2,4-DIARYL-2,3-DIHYDRO-1H-PYRIMIDO[5,6-b]-1,5-DIAZEPINES

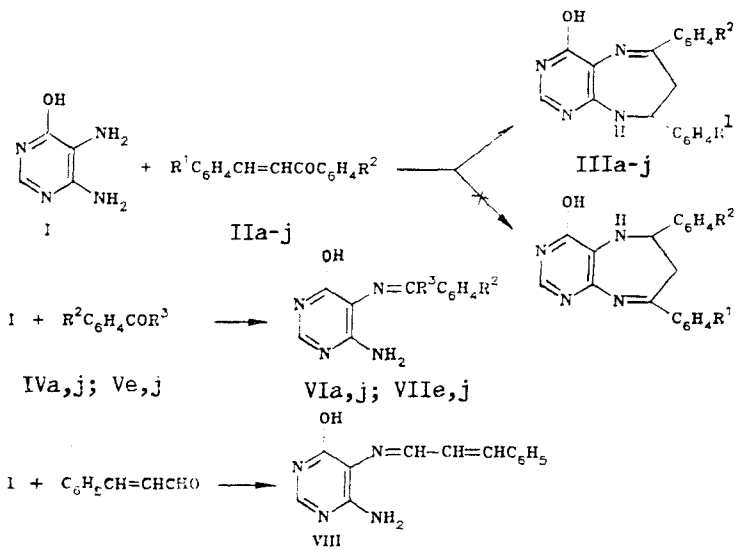
V. D. Orlov, N. N. Kolos, E. V. Zhidkova, and I. Z. Papiashvili

UDC 547.892'859.07:543.51'422

It has been shown that chalcones react with 5,6-diamino-4-hydroxypyrimidine to form 2,3-dihydro-1H-pyrimido[5,6-b]-1,5-diazepines but aromatic aldehydes and methyl ketones give the monoazomethines. The mechanism and tendency to form the 7-membered ring are discussed.

It has previously been shown [1] that reaction of 5,6-diamino-1,3-dimethyluracil with α,β-unsaturated ketones, depending on the nature of the carbonyl component, forms a 2,3-dihydro-1,5-diazepine (or 2,3-dihydro-1,5-oxazepine) ring annelated to the pyrimidine nucleus. Extending this investigation, we have studied the reactions of 5,6-diamino-4-hydroxypyrimidine (I) with chalcones IIa-j, aromatic aldehydes IVa, i, and methyl ketones Ve, j.

It was shown that refluxing equimolar amounts of I and IIa-j in methanol for 3.5-4 h with catalytic additions of acetic acid forms 2,4-diaryl-6-hydroxy-2,3-dihydro-1H-pyrimido[5,6-b]-1,5-diazepines (IIIa-j). A similar result was achieved by refluxing compounds I and IIa in DMF for 2-2.5 h. Catalysis by triethylamine, used in the synthesis of dihydrobenzodiazepines [2], proved ineffective.



II—VII a R^1=H, b R^1=2-OH, c R^1=4-Br, d R^1=4-NO_2, e-j R^1=H; a-d R^2=H, e R^2=2-OH, f R^2=4-CH_3, g R^2=4-OCH_3, h R^2=4-Cl, i R^2=4-Br, j R^2=4-NO_2; IV, VI R^3=H; V, VII R^3=CH_3

The basic spectral criteria for 2,3-dihydrodiazepines noted in [1, 2] are repeated for compounds IIIa-j. Thus $\nu_{C=N}$ and ν_{N-H} IR spectral bands are given in Table 1. Introduction of the 2-hydroxy group as the R^1 substituents causes a lowering, and as the R^2 substituent an increase in the ν_{N-H} frequency. Both effects are due to the formation of intramolecular hydrogen bonds (IMHB), but in the first case the NH group is a direct participant in the IMHB (—N—H · · · O—), and in the second this group receives the effect of the azomethine fragment, taking part in the process —CN · · · H—O—. The IR spectra of IIIa-j could not identify a clearly defined ν_{O-H} band, probably because of the considerable broadening and low-frequency shift of these bands which can occur through an intermolecular association involving this group. In addition, the IR spectra of IIIa-j do not show amide type $\nu_{C=O}$ bands; hence an alternative amide-type tautomer can be excluded in the crystalline state.

A. M. Gorkii State University, Khar'kov. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 250-255, February, 1991. Original article submitted June 27, 1989.

