

## Conformations and $^1\text{H}$ NMR Spectra of 5-Alkoxy-, 5-Hydroxy-, and 5-Amino- $\Delta^2$ -1,2,3-triazolines

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$^1\text{H}$  NMR spectroscopy (and in a single case X-ray results) shows that 5-alkoxy- and 5-hydroxy- $\Delta^2$ -1,2,3-triazolines prefer an envelope conformation with the hetero substituent at C-5 pseudo-axial at the flap and the N-1 substituent pseudoequatorial, probably due to the anomeric effect.

1-(*p*-Nitrophenyl)-5-amino- $\Delta^2$ -1,2,3-triazolines with  $\text{R}^5 = \text{H}$  prefer the same conformation, but for  $\text{R}^5 \neq \text{H}$  there seems to be more than one important conformation. In aminotriazolines steric effects, rather than the anomeric effect, seem to be dominating.

5-Amino- $\Delta^2$ -1,2,3-triazolines unsubstituted in the amino group have been prepared for the first time.

During  $^1\text{H}$  NMR investigations on 5-hydroxy- and 5-amino- $\Delta^2$ -1,2,3-triazolines we observed that the chemical shifts of protons and methyl groups at C-4 depend in a characteristic manner on the orientation relative to the hetero substituent (X) at C-5. This was extensively used by us for assignments of relative configurations at C-4 and C-5 in both 5-hydroxy- and 5-amino- $\Delta^2$ -1,2,3-triazolines,<sup>1-3</sup> and subsequently by other authors<sup>4</sup> in some 5-dialkylamino- $\Delta^2$ -1,2,3-triazolines.

For all hydroxytriazolines and most aminotriazolines one observes that a *cis*\* oriented proton (or methyl group) at C-4 resonates at lower field than that in *trans*. This may be due to a non-planar conformation of the triazoline ring. Thus with  $\Delta^1$ -pyrazolines ring-puckering has been assumed to explain chemical shift differences for protons or methyl groups

adjacent to the N=N double bond.<sup>5-7</sup> These differences have been proposed to stem from the different positions of the protons in the strongly anisotropic field due to the N=N bond.<sup>8</sup> The anisotropy of single bonds (C-C, C-H, and C-N) cannot be ignored, however, and we prefer to consider only the sum of these contributions, the total anisotropy of the ring. Quantitative calculations on this<sup>9</sup> (*cf.* Refs. 10-12) seems unjustified in view of the difficulties encountered even in simple hydrocarbons. The total effect seems to be consistent; a pseudo-axial proton or methyl group resonates at higher field than a pseudo-equatorial (henceforth abbreviated to axial and equatorial). By analogy the chemical shift differences of C-4 groups in  $\Delta^2$ -1,2,3-triazolines might be due to folding of the ring system so as to shield the axial relative to the equatorial group.

A near planar ring probably represents an energy maximum due to eclipsing of the C-4 and C-5 substituents; however, the eclipsing energy may be smaller than in straight-chain hydrocarbons, since the small ring angles at C-4 and C-5 must result in larger distances between the interfering substituents. The preference of nitrogen (N-1) for being in the  $sp^3$  state, rather than in the  $sp^2$  state,<sup>13</sup> would further destabilize the planar structure. The planar conformation of cyclopentene represents an energy barrier of 0.6 kcal/mol<sup>14</sup> between the two equivalent folded conformations, but the barrier might well be higher in the triazolines.

Four non-planar ring conformations are possible (Fig. 1), and at room temperature they might equilibrate so fast as to give time-

\* Used without specification *cis* and *trans* refer to position relative to X.

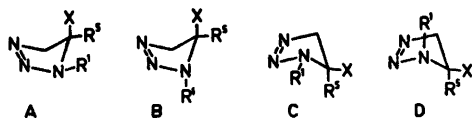


Fig. 1.

averaged NMR spectra. The factors that determine the preferred conformation may be divided into electronic effects, steric effects, and hydrogen bonding. The electronic effects include stabilization by conjugation in the triazene part of the ring. This does not necessarily involve strong preference for a planar arrangement of the ring atoms and  $R^1$ ; but it should favor A and C over B and D, since in the lone-pair orbital of N-1 the  $p$  orbital component that is in a position to overlap with the N-2  $p$  orbital is largest when the lone-pair is axial.<sup>13</sup>

