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IMINE—ENAMINE TAUTOMERISM OF DIHYDROAZOLOPYRIMIDINES. 3.* 5-ARYL-SUBSTITUTED 4,7(6,7)-DIHYDRO-1,2,4-TRIAZOLO[1,5-*a*]PYRIMIDINES

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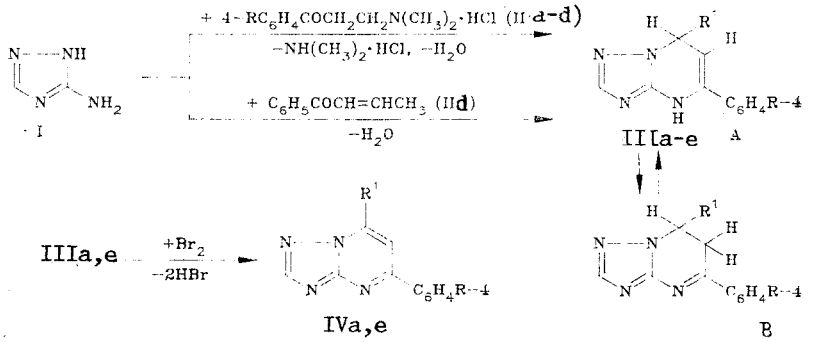
5-Aryl-substituted 4,7(6,7)-dihydro-1,2,4-triazolo[1,5-a]pyrimidines were obtained by condensation of 3-amino-1,2,4-triazole with β-dimethylaminopropiophenone hydrochlorides or crotophenone. The effect of steric and electronic factors on the position of the imine—enamine equilibrium in solutions of the synthesized substances is examined. 5-Phenyl-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine was subjected to x-ray diffraction analysis.

We have previously established [1] that the steric and electronic effects of substituents in the pyrimidine ring of dihydropyrimido[1,2-*a*]benzimidazoles may have a substantial effect on the position of the imine—enamine tautomeric equilibrium. The aim of the present research was to investigate this phenomenon in a series of aromatic substituted 4,7(6,7)-dihydro-triazolo[1,5-*a*]pyrimidines IIIa-e.

Substances IIIa-d were obtained by condensation of 3-amino-1,2,4-triazole (I) with β-dimethylaminopropiophenone hydrochlorides IIa-d, while 7-methyl-substituted IIIe was obtained by the reaction of amine I with 1-phenyl-2-buten-1-one (IIe) in DMF. In the synthesis of IIId under these conditions we observed appreciable resinification, which markedly decreases the yield of the reaction product (Table 1) and can be avoided by using isopropyl alcohol as the solvent. Ketones IIa-c also react with amine I in isopropyl alcohol, while crotophenone (IIe) is not sufficiently reactive and, like chalcones [2], does not react with amine I.

The dehydrogenation of IIIa, e to give their heteroaromatic analogs IVa, e was accomplished by the action of bromine in acetic acid.



II—IVa, e R=H, b R=CH_3, c R=Cl, r R=NO_2; a-d R^1=H, e R^1=CH_3

*See [1] for Communication 2.

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TABLE 1. Characteristics of IIIa-e and IVe*

Compound	Empirical formula	mp, °C	$\nu_{C=C}$, cm^{-1} (in KBr)	$\nu_{C=C}$, cm^{-1} (in KBr)	Yield, %	
					A	B
IIIa	$C_{11}H_{10}N_4$	201...203	1655	285 (3,4)	70	35
IIIb	$C_{12}H_{12}N_4$	178...180	1652	281 (3,6)	65	43
IIIc	$C_{11}H_9ClN_4$	208...210	1654	281 (3,4)	69	52
IIId	$C_{11}H_9N_5O_2$	242...244	1655	271 (13,5); 341 (3,5)	25	65
IIIe	$C_{12}H_{12}N_4$	175	1656	289 (4,1)	66	
IVe	$C_{12}H_{10}N_4$	158...159	—	247 (22,2); 293 (15,3)	75	

*Compound IVa was characterized in [3]; UV spectrum: 251 (17.9), 300 (14.6).

