the dihydropyrimidine ring. Katritzky and coworkers [8] proposed $J_{(aa)}$ = 11.5 Hz and $J_{(ae)}$ = 2.0 Hz. The fractions of the conformer with an axial orientation of the 6-CH_3 group obtained from Eq. (1) for the anti isomer are appreciably greater than for the syn isomer (Table 1). The reason for this is evidently the unfavorable steric repulsion between substituent R in the N-aryl ring and the equatorially oriented 6-CH_3 group in the anti isomer. For the syn isomer the above-mentioned unfavorable steric contacts occur in the conformation with an axial 6-CH_3 group, and the population of this conformer is therefore decreased as compared with the anti isomer. The conformational equilibrium simultaneously depends appreciably on the volume of substituent R in the aryl ring. Thus, the change in the volume of substituent R in the order Br < CL < CH_3 leads to an increase in the population of the conformer with an equatorial 6-CH_3 group in the syn isomer (Table 1) and to a decrease in the population in the anti isomer. In addition, it may be noted that, in both the syn and anti isomers the populations of the conformations with an axial 6-CH_3 group prevail. This is in agreement with the results of x-ray diffraction analysis [1].

The presence of an oxime bond at the $C_{(4)}$ atom does not affect the primary conformation of the dihydropyrimidine ring, and thus the introduction of substituents into the 3 position does not change it substantially. The results of analysis of the chemical shifts (CS) and SSCC for these compounds also provide evidence in favor of this.

To determine the energy parameters of rotation of a 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 corresponding to the 6-CH_3 groups in the syn and anti isomers are broadened and subsequently merge. For Va-j the coalescence points (T_c) reach 320-341°K, depending on the substituent in the phenyl group. The free energies of activation were calculated from Eyring's equation (Table 1). The coalescence points could not be reached for 2-thiono analogs VIa-g, i. According to our evaluation, the

lower limit of the barrier to rotation is ~19.4 kcal/mole. The introduction of substituents into the dihydropyrimidine ring does not have a substantial effect on the $\Delta G^{\neq}$ value; this constitutes evidence for the steric nature of the measured energy barrier.

In contrast to classical dynamic NMR spectroscopy, two-dimensional (2D) NMR spectroscopy makes it possible to unambiguously determine the pathways and energy characteristics of exchange processes. An advantage of this method is the fact that the character of an exchange process can be established as a result of a single, nonselective, multipulse experiment, while the free energy of activation can be determined by measuring the intensities of the diagonal and cross peaks in the 2D spectrum (Fig. 2). The $\Delta G_T^{\neq}$ values obtained by this method for Vi (16.9 kcal/mole) are in good agreement with the results of the determination of $\Delta G_C^{\neq}$ by the traditional method of studying the temperature dependences of the NMR spectra (17.0 kcal/mole).

We also studied the ^{13}C NMR spectra for the compounds under consideration (Table 2). In the ^{13}C NMR spectra we also observed doubled character of the signals of the C atoms of the substituted phenyl group and the dihydropyrimidine ring, which also confirms the presence of two rotational isomers due to retarded rotation of the phenyl ring about the $N_{(1)}$–$C_{(1')}$ bond. The assignment of the signals was made taking into account the data in [6, 10] and also directly from the multiplicity of the signals in the spectra recorded without suppression of spin-spin coupling with the protons; in addition, we used the differences in the intensities of the signals corresponding to the different isomers and the presence of cross peaks in the exchange 2D spectra (Fig. 2). In assigning the aromatic C atoms we took into account the constants of SSC with the protons and the changes in the chemical shifts (CS) on passing from one isomer to another. We did not find a clear dependence of the ^{13}C CS of the carbons of the dihydropyrimidine ring on the substituents in the phenyl ring. Replacement of the carbonyl group by a thiocarbonyl group leads to a weak-field shift of the $C_{(2)}$ signal. A comparison of the ^{13}C CS for the two isomers shows that for the anti isomer the signals corresponding to the $C_{(5)}$ and $C_{(6)}$ atoms, as well as the 6-CH_3, $C_{(2')}$, and $C_{(4')}$ atoms are located at stronger field as compared with the signals of the corresponding carbon atoms in the syn isomer, while the signals of the $C_{(1')}$, $C_{(3')}$, and $C_{(5')}$ atoms are shifted to weaker field. This is probably due to the relative orientation of the 6-CH_3 group of the dihydropyrimidine ring and the substituent in the phenyl group. As expected, the greatest changes in the CS on passing from the anti isomer to the syn isomer are observed for the o-oriented carbon atoms of the phenyl ring; this is associated with steric interaction with the 6-CH_3 group of the dihydropyrimidine ring. For the $C_{(2)}$ atom this change in the CS is ~1.8 ppm, whereas it is on the order of 1.0 ppm for the $C_{(6)}$ atom. The introduction of substituents into the dihydropyrimidine ring does not substantially change the CS of the carbon atoms of the dihydropyrimidine ring; this confirms the invariability of the primary conformation.

