Chemistry of Heterocyclic Compounds Vol. 30, No. 7, 1994

SYNTHESIS AND STRUCTURE OF 4,5,6,7-TETRAHYDRO-1,2,4-TRIAZOLO[1,5-*a*]PYRIMIDINES

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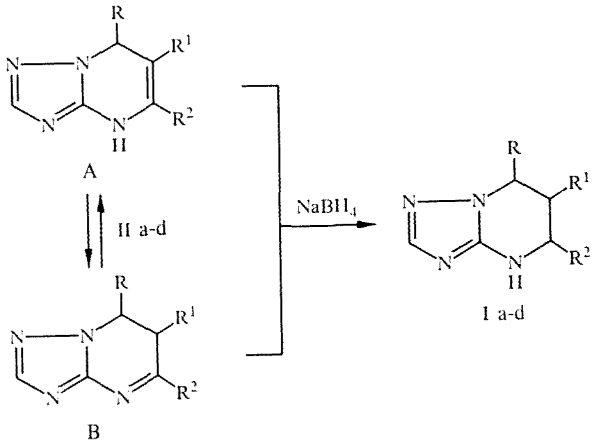
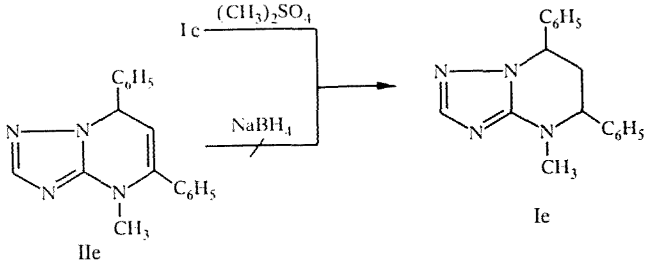
The sodium borohydride reduction of dihydroazolopyrimidines gave substituted 4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidines. X-ray diffraction structural analysis, PMR spectroscopy, and molecular mechanics calculations were used to analyze the three-dimensional structure of these compounds.

A study was carried out on 4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidines differing in the steric strain in the tetrahydropyrimidine system. Products Ia-Id were obtained by the sodium borohydride reduction of previously synthesized dihydro derivatives IIa-IId [1, 2]. We should note that dihydrotriazolopyrimidine IIe is not reduced under these circumstances. This failure is probably related to the circumstance that the reduction of analogs IIa-IIc proceeds through prior conversion to imine tautomer form B, which is impossible for IIe. The synthesis of 4-methyl-5,7-diphenyl-4,5,6,7-tetrahydro-1,2,4-triazolo-[1,5-*a*]pyrimidine Ie was achieved by the alkylation of Ic using dimethyl sulfate. The addition of the methyl group at $N_{(4)}$ rather than at $N_{(1)}$ or $N_{(3)}$ was demonstrated by x-ray diffraction structural analysis.





I, II a R = CH_3, R^1 = H, R^2 = Ph; b R = Ph, R^1 = H, R^2 = CH_3; c R = R^2 = Ph, R^1 = H; d R = R^2 = Ph, R^1 = CH_3

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TABLE 1. PMR Spectra of Ia-Ie Isomers

Compound	Proton chemical shifts, δ, ppm					Coupling contants (J), Hz				
	2-H	5-H	6-H	7-H	CH_3	J_{56A}	J_{56B}	J_{B6A6}	J_{6A7}	J_{6B7}
Ia	8,20	4,86	2,60 (A) 2,19 (B)	4,58	1,73	3,0	11,6	-14,4	4,0	10,8
Ib	8,45	3,69	2,39 1,83	5,32	1,23	3,1	9,7	-14,1	4,8	11,0
Ic	8,35	5,12	2,82 (A) 2,67 (B)	5,61	—	3.5	10,5	-14,0	4,5	11,0
Id	8,11	5,13	2,44	5,67	0,57	2,4	—	—	4,0	—
Ie	8,34	4,97	2,79	5,56	2.70	7.1	7.1	—	7,5	7,5

The existence of two or more chiral sites in Ia-Id raises the question of the stereoselectivity of their synthesis. This question was answered by PMR spectroscopy (Table 1). Each spectrum, including those of samples not yet purified by crystallization, characterizes a single isomer. Signals for the methine and methylene protons of the tetrahydropyrimidine system are readily identified in all the spectra. The signals for 7-H and 5-H in the spectra of Ia and Ib, respectively, are further split due to coupling with a methyl group and shifted upfield in comparison to the signals of the second methine proton, which makes their assignment unequivocal. The assignment of these signals for tetrahydrotriazolopyrimidines Ic-Ie was carried out by the comparison of their spectra with those of analogs Ia and Ib.