Substances IIIa-e and IVe were identified by spectral methods (Tables 1 and 2). Compound IVa was identical to a comparison sample obtained by the method in [3]. The IR spectra of dihydro derivatives IIIa-e (in KBr pellets) contain $\nu_{C=C}$ bands (1652-1659 cm^{-1}), which indicates their 4,7-dihydro structure in the solid phase. The electronic absorption spectra of IIIa-e are similar to the spectra of other 4,7-dihydrotriazolo[1,5-*a*]pyrimidines [2] and are characterized by the presence of a low-intensity absorption band at 281-341 nm (see Table 1). The absence of longer-wave absorption indicates, in conformity with [1, 2], the absence of imino form **B** also in alcohol solutions of these substances. Heteroaromatization of IIIa, e leads to the disappearance of bands of vibrations of C=C bonds in the IR spectra and to the appearance in the UV spectra of IVa, e of an intense band at 293-300 nm (see Table 1), which is typical for the spectra of 5-aryl-substituted 1,2,4-triazolo[1,5-*a*]pyrimidines [2, 3].

Unambiguous information regarding the tautomeric composition of IIIa, e in solution in d_6-DMSO and CF_3COOD is provided by their PMR spectra (see Table 2). Dihydro forms **B** have one hydrogen atom more in the 6 position of the bicyclic system than tautomers **A**, and their spectra differ substantially in the region of resonance of aliphatic protons (see Table 2). The spectra of solutions of IIId, e in d_6-DMSO characterize the individual dihydro forms **A** of the substances. In the spectra of IIIa-c, however, the signal of the proton of the triazole ring is split (the signal of the protons of the CH_3 group is also split in the case of IIIb). In addition, signals of protons of the $CHCH_2$ and CH_2CH_2 fragments of tautomers **A** and **B**, respectively, are present in them. A comparison of the integral intensities of these groups of signals made it possible to evaluate the tautomeric compositions of IIIa-c (see Table 2). In the case of measurements of solutions in CF_3COOD signals of the protons in the 6 position of the bicyclic systems of both tautomeric forms of IIIa-c, e do not appear because of rapid deuterium exchange. In these cases the existence in the solutions of mixtures of tautomers was manifested in splitting of the signals of the triazole protons, the protons in the 7 position of the bicyclic systems, and, in the case of IIIb, e, the protons of the methyl group (see Table 2). In IIId, which exists under these conditions exclusively in dihydro form **A**, deuterium exchange of the vinyl proton proceeds quite slowly (at 20°C, $t_{1/2} \approx 15$ min), which made it possible to record the signals of this proton also (see Table 2).

An analysis of the data presented in Table 2 makes it possible primarily to note an increase in the equilibrium concentration of tautomer **A** with intensification of the electron-acceptor character of substituent R (IIIa-d). Similar principles were observed for other dihydroazolopyrimidine systems [1, 2] and were linked with the manifestation of conjugation effects. 5,7-Diphenyldihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (III, R = H, $R^1 = C_6H_5$) exists in d_6-DMSO and CF_3COOH completely in 4,7-dihydro form **A** [2]. Taking this fact into account, an analysis of the tautomeric compositions of IIIa, e (see Table 2) shows that the introduction of a methyl and, particularly, a phenyl substituent into the 7 position of dihydrotriazolopyrimidines leads to relative stabilization of enamine tautomeric forms **A**. Considering that the electronic effect of the substituent in the 7 position of the dihydrotriazolopyrimidine bicyclic system cannot be great, the observed phenomenon should be associated with steric factors.

Let us also note the substantial effect of protonation processes on the tautomeric compositions (see Table 2). The observed increase in the concentrations of tautomers **B** on passing from solutions in d_6-DMSO to solutions in CF_3COOD is associated, in our opinion, with the greater basicities of these tautomeric forms.

An x-ray diffraction analysis of IIIa (Fig. 1, Tables 3 and 4) unequivocally confirmed its 4,7-dihydro structure in the solid phase. In the crystals the molecules of IIIa form centrosymmetric dimers that are linked by $N_{(4)}H_{(N4)}\cdots N_{(3')}$ hydrogen bonds [the $N_{(4)}\cdots N_{(3')}$, $N_{(4)}\cdots H_{(N4)}$, and $H_{(N4)}\cdots N_{(3')}$ distances are 2.96(5), 0.90(2), and 2.06(6) Å, respectively, and angle $N_{(4)}H_{(N4)}N_{(3')}$ is 171.6(2)°]. The formation of intermolecular hydrogen bonds is probably one of the factors that promote stabilization of enamine tautomeric forms **A** of IIIa-e in the solid phase.