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 free energy of activation of retarded rotation of the phenyl group about the $N_{(1)}$–$C_{(1')}$ bond for Vi was determined from the two-dimensional NOESY spectrum. A sequence of three pulses – 90°–t_1–90°–t_m – 90° – t_2 – was used. The mixing time t_m = 0.35 sec. The experiments were carried out at 303°K. To determine the exchange-rate constants we measured the intensities of the diagonal and cross peaks. We used the relationship between the matrices of the normalized amplitudes and the matrix containing the dynamic parameters [11]

$$\hat{A} = \begin{pmatrix} a_{AA}/A_0 & a_{AB}/B_0 \\ a_{BA}/A_0 & a_{BB}/B_0 \end{pmatrix},$$

where a_{AA} and a_{BB} are the intensities of the diagonal peaks, a_{AB} and a_{BA} are the intensities of the cross peaks, and A_0 is the intensity of the diagonal peaks when $t_m = 0$.

As a result of the experiments, we obtained the matrix

$$\hat{A} = \begin{pmatrix} 38.6 & 29.2 \\ 12.6 & 19.1 \end{pmatrix}.$$

The values of the dynamic parameters were obtained after calculation of the diagonal matrix of eigenvalues $\hat{D}$

$$\hat{D} = \begin{pmatrix} 50.3 & 0 \\ 0 & 7.3 \end{pmatrix},$$

as well as the matrix of the eigenvectors $\hat{X}$ and its inverse matrix $\hat{X}^{-1}$

$$\hat{X} = \begin{pmatrix} 1 & 1 \\ 0.40 & -1.07 \end{pmatrix}, \quad \hat{X}^{-1} = \begin{pmatrix} 0.73 & 0.68 \\ 0.27 & -0.68 \end{pmatrix}.$$

After calculation of the $\hat{R}$ matrix – $-\hat{R} = (1/t_m)\hat{X}(\ln \hat{D})\hat{X}^{-1}$ – we obtain the following rate constants: K_{AB} = 67 sec^{-1}, and K_{BA} = 6.3 sec^{-1}.

TABLE 1. Parameters of the PMR spectra and Free Energies of Activation of 1-Aryl-6-methyldihydropyrimidine-2,4-diones and 1-Aryl-6-methyldihydropyrimidin-4-one-2-thiones