The electronegativity of  $R^1$  determines the electron density in the N-1 lone-pair orbital, which in turn must influence the degree of conjugation within the triazene part (*cf.* Ref. 15) and possibly also the interaction with X. This latter interaction is reminiscent of the anomeric effect (rabbit ear effect, dipolar effect<sup>16-19</sup>) and would act so as to favor conformation A. Other authors<sup>20</sup> have also suggested the operation of an anomeric effect between a hydroxy group and a nitrogen atom of a five-membered heterocyclic ring.  $n-\pi$  Repulsive forces<sup>21</sup> between X and the N=N  $\pi$ -system would tend to place X equatorially.

Steric effects must play an important role. The interactions of the C-5 substituents with the N=N  $\pi$ -system are probably smaller than

with the C-4 substituents, and the axial position of the larger C-5 group may thus be favored.

Interaction of  $R^1$  with the C-4 substituents would be expected to favor an equatorial position of  $R^1$ , whereas its interaction with the C-5 substituents would favor an axial position, particularly if both C-5 groups are very bulky.

Hydrogen bonding between X and the N=N  $\pi$ -system<sup>22</sup> would favor an axial position of X.

The data used to solve the conformational problem include vicinal coupling constants, chemical shifts, and one X-ray structure. Most NMR data have been gathered from the literature; only the section on aminotriazolines contains mostly new NMR data.

*5-Alkoxy- $\Delta^2$ -1,2,3-triazolines.* The conformation of the triazolone ring in 5-alkoxytriazolines may be inferred from vicinal coupling constants. Table 1 reveals that the *cis* and *trans* coupling constants are very constant, being 7.0–7.5 Hz and 2.0–2.8 Hz, respectively. The small value of the *cis* coupling constant is not compatible with a planar triazolone ring, since  $J^0$  would then be expected to be 13 Hz or larger, based on the *cis* coupling constant in 1-phenyl-4-carbomethoxy- $\Delta^2$ -1,2,3-triazoline ( $J_{cis} = 13.03$  Hz,  $J_{trans} = 9.87$  Hz<sup>25</sup>). Further, in a non-planar structure (Fig. 1) the alkoxy group cannot take the equatorial position (as in C or D), since this should give rise to a *trans* coupling constant much larger than 3 Hz, the dihedral angle being considerably larger than 120°. The alkoxy group must therefore occupy the axial position, and one or both of such conformations (A or B) predominate.

Three alkoxytriazolines deserve special mention. With Ic (Table 1) there is no *trans* coupling on which to base assumptions as to the

Table 1. <sup>1</sup>H NMR data of 1-(*p*-nitrophenyl)-5-alkoxy- $\Delta^2$ -1,2,3-triazolines (CDCl<sub>3</sub>).

	$R^4_{cis}$	$R^4_{trans}$	$R^5$	X	$R^4_{cis}$	$R^4_{trans}$	$J_{cis}^a$	$J_{trans}^a$	Ref.
Ia	H	H	H	OEt	4.61	4.29	7.2	2.8	
Ib	H	H	H	OBu	4.65	4.25	7.0	2.7	23
Ic	Me	H	H	OPr	1.67	4.27	7.5		24
Id	H	Me	H	OPr	4.65	1.36		2.0	24
Ie	H	H	Me	OEt	4.72	4.19			23

<sup>a</sup>  $J_{cis}$  is the coupling constant between  $R^4_{trans} = H$  and  $R^5 = H$ ,  $J_{trans}$  that between  $R^4_{cis} = H$  and  $R^5 = H$ .

conformation. The degree of ring folding seems nevertheless to be approximately the same in Ic as in Ia or Ib, as judged from the nearly identical *cis* vicinal coupling constants.

In Id conformation C would be expected on steric grounds, since here both  $R^1$  and  $R^4_{trans} = \text{Me}$  are equatorial. However, even here X and consequently also  $R^4_{trans}$  must be preferentially axial, the *trans* coupling constant being only 2.0 Hz. Hence the axial position of  $R^4_{trans} = \text{Me}$  does not seem to be particularly unfavorable or, alternatively, the tendency of X to be axial must be very strong. The axial position of  $R^4_{trans}$  is best compatible with an equatorial position of  $R^1$ , *i.e.* Id presumably adopts conformation A.