0009-3122/91/2702-0205$12.50

TABLE 1. Properties of Synthesized Compounds

Compound	Empirical formula	Mp, °C	R_f	IV spectrum, λ_{max}, nm ($\varepsilon 10^{-2}$)	IR spectrum (KBr), ν, cm^{-1}		Yield, %
					C=N	N–H	
IIIa	$C_{19}H_{16}N_4O$	208...209	0.48	274 (7,4), 370 (7,2)	1642	3236	72
IIIb	$C_{19}H_{18}N_4O_2$	171	0.52	297 (13,1), 357 (11,4)	1642	3216	41
IIIc	$C_{19}H_{15}BrN_4O$	235...236	0.50	273 (11,5), 375 (10,9)	1638	3243	76
IIId	$C_{19}H_{15}N_5O_3$	228...229	0.51	272 (16,5), 369 (6,3)	1625	3236	72
IIIe	$C_{19}H_{16}N_4O_2$	248...250	0.45	277 (14,8), 379 (10,2), 400 (4,7)	1652	3263	59
IIIf	$C_{20}H_{18}N_4O$	240...241	0,49	274 (10,2), 370 (9,5)	1638	3243	55
IIIg	$C_{20}H_{18}N_4O_2$	250...251	0,47	282 (10,4), 373 (8,1)	1635	3229	64
IIIh	$C_{19}H_{15}ClN_4O$	234	0,51	297 (10,5), 374 (9,9)	1628	3242	77
IIIi	$C_{19}H_{15}BrN_4O$	237	0,53	297 (12,8), 375 (8,8)	1642	3236	69
IIIj	$C_{19}H_{15}N_5O_3$	279...282	0,46	261 (24,2), 313 (15,1), 409 (5,3)	1642	3246	80
VIa	$C_{11}H_{10}N_4O$	275	0,45	283 (8,7), 360 (14,8)	1628	3290*, 3469	83
VIj	$C_{11}H_9N_5O_3$	>300	0.49	269 (7,6), 403 (3,3)	1625	3283, 3463	96
VIIe	$C_{12}H_{12}N_4O_2$	272...273	0,39	258, 357**	1625	3303, 3403	85
VIIj	$C_{12}H_{11}N_5O_3$	>300	0.33	264, 307, 405	1628	3315, 3422	70
VIII	$C_{15}H_{12}N_4O$	236...238	0,85	279, 380	1615	3285, 3435	89

*Separation of NH_2 and OH stretching bands very difficult.
**Spectrum qualitative because of low solubility.

TABLE 2. PMR Spectra* of Compounds IIIa, d, g

Compound	Chemical shift, δ, ppm						J, Hz		
	CH_2–CH			N–H, s	OH, s	H**, s	AB	AX	BX
	A, dd	B, dd	X, dd						
IIIa	2,88	3,66	5,18	4,28	11,60	7,79	13,8	5,2	6,2
IIId	2,89	3,82	5,39	4,36	11,48	8,01	14,6	5,2	6,6
IIIg	2,81	3,70	5,18	4,30	11,62	7,79	14,0	5,0	6,0

*Aromatic proton multiplets occur in the region 7.24-7.76 ppm.
**Pyrimidine ring proton.

Electronic absorption spectra of IIIa-j are typical for annelated dihydrodiazepines systems [1, 2] and are characterized by the presence in the near UV of two basic, resolved π–π^*-type bands (Table 1).

The PMR spectra (DMSO) of IIIa, d, g uniquely identify all of the heterocycle proton signals with the expected multiplicity (Table 2). Comparison of the spectral characteristics for CH_2CH in IIIa and 2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine (IX, δ_A 2.90, δ_B 3.08, δ_X 4.99 ppm, J_{AB} = 13.6, J_{AX} = 3.56, and J_{BX} = 8.85 Hz [3]) draws attention to the marked paramagnetic shift of one of the protons of the methylene group ($\Delta\delta_B$ = 0.58 ppm) in the spectrum of IIIa and the change in vicinal coupling constant J. On their basis the dihedral angles formed by the vicinal C–H bonds (θ_{AX} and θ_{BX}) were found to be 48 and 168° for IX and 37 and 146° for IIIa. Undoubtedly this is partly due to an increase in the electron-acceptor effect of the pyrimidine ring on the seven-membered heterocycle when compared with the o-phenylene nucleus. On the other hand, the change in θ_{AX} and θ_{BX} supports the proposal that exchange of the benzene ring for pyrimidine is also reflected in the conformation of the dihydrodiazepine ring. According to [3, 4], this ring in molecule IX is a slightly distorted boat in which the 2-phenyl occupies an equatorial (in solution, by NMR or dipole moments) or axial position (in the crystal, x-ray diffraction). Judged by the values of θ_{AX} and θ_{BX}, the molecule IIIa occurs as a slightly flattened boat.