Compound	Isomer ratio (anti: syn, %)	Chemical shifts, δ, ppm							SSCC, J. Hz				P_A*	J, Hz	T_s, K	$\Delta G^{\neq}$, kcal/mole
		6-CH_3	5a	5e	6-H	Ph	NH	R	5e6	5a6	5a5e	6H, CH_3				
anti-Va	2,91	1,15	2,47	3,03	3,75	7,25	11,80	2,19	5,7	3,9	16,0	6,3	0,47	14,30	327	17,2
syn-Va	2,10	0,99	2,51	2,98	4,08		8,60	2,16	5,1	6,5	16,0	6,3	0,20			
anti-Vb	5,40	1,11	2,46	3,02	3,71	7,12	10,30	2,16; 2,30	5,8	3,9	16,5	6,6	0,26	13,70	335	17,4
syn-Vb	4,10	0,96	2,50	2,97	4,03		10,30	2,13; 2,30	5,4	4,5	16,5	6,4	0,20			
anti-Vc	85,80	1,15	2,45	3,02	3,72	6,9...7,3	10,34	2,14; 2,29	5,8	3,8	16,3	6,7	0,35	14,60	338	17,5
syn-Vc	62,20	1,00	2,51	2,99	4,06		10,32	2,12; 2,29	5,5	5,3	16,4	6,7	0,19			
anti-Vd		1,05	2,45	2,93	3,82	6,9...7,3	9,38	3,27	5,5	5,3	16,1	6,4				
anti-Ve		1,06	2,47	2,92	3,85	6,9...7,4	10,80	1,32; 4,07	5,9	4,0	15,5	6,1				
anti-Vf		1,06	2,48	2,89	3,87	6,9...7,4	8,60	0,97; 2,00; 3,77	5,6	4,8	16,0	6,5				14,9
anti-Vg		1,05	2,40	2,78	3,87	6,9...7,2	11,50	6,5...7,0; 5,15	5,6	4,9	16,0	6,5				14,9
anti-Vh		1,54	2,91	3,10	4,88	7,0...7,5	9,33	7,5; 8,15	7,8	6,3	16,1	7,0				
anti-Vi	5,5	1,12	2,50	3,00	3,87	7,40	10,50		5,5	4,8	16,0	6,1	0,29	7,75	320	17,0
syn-Vi	2,9	1,02	2,53	2,99	4,10	7,60	10,42		5,5	5,5	16,1	6,1	0,37			
anti-Vj	14,4	1,13	2,50	3,03	3,85	7,2...7,7	9,37		5,5	4,4	16,0	6,5	0,25	12,30	338	17,4
syn-Vj	8,2	1,02	2,55	2,95	4,10		9,30		5,0	5,9	16,2	6,5	0,21			
anti-VIa	2,2	1,21	2,57	3,11	3,94	7,1...7,4	9,35	2,19	6,1	3,9	16,7	6,5	0,20			
syn-VIa	1,0	1,02	2,62	3,05	4,22		9,30	2,23	5,3	7,4	16,7	6,5	0,57			
anti-VIb	100,5	1,19	2,55	3,10	3,89	7,0...7,2	10,48	2,14; 2,29	5,8	3,6	16,5	6,1	0,17			
syn-VIb	13,9	1,02	2,60	3,05	4,18		10,52	2,19; 2,29	5,7	7,1	16,4	6,1	0,54			
anti-VIc	24,3	1,23	2,55	3,11	3,92	7,0...7,3	9,24	2,14; 2,30	6,1	3,5	16,2	6,1	0,16			
syn-VIc	0,9	1,04	2,60	3,07	4,20		9,28	2,19; 2,30	3,9	6,6	16,0	6,5	0,48			
anti-VId	21,5	1,13	2,47	3,14	3,92	7,1...7,4	8,30	3,82	5,8	4,4	16,4	6,1	0,25			
syn-VId	8,4	1,09	2,56	2,90	4,06		8,20	3,78	5,5	4,7	16,2	6,1	0,28			
anti-VIe	5,0	1,16	2,48	3,15	3,92	6,9...7,4	8,25	1,32; 4,09	5,7	3,9	16,0	6,0	0,21			
syn-VIe	2,0	1,13	2,59	2,95	4,09		8,35	1,30; 4,05	5,7	5,0	16,0	6,0	0,23			

anti-VIf		1,16	2,44	3,14	3,93	6,9 . . . 7,4	7,70		5,9	4,5	16,2	6,5	0,26			
syn-VIf		1,11	2,59	2,90	4,06	6,9 . . . 7,4	7,80		5,8	5,0	16,2	6,5	0,23			
anti-VIg	72,7	1,15	2,43	3,14	3,94	7,4 . . . 7,5	8,35	5,12; 6,9 . . . 7,2	5,7	4,1	16,0	6,6	0,22			
syn-VIg	8,4	1,08	2,51	2,73	4,08		8,30	5,19	5,7	4,6	16,0	6,3	0,27			
anti-VIi	5,3	1,19	2,60	3,09	4,02	7,4 . . . 7,7	10,28		5,7	4,5	16,5	6,7	0,26			
syn-VIi	0,6	1,07	2,64	3,06	4,26		10,15		4,4	7,6	16,2	6,5	0,59			
anti-VIIb	13,8	1,12	2,59	3,12	3,68	7,4 . . . 7,6		2,12; 2,30; 3,08	5,7	4,0	15,7	6,2	0,22	13,50	337	17,5
syb-VIIb	11,0	0,97	2,63	3,09	4,00			2,15; 2,30; 3,05	5,7	7,0	15,7	6,2	0,55			
anti-VIIc	13,7	1,12	2,60	3,13	3,72	7,0 . . . 7,2		2,15; 2,29; 3,08	5,8	3,8	15,5	6,5	0,20	13,50	338	17,6
syn-VIIc	11,3	0,98	2,64	3,09	4,23			2,24; 2,31; 3,64	5,7	6,6	15,7	6,2	0,51			
anti-VIIIb	2,6	1,25	2,79	3,44	4,00	7,0 . . . 7,3		2,14; 2,23; 7,5 . . . 7,8	5,0	4,5	16,2	6,0	0,27	10,86	333	17,5
syn-VIIIb	2,1	1,11	2,87	3,42	4,30				5,0	6,1	16,2	6,0	0,45			
anti-IXb	9,8	1,12	2,37	2,88	3,63	7,0 . . . 7,2	8,52	2,11; 2,30	4,6	3,5	15,5	6,3	0,16	12,91	330	17,2
syn-IXb	7,0	0,97	2,38	2,86	3,98		8,50	2,13; 2,30	4,6	6,5	15,5	6,3	0,50			
anti-IXc	7,8	1,12	2,38	2,88	3,64	7,1 . . . 7,3	8,59	2,09; 2,28	5,5	3,8	15,5	6,3	0,20	13,50	330	17,2
syn-IXc	6,6	0,98	2,40	2,86	3,99		8,57	2,13	5,5	6,7	15,5	6,2	0,52			
anti-Xb	8,8	1,15	2,51	3,05	3,73	7,0 . . . 7,2	9,5	2,12; 2,29; 2,15	5,4	3,7	15,6	7,0	0,18	12,91	335	17,2
syn-Xb	7,8	1,02	2,53	3,02	4,03		9,5	2,16; 2,29; 2,15	5,1	6,9	15,6	7,0	0,54	11,74		
anti-Xc	8,3	1,15	2,51	3,06	3,73	7,3 . . . 7,5	9,8	2,11; 2,28; 2,15	5,0	3,9	16,0	6,4	0,21	12,91	332	17,3
syn-Xc	7,2	1,02	2,54	3,02	4,05		9,8	2,14; 2,27; 2,15	5,0	6,5	16,0	6,5	0,50			