In the triazoline<sup>23</sup> prepared from *p*-nitrophenyl azide and 3,4-dihydro-2H-pyran we have measured the coupling constants of  $R^4_{trans} = \text{H}$  with the two adjacent methylene protons of the tetrahydropyran ring to be 5.4 and 2.8 Hz. This indicates a *gauche* relationship to both methylene protons, which in turn implies that the oxygen atom at C-5 is axially oriented, if the tetrahydropyran ring is to adopt the usual chair conformation. The *cis* vicinal coupling constant between  $R^4_{trans} = \text{H}$  and  $R^5 = \text{H}$  is 7.1 Hz, *i.e.* of the same magnitude as for the examples in Table 1.

Chemical shifts of the C-4 protons in the 1-*p*-nitrophenyltriazolines clearly distinguish a *cis* (4.61–4.72 ppm) from a *trans* proton (4.19–4.29 ppm).

In all discussed examples conformation A seems to predominate at equilibrium. Since the chemical shift between the C-4 protons is not diminished by the introduction of a methyl group at C-5 (Ie), conformation A seems to be favored by an anomeric effect rather than by steric effects involving the C-5 substituents. Unfortunately, two experiments designed to verify this were inconclusive. Thus the conformation (or predominating conformation) of Ia seemingly did not change on going from  $\text{CDCl}_3$  to the much more polar solvent acetonitrile, the coupling constants remaining largely unaltered (7.9 and 2.9 Hz). Also, reduction of the nitro group in Ia to an amino group did not lead to a change in coupling constants or chemical shift difference between the C-4 protons (NMR data for the reduced compound: 4.42 and 4.10 ppm; 7.5 and 2.8 Hz). Both

experiments suggest that the degree of folding of the triazoline ring remains the same.

*5-Hydroxy- $\Delta^2$ -1,2,3-triazolines.* An X-ray crystallographic investigation<sup>26</sup> on 1,4-dimethyl-5-ethyl-5-hydroxy- $\Delta^2$ -1,2,3-triazoline confirmed that there was a significant degree of conjugation within the triazene chain, as evidenced by a substantial shortening of the N-1...N-2 bond (1.357 Å as opposed to 1.44 Å for a normal N–N single bond<sup>27</sup>). In spite of this the triazoline ring was strongly puckered, the angle between the plane containing N-1, N-2, N-3, and C-4 and that defined by C-4, C-5, and N-1 being 27.5°. The molecule adopted conformation A, the OH group being axial and  $R^1$  equatorial. Of course, the conformation is not necessarily the same in solution and crystal, even when there are no exceptionally strong interactions between the individual molecules. But it is presumably the more common and has often been assumed by other authors (*cf.* references given in Refs. 17 and 28).

Unfortunately, data for vicinal coupling constants in hydroxytriazolines are not available, since hydroxytriazolines with  $R^5 = \text{H}$  are unknown. However, support for a puckered triazoline ring may be obtained indirectly from the coupling constants of  $R^4_{cis} = \text{H}$  in 4,5-tetramethylene-5-hydroxy- $\Delta^2$ -1,2,3-triazolines.<sup>1,2</sup> The cyclohexane ring is likely to adopt a chair conformation, thus excluding a planar structure of the triazoline ring. The chair conformation may be attained in two ways, as shown in Fig. 2. The coupling constants between  $R^4_{cis} = \text{H}$  and the adjacent methylene protons of the cyclohexane ring are 7.2 and 10.2 Hz for  $R^1$  being methyl or benzyl; for  $R^1$  being phenyl they are 7.2 and 8.5 Hz. These coupling constants may easily be interpreted in terms of conformation E and are incompatible with conformation F, which should give coupling constants below 6 Hz,<sup>29</sup> these dihedral angles being around 60°. Since  $R^1$  (methyl or benzyl) has the same chemical shift in these molecules as in those where  $R^4_{trans}$  is

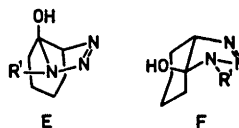


Fig. 2.

not part of a cyclohexane ring (the same applies to pyridine solvent shifts for  $R^1$  and  $R^4_{cis}$ ),<sup>1,2</sup> the conformation is probably the same in all these cases, *i.e.* puckered in such a way as to place the hydroxy group axially.