TABLE 3. Mass Spectra of Pyrimido[5,6-b]-1,5-diazepines

Compound	m/z (I, %)*
IIIa	*316* (100), 301 (24), 239 (32), 212 (60), 206 (30), 191 (12), 137 (21), 110 (32), 104 (40), 103 (25), 89 (8), 77 (29)
IIIc	*394*• (100), 379• (53), 290• (67), 239 (44), 213 (47), 212 (59), 182• (45), 137 (88), 110 (90), 104 (47), 102 (47), 77 (43)
IIId	*361* (100), 346 (24), 315 (19), 284 (21), 257 (25), 252 (67), 239 (47), 212 (46), 211 (42), 189 (19), 137 (30), 110 (90), 104 (60), 103 (51), 77 (44)
IIIg	*346* (100), 345 (65), 331 (50), 269 (45), 242 (32), 212 (69), 137 (41), 134 (15), 107 (15), 104 (65), 77 (45)
IIIh	*350*• (100), 349• (23), 335• (34), 273• (19), 247• (25), 246• (76), 240 (44), 239 (38), 213 (33), 212 (32), 189 (21), 139• (24), 137• (18), 125 (19), 115 (21), 111• (30), 110 (92), 104 (53), 77 (53)
IIIi	*394*• (100), 379• (20), 290• (41), 239 (41), 212 (46), 211 (15), 182• (40), 137 (73), 110 (90), 104 (47), 102 (51), 77 (60)

*Monoisotopic ion peaks are given. The molecular ion peaks are given in italics. The asterisk indicates the ion containing the lighter halogen isotope.

In most examples reported in [5], it was shown that fragmentation of 2-R-4-$R^1C_6H_4$-2,3-dihydro-1H-1,5-benzodiazepines under electron impact occurs by three preferred routes: contraction of the diazepine ring to pyrazine (with loss of CH_3•) of imidazole (with loss of R-styrene), and loss of the R^1-radical. This was confirmed in later work [6]. Analysis of their mass spectra also shows that similar processes also dominate in III (Table 3). An important feature of these spectra is the fact that the maximum intensity characterizing the molecular ion peaks is a result of the high thermodynamic stability of the M^+• when compared with dihydrobenzodiazepines. In addition, in the spectra of the III molecules, the intensity of the $[M-R^2C_6H_4CH=CH_2]^+$• ions is only slightly greater than that of the $[M-R^1C_6H_4CH=CH_2]^+$• ions. As a result, the spectra of the isomeric IIIc and IIIi are extremely similar. However, in our opinion, this does not mean that formation of purine ions under electron impact takes place as selectively as for benzimidazoles. It is more likely, for reasons mentioned above, that the volatility of III is reduced by intermolecular association, and this results in an increase in the inlet temperature needed ($\geq$150°C) and a resulting increase in the likelihood of thermolysis [5].

Thus, combination of the spectral characteristics and elemental analytical data for nitrogen shows that the hydrolysis of the 6-amino group accompanying the reaction of 5,6-diamino-1,3-dimethyluracil with chalcones [1] is not typical for I. It can be explained by a preference for I to exist in the 4-hydroxy form, inhibiting the formation of the 6-imino tautomer which takes part in the hydrolysis process as proposed in [1].

The data given above do not answer the question of the direction of the reaction relative to the nonequivalent amino groups in I. A similar problem was solved [7] by comparison of the electronic absorption spectra of the dihydrodiazepines with model azomethines.

Diamine I readily reacts with aromatic aldehydes IVa, j by a short reflux of the starting reagents in ethanol to form the monoazomethines VIa, j (Table 1). The aldehydes were chosen because the change from R^2 = H to 4-NO_2 achieves a maximum bathochromic effect for the long-wavelength band in the azomethine spectra. The properties of the pyrimidine 5- and 6-amino groups are so different (the 5-amino group being most typical of aromatic amines [8]) that a preference for formation of the monoazomethine at the 5-amino group is not in doubt.

Supportive evidence comes from the quantum chemical calculations for the spectra of VIa and the alternative 6-azomethine (VIa') (Table 4) with the better agreement with experiment being obtained for the 5-azomethine structure. There is good agreement between the UV spectra of VIa, j and IIIa, j (Table 1); hence they have the same chromophoric system, and this confirms the structure of all the dihydropyrimidinodiazepines III.