*P_A is the fraction of the conformer with an axially oriented 6-CH_3 group.

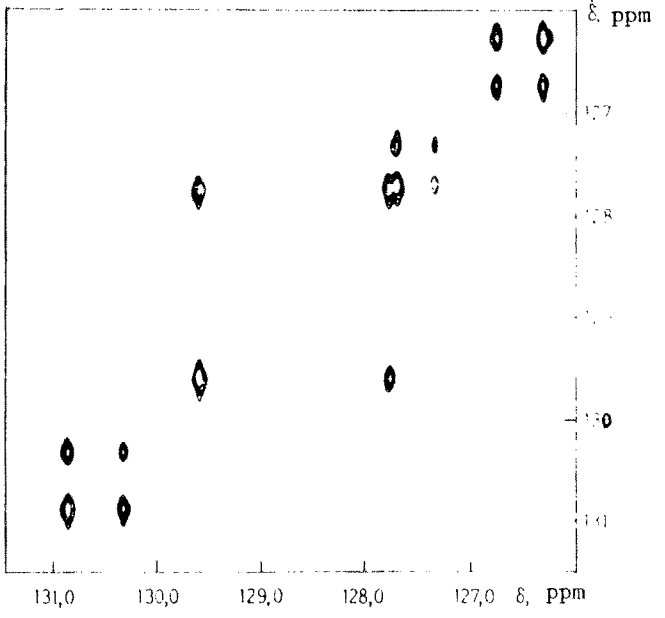


Fig. 2

TABLE 2. ^{13}C NMR Spectra of 1-Aryl-6-methyldihydropyrimidines and 1-Aryl-6-methyl-2-thionodihydropyrimidines