Also chemical shift data, and particularly their systematic variations with substituents, provide evidence for a non-planar conformation in solution. The effect on equal substituents at C-4 of changing  $R^1$  (Table 2) would not be

Table 2. Chemical shifts of methyl groups at C-4 in 4,4-dimethyl-5-hydroxy-5-isopropyl- $\Delta^2$ -1,2,3-triazolines (CDCl<sub>3</sub>).<sup>1,2</sup>

$R^1$	$R^4_{cis} = \text{Me}$	$R^4_{trans} = \text{Me}$
Me	1.52	1.13
Benzyl	1.55	1.21
<i>p</i> -NH <sub>2</sub> -Ph	1.60	1.29
<i>p</i> -MeO-Ph	1.60	1.30
Ph	1.58	1.33
<i>p</i> -Br-Ph	1.58	1.33
<i>p</i> -NO <sub>2</sub> -Ph	1.56	1.44

understandable on the basis of a planar arrangement of the ring and N-1... $R^1$  bond.  $R^4_{cis} = \text{Me}$  is seen to be largely unaffected, whereas  $R^4_{trans} = \text{Me}$  varies monotonically with the electronegativity of  $R^1$ . This variation is probably caused by electronic effects, possibly involving the N-1 lone-pair, since steric variations in  $R^1$  are negligible, at least in the aromatic series.

The remarkably constant chemical shift of  $R^1 = \text{Me}$  in 1-methyl-5-hydroxy- $\Delta^2$ -1,2,3-triazolines ( $3.26 \pm 0.02$  ppm, unless  $R^5$  is particularly bulky ( $\text{Bu}^t$ ) or anisotropic (Ph)<sup>1,2</sup> points to a constant conformation of the ring in these triazolines. Again, this conformation cannot be planar, since this would involve eclipsing of vicinal alkyl groups in the cases where  $R^4_{trans}$  is methyl. In addition, the insensitivity of the chemical shift of  $R^1$  to variations in the C-4 substituents indicates that  $R^1$  is well separated from these. This is also supported by the fact that the equilibrium position between diastereomeric hydroxytriazolines ( $R^4_{cis} \neq R^4_{trans}$ ) is rather indifferent to the steric requirements of  $R^1$ .<sup>1,2</sup> Therefore  $R^1$  must be equatorially disposed, and conformation A is

most probable on the reasonable assumption that the OH group is axial.

The effect of varying the size of  $R^5$  is shown in Table 3. The constant chemical shift of  $R^4_{cis} = \text{Me}$  is yet another indication that the triazoline ring has a constant conformation.

Table 3. Chemical shift variations in some 1,4-dimethyl-5-hydroxy- $\Delta^2$ -1,2,3-triazolines as a function of  $R^5$ .<sup>1,2</sup>

$R^5$	$R^4_{cis} = \text{Me}$	$R^4_{trans} = \text{H}$	$R^1 = \text{Me}$
Me	1.44	3.63	3.27
Et	1.44	3.78	3.24
Pr <sup>i</sup>	1.44	3.84	3.24
Bu <sup>t</sup>	1.41	4.10	3.37

The fact that  $R^4_{trans} = \text{H}$  is influenced by the steric requirements of the proximate  $R^5$  is quite reasonable (*cf.* Ref. 30).

In summary, conformation A seems to predominate with hydroxytriazolines in solution. We propose the anomeric effect to be responsible for this. The fact that  $R^5$  is larger than the OH group does probably not stabilize conformation A. Intramolecular OH... $\pi$  bonding<sup>23</sup> is also presumed to be of minor importance. The free OH stretching frequency is rather low ( $3580 - 3595 \text{ cm}^{-1}$  in CHCl<sub>3</sub>, as opposed to the normal  $3625 \text{ cm}^{-1}$ <sup>22</sup>), but this may well be due to the nitrogen atom attached to C-5. The intensity of the free OH band varies with the concentration, thus excluding any exceptionally strong OH... $\pi$  interaction;<sup>21</sup> the puckering of the ring is probably too small.<sup>22</sup> The occasional appearance of the OH stretching frequency as a doublet or asymmetric band is probably better explained in terms of rotational isomerism around the C-5...O bond.<sup>21</sup>

With regard to the conformation at the N-1... $R^1$  bond, it was observed that the diastereotopic benzylic protons in 1-benzyl-5-hydroxy- $\Delta^2$ -1,2,3-triazolines appeared in two