The $N_{(4)}$ atom is plane-coordinated [its deviation from the $C_{(2)}C_{(3)}H_{(N4)}$ plane does not exceed 3σ], which indicates its sp^2 hybridization. In addition, The lengths of the $C_{(2)}\cdots N_{(4)}$ and $N_{(4)}\cdots C_{(3)}$ bonds, which are 1.354(2)

TABLE 2. PMR Spectra of Tautomers **A** and **B** of IIIa-e

Compound	Solvent	Arom. protons, m	Tautomer	Chemical shifts, δ, ppm (J, Hz)					Tautomer amt., %
				2-H (1H, s)	6-H	7-H	NH (1H, s)	CH_3	
IIIa	d_6-DMSO	7,3...7,6	A	7,67	5,16 (1H, t, J=3,2)	4,88 (2H, d)	9,6	—	85
			B	7,92	4,43 (2H, t, J=8,0)	3,47 (2H, t)	—	—	15
	d_6-DMSO	7,5...8,3	A	8,42	—	5,19 (2H, s)	—	—	50
			B	8,60	—	4,76 (2H, s)	—	—	50
IIIb	d_6-DMSO	7,1...7,5	A	7,68	5,10 (1H, t, J=3,4)	4,86 (2H, d)	9,6	2,31 (3H, s)	75
			B	7,90	4,39 (2H, t, J=8,2)	3,44 (2H, d)	—	2,38 (3H, s)	25
	d_6-DMSO	7,1...8,2	A	8,32	—	5,08 (2H, t)	—	2,46 (3H, s)	30
			B	8,49	—	4,64 (2H, s)	—	—	70
IIIc	d_6-DMSO	7,3...7,6	A	7,69	5,19 (1H, t, J=3,2)	4,87 (2H, d)	9,7	—	90
			B	7,97	4,34 (2H, t, J=8,4)	3,42 (2H, t)	—	—	10
	d_6-DMSO	7,1...8,3	A	8,39	—	5,16 (2H, s)	—	—	60
			B	8,58	—	4,73 (2H, s)	—	—	40
IIId	d_5-DMSO	7,5...8,4	A	7,77	5,40 (1H, m, J=3,5)	4,87 (2H, d)	9,8	—	100
	CF_3COOD	7,6...8,4	A	8,45	5,64 (1H, t, J=3,1)	5,21 (2H, d)	—	—	100
IIIe	d_6-DMSO	7,2...7,6	A	7,66	5,10 (1H, d, J=2,8)	5,15 (1H, m)	9,7	1,50 (d J=6,0)	100
			A	8,34	—	5,42 (1H, q)	—	1,79 (d J=5,9)	55
	CF_3COOD	7,4...8,3	B	8,53	—	4,89 (1H, q)	—	1,81 (d J=5,9)	45