Quantum chemical calculation also shows that the long-wavelength band in the spectra of III and VI is due to the single-electron transition 0 → 1 which is localized on the N–Pyr–N=C–Ph fragment. The transition is accompanied by a significant (0.5 e) transfer of electron density from the imino group and the pyrimidine ring to the phenylazomethine fragment. Hence it follows that introduction of electron-acceptor substituents (especially R^2 = 4-NO_2) facilitates this charge transfer and is accompanied by a bathochromic shift of the long-wavelength absorption band. This band is also sensitive to conformational changes of the chromophore; hence, inclusion in a seven-membered ring shows a small bathochromic effect (Table 1).

The second experimentally observed band is assigned to the 0 → 4 transition and is characterized by preferred localization of the transition on the pyrimidine fragment.

TABLE 4. Calculations for the Planar Model Monoazomethine VIa and Alternative VIa'

Electronic transition	UV spectral band	E_{calc}, eV	f_{calc}	E_{exp}, eV	f_{exp}	Transition localization, %				Change in electron density,			
						N	Pyr	N=C	Ph	N	Pyr	N=C	Ph
					Compound	*VI*							
1	1	3,29	0,61	3,44	0,42	23	27	17	33	−0,2	−0,03	0,34	0,16
2		4,03	0,08	—	—	13,5	61,5	6,9	18,1	−0,09	−0,11	0,06	0,14
3		4,4	0,002	—	—	1,1	10,6	9,3	79,0	−0,03	−0,13	−0,01	0,17
4	2	4,59	0,51	4,38	0,60	22,0	43,6	20,9	13,5	−0,07	−0,11	0,15	0,3
					Compound	*VIa'*							
1	1	3,11	0,44			18,9	38,5	27,8	14,8	−0,22	−0,36	0,19	0,39
2		4,03	0,004			10,1	18,5	1,0	70,4	−0,07	−0,15	0,2	0,02
3		4,35	0,04			2,7	71,2	9,9	16,2	−0,02	−0,08	0	0,1
4	2	4,42	0,32			19,4	29,7	26,4	24,5	−0,01	−0,15	0,16	0

The electronic absorption spectrum of IIIe (R^2 = 2-OH, Table 1) is a special case. The presence in this molecule of a rather strong IMHB, formed by the ortho-hydroxy group and the azomethine nitrogen, probably leads to the electron transition being principally localized on the arylazomethine fragment: a phenomenon seen in o-hydroxybenzalanilines [9].

An important question in the reaction of unsaturated ketones with dinucleophiles concerns the successive stages of β-addition and condensation. It is known [10] that dihydrodiazepine ring formation can occur by both routes. In a number of cases it was possible to obtain unambiguous answers by identifying the process intermediates. Spectroscopic monitoring of the reaction of I and IIa shows that the electronic spectrum after 1.5 h shows both the chalcone band at 312 nm and a band near 380 nm which eventually disappears to give a band with λ_{max} 370 nm. We propose that the band at 380 nm can be assigned to the azomethine formed by diamine I and chalcone IIa (the possible β-adduct does not have such an extended chromophoric system) and we have synthesized the monoazomethine VIII from diamine I and cinnamaldehyde with measurement of its UV spectrum. As expected, this spectrum (Table 1) is identical to that of the intermediate. These results agree with the previously expressed proposition [10] that the first stage of the condensation is primarily characterized by an acid catalyzed reaction of diamines with unsaturated ketones.

Additional information concerning the reactivity of the amino groups in I results from a study of its reaction with acetophenone (Va) and substituted analogs Ve, j. Reaction to form monoazomethines VIIe, j could be seen only when refluxing the starting materials in alcohol with catalytic addition of concentrated sulfuric acid. Acetophenone was returned unchanged in all cases, but the acetones formed an oily material, presumably products of its self-condensation. Formation of the dihydrodiazepines was not observed in any conditions. This can be explained by a lowering of the ability of the 6-amino group to react by condensation which, in the given case, is of primary importance since the mechanism of seven-membered ring formation in the reaction of methyl ketones with o-diamines includes a bisazomethine stage [10].

EXPERIMENTAL

IR spectra were measured on a Specord IR-75 (KBr tablets), electronic absorption spectra on a Specord M-40 [in ethanol solvent at a concentration of $(2\text{-}3) \cdot 10^{-5}$ M], and PMR spectra on a Varian XL-100 instrument using DMSO-D_6 as solvent and TMS as internal standard. Mass spectra were recorded on a Varian MAT-311 instrument with ionizing energy 70 eV. The purity of the materials was monitored by TLC using Silufol-254 plates with chloroform eluent. Quantum chemical calculations were carried out using the PPP-50 program with a standard parameter set.