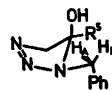


Fig. 3.

ranges, 4.6–4.7 ppm and 4.8–5.0 ppm, provided that  $R^5 \neq \text{Ph}$ . This is consistent with conformation A. Of the three possible rotational isomers the one with the benzylic phenyl group pointing away from  $R^5$  and OH (Fig. 3) is most likely, and the observed shielding by  $R^5 = \text{Ph}$  of the benzylic proton that normally resonates most downfield suggests that this is the one located nearest  $R^5$ , namely B. The normal shielding of proton A relative to proton B is most likely due to its position in a shielding region of the triazoline ring rather than to an effect from the benzylic phenyl group.<sup>32</sup> The pyridine induced solvent shifts of protons A and B<sup>3</sup> are also consistent with this model. Thus the shift of proton A is very constant for different  $R^5$  groups, whereas the shift of proton B is strongly dependent on  $R^5$ , being small when  $R^5$  is large (Ph or Bu<sup>t</sup>).

**5-Amino- $\Delta^2$ -1,2,3-triazolines.** In order to elucidate the conformation of 5-aminotriazolines, we have prepared series of homologous triazolines where the C-4 and C-5 substituents are varied systematically while  $R^1$  is kept constant (*p*-nitrophenyl). In this connection triazolines with an unsubstituted amino group have been prepared for the first time.

Pertinent <sup>1</sup>H NMR data, measured by us or gathered from the literature, are presented in Tables 4 and 5. Assignments of signals are based on trends within homologous series in conjunction with considerations on equilibria positions<sup>1</sup> as well as on absolute  $\delta$ -values.

As with the alkoxytriazolines, the small *trans* coupling constants (3.0–3.4 Hz, Table 4) suggest that X is preferentially axial, even

though this also places  $R^4_{trans}$  axially, irrespectively of its being H, Me, or Et. This is only compatible with  $R^1$  being equatorially oriented, as in conformation A (*cf.* the section on alkoxytriazolines).

Informations may also be obtained from aminotriazolines fused with a cyclohexane ring. For X = NH<sub>2</sub> (IIIp, Table 7 in the experimental part)  $R^4_{cis} = \text{H}$  couples with the adjacent methylene protons with identical coupling constants of 6.2 Hz; for X = NMe<sub>2</sub> (IIIq) these are 5.0 and 3.1 Hz. This suggests that, compared with the corresponding hydroxytriazolines, a larger fraction of molecules with equatorial X is present.

Chemical shifts also provide information on the conformation of aminotriazolines.  $\delta$ -Values for C-4 protons in triazolines where  $R^4_{cis} = R^4_{trans} = \text{H}$  ( $R^5$  is an alkyl group) are particularly informative and have been summarized in Table 6. The rule that  $R^4_{cis}$  resonates at lower field than  $R^4_{trans}$ , generally followed by the hydroxytriazolines, is not valid for the aminotriazolines (see values marked \* in Table 6).

If the difference in chemical shift of the C-4 protons were due to deshielding of  $R^4_{cis} = \text{H}$  by the lone-pair of the amino group, as postulated by other authors,<sup>4</sup> assuming a planar geometry of the triazoline ring, it is difficult to explain why the *cis* proton resonates at highest field in the starred triazolines in Table 6. Also the fact that it is  $R^4_{trans} = \text{H}$ , and not  $R^4_{cis} = \text{H}$ , that suffers the greatest change when the size of the amino group is varied, remains unexplained. Thus for

Table 4. PMR data of 1-(*p*-nitrophenyl)-5-amino- $\Delta^2$ -1,2,3-triazolines where  $R^4_{cis} = R^5 = \text{H}$ .