TABLE 3. Some Bond (ω) and Torsion (τ) Angles in the IIIa Molecule

Angle	ω°	Angle	τ°
$N_{(2)}N_{(1)}C_{(1)}$	101,5(1)	$N_{(2)}N_{(1)}C_{(1)}N_{(3)}$	0,5(2)
$N_{(1)}C_{(1)}N_{(3)}$	116,0(2)	$N_{(1)}C_{(1)}N_{(3)}C_{(2)}$	−0,4(2)
$C_{(1)}N_{(3)}C_{(2)}$	101,9(2)	$C_{(1)}N_{(3)}C_{(2)}N_{(2)}$	0,1(2)
$N_{(3)}C_{(2)}N_{(2)}$	110,8(1)	$N_{(3)}C_{(2)}N_{(2)}N_{(1)}$	0,2(1)
$C_{(2)}N_{(2)}N_{(1)}$	110,0(1)	$N_{(2)}C_{(2)}N_{(4)}C_{(3)}$	−5,2(2)
$N_{(2)}C_{(2)}N_{(4)}$	121,6(2)	$C_{(2)}N_{(4)}C_{(3)}C_{(4)}$	5,0(2)
$C_{(2)}N_{(4)}C_{(3)}$	118,0(1)	$N_{(4)}C_{(3)}C_{(4)}C_{(5)}$	−0,9(2)
$N_{(4)}C_{(3)}C_{(4)}$	120,8(2)	$C_{(3)}C_{(4)}C_{(5)}N_{(2)}$	−2,7(1)
$C_{(3)}C_{(4)}C_{(5)}$	124,9(2)	$C_{(4)}C_{(5)}N_{(2)}C_{(2)}$	2,6(2)
$C_{(4)}C_{(5)}N_{(2)}$	108,0(2)	$C_{(5)}N_{(2)}C_{(2)}N_{(4)}$	1,2(1)
$C_{(5)}N_{(2)}C_{(2)}$	126,5(1)	$C_{(3)}C_{(4)}C_{(5)}H_{(5A)}$	117,5(7)
$C_{(7)}C_{(6)}C_{(11)}$	117,9(2)	$C_{(3)}C_{(4)}C_{(5)}H_{(5B)}$	−119,7(8)
$C_{(6)}C_{(11)}C_{(10)}$	121,2(2)	$C_{(4)}C_{(3)}C_{(6)}C_{(11)}$	−32,6(2)
$C_{(6)}C_{(7)}C_{(8)}$	120,7(2)	$N_{(4)}C_{(3)}C_{(6)}C_{(7)}$	−30,4(1)

TABLE 4. Coordinates of the Nonhydrogen Atoms ($\cdot 10^4$) and Hydrogen Atoms ($\cdot 10^3$) of the IIIa Molecule

Atom	x	y	z	Atom	x	y	z
$N_{(1)}$	−3725(2)	3958(2)	−4147(1)	$C_{(10)}$	2745(2)	4291(4)	−672(2)
$N_{(2)}$	−2601(1)	3826(2)	−3522(1)	$C_{(11)}$	1471(2)	4333(3)	−1101(2)
$N_{(3)}$	−1837(2)	4534(2)	−5024(1)	$H_{(1)}$	−387(2)	462(3)	−565(2)
$N_{(4)}$	−262(2)	4094(2)	−3613(1)	$H_{(N_4)}$	−42(2)	455(3)	−397(2)
$C_{(1)}$	−3202(2)	4390(3)	−5026(2)	$H_{(4)}$	−110(2)	317(3)	−127(2)
$C_{(2)}$	−1507(2)	4167(2)	−4054(1)	$H_{(5A)}$	−308(2)	15(3)	−237(2)
$C_{(3)}$	−155(2)	3794(3)	−2553(1)	$H_{(5B)}$	−323(2)	434(3)	−210(2)
$C_{(4)}$	−1243(2)	3453(3)	−2011(2)	$H_{(7)}$	213(2)	281(3)	−337(2)
$C_{(5)}$	−2640(2)	3380(3)	−2441(2)	$H_{(8)}$	433(2)	278(3)	−267(2)
$C_{(6)}$	1223(2)	3793(3)	−2675(2)	$H_{(9)}$	470(2)	365(3)	−93(2)
$C_{(7)}$	2311(2)	3228(3)	−2108(1)	$H_{(10)}$	291(2)	468(3)	3(2)
$C_{(8)}$	3591(2)	3197(3)	−2242(2)	$H_{(11)}$	71(2)	479(3)	−74(2)
$C_{(9)}$	3811(2)	3716(3)	−1241(2)				

Å and 1.404(2) Å, respectively (see Fig. 1), provide evidence for substantial conjugation of the unshared electron pair of the $N_{(4)}$ atom with the π systems of the triazole ring and the double bond, which is manifested, in particular, in the acidic character of the imino proton of the aromatic substituted 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines [5].

