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Preparation and Characterization of 1-Alkyl-5-hydroxy-Δ^2-1,2,3-triazolines

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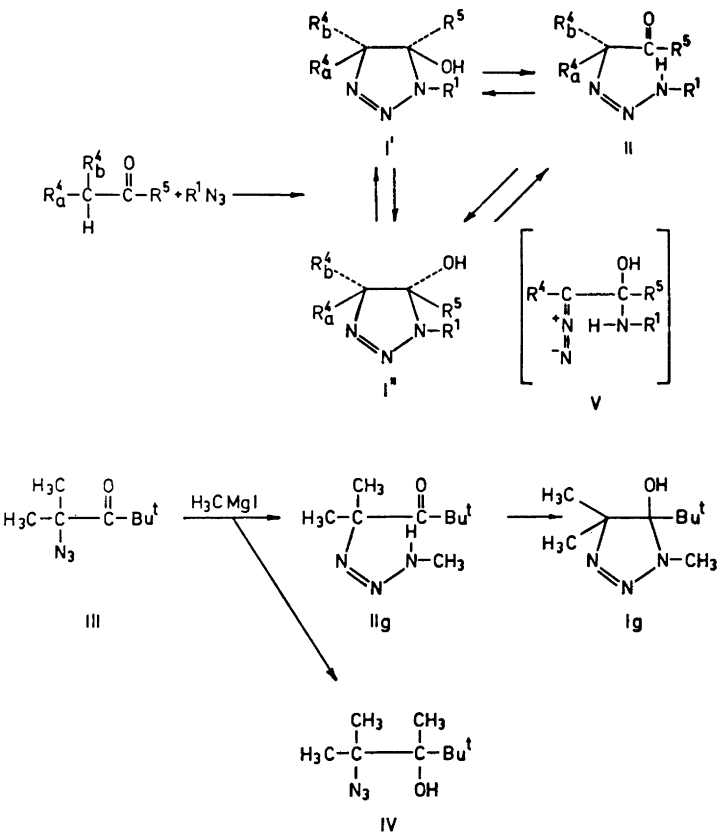
A number of 1-methyl- and 1-benzyl-5-hydroxy-Δ^2-1,2,3-triazolines have been prepared by reaction of ketones with methyl or benzyl azide in the presence of potassium *tert*-butoxide. Some of the triazolines exist in solution as an equilibrium mixture of diastereomers, most likely interconvertible *via* triazenes. The structures of the triazolines, including the diastereomeric pairs, have been determined by NMR spectroscopy in chloroform and pyridine.

The reaction of alkyl or aryl azides with ketones in the presence of potassium *tert*-butoxide leads to the formation of 5-hydroxy-Δ^2-1,2,3-triazolines (I), as described in a preliminary communication.[1] The reaction has now been further studied, and the products obtained by treating a number of ketones with methyl and benzyl azide are described in the present paper. The analogous reaction with aryl azides forms the subject of a forthcoming paper.

Methyl or benzyl azide react smoothly with ketones and potassium *tert*-butoxide at room temperature to give 1-methyl- or 1-benzyl-5-hydroxy-Δ^2-1,2,3-triazolines (I) in mostly good yields (Table 1). Sterically unhindered ketones react with azides in the course of a few hours whereas hindered ketones, such as diisopropyl ketone, require longer reaction times. For certain ketones the reaction takes a different course.[2,3]

The highly hindred triazoline (Ig) was prepared by treatment of the α-azido ketone (III) with methyl magnesium iodide, a reaction probably proceeding with the triazene (IIg) as an intermediate,[4] which subsequently undergoes ring-closure to (Ig). The α-azido alcohol (IV) was obtained as a by-product from this reaction.

Triazolines in which R_a[4] and R_b[4] are different may obviously exist in two diastereomeric forms (I′) and (I″), and NMR spectra in fact showed that many of the compounds in Table 1 gave a mixture of two products when dissolved in chloroform or pyridine. When an NMR spectrum of 1-benzyl-4,5-dimethyl-5-hydroxy-Δ^2-1,2,3-triazoline (Ik) was determined immediately after it was dissolved in deuteriochloroform almost only one isomer (I′k) was present.



After a few minutes, however, an equilibrium mixture of (I'k) and (I''k) had been formed. This indicates that in the crystalline phase only (I'k) is present, whereas in solution it isomerizes to a mixture of (I'k) and (I''k). Presumably all the triazolines listed in Table 1 crystallize as the I'-isomers (the assignment of structures to the (I') and (I'') isomers is described below).

The equilibrium mixtures of (I') and (I'') were determined in deuteriochloroform solution by NMR spectroscopy (Table 2). The position of the equilibrium is determined by the interaction of R^5 with R_a^4 and R_b^4. When the two substituents at C-4 are different R_b^4 is chosen to be the smaller of the two groups (Table 1).

