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IMINE—ENAMINE TAUTOMERISM OF DIHYDROAZOLOPYRIMIDINES

5.* STERIC EFFECTS AND THE TAUTOMERIC EQUILIBRIUM FOR DIHYDRO-1,2,4-TRIAZOLO[1,5-*a*]PYRIMIDINES

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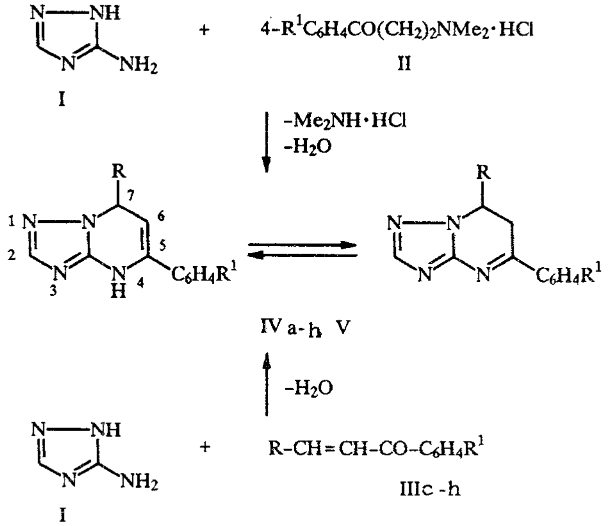
The reaction of 3-amino-1,2,4-triazole with β-dimethylaminopropiophenones or unsaturated ketones gives 5,7-disubstituted 4,7(6,7)-dihydro-1,2,4-triazolo[1,5-a]pyrimidines. An increase in the bulk of the substituent at $C_{(7)}$ in the bicyclic system leads to relative stabilization of the enamine tautomer of these compounds. An x—ray diffraction structural analysis of 7-tert-butyl-5-(4-methoxyphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-a]pyrimidine showed that the introduction of a tert-butyl group into the dihydropyrimidine ring leads to significant loss of planarity of this system.

In a continuation of a study of the effect of structural factors on the imine—enamine tautomeric equilibrium in dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines, we investigated derivatives containing substituents of various size at $C_{(7)}$. Products IVa-IVh were obtained by the reaction of 3-amino-1,2,4-triazole (I) with the hydrochloride salts of β-dimethylaminopropiophenones IIa and IIb or unsaturated ketones IIIc-IIIh according to a procedure described in our previous work [2].



II—IV a,b, R = H; c,d R = CH_3; e,f R = $(CH_3)_3C$; g,h R = C_6H_5; a,c,e,g R^1 = H; b,d,f,h R^1 = CH_3O; V R = $4\text{-}CH_3C_6H_4$, R^1 = H

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*For Communication 4, see [1].

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TABLE 1. Physical Indices of IVb, IVd-IVf, and IVh*1

Compound	Chemical formula	Mp, °C	IR spectrum, cm^{-1} $\nu_{C=C}$	UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	Yield, %
IVb	$C_{12}H_{12}N_4O$	162...164	1652	279 (5,5)*2, 325 (3,9)*2	70
IId	$C_{13}H_{14}N_4O$	149	1658	278 (4,5)	65
IVe	$C_{15}H_{18}N_4$	176...177	1652	281 (2,7)	62
IVf	$C_{16}H_{20}N_4O$	170...172	1666	284 (5,4)	68
IVh	$C_{18}H_{16}N_4O$	205	1668	282 (5,2)	70

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*1IVa, IVc, IVg, and V were characterized in our previous work [2, 3].

*2The determination of ε is difficult in light of the unknown tautomeric composition. Values of $[D_{max}/l \cdot (C_{"A"} + C_{"B"})] \cdot 10^{-3}$ are given.

Products IVb, IVd-f, and IVh were identified by spectral methods (Table 1), while IVa, IVc, and IVg were described in our previous work [2, 3]. The IR spectra of these products have strong $\nu_{C=C}$ bands at 1652-1668 cm^{-1}, indicating their 4,7-dihydro structure in the solid phase. The electronic absorption spectra of solutions of IVd-IVf and IVh are analogous to the spectra of other 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines, including IVa, IVc, and IVg [2, 3]. These spectra have weak bands at 279-284 nm. The lack of bands at longer wavelength indicates the absence of imine form B in solution [1, 4]. The spectrum of IVb differs from the spectra of the other products and has an additional band with λ_{max} 225 nm, probably related to the imine tautomer form.