The coupling constants of the methine protons in Ia-Ic (Table 1) show that both have close-to-axial orientation (one of the vicinal coupling constants of these protons is in the range 9.7-11.0 Hz, which is typical for J_{aa} [3]). Thus, tetrahydro derivatives Ia-Ic should be assigned *cis* structure, which is in accord with the x-ray diffraction structural data for Ie. The substituents at $C_{(5)}$ and $C_{(7)}$ in the bicyclic system have equatorial orientation in the predominant conformers. A molecular mechanics calculation also indicated that the diequatorial conformer is the most stable (Table 2). Satisfactory accord was also obtained between the vicinal coupling calculated using the Karplus equation and the experimental values in the case of equatorial orientation of substituents in Ia-Ic.

The question concerning the structure of trisubstituted tetrahydrotriazolopyrimidine Id is somewhat more complicated. Four isomeric structures (*cis–cis, cis–trans, trans–cis,* and *trans–trans*) are possible for this compound. The values of J_{56} and J_{67} (see Table 1) correspond equally to J_{ee} and J_{ae} coupling constants [3]. Thus, only the *eee* conformer of the *trans–trans* may be excluded on the basis of the spin—spin coupling constants of Id. Nevertheless, indirect evidence given below suggests that the *cis–cis* structure is most likely for Id and the R, R^1, and R^2 substituents have *eae* orientation in the predominant conformation. Thus, the conditions for the synthesis of Id are identical to the corresponding conditions for Ia-Ic. Hence, *cis* configuration of the R and R^2 substituents (in the case of their diequatorial or diaxial orientation) is also found for Id. Furthermore, the chemical shifts for 5-H and 7-H hardly change in going from Ic to Id. This behavior indicates retention of the diaxial orientation of these protons in Id (in particular, change in the orientation of 7-H is related to a significant change in its position relative to the triazole ring and should have a marked effect on its anisotropic shielding by this ring and, thus, on the chemical shift of this proton). Finally, the signal for the CH_3 group of Id is found at anomalously high field (0.57 ppm, see Table 1). The only reason for such an effect may be anisotropic shielding of the CH_3 group by suitably oriented substituents $R = R^2 = C_6H_5$. A molecular mechanics calculation of possible equilibrium conformations showed that such an arrangement may be achieved only in the *eae* conformer of the *cis-cis* isomer of Id.

The PMR spectrum of Ia-Ic of N-methyl derivative Ie, in which broadening of the vicinal coupling constants is noted (J_{56A} and J_{56B}, J_{6A7} and J_{6B7}) also differs markedly from the spectra of Ia-Ic. Furthermore, the methylene group protons become magnetically equivalent. Since alkylation of Ic cannot lead to its conversion from *cis* to *trans*, the observed spectral effects should be attributed to a change in the conformational composition upon going from Ic to Ie. In the case of N-methyl derivative Ie, an *aa* ⇄ *ee* conformational equilibrium with similar concentrations of both conformers is most likely.

The three-dimensional structure of Ie was established by x-ray diffraction structural analysis (see Tables 3 and 4 and Fig. 1). The tetrahydropyrimidine ring system has distorted half-chair conformation (fold parameters [4]: $S = 0.72$, $\psi = 7.6°$, $\theta = 63.°$). $C_{(5)}$ and $C_{(6)}$ extrude from the mean-square plane of $N_{(8)}$, $C_{(3a)}$, $N_{(4)}$, and $C_{(7)}$ by −0.24(1) and 0.40(1) Å, respectively. $N_{(4)}$ of the imino group has trigonal-pyramidal configuration; the sum of the bond angles is 349.5(4)°. However, the $C_{(3a)}$—$N_{(4)}$ bond length (1.340(7) Å), which is similar to the length of the analogous bond in 3-amino-1,2,4-triazole (1.342 Å [5]), suggests conjugation of the unshared electron pair of $N_{(4)}$ and the π-system of the triazole ring. Both phenyl substituents