X	$R^4_{trans}$	$R^1$	Me in	$R^4_{trans}$	$R^4_{cis} = \text{H}$	$R^5 = \text{H}$	$J_{cis}^a$	$J_{trans}^a$	Remarks		
		<i>ortho</i>	<i>meta</i>	X							
IIa	NH <sub>2</sub>	H									
IIb	NHMe	H									
IIc	NMe <sub>2</sub>	H	7.60	8.30	2.12	4.02	4.55	5.05	9.8	3.3	<i>cf.</i> Ref. 4
IId	NH <sub>2</sub>	Me									
IIe	NHMe	Me	7.46	8.25	2.01	1.34	4.47	4.74		3.0	(not pure)
IIf	NMe <sub>2</sub>	Me <sup>b</sup>	7.56	8.24	2.12	1.31	4.55	4.51	<sup>b</sup>	3.4	<i>cf.</i> Ref. 4
IIg	NH <sub>2</sub>	Et									
IIh	NHMe	Et	7.52	8.34	2.02		4.38	4.81		3.2	
IIi	NMe <sub>2</sub>	Et					4.46			3	Ref. 4

<sup>a</sup> *cf.* note in Table 1. <sup>b</sup> 4.12 ppm for  $R^4_{trans} = \text{H}$  and  $J_{cis} = 9$  cps have been reported<sup>4</sup> for the diastereomeric form of IIf. We were unable to observe this form.

Table 5.  $^1\text{H}$  NMR data for 1-(*p*-nitrophenyl)-5-alkyl-5-amino- $\Delta^2$ -1,2,3-triazolines (the C-4 groups are hydrogen or methyl). III d–f were measured in mixture with structure–isomeric triazolines. III j–o were measured as mixtures of stereoisomeric triazolines.

X	$\text{R}^4_{cis}$	$\text{R}^4_{trans}$	$\text{R}^5$	$\text{R}^1$		Me in X	$\text{R}^4=\text{Me}$		$\text{R}^4=\text{H}$		$\text{R}^5$	Remarks
				<i>ortho</i>	<i>meta</i>		<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>		
IIIa	$\text{NH}_2$	H	H	Me	7.68	8.30			4.40	4.40	1.77	
IIIb	$\text{NHMe}$	H	H	Me	7.66	8.28	2.01		4.50	4.18	1.80	
IIIc	$\text{NMe}_2$	H	H	Me	7.90	8.31	2.17		4.68	3.94	1.74	cf. Ref. 4
III d	$\text{NH}_2$	H	H	Et					4.34	4.46		
III e	$\text{NHMe}$	H	H	Et	7.61	8.25	2.04		4.40	4.25	0.87 (t)	
III f	$\text{NMe}_2$	H	H	Et	7.90	8.30	2.16		4.58	3.96	0.66 (t)	cf. Ref. 4
III g	$\text{NH}_2$	H	H	$\text{Pr}^i$	7.68	8.27			4.18	4.50	0.74 (d)	
III h	$\text{NHMe}$	H	H	$\text{Pr}^i$	7.65	8.30	2.02		4.27	4.27	1.12 (d)	
III i	$\text{NMe}_2$	H	H	$\text{Pr}^i$	7.76	8.25	2.21		4.37	4.18	1.12 (d)	cf. Ref. 4
											0.98 (d)	
III j	$\text{NH}_2$	Me	H	Me	7.68	8.24		1.51		4.10	1.74	
		H	Me						1.40	4.29	1.47	
III k	$\text{NHMe}$	Me	H	Me	7.63	8.24	1.87	1.54		3.98	1.81	Ref. 1
		H	Me				2.12		1.38	4.47	1.57	
III l	$\text{NMe}_2$	Me	H	Me	7.79	8.20	2.16					
		H	Me						1.37	4.56	1.52	
III m	$\text{NH}_2$	Me	H	Et	7.85	8.45		1.50		4.35	0.89 (t)	
		H	Me									
III n	$\text{NHMe}$	Me	H	Et	7.64	8.30	1.89	1.53		4.11	0.93 (t)	
		H	Me									
III o	$\text{NMe}_2$	Me	H	Et	7.65	8.24	2.33	1.57?		4.18		cf. Ref. 39
		H	Me		7.91		2.19		1.57	4.57	0.59 (t)	

Table 6. Chemical shifts for  $\text{R}^4_{cis}=\text{H}$  and  $\text{R}^4_{trans}=\text{H}$  in 1-(*p*-nitrophenyl)-5-alkyl-5-amino- $\Delta^2$ -1,2,3-triazolines (cf. Table 5). \* Exceptions from the rule that  $\text{R}^4_{cis}$  resonates at lower field than  $\text{R}^4_{trans}$  (cf. text).