PMR spectra gave unequivocal information on the tautomeric composition of IV in $CDCl_3$, DMSO-d_6, and CF_3CO_2D (Table 2). Dihydro form B has one hydrogen atom more at $C_{(6)}$ than tautomer A and, hence, the spectra of form B are significantly different in the aliphatic proton region. Comparison of the integral intensities of the corresponding groups of signals gave the tautomeric composition of these compounds (Table 3). The signals for 6-H in CF_3CO_2D solution do not appear due to their deuteroexchange. In this case, the formation of a mixture of tautomeric forms is seen in a double set of signals for 2-H, 7-H, and the substituents (when R = CH_3, $(CH_3)_3C$ or R^1 = CH_3O). The assignment of signals to specific protons was carried out using the position and integral intensity of the 7-H signal, which is found downfield in dihydro forms A relative to tautomers B by 0.04-0.6 ppm due to its allylic nature in forms A (Table 2).

Analysis of the data in Table 3 showed a steady increase in the equilibrium concentration of tautomers B upon introducing a methoxy group into the aryl substituent. A similar effect was observed in our previous work [2] and should be attributed to conjugation effects of the electron-donor R^1 substituent with the azomethine group and triazole system. The imine tautomer structure of dihydropyrimidines facilitates the manifestation of these conjugation effects.

A decrease in the concentration of tautomer A is observed in the series R = H, CH_3, $(CH_3)_3C$, and C_6H_5 in the case of identical R^1. In our previous work [1], we found in an analysis of the tautomeric composition of derivatives of IV with different R = Ar that there is only a slight shift in the equilibrium toward form B with increasing electron-donor capacity of R. Hence, the variation in the equilibrium composition for IVa-IVh cannot be attributed exclusively to the electronic effects of substituent R. In our view, steric factors play the predominant role in this effect (when R = CH_3, these effects may be partially compensated by electronic effects). The reason for the relative stabilization of dihydro forms A upon the introduction of bulky substituents R probably should be sought in the different conformational behavior of 4,7- and 6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines.

Using structural data for imine tautomer forms of dihydroazolopyrimidines, we have shown that the three-dimensional structure of their dihydropyrimidine fragment is hardly sensitive to the introduced substituents [5]. On the other hand, literature data on 1,4-dihydroaromatic systems indicated that dihydro forms A might have high conformational lability, permitting bulky substituents to occupy a more favorable position than in form B. In order to check this hypothesis, we carried out an x—ray diffraction structural analysis of IVf and these results were compared with the our previous data for IVa and V [2].

The triazole ring in IVf is planar. The bond lengths (Fig. 1) and bond angles (Table 4) are similar to those observed in other such compounds: 5-phenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (IVa) [3] and 5-phenyl-7-(4-methyl-phenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (V) [2].