Compound	Chemical shifts, δ, ppm											
	$C_{(2)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	6-CH_3	$C_{(1')}$	$C_{(2')}$	$C_{(3')}$	$C_{(4')}$	$C_{(5')}$	$C_{(6')}$	remaining shifts
anti-Va	151,35	170,01	37,96	50,03	18,44	139,00	129,62	126,33	127,73	130,89	135,77	17,36 (6′-CH_3)
syn-Va	151,05	169,93	38,33	51,22	18,81	139,30	127,73	126,76	127,38	130,35	136,85	17,90 (6′-CH_3)
anti-Vb	151,40	170,01	37,96	50,06	18,44	136,58	129,35	126,84	136,98	131,38	135,36	17,28 (6′-CH_3); 20,51 (4′-CH_3)
syn-Vb	151,08	169,93	38,31	51,22	18,79	136,71	127,54	127,30	136,41	130,89	136,41	17,82 (6′-CH_3); 20,51 (4′-CH_3)
anti-Vc	151,32	170,01	37,96	50,03	18,49	138,81	129,97	135,55	128,19	130,64	131,42	16,93 (6′-CH_3); 20,32 (3′-CH_3)
syn-Vc	150,97	169,90	38,28	51,25	18,81	139,08	128,38	136,01	128,03	130,13	133,56	17,49 (6′-CH_3); 20,32 (3′-CH_3)
anti-Vd	151,54	170,03	38,01	50,25	18,60	130,48	128,95	120,18	128,51	112,88	154,80	55,72 (OCH_3)
anti-Ve	151,54	170,09	37,96	50,28	18,49	130,51	128,84	120,24	128,73	113,17	154,58	63,68 (OCH_2); 14,58 (CH_3)
anti-Vg	151,57	170,01	37,93	50,30	18,63	130,59	128,89	120,67	128,41	113,58	154,42	136,90 (*ipso*-C); 128,41 (*o*-C); 127,81 (*p*-C); 127,36 (*m*-C); 69,71 (OCH_2)
anti-Vf	151,57	169,95	38,04	50,28	18,63	130,48	128,89	120,18	128,57	112,88	154,80	74,00 (OCH_2); 27,87 (CH); 19,03 (CH_3)
anti-Vi	151,46	169,84	37,85	50,01	18,48	137,14	132,18	127,79	129,57	129,98	132,05	
syn-Vi	150,97	169,84	38,36	51,30	18,73	137,76	130,43	128,22	129,24	129,70	133,42	
anti-Vj	151,30	169,84	37,82	50,11	18,36	138,71	132,15	128,41	129,84	133,15	122,93	
syn-Vj	151,13	169,79	38,58	51,00	18,89	139,27	130,46	128,81	129,43	132,83	124,55	
anti-VIa	177,99	166,34	37,20	53,51	17,71	142,02	128,81	126,41	128,06	131,02	134,72	17,41 (6′-CH_3)
syn-VIa	178,15	166,45	37,63	54,91	18,19	142,02	127,36	127,11	127,81	130,48	136,01	18,11 (6′-CH_3)
anti-VIb	178,07	166,37	37,17	53,59	17,68	139,62	128,51	127,03	137,95	131,53	134,31	17,33 (6′-CH_3); 20,54 (4′-CH_3)
syn-VIb	178,15	166,50	37,58	54,99	18,47	139,65	127,09	127,68	137,33	131,05	135,58	18,06 (6′-CH_3); 21,05 (4′-CH_3)
anti-VIc	177,88	166,37	37,20	53,57	17,76	141,91	128,97	135,71	128,73	130,81	131,43	17,01 (6′-CH_3); 20,35 (3′-CH_3)
anti-VIe	178,55	166,45	36,93	53,62	17,55	130,46	130,46	120,05	129,27	113,61	153,29	63,92 (OCH_2); 14,61 (CH_3)
syn-VIe	178,55	166,64	37,52	55,21	17,65	130,46	129,00	120,83	129,00	113,31	154,26	63,62 (OCH_2); 14,61 (CH_3)
anti-VIIb	151,65	169,12	38,12	48,87	18,33	137,09	129,19	126,95	136,68	131,45	135,31	27,17 (N—CH_3); 17,30 (2′-CH_3)
syn-VIIb	151,52	169,12	38,49	49,95	18,68	137,20	127,52	127,36	135,31	130,97	136,31	27,28 (N—CH_3); 17,79 (2′-CH_3); 20,54 (4-CH_3)
anti-VIIc	151,84	169,09	38,12	48,82	18,33	139,30	129,81	135,63	128,49	130,73	132,37	27,14 (N—CH_3); 20,35 (6′-CH_3); 16,95 (2′-CH)
syn-VIIc	151,57	169,09	38,47	49,95	18,68	139,54	128,14	136,09	128,14	130,19	133,45	27,25 (N—CH_3); 20,35 (6′-CH_3); 17,44 (2′-CH_3)
anti-VIIIb	153,83	170,19	38,14	49,86	18,77	137,22	129,30	127,06	136,47	133,31	135,36	169,20 (CO); 134,93 (*ipso*-C); 129,94 (*o*-C); 127,54 (*p*-C); 129,30 (*m*-C); 17,33, 17,71 (2′-CH_3)
syn-VIIIb	153,83	169,20	38,25	51,35	18,85	137,63	127,54	127,54	135,77	132,26	136,17	
anti-IXb	150,08	142,80	31,19	51,03	18,17	136,68	129,43	126,79	136,55	131,32	135,36	17,30 (6′-CH_3); 20,54 (4′-CH_3)
syn-IXb	149,70	142,80	31,67	52,41	18,65	137,25	127,60	127,22	135,31	130,81	136,28	17,84 (6′-CH_3); 20,54 (4′-CH_3)
anti-IXc	149,97	142,78	31,22	49,87	18,77	137,22	129,94	135,77	129,94	131,56	132,26	20,54 (5′-CH_3); 17,33 (2′-CH_3)
syn-IXc	149,62	142,78	31,65	51,35	18,84	137,63	127,54	136,17	129,34	131,05	133,31	20,54 (5′-CH_3); 17,71 (2′-CH_3)
syn-IXc	150,86	149,89	30,92	50,55	18,03	137,03	129,35	126,92	136,74	131,43	135,36	167,47 (CO); 20,54 (4′-CH_3); 17,33 (2′-CH_3)
anti-Xb	150,83	149,44	31,24	52,06	18,41	137,63	127,67	127,38	136,39	130,91	136,39	167,47 (CO); 20,54 (4′-CH_3); 17,87 (2′-CH_3)
syn-Xb	150,84	149,20	30,95	50,52	18,11	139,16	129,93	135,63	128,07	130,70	132,42	20,38 (5′-CH_3); 19,41 (CH_3); 17,01 (2′-CH_3)
anti-Xc	150,82	149,79	31,22	52,11	18,41	139,50	128,27	136,12	128,06	130,16	133,53	20,38 (5′-CH_3); 19,41 (CH_3); 17,55 (2′-CH_3)
syn-Xc												