TABLE 2. Relative Steric Energies and Conformation Parameters of the Tetrahydropyrimidine System and Calculated Coupling Constants in Ia-Id

Compound	Conformer	ΔE_{ster}, Kcal/mole	Fold parameters of tetrahydro ring system			Calculated coupling constants (J), Hz			
			S	θ	ψ	J_{56A}	J_{56B}	J_{76A}	J_{76B}
Ia	*aa*	1,96	0,65	54,7	0,8	1,7	5,4	1,6	5,7
	ee	0,00	0,71	55,8	3,4	3,0	11,8	3,3	11,8
	ae	0,56	0,68	55.3	0,1	3,3	11,8	1,7	5,4
	ea	0,85	0,72	54,9	1,5	3,0	11,8	1,9	4,8
Ib	*aa*	2,00	0,65	54,7	0,1	3,3	3,3	3,6	3,0
	ee	0,00	0,71	55,8	3,4	3,0	11,8	3,3	11,8
	ae	0,77	0,69	56,2	4.3	1,9	5,0	3,3	11,8
	ea	0,91	0,68	54,6	4,9	2,8	11,8	1,6	5,6
Ic	*aa*	3.14	0,68	54,1	11,1	2,1	4,9	1,6	5,8
	ee	0,00	0,72	55,9	2.5	3,0	11,8	3,1	11,8
	ae	2,17	0,74	55,9	4.4	2,3	4,5	2,4	11,8
	ea	2,35	0,72	54,1	0,5	2,5	11,8	5,0	1,9
Id	*aaa*	2,27	0,67	54,9	10,2	1,3	—	1,0	—
	aae	2.31	0.74	56,8	8.7	1,7	—	2,8	—
	eea	0,00	0,66	54,8	4.7	—	5,2	—	11,3
	eee	0.68	0.72	56.5	3.6	—	11,5	—	11,3
	aea	5,00	0,64	53,8	14,1	—	4,5	—	5,5
	aee	1,62	0,57	56,0	2,2	—	11,1	—	6,0
	eaa	0,03	0,66	56,4	[illegible]	11,3	—	5,2	—
	eae	0,88	0,71	56,4	3.8	3,3	—	3,0	—

have equatorial orientation [torsion angles $C_{(3a)}N_{(4)}C_{(5)}C_{(9)}$ 171.2(4)°, $C_{(3a)}N_{(4)}C_{(5)}H_{(5)}$ 66(1)°, $C_{(3a)}N_{(8)}C_{(7)}C_{(16)}$ 167.4(4)°, $C_{(3a)}N_{(8)}C_{(7)}H_{(7)}$ 65(1)°]. This molecule has short intramolecular contacts: $C_{(17)}\cdots N_{(8)}$ 2.93(1) Å, $H_{(17)}\cdots N_{(8)}$ 2.60(1) Å, $H_{(5)}\cdots C_{(17)}$ 1.57(1) Å (the sums of the van der Waals radii are 3.21, 2.66, and 2.87 Å, respectively [6]). These contacts indicate definite steric hindrance.

EXPERIMENTAL

X-Ray Diffraction Structural Analysis. The unit cell parameters of monoclinic crystals of 4-methyl-5,7-diphenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine (Ie) at 20°C: a = 14.806(2), b = 8.531(3), c = 12.805(4) Å, β = 109.67(2)°, V = 1523(1) Å^3, d_{calc} = 1.214 g/cm^3, space group $P2_1/c$. The unit cell parameters and intensities of 1184 independent reflections were measured on a Syntex $P2_1$ automatic four-circle diffractometer using λMoK_α radiation, graphite monochromator, and $\theta/2\theta$ scanning, $2\theta < 50°$. A profile analysis of the data obtained was carried out according to Strel'tsov and Zavodnik [7], which permitted improvement of its quality.

The structure was solved by the direct method using the SHELXTL PLUS program package [8]. The positions of the hydrogen atoms were calculated geometrically and not refined. Anisotropic refinement of the nonhydrogen atoms gave R = 0.068 (R_w = 0.071, S = 2.54). The atomic coordinates are given in Table 4.

The PMR spectra were taken on a Gemini 200 spectrometer in CF_3CO_2D with TMS as the internal standard. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates using acetone as the eluent.

The nitrogen content in the compounds obtained corresponded to the calculated amounts.