$\text{R}^5$	$\text{R}^4$	X= $\text{NH}_2$	X= $\text{NHMe}$	X= $\text{NMe}_2$
Me	<i>cis</i>	4.40*	4.50	4.68
	<i>trans</i>	4.40*	4.18	3.94
Et	<i>cis</i>	4.34*	4.40	4.58
	<i>trans</i>	4.46*	4.25	3.96
$\text{Pr}^i$	<i>cis</i>	4.18*	4.27*	4.37
	<i>trans</i>	4.50*	4.27*	4.18

$\text{R}^5=\text{Me}$  one observes a 0.46 ppm upfield shift for  $\text{R}^4_{trans}=\text{H}$  but only a 0.28 ppm downfield shift for  $\text{R}^4_{cis}=\text{H}$  on proceeding from X= $\text{NH}_2$

to X= $\text{NMe}_2$ . The presence of lone-pairs on X is seemingly not essential for this. Quite analogous effects are observed on increasing the size of  $\text{R}^5$ , the proton *trans* to  $\text{R}^5$  here suffering a large upfield shift and the other a smaller downfield shift.

Deshielding of the *cis* proton by the lone-pair(s) on X is clearly inadequate to explain these observations, and, also, the effect of hydroxy or amino groups on vicinal protons is not at all clearcut. Admittedly, there are examples of even very large deshieldings of this sort, but this requires either extreme steric compression<sup>33</sup> or that a lone-pair points directly toward the affected proton.<sup>34</sup> In fact, if the hetero group is freely rotating, it is more common that the *trans* oriented proton resonates at lowest field.<sup>20,25–28</sup>

It is more likely that the observed chemical shift variations are the result of conformational

changes. Rotational isomerism about the C-5...X bond (*cf.* Ref. 4) is one possibility, which would, however, also fail to explain, at least in a straightforward manner, the large shieldings experienced by a proton at C-4, when the C-5 group *trans* to it increases in size. We favor an explanation based on a variation in the equilibrium composition of conformations A, B, C, and D, and propose that a large C-5 substituent prefers the axial to the equatorial position, because it then avoids being *gauche* to both C-4 protons (*cf.* Ref. 7). This forces the C-4 proton situated *trans* to the C-5 group with the largest steric requirements into the axial position, where it will be shielded by the triazoline ring.

This picture explains the tendency of amino-triazolines with  $R^5 = H$  to adopt conformation A, and also the "trans shielding effect" exerted by an alkyl as well as an amino group at C-5. The anomeric effect, which seemed to determine the conformation of alkoxy- and hydroxy-triazolines, would not account for these effects.

For  $R^5$  being an alkyl group we have not been able to conclude which are the participating conformers. A and C are the most likely candidates, but the coexistence of B or D is also possible in view of the increasing steric congestion along the N-1...C-5 bond with increasing size of C-5 substituents.

## EXPERIMENTAL

$^1H$  NMR spectra were recorded on a JEOL JNM-C-60HL instrument, using TMS as internal standard. Chemical shifts (in  $CDCl_3$  at magnet temperature, unless otherwise stated) are given as  $\delta$ -values. AB systems were treated in a second order manner.<sup>41</sup>  $\delta$ -Values for *p*-nitrophenyl groups are just the centers of the characteristic 'doublets'.

*1-(p-Nitrophenyl)-5-ethoxy- $\Delta^2$ -1,2,3-triazoline* (Ia) was prepared by dissolving 1.64 g of *p*-nitrophenyl azide in 8 ml of ethyl vinyl ether. After 11 days the product had separated in 99% yield. After recrystallization from ethyl acetate the m.p. of the slightly yellowish crystals was 135°C. (Found: C 50.77; H 5.23; N 23.80. Calc. for  $C_{10}H_{12}N_4O_2$ : C 50.86; H 5.12; N 23.72).

*1-(p-Aminophenyl)-5-ethoxy- $\Delta^2$ -1,2,3-triazoline* was obtained in quantitative yield by catalytic hydrogenation of Ia (0.356 g in 3 ml of methanol) for 1 h at 2.5 atm  $H_2$  pressure, using  $PtO_2$  (3 mg) as the catalyst. After treatment with activated carbon and crystallization from ether, yellow crystals of m.p. 71–76°C were obtained. (Found: C 58.26; H 6.63; N 27.35. Calc. for  $C_{10}H_{14}N_4O_2$ : C 58.24; H 6.84; N 27.17).