TABLE 3. Physicochemical Characteristics of II and V-X

Compound	mp,* °C	IR spectrum, cm^{-1}		Empirical formula	Yield, %
		NH	C=O		
IIa	166...168			$C_{11}H_{15}NO_2 \cdot HCl$	31.4
IIb	173...175			$C_{12}H_{17}NO_2 \cdot HCl$	22.3
IIc	171...173			$C_{12}H_{17}NO_2 \cdot HCl$	37.1
IId	143...144			$C_{11}H_{15}NO_3 \cdot HCl$	40.9
IIe	180...181			$C_{12}H_{17}NO_3 \cdot HCl$	65.4
IIg	92...93			$C_{17}H_{19}NO_3$	56.8
IIi	142...144			$C_{10}H_{12}ClNO_2 \cdot HCl$	42.1
IIj	140...142			$C_{10}H_{12}BrNO_2 \cdot HCl$	29.1
Va	183...185	3195	1725, 1675	$C_{12}H_{14}N_2O_2$	78.0
Vb	200...201	3195	1730, 1695	$C_{13}H_{16}N_2O_2$	75.8
Vc	193...194	3205	1740, 1695	$C_{13}H_{16}N_2O_2$	75.4
Vd	191...193	3190	1735, 1700	$C_{12}H_{14}N_2O_3$	54.2
Ve	166...167	3230	1715, 1705	$C_{13}H_{18}N_2O_3$	55.2
Vf	134...136	3195	1730, 1695	$C_{15}H_{20}N_2O_3$	34.1
Vg	145...147	3200	1720, 1695	$C_{18}H_{18}N_2O_3$	35.1
Vh	145...147			$C_{17}H_{17}N_3O_2$	8.2
Vi	238...240	3190	1725, 1690	$C_{11}H_{11}ClN_2O_2$	67.0
Vj	236...238	3190	1720, 1690	$C_{11}H_{11}BrN_2O_2$	63.6
VIa	173...174	3130	1730	$C_{12}H_{14}N_2OS$	41.0
VIb	207...209	3230	1710	$C_{13}H_{16}N_2OS$	35.9
VIc	205...206	3210	1740	$C_{13}H_{16}N_2OS$	50.0
VId	174...176	3215	1710	$C_{12}H_{14}N_2O_2S$	32.0
VIe	200...202	3215	1705	$C_{13}H_{16}N_2OS$	58.4
VIf	169...171	3275	1715	$C_{15}H_{20}N_2O_2S$	13.1
VIg	201...203	3220	1710	$C_{18}H_{18}N_2O_2S$	24.7
VIi	195...196	3210	1720	$C_{11}H_{11}ClN_2OS$	41.9
VIIb	89...90		1730, 1680	$C_{14}H_{18}N_2O_2$	11.3
VIIc	118...120		1725, 1670	$C_{14}H_{18}N_2O_2$	66.7
VIIIb	123...124		1760, 1725, 1680	$C_{20}H_{20}N_2O_3$	44.6
VIIIc	132...133		1760, 1715, 1685	$C_{20}H_{20}N_2O_3$	56.6
IXb	244 (dec.)	3240,** 3110	1710	$C_{13}H_{17}N_3O_2$	93.0
IXc	230 (dec.),	3280, 3090**	1695	$C_{13}H_{17}N_3O_2$	79.3
Xb	201...203	3200	1780, 1680	$C_{15}H_{19}N_3O_3$	65.0
Xc	215...217	3205	1780, 1680	$C_{15}H_{19}N_3O_3$	42.1

*The compounds were crystallized: IIa-d, i, Vc, j, and Xb, c from CH_3COOH; IIe, j, Va, b, d-g, VIa-g, VIIc, and VIIIb, c from C_2H_5OH; IIg from hexane; Vi, VIi, and IXb, c from dioxane; VIIb from ether.