TABLE 2. PMR Spectra of Tautomers A and B of IVa-IVh*

Compound	Solvent	Tautomer	Chemical shifts, δ, ppm, coupling constant, J, Hz				
			2-H (1H, s)	6-H	7-H	NH (1H, s)	CH_3 (3H, s)
IVa	$CDCl_3$	A	7,62	4,95 (1H t, 3,2)	4,89 (2H, d)	9,8	—
		B	7,86	3,28 (2H, t, 8,2)	4,34 (2H, d)		
IVb	$CDCl_3$	A	7,83	6H + 7H: 4,87 (3H, br.s)		9,5	3,80
		B	7,99	3,23 (2H, t, 8,2)	4,31 (2H, t)	—	3,85
		A	7,72	5,05 (1H, t, 3,2)	4,85 (1H, d)	9,6	3,77
		B	7,90	3,59 (2H, t, 8,2)	4,33 (2H, t)	—	3,85
	CF_3COOD	A	8,30	—	5,16 (2H, s)	—	3,94
		B	8,43	—	4,60 (2H, s)	—	3,97
IVc	$CDCl_3$	A	7,70	4,90 (1H, d, 3,3)	5,10 (1H, m)	9,7	1,50 (d, 6,3)
		B	7,90	H_A: 2,89 (1H dd) H_B: 3,40 (1H, dd) J_{AB} = -17,6	H_X: 4,42 (1H, m) J_{AX} = 8,4 J_{BX} = 7,1	—	1,46 (d, 6,4)
IVd	$CDCl_3$	A	7,83	4,81 (1H, d, 3,2)	5,13 (1H, m)	9,6	1,55; 3,78
		B	8,00	H_A: 2,88 (1H, dd) H_B: 3,33 (1H, dd) J_{AB} = -17,4	H_X: 4,48 (1H, m) J_{AX} = 8,6 J_{BX} = 7,0	—	1,51 (d, 6,2) 3,81
		A	7,65	4,99 (1H, d, 3,0)	5,11 (1H, m)	9,6	1,49 (d, 6,4) 3,77
		B	7,85	3,20 (2H, d, 6,9)	4,58 (1H, m)	—	1,46 (d, 6,4) 3,85
	CF_3COOD	A	8,35	—	5,38 (1H, q)	—	1,74 (d, 6,5) 3,94
		B	8,42	—	4,77 (1H, q)		1,71 (d, 6,6) 3,96
IVe	$CDCl_3$	A	7,80	5,06 (1H, d, 4,6)	4,81 (1H, d)	9,9	1,00 (9H)
		A	7,65	5,07 (1H, d, 4,0)	4,78 (1H, d)	9,7	0,93 (9H)
	CF_3COOD	A	8,41	5,56 (1H, d, 4,6)	5,13 (1H, d)	—	1,21 (9H)
		B	8,55	—	4,78 (1H, s)	—	1,15 (9H)
IVf	$CDCl_3$	A	7,85	4,95 (1H, d, 4,6)	4,79 (1H, d)	9,9	1,01 (9H) 3,85
		B	8,15	H_A: 3,01 (1H, dd) H_B: 3,64 (1H, dd) J_{AB} = -17,8	H_X: 4,31 (1H, dd) J_{AX} = 9,0 J_{BX} = 1,6	—	0,95 (9H) 3,89
		A	7,65	4,97 (1H, d, 4,6)	4,75 (1H, d)	9,7	0,92 (9H) 3,77
	CF_3COOD	A	8,45	—	5,03 (1H, s)	—	1,12 (9H) 4,02
		B	8,55	—	4,66 (1H, s)	—	1,08 (9H) 4,04
IVg	$CDCl_3$	A	7,59	4,88 (1H, d, 3,5)	5,98 (1H, d)	10,4	—
	CF_3COOD	A	8,34	—	6,29 (1H, s)	—	—
		B	8,58	—	5,88 (1H, s)	—	—
IVh	$CDCl_3$	A	7,47	4,80 (1H, d, 3,3)	5,95 (1H, d)	10,6	3,61
		B	7,72	H_A: 3,28 (1H, dd) H_B: 3,35 (1H, dd) J_{AB} = -17,4	H_X: 5,40 (1H, d, d) J_{AX} = 6,0 J_{BX} = 7,8	—	3,64
		A	7,62	5,10 (1H, d, 3,6)	6,16 (1H, d)	9,9	3,76
	CF_3COOD	A	8,30	—	6,30 (1H, s)	—	3,95
		B	8,52	—	5,78 (1H, s)	—	3,98

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*The spectra of IVa and IVc in DMSO-d_6 and CF_3CO_2D and of IVg in DMSO-d_6 are given in our previous work [2, 3]. The aromatic proton signals for IVa-IVh are found at 6.8-8.4 ppm.

TABLE 3. Content of Tautomer A (%) in Solutions of IVa-IVh

Solvent	R^1	R			
		H	CH_3	$(CH_3)_3C$	C_6H_5
$CDCl_3$	H	80	80	100	100
DMSO-D_6		85*	100*	100	100*
CF_3COOD		50*	55*	90	85
$CDCl_3$	OCH_3	35	35	70	65
DMSO-D_6		60	90	100	100
CF_3COOD		10	10	35	40

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*According to our previous data [2, 3].