*1-(p-Nitrophenyl)-4,5-tetrahydropyrano- $\Delta^2$ -1,2,3-triazoline* was prepared according to the literature.<sup>23</sup>

*5-Hydroxy- $\Delta^2$ -1,2,3-triazolines* have been described previously.<sup>1,2</sup>

*5-Amino- $\Delta^2$ -1,2,3-triazolines* are prepared by adding either *ca.* 0.3 g of liquid ammonia and 2 g of anhydrous sodium sulfate, 1.5 ml of 40% aqueous methylamine, or *ca.* 0.5 g of dimethyl-

Table 7. Data of preparative interest for new amino triazolines in Tables 4 and 5.

R <sup>4</sup>	R <sup>5</sup>	X	Reac- tion time	Yield %	M.p. °C	Formula	Analyses			Calculated			
							Found C	H	N	C	H	N	
IIIh	Et	H	NHMe	6 d	100	108–109	$C_{11}H_{15}N_5O_2$	53.00	6.07	28.10	53.15	6.10	27.98
IIIa	H	Me	NH <sub>2</sub>	3 d	25	123–124 <sup>a</sup>	$C_9H_{11}N_5O_2$	48.86	5.01	31.66	48.72	5.24	31.82
IIIb	H	Me	NHMe	24 h	90	124–126	$C_{10}H_{13}N_5O_2$	51.06	5.57	29.77	51.01	5.53	29.77
IIIg	H	Pr <sup>1</sup>	NH <sub>2</sub>	7 d	— <sup>b</sup>	122–124 <sup>a</sup>	$C_{11}H_{15}N_5O_2$	53.00	6.07	28.10	53.17	6.33	28.27
IIIh	H	Pr <sup>1</sup>	NHMe	2 d	100	144–145	$C_{12}H_{17}N_5O_2$	54.74	6.51	26.60	54.70	6.51	26.67
IIIj	Me	Me	NH <sub>2</sub>	2 d	— <sup>b</sup>	153–155	$C_{10}H_{13}N_5O_2$	51.06	5.57	29.77	51.23	5.70	29.72
IIIi	Me	Me	NMe <sub>2</sub>	3 d <sup>c</sup>	— <sup>b</sup>	119–120	$C_{12}H_{17}N_5O_2$	54.74	6.51	26.60	54.97	6.62	26.54
IIIm	Me	Et	NH <sub>2</sub>	4 d	80	131–132	$C_{11}H_{15}N_5O_2$	53.00	6.07	28.10	52.95	5.98	28.03
IIIn	Me	Et	NHMe	2 d	96	109–111	$C_{12}H_{17}N_5O_2$	54.74	6.51	26.60	54.86	6.60	26.84
IIIp	—(CH <sub>2</sub> ) <sub>4</sub> —	NH <sub>2</sub>		24 h	100	129–130	$C_{12}H_{15}N_5O_2$	55.16	5.79	26.80	55.23	5.86	26.94
IIIq	—(CH <sub>2</sub> ) <sub>4</sub> —	NMe <sub>2</sub>		2.5 h <sup>c</sup>	100	84–86	$C_{14}H_{19}N_5O_2$	58.12	6.62	24.21	58.18	6.63	24.01

<sup>a</sup> Ethyl acetate-pentane was used for recrystallization. <sup>b</sup> Two isomeric triazolines were formed due to enamine formation in two directions;<sup>40</sup> only the shown triazoline was isolated in a pure state. <sup>c</sup> The reaction was carried out in chloroform in place of ether.

amine to a solution of 0.82 g of *p*-nitrophenyl azide and the appropriate aldehyde (ca. 100 % excess) or ketone (ca. 20 % excess) in 7 ml of diethyl ether. The mixture is allowed to stand at room temperature for the specified time (Table 7) in a stoppered flask.

If the product separates during the reaction, it is just filtered off, washed with pentane, and recrystallized from methanol; if not, the product will crystallize on removal of the solvent from the organic phase and triturating the residue with pentane. Recrystallization is performed, using methanol as solvent, until a constant melting point is obtained. Sodium sulfate used in conjunction with ammonia is first removed by dissolving the product in chloroform and filtering. Yields (referring to unrecrystallized product), melting points, and analyses are given in Table 7. The triazolines are yellow to brown. 5-Methylaminotriazolines in particular are often unstable and decompose on standing at room temperature.

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Received December 3, 1973.