**Signals of the OH and NH groups.

The IR spectra of KBr pellets were recorded with a UR-20 spectrometer. Monitoring of the course of the reactions and the purity of the compounds obtained was accomplished by means of TLC on Silufol UV-254 plates; development was carried out in UV light or with iodine.

The characteristics of the compounds obtained are presented in Table 3.

Hydrochlorides of N-Substituted β-Methyl-β-alanines (IIa-e, i, j). A mixture of 0.2 mole of the corresponding amine I, 25.8 g (0.3 mole) of crotonic acid, 0.5 g of hydroquinone, and 30 ml of toluene was refluxed for 12 h, after which the mixture was cooled and treated with 10% sodium hydroxide solution until it was alkaline, and the residual amine was extracted with toluene or diethyl ether (four 50-ml portions). The alkaline solution was acidified to pH 6 with acetic acid, and the liberated oily β-alanine was extracted with 150 ml of diethyl ether. A stream of dry HCl was passed through the ether solution until it was saturated, and the resulting precipitate was removed by filtration and washed with acetone and ether.

N-(2-Benzyloxyphenyl)-β-methyl-β-alanine (IIg). A mixture of 19.9 g (0.1 mmole) of 2-benzyloxyaniline, 12.9 g (0.15 mole) of crotonic acid, and 50 ml of toluene was refluxed for 6 h, after which the mixture was cooled and treated with 10% sodium hydroxide solution until it was alkaline, and the unchanged amine was extracted with toluene or diethyl ether (four 50-ml portions). The alkaline solution was acidified to pH 6 with acetic acid, and the liberated oily β-alanine IIg

was washed three times with water. The mass crystallized on standing. Compound IIg was removed by filtration, washed with water, and dried.

1-Aryl-6-methyldihydropyrimidine-2,4-diones (Va-e, g, i, j). A mixture of 0.05 mole of the corresponding N-substituted β-methyl-β-alanine II or its hydrochloride, 4.2 g (0.07 mole) of urea, and 15 ml of acetic acid was refluxed for 14 h, after which concentrated HCl was added to pH 1-2, and the mixture was refluxed for another 5 min. The mixture was diluted with 50 ml of water and allowed to stand at 20°C for 12 h. The liberated crystals of V were removed by filtration and washed with water. To purify V to remove the N-substituted ureas the crystals were dissolved by heating in 30 ml of 10% sodium hydroxide solution, after which the solution was cooled and filtered. The filtrate was heated to the boiling point and treated with 10 ml of hydrochloric acid, and the mixture was refluxed for 5 min. It was then cooled, and the precipitated V was removed by filtration, washed with water, and dried.

6-Methyl-1-(2-phenylaminophenyl)dihydropyrimidine-2,4-dione (Vh). A mixture of 18.4 g (0.1 mole) of 2-aminodiphenylamine, 12.9 g (0.15 mole) of crotonic acid, and 30 ml of toluene was refluxed for 12 h, after which it was treated with 10% sodium hydroxide solution until it was alkaline, and the residual amine was extracted with toluene or diethyl ether. The alkaline solution was acidified to pH 6 with acetic acid, and the liberated β-alanine IIh was separated, washed with water, and dissolved in 30 ml of acetic acid. A 12-g (0.2 mole) sample of urea was added to the solution, and the mixture was refluxed for 14 h. Concentrated HCl was then added to pH 1, and the mixture was refluxed for another 5 min. The mixture was diluted with water (1:4), and the liberated mass was separated, washed with water, and dried. The mixture was passed through a column packed with Silpearl UV-245 silica gel by elution with ether–hexane (10:1), and the fraction with R_f 0.82 was collected.

6-Methyl-1-(2-isobutoxyphenyl)dihydropyrimidine-2,4-dione (Vf). This compound was obtained from 16.5 g (0.1 mole) of 2-isobutoxyaniline by the method used to obtain Vh and was purified as in the case of Va.

1-Aryl-6-methyldihydropyrimidin-4-one-2-thiones (VIa-e, g, i, j). A mixture of 0.05 mole of the corresponding β-alanine II or its hydrochloride, 5.8 g (0.06 mole) of potassium thiocyanate, and 15 ml of acetic acid was refluxed for 14 h, after which 20 ml of 18% hydrochloric acid was added, and the mixture was refluxed for another 5 min. The mixture was diluted with 30 ml of water and allowed to stand at 20°C, after which the liberated crystals of VI were removed by filtration, washed with water, and purified as in the case of V.