Comparison of the structures of the dihydropyrimidine system in IVf, IVa, and V showed that variation of the size of the substituent at $C_{(5)}$ leads to change in the puckering of the partially hydrogenated ring without affecting its conformation. Such loss of planarity of the dihydropyrimidine ring eliminates unfavorable nonbonding interactions even upon the introduction of a bulky substituent such at the *tert*-butyl group.

The dihydropyrimidine system in IVf exists as a nonuniformly compressed boat [Table 4). The folding parameters are $S = 0.34$, $\theta = 64.3°$, and $\psi = 9.8°$ [6]. The extrusions of $N_{(4)}$ and $C_{(5)}$ from the $N_{(2)}C_{(2)}C_{(3)}C_{(4)}$ plane are 0.12(1) and 0.30(1) Å, respectively, indicating considerable compression of the nitrogen-containing fragment in the dihydropyrimidine system. This is attributed to conjugation of the unpaired electron pair of $N_{(4)}$ with the π-systems of the triazole ring and double bond as indicated by shortening of the $N_{(4)}$—$C_{(2)}$ (1.358(4) Å) and $N_{(4)}$—$C_{(3)}$ bonds (1.397(4) Å).

The length of the $C_{(3)}$—$C_{(6)}$ bond (1.469(4) Å) indicates retention of the conjugation of the $C_{(3)}$—$C_{(4)}$ double bond and the *p*-methoxyphenyl substituent despite the twist of the aromatic ring by 36.1(5)°. The methoxy group is somewhat extruded from the plane of the phenyl ring (the $C_{(10)}C_{(9)}O_{(1)}C_{(16)}$ torsion angle is $-6.0(5)°$). However, the $C_{(9)}$—$O_{(1)}$ bond length (1.361(3) Å) indicates conjugation of the unshared electron pair of the oxygen atom and the aromatic π-system.

The *tert*-butyl group occupies a pseudoaxial position (the $C_{(2)}N_{(2)}C_{(5)}C_{(12)}$ torsion angle is $-99.8(3)°$ and the $C_{(2)}N_{(2)}C_{(5)}H_{(5)}$ torsion angle is 139.6(5)°). The repulsion of the atoms of the azole ring and hydrogen atoms at $C_{(14)}$ leads to a twist of this substituent from the $H_{(5)}C_{(5)}C_{(12)}$ plane toward $C_{(4)}$ (torsion angles $H_{(5)}C_{(5)}C_{(12)}C_{(13)} = -71.8(6)°$, $H_{(5)}C_{(5)}C_{(12)}C_{(14)} = 168.5(5)°$, $H_{(5)}C_{(5)}C_{(12)}C_{(15)} = 45.8(6)°$).

As in the case of IVa and V [2, 3], centrosymmetric dimers are formed in the crystal of IVf due to $N_{(4)}$—H$\cdots N_{(3')}$ (1.98(1) Å, N—H$\cdots$N bond angle 171.6(6)°).

EXPERIMENTAL

X—ray diffraction structural analysis. The unit cell parameters of triclinic crystals of 7-*tert*-butyl-5-(4-methoxyphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (IVf) at 20°C: $a = 7.145(2)$, $b = 10.4666(2)$, $c = 11.034(3)$ Å, $\alpha = 96.42(2)°$, $\beta = 101.50(2)°$, $\gamma = 93.81(2)°$, $V = 768.9(3)$ Å^3, $Z = 4$, $d_{calc} = 1.228$ g/cm^3, space group P1. The unit cell parameters and intensities of 1445 independent reflections were measured on a Siemens P3/PC automatic four-circle diffractometer using λMoK_α radiation, graphite monochromator, and $\theta/2\theta$ scanning; $2\theta = 50°$.

The structure was solved by the direct method using the SHELXTL PLUS program package. All the hydrogen atoms were revealed in the difference map. The anisotropic refinement for the nonhydrogen atoms (isotropic refinement for the hydrogen atoms) was carried out to $R = 0.053$, $R_w = 0.062$, $S = 1.42$. The atomic coordinates are given in Table 4.