The three-dimensional structure of Ia-Id was calculated using the MMX method [9] and the PCMODEL program. The conformation of the tetrahydropyrimidine ring system was characterized using fold parameters according to Zefirov, Palyulin, and Dashevskaya [4], where S is the extent of ring folding, and θ and ψ are polar angles describing the conformation type.

7-Methyl-5-phenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine (Ia, $C_{12}H_{14}N_4$). A sample of 3.75 g (0.1 mole) $NaBH_4$ was added to a suspension of 2.1 g (10 mmoles) 7-methyl-5-phenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine IIa (obtained according to our previous procedure [2]) in 20 ml methanol. After gaseous products were no longer evolved, the

TABLE 3. Some Bond Angles (ω) and Torsion Angles (τ) in Ie

Bond angle	ω	Bond angle	τ
$N_{(8)}—N_{(1)}—C_{(2)}$	101,4(4)	$N_{(8)}—C_{(3a)}—N_{(4)}—C_{(5)}$	16,0(8)
$N_{(1)}—N_{(8)}—C_{(3a)}$	111,4(4)	$C_{(3a)}—N_{(4)}—C_{(5)}—C_{(6)}$	-38,2(8)
$C_{(3a)}—N_{(8)}—C_{(7)}$	124,7(4)	$N_{(4)}—C_{(5)}—C_{(6)}—C_{(7)}$	54,8(6)
$C_{(2)}—N_{(3)}—C_{(3a)}$	102,7(5)	$C_{(5)}—C_{(6)}—C_{(7)}—N_{(8)}$	-44,5(6)
$C_{(3a)}—N_{(4)}—C_{(5)}$	116,8(5)	$C_{(6)}—C_{(7)}—N_{(8)}—C_{(3a)}$	20,6(7)
$N_{(1)}—C_{(2)}—N_{(3)}$	116,2(4)	$C_{(7)}—N_{(8)}—C_{(3a)}—N_{(4)}$	-7,0(8)
$N_{(8)}—C_{(3a)}—N_{(3)}$	108,2(4)	$C_{(5)}—C_{(6)}—C_{(7)}—H_{(7)}$	68(1)
$N_{(8)}—C_{(3a)}—N_{(4)}$	124,2(4)	$C_{(5)}—C_{(6)}—C_{(7)}—C_{(16)}$	-168,3(4)
$N_{(4)}—C_{(5)}—C_{(6)}$	109,5(4)	$N_{(4)}—C_{(5)}—C_{(9)}—C_{(10)}$	36,8(7)
$C_{(5)}—C_{(6)}—C_{(7)}$	115,2(4)	$C_{(6)}—C_{(5)}—C_{(9)}—C_{(10)}$	91,1(6)
$N_{(8)}—C_{(7)}—C_{(6)}$	106,9(4)		

TABLE 4. Coordinates of Nonhydrogen Atoms ($\times 10^4$) in Ie

Atom	x	y	z	Atom	x	y	z
$N_{(1)}$	829(3)	3589(6)	8080(3)	$C_{(8)}$	5616(4)	2515(7)	13124(5)
$N_{(2)}$	1662(3)	3491(5)	8969(3)	$C_{(9)}$	6274(4)	3105(8)	12651(5)
$N_{(3)}$	1898(3)	1920(6)	7744(4)	$C_{(10)}$	5959(4)	3456(7)	11546(5)
$N_{(4)}$	3144(3)	2097(5)	9515(3)	$C_{(11)}$	5021(4)	3263(7)	10893(5)
$C_{(1)}$	1013(4)	2655(7)	7380(4)	$C_{(12)}$	1454(4)	5888(6)	9948(4)
$C_{(2)}$	2286(4)	2460(6)	8775(4)	$C_{(13)}$	1094(4)	6490(6)	0735(4)
$C_{(3)}$	3305(4)	2524(6)	0677(4)	$C_{(14)}$	926(4)	8079(7)	0753(5)
$C_{(4)}$	2841(3)	4103(6)	10718(4)	$C_{(15)}$	1075(4)	9070(7)	10000(5)
$C_{(5)}$	1784(3)	4214(6)	10039(4)	$C_{(16)}$	1401(4)	8482(7)	9186(5)
$C_{(6)}$	4361(4)	2655(6)	11354(4)	$C_{(17)}$	1589(4)	6912(6)	9159(5)
$C_{(7)}$	4682(4)	2283(6)	12462(4)	$C_{(18)}$	3566(4)	624(6)	9325(5)