6-Methyl-1-(2-isobutoxyphenyl)dihydropyrimidin-4-one-2-thione (VIf). This compound was obtained from 16.5 g (0.1 mole) of 2-isobutoxyaniline as in the preparation of Vf using potassium thiocyanate instead of urea.

3,6-Dimethyl-1-(2,4-dimethylphenyl)- and 3,6-Dimethyl-1-(2,5-dimethylphenyl)dihydropyrimidine-2,4-dione (VIIb, c). A 4.4-g (0.035 mole) sample of dimethyl sulfate was added to a boiling mixture of 5.8 g (0.025 mole) of the corresponding dihydropyrimidinedione Vb, c, 1.4 g (0.03 mole) of sodium hydroxide, and 25 ml of water, and the mixture was refluxed until it became acidic (pH 6). The crystals of VIIb, c that precipitated on standing at 20°C were removed by filtration and washed with water.

3-Benzoyl-1-(2,4-dimethylphenyl)- and 3-Benzoyl-1-(2,5-dimethylphenyl)-6-methyldihydropyrimidine-2,4-dione (VIIIb, c). A mixture of 2.3 g (0.01 mole) of the corresponding dihydropyrimidinedione Vb, c, 2.8 g (0.02 mole) of benzoyl chloride, and 5 ml of pyridine was refluxed for 3 h, after which it was diluted with water (1:4). The liberated oily mass was washed with water and crystallized from 15 ml of ethanol.

4-Hydroxyimino-6-methyl-1-(2,4-dimethyl)- and 4-Hydroxyimino-1-(2,5-dimethylphenyl)dihydropyrimidin-2-one (IXb, c). A 2.3-g (0.01 mole) sample of the corresponding dihydropyrimidinedione Vb, c and 2.1 g (0.03 mole) of hydroxylamine hydrochloride were refluxed in a mixture of 10 ml of pyridine and 5 ml of 2-propanol for 5 h, after which the mixture was diluted with water (1:4). The IXb or IXc that precipitated on standing at 20°C was removed by filtration and washed with water and ethanol.

4-Acetoxyimino-6-methyl-1-(2,4-dimethylphenyl)- and 4-Acetoxyimino-6-methyl-1-(2,5-dimethylphenyl)dihydropyrimidin-2-one (Xb, c). A mixture of 2.45 g (0.01 mole) of the corresponding pyrimidinone IXb, c and 30 ml of acetic anhydride was refluxed for 30 min, after which the liquid fractions were removed by distillation in vacuo, and the residue was treated with water, removed by filtration, and washed with water and ethanol.

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CONFORMATION OF 2,5-SUBSTITUTED 1,3,2-DIOXABORINANES STUDIED BY NMR

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The conformation of a series of 2,5-substituted 1,3,2-dioxaborinanes is studied by PMR. The preferred conformation for the majority of compounds has an equatorial group on atom $C_{(5)}$. The 5-nitroderivative exists in the conformation with an axial nitro group.

The conformations of 1,3,2-dioxaborinanes are largely determined by the electronic interactions in the B–O bonds. Thus, the majority of these molecules have a preferred half-planar shape [1-3]. Quantum chemical calculations confirm the suitability of this conformation [4]. The present work reports an NMR study of the conformation of 2,5-substituted 1,3,2-dioxaborinanes with different substituents on atom $C_{(5)}$ (Table 1).

It has already been noted that the heteroatomic fragment increases (in comparison to the analogs without boron, 1,3-dioxanes) the conformational energy of the alkyl substituent on $C_{(5)}$ [3]. For a methyl group, the experimental values are ΔG^0 = 3.3-4.2 kJ/mole for 1,3-dioxanes [9] and at least 10.5 kJ/mole for 1,3,2-dioxaborinanes. The latter values were obtained from data for the configurational isomerization of 2-isopropyl-4,5-dimethyl-1,3,2-dioxaborinane [10]. It seemed interesting to measure the energy by an independent method using averaged and standard SSCC and the equation [11]

$$^3J_{AX}+{}^3J_{BX}=N(J_{aa}+J_{ae})+(1-N)(J_{ea}+J_{ee}),$$

where N is the fraction of equatorial conformer, $^3J_{AX}$ and $^3J_{BX}$ are the observed (averaged) SSCC in the molecule studied, and J_{ae}, J_{ee}, J_{aa}, and J_{ea} are the standard SSCC. Using the constants from the spectra of cis- and trans-2-isopropyl-4,5-dimethyl-1,3,2-dioxaborinane (J_{aa} = 10.5, J_{ae} = 4.4, J_{ea} = 7.4, J_{ee} = 4.2 Hz [3]), we find that N = 0.97 for compound I. This means that at room temperature in the equilibrium system

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