Elemental analytical data for N agreed with that calculated.

2,4-Diphenyl-6-hydroxy-2,3-dihydropyrimido[5,6-b]-1H-1,5-diazepine (IIIa). A. A solution of I (1.0 g, 7.9 mmoles) and chalcone (1.65 g, 7.9 mmoles) in a mixture of methanol (30 ml) and acetic acid (1 ml) was refluxed for 4 h, filtered hot with removal of unreacted diamine, and cooled to precipitate yellow crystals of IIIa (1.8 g). Compounds IIIb-j were obtained similarly. B. A solution of I (1.0 g, 7.9 mmoles) and chalcone (1.65 g, 7.9 mmoles) in DMF (10 ml) was refluxed for 2.5 h, mixed with methanol (20 ml), and filtered to give IIIa (2.0 g, 80%).

Condensation of Diamine I with Aromatic Aldehydes. A solution of I (1.26 g, 10 mmoles) and benzaldehyde (1.06 g, 10 mmoles) in methanol (40 ml) was refluxed for 5-10 min. Yellow crystalline VIa precipitated from the hot solution.

Compounds VIj and VIII were obtained similarly.

Condensation of Diamine I with Acetophenones. A solution of I (1.26 g, 10 mmoles) and o-hydroxyacetophenone (1.36 g, 10 mmoles) in a mixture of methanol (40 ml) and concentrated H_2SO_4 (2 ml) was refluxed for 4 h. After cooling, the reaction mixture was neutralized with ammonia solution and the precipitate filtered off to give VIIe (2.07 g).

Compound VIIj was obtained similarly.

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NITROAZINES.

12.* REACTION OF 6-NITROAZOLO[1,5-*a*]PYRIMIDINES WITH ACETONITRILES

O. N. Chupakhin, V. L. Rusinov, A. A. Tumashov, T. L. Pilicheva, E. O. Sidorov, and I. V. Karpin

UDC 547.859.3.04'828'792.8.04: 543.422

Reaction of 6-nitroazolo[1,5-a]pyrimidines with cyanoacetamide, cyanoacetthioamide, or benzoylacetonitrile results in the conversion of the pyrimidine ring into a pyridine ring with the formation of 2-azolylamino-5-nitropyridines. Treatment of the latter with alcoholic sodium carbonate, or reaction of the azolopyrimidines with acetonitriles in an alkaline medium, affords 7-nitroazolo]1,5-a]pyrido[2,3-d]pyrimidines.

6-Nitroazolo[1,5-*a*]pyrimidines are, somewhat unexpectedly, converted into 2-azolylamino-3-ethoxycarbonyl-5-nitropyridines on treatment with cyanoacetic ester [1]. Unlike the reactions of monocyclic nitropyrimidines with cyanoacetic ester [2, 3], this reaction does not involve elimination of a C—N fragment from the pyrimidine ring, nor does it require further activation of either the reactant or the substrate.

We here consider the reactions of azoloannelated nitropyrimidines with other acetonitriles in order to determine the range of applicability of these reactions, and to obtain information on some of the properties of the transformation products.

It has been found that 6-nitro-1,2,4-triazolo- and 6-nitropyrazolo-[1,5-*a*]pyrimidines (Ia-j), on heating with cyanoacetamide (II), cyanoacetthioamide (III), or benzoylacetonitrile (IV), are converted into the 2-azolylamino-3-R-5-nitropyridines (VI)-(VIII) (Table 1) (see scheme on page 211).

The transformation products (VIa-f, i, j) and (VIIIa, b, e) are obtained readily on boiling the reactants for 30 min in ethanol. The reactions of the less electrophilic 2-amino- and 2-diethylamino-6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidines (Ig, h) with cyanoacetamide do not proceed so readily, (VIg, h) being obtained only on heating at 100°C in DMSO. The 2-triazolylamino-5-nitronicotinothioamides (VIIa, b) were obtained when the reactions with (III) were carried out in absolute ethanol. When these reactions were carried out in solvents containing water, hydrolysis of the thioamide group occurred with the formation of the nicotinamides (VI).

The less CH-acidic chloroacetonitrile, tosyloxyacetonitrile, benzyl cyanide, and cyanomethoxybenzimidazole failed to react with the azolopyrimidines (Ia-j) under these conditions.

*See [1] for communication 11.

S. M. Kirov Urals Polytechnic Institute, Sverdlovsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 256-291, February, 1991. Original article submitted June 5, 1989.

 0009-3122/91/2702-0210$12.50