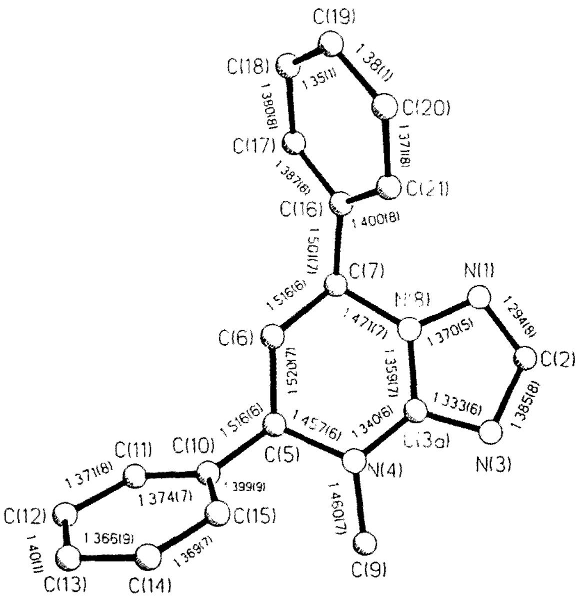

Fig. 1. Molecular structure of Ie (without hydrogen atoms) with bond lengths (Å).

reaction mixture was heated at reflux for 15 min. Then, 100 ml water was added and the mixture was filtered to give 1.8 g (86%) Ia, mp 175-176°C (from 2-propanol). Products Ib-Id were obtained analogously.

Product Ib, $C_{12}H_{14}N_4$ was obtained in 50% yield, mp 150-151°C [10].

Product Ic, $C_{17}H_{16}N_4$ was obtained in 71% yield, mp 199-200°C [10].

Product Id, $C_{18}H_{18}N_4$ was obtained in 53% yield, mp 218°C.

4-Methyl-5,7-diphenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine (Ie, $C_{18}H_{18}N_4$). A sample of 0.8 g (3 mmoles) 5,7-diphenyl-4,5,6,7-tetrahydro-1,2,4-triazolo[1,5-*a*]pyrimidine Ic and 0.87 g (6 mmoles) dimethyl sulfate were added to a suspension of 0.9 g KOH in 10 ml DMF. The reaction mixture was maintained for 1 h at room temperature. Then, 50 ml water was added. The mixture was neutralized to pH 7 by adding acetic acid and extracted with chloroform. The extract was dried over sodium sulfate and evaporated. The residue was dissolved in 10 ml 2-propanol and cooled. Product Ie was filtered off, mp 148°C (from 2-propanol). The yield of Ie was 0.5 g (60%).

REFERENCES

1. V. D. Orlov, S. M. Desenko, K. A. Potekhin, and Yu. T. Struchkov, Khim. Geterotsikl. Soedin., No. 2, 229 (1988).
2. S. M. Desenko, V. D. Orlov, V. V. Lipson, O. V. Shishkin, S. V. Lindeman, and Yu. T. Struchkov, Khim. Geterotsikl. Soedin., No. 11, 1539 (1991).
3. A. Junke, Nuclear Magnetic Chemistry in Organic Chemistry, [Russian translation], Mir, Moscow (1974), p. 84.
4. N. S. Zefirov, V. A. Palyulin, and E. E. Dashevskaya, J. Phys. Org. Chem., 3, 147 (1990).
5. G. L. Starova, O. V. Frank-Kamenetskii, V. V. Makarskii, and V. L. Lopyrev, Kristallografiya, 23, 849 (1978).
6. Yu. V. Zefirov and P. M. Zorkii, Usp. Khim., 58, 713 (1989).
7. V. A. Strel'tsov and V. E. Zavodnik, Kristallografiya, 34. 1369 (1989).
8. G. M. Sheldrick, SHELXTL PLUS PC Version. A System of Computer Programs for the Determination of Crystal Structure from X-Ray Data, Rev. 4.2 (1992).
9. K. B. Lipkowitz, A. M. Naylor, and W. B. Melchior, Tetrahedron Lett., 25, 2297 (1984).
10. S. M. Desenko, V. D. Orlov, and V. V. Lipson, Khim. Geterotsikl. Soedin., No. 12, 1638 (1990).