As in other dihydrotriazolo[1,5-*a*]pyrimidines [2], the triazole ring in the IIIa molecule is planar (see the torsion angles in Table 3). With an accuracy of no less than 3σ, the $N_{(2)}$, $C_{(2)}$, $C_{(3)}$, and $C_{(4)}$ atoms of the dihydropyrimidine ring are also located in a single plane, while the $C_{(5)}$ and $C_{(4)}$ atoms deviate from this plane on the same side by 0.033(3) Å and 0.05(3) Å, which indicates that the dihydropyrimidine ring exists in the form of a markedly flattened boat. The puckering parameter S of IIIa calculated in conformity with [4] is 0.007, which is significantly smaller than the corresponding value for 7-(4-methylphenyl)-5-phenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (III, R = H, R^1 = 4-$CH_3C_6H_4$, S = 0.25). This fact constitutes evidence that the substituent attached to the sp^3-hybridized carbon atom has a substantial effect on the degree of flattened character of the dihydropyrimidine ring in 4,7-dihydrotriazolopyrimidine derivatives. This result also reflects the high conformational lability of 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines, which, in our opinion, is also the reason for the above-noted relative stabilization of the 4,7-dihydro forms when bulky substituents R^1 are introduced.

EXPERIMENTAL

X-ray Diffraction Study. The IIIa crystals were monoclinic and had the following parameters at 20°C: a = 9.968(2), b = 7.354(1), c = 13.065(3) Å, β = 91.61(3)°, Z = 4, d_{calc} = 1.375 g/cm^3, space group $P2_1/C$. The cell parameters and intensities of 1235 reflections with $|F| > 4\sigma(F)$ were measured with a Hilger—Watts automatic four-circle diffractometer with a graphite monochromator in Mo K_α emission.

The structure was decoded by the direct method by means of the complex of SHELXTL PLUS programs. All of the hydrogen atoms were revealed by differential synthesis. The refinement within the anisotropic (isotropic for the hydrogen atoms) approximation was carried out up to R = 0.043 (R_w = 0.050). The coordinates of the atoms are presented in Table 4.

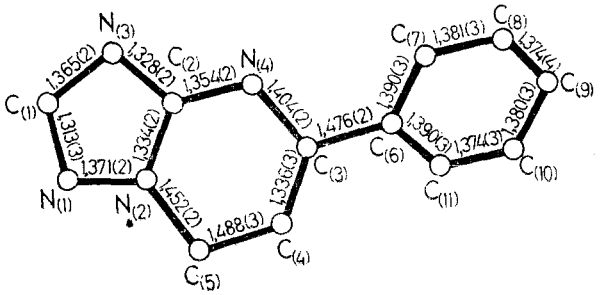

Fig. 1. Structure of the IIIa molecule (without the hydrogen atoms) with the bond lengths.

The IR spectra of KBr pellets of IIIa-e and IVa, e were recorded with a Specord IR-75 spectrometer. The UV spectra of solutions in ethanol [(3-5)·10^{-5} mole/liter] were recorded with a Specord M-40 spectrophotometer. The PMR spectra of solutions in CF_3COOD and d_6-DMSO were recorded with a Gemini-200 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The progress of the reactions and the purity of the substances formed were monitored by TLC on Silufol UV-254 plates with chloroform and acetone as the eluents.

The nitrogen percentages in the substances obtained were in agreement with the calculated values.

5-Phenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (IIIa). A. A solution of 1.1 g (5 mmole) of β-dimethylaminopropiophenone hydrochloride and 0.42 g (5 mmole) of 3-amino-1,2,4-triazole in 1 ml of DMF was refluxed for 30 min, after which it was cooled, and the resulting precipitate was removed by filtration to give 0.7 g (70%) of IIIa with mp 201-203°C (from isopropyl alcohol).

Compounds IIIb-e were similarly obtained.

B. The synthesis was carried out as in method A using isopropyl alcohol (5 ml) instead of DMF. Workup gave 0.35 g (35%) of IIIa.

Compounds IIIb-e were similarly obtained.

5-Phenyl-1,2,4-triazolo[1,5-*a*]pyrimidine (IVa, $C_{11}H_8N_4$). A mixture of 0.8 g of bromine and 5 ml of acetic acid was added with stirring to a solution of 1 g (5 mmole) of IIIa in 10 ml of acetic acid, after which the mixture was allowed to stand for 20 min and then mixed with 100 ml of water. The resulting precipitate was removed by filtration and chromatographed with a column packed with Al_2O_3 (diameter 1 cm, packing height 30 cm, chloroform as the eluent). The fraction with R_f 0.8 was collected to give 0.75 g (75%) of IVa with mp 186-188°C [3].

Compound IIIe was similarly obtained.

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