The IR spectra were taken on a Specord IR-75 spectrometer for KBr pellets. The electronic absorption spectra were taken on a Specord M-40 spectrophotometer in ethanol with concentration from $2 \cdot 10^{-5}$ to $4 \cdot 10^{-5}$ mole/liter. The PMR spectra were taken on a Gemini-200 spectrometer in DMSO-d_6, $CDCl_3$, and CF_3CO_2D with TMS as the internal standard. The reaction course and purity of the products were checked using thin-layer chromatography on Silufol UV-254 plates with 10:1 benzene—methanol as the eluent.

TABLE 4. Coordinates of the Non-Hydrogen Atoms ($\times 10^4$) and Hydrogen Atoms ($\times 10^3$) in IVf

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
$O_{(1)}$	-3260(4)	-5232(3)	-6429(3)	$H_{(1)}$	184(1)	375(1)	143(1)
$N_{(1)}$	2572(4)	3322(3)	-330(3)	$H_{(4)}$	193(1)	27(1)	-423(1)
$N_{(2)}$	2269(4)	2080(3)	-1257(3)	$H_{(4N)}$	30(1)	-71(1)	-122(1)
$N_{(3)}$	1024(4)	1747(3)	315(3)	$H_{(5)}$	281(1)	249(1)	-284(1)
$N_{(4)}$	822(4)	-110(3)	-1622(3)	$H_{(7)}$	-231(1)	-173(1)	-292(1)
$C_{(1)}$	1802(5)	3036(3)	560(3)	$H_{(8)}$	-417(1)	-378(1)	-451(1)
$C_{(2)}$	1358(4)	1181(3)	-856(3)	$H_{(10)}$	10(1)	-417(1)	-651(1)
$C_{(3)}$	983(4)	-423(3)	-2911(3)	$H_{(11)}$	193(1)	-212(1)	-491(1)
$C_{(4)}$	1979(4)	459(3)	-3298(3)	$H_{(13A)}$	750(1)	131(1)	-309(1)
$C_{(5)}$	3108(4)	1768(3)	-2406(3)	$H_{(13B)}$	547(1)	164(1)	-395(1)
$C_{(6)}$	-58(4)	-1711(3)	-3794(3)	$H_{(13C)}$	547(1)	21(1)	-370(1)
$C_{(7)}$	-1846(5)	-2234(3)	-3678(3)	$H_{(14A)}$	726(1)	89(1)	-97(1)
$C_{(8)}$	-2855(5)	-3402(3)	-4548(3)	$H_{(14B)}$	553(1)	125(1)	-30(1)
$C_{(9)}$	-2131(5)	-4104(3)	-5597(3)	$H_{(14C)}$	520(1)	-10(1)	-159(1)
$C_{(10)}$	-331(5)	-3628(3)	-5707(3)	$H_{(15A)}$	786(1)	323(1)	-120(1)
$C_{(11)}$	661(4)	-2456(3)	-4822(3)	$H_{(15B)}$	600(1)	374(1)	-207(1)
$C_{(12)}$	5319(4)	1751(3)	-2048(3)	$H_{(15C)}$	605(1)	369(1)	-58(1)
$C_{(13)}$	5988(5)	1169(4)	-3298(4)	$H_{(16A)}$	-127(1)	-616(1)	-730(1)
$C_{(14)}$	5814(5)	890(4)	-1165(3)	$H_{(16B)}$	-375(1)	-667(1)	-821(1)
$C_{(15)}$	6353(5)	3182(4)	-1407(4)	$H_{(16C)}$	-270(1)	-536(1)	-817(1)
$C_{(16)}$	-2653(6)	-5921(4)	-7567(4)				

TABLE 5. Some Bond Angles (ω) and Torsion Angles (τ) in IVf

Angle	ω	Angle	τ
$N_{(2)}$—$N_{(1)}$—$C_{(1)}$	100,9(3)	$N_{(2)}$—$C_{(2)}$—$N_{(4)}$—$C_{(3)}$	-9,6(4)
$N_{(1)}$—$N_{(2)}$—$C_{(2)}$	109,7(3)	$C_{(2)}$—$N_{(4)}$—$C_{(3)}$—$C_{(4)}$	-12,7(4)
$C_{(2)}$—$N_{(2)}$—$C_{(5)}$	125,3(2)	$N_{(4)}$—$C_{(3)}$—$C_{(4)}$—$C_{(5)}$	4,9(5)
$C_{(1)}$—$N_{(3)}$—$C_{(2)}$	101,1(3)	$C_{(3)}$—$C_{(4)}$—$C_{(5)}$—$N_{(2)}$	-21,8(4)
$C_{(2)}$—$N_{(4)}$—$C_{(3)}$	118,1(3)	$C_{(4)}$—$C_{(5)}$—$N_{(2)}$—$C_{(2)}$	25,5(4)
$N_{(1)}$—$C_{(1)}$—$N_{(3)}$	117,3(3)	$C_{(5)}$—$N_{(2)}$—$C_{(2)}$—$N_{(4)}$	-11,9(5)
$N_{(2)}$—$C_{(2)}$—$N_{(3)}$	111,0(3)	$C_{(2)}$—$N_{(2)}$—$C_{(5)}$—$C_{(12)}$	-99,8(3)
$N_{(2)}$—$C_{(2)}$—$N_{(4)}$	121,0(3)	$C_{(2)}$—$N_{(2)}$—$C_{(5)}$—$H_{(5)}$	139,6(5)
$N_{(4)}$—$C_{(3)}$—$C_{(4)}$	120,1(2)	$N_{(2)}$—$C_{(5)}$—$C_{(12)}$—$C_{(13)}$	169,6(3)
$N_{(4)}$—$C_{(3)}$—$C_{(6)}$	116,5(3)	$N_{(2)}$—$C_{(5)}$—$C_{(12)}$—$C_{(14)}$	49,9(3)
$C_{(3)}$—$C_{(4)}$—$C_{(5)}$	124,5(3)	$N_{(2)}$—$C_{(5)}$—$C_{(12)}$—$C_{(15)}$	-72,8(4)
$N_{(2)}$—$C_{(5)}$—$C_{(4)}$	105,1(3)	$C_{(4)}$—$C_{(3)}$—$C_{(6)}$—$C_{(7)}$	-141,8(4)
$N_{(2)}$—$C_{(5)}$—$C_{(12)}$	112,3(2)	$C_{(2)}$—$N_{(4)}$—$C_{(3)}$—$C_{(6)}$	-164,5(3)
$C_{(4)}$—$C_{(5)}$—$C_{(12)}$	114,6(3)		

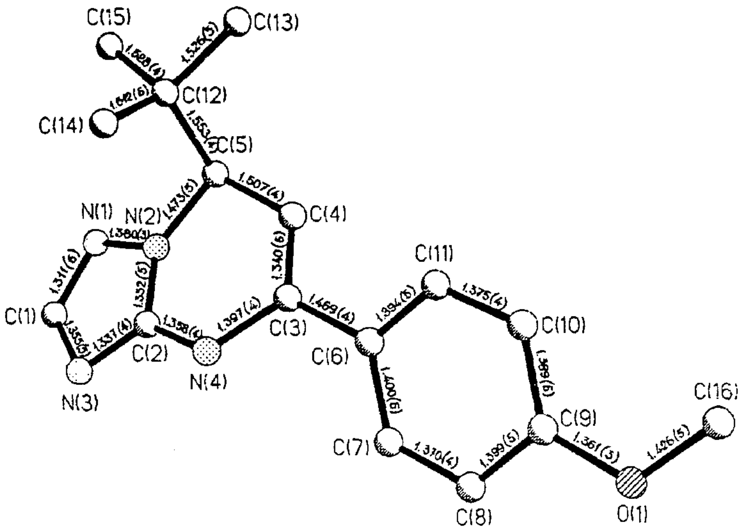

Fig. 1. Molecular structure and bond lengths of IVf (without hydrogen atoms).

The nitrogen content in the products corresponded to the calculated values.

5-(4-Methoxyphenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (IVb). A solution of 1.1 g (5 mmoles) hydrochloride salt of *p*-methoxy-β-dimethylaminopropiophenone and 0.42 g (5 mmoles) 3-amino-1,2,4-triazole in 0.5 ml DMF was heated at reflux for 1 h, cooled, mixed with 5 ml 2-propanol, and filtered to give 0.8 g (70%) IVb, mp 149°C (from 2-propanol).

Analogous procedures gave IVd-IVf and IVh. The syntheses of IVa, IVc, and IVg were described in our previous work [2, 3].

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