The reversible isomerization of (I') and (I'') in solution probably proceeds *via* the triazenes (II). When R^1 is an aryl group, the latter can be detected through IR and NMR spectra.[1] The hydroxy-triazolines described in the present paper (R^1 = methyl or benzyl), however, did not contain the triazene (II) in amounts sufficiently large to be detected. This even applies to the highly hindered compound (Ig). Since the 1-phenyl-triazoline corresponding to (Ig) is almost entirely on the triazene form[2] it may be concluded that the

Table 1. 1-Alkyl-5-hydroxy-Δ^2-1,2,3-triazolines (I).

I	R^1	R_b^4	R_a^4	R^5	Reaction time, h	Isolation procedure	% Yield	m.p. °C.	Formula	C % Calc.	C % Found	H % Calc.	H % Found	N % Calc.	N % Found
a	Me	H	Me	Me	3	D	33	106–7	$C_5H_{11}N_3O$	46.48	46.56	8.59	8.48	32.53	32.37
b	Me	H	Me	Et	7	D	58	94–95	$C_6H_{13}N_3O$	50.32	50.35	9.15	9.07	29.35	29.25
c	Me	H	Me	i-Pr	24	C	74	109–10	$C_7H_{15}N_3O$	53.48	53.62	9.62	9.44	26.74	26.80
d	Me	H	Me	*t*-Bu	150	C	77	134–35	$C_8H_{17}N_3O$	56.12	56.25	10.01	9.80	24.55	24.78
e	Me	H	$-(CH_2)_4-$		18	D	78	120–22[a]	$C_7H_{13}N_3O$	54.17	54.27	8.44	8.21	27.08	27.28
f	Me	Me	Me	i-Pr	900	C	75	100–01	$C_8H_{17}N_3O$	56.12	56.21	10.01	10.16	24.55	24.47
g[b]	Me	Me	Me	*t*-Bu			32	118–20	$C_9H_{19}N_3O$	58.33	58.40	10.33	10.10	22.68	22.85
h	Me	H	Me	Ph	3	C	84	138–39[a]	$C_{10}H_{13}N_3O$	62.81	62.72	6.85	6.84	21.98	22.04
i	Me	H	Et	Ph	26	C	78	112–13[a]	$C_{11}H_{15}N_3O$	64.35	64.38	7.37	7.43	20.47	20.38
j	Me	Me	Me	Ph	220	C	63	190–91[a]	$C_{11}H_{15}N_3O$	64.35	64.54	7.37	7.30	20.47	20.69
k	$PhCH_2$	H	Me	Me	7	B	57	108–9[a]	$C_{11}H_{15}N_3O$	64.35	64.21	7.37	7.38	20.47	20.63
l	$PhCH_2$	H	Me	Et	3	A	65	104–5	$C_{12}H_{17}N_3O$	65.72	65.71	7.81	7.62	19.16	19.33
m	$PhCH_2$	H	Me	i-Pr	28	A	72	110–11[a]	$C_{13}H_{19}N_3O$	66.92	67.07	8.21	8.06	18.02	18.17
n	$PhCH_2$	H	Me	*t*-Bu	100	A	73	130–31[a]	$C_{14}H_{23}N_3O_2$[d]	63.38	63.30	8.74	8.64	15.84	16.00
o	$PhCH_2$	H	$-(CH_2)-$		8	A	81	121–22[a]	$C_{13}H_{17}N_3O$	67.50	67.33	7.41	7.28	18.17	18.11
p	$PhCH_2$	Me	Me	i-Pr	600	B[c]	91	99–102[a]	$C_{14}H_{21}N_3O$	68.00	68.15	8.56	8.47	16.99	17.19
q	$PhCH_2$	H	Me	Ph	7	A	92	153[a]	$C_{16}H_{17}N_3O$	71.89	71.76	6.41	6.22	15.72	15.84
r	$PhCH_2$	Me	Me	Ph	220	A	74	134–35[a]	$C_{17}H_{19}N_3O$	72.58	72.58	6.81	6.77	14.94	14.89

[a] Melts with evolution of nitrogen. [b] Prepared from the α-azido ketone (III) and Grignard reagent. [c] Recrystallized from cyclohexane. [d] Contains one mol water of crystallization.

equilibrium between triazolines (I) and triazenes (II) is determined largely by electronic factors.

Since some Δ^2-1,2,3-triazolines can undergo ring opening to diazo compounds (V),[5] such intermediates might conceivably also account for the interconversion of (I′) and (I″). However, when (Ia) was dissolved in deuterium oxide it gave a mixture of (I′a) and (I″a) without exchange of H-4 with deuterium. In the presence of a trace of potassium hydroxide the isomerization took place at such a rate that an averaged NMR spectrum of the two diastereomers was obtained; yet, no deuterium was incorporated at C-4. This necessarily excludes (V) as an intermediate in the interconversion.

In Tables 3 and 4 are presented NMR data of all the 5-hydroxy-Δ^2-1,2,3-triazolines (I) described in the present paper. In the cases where two diastereomers are present in solution (Table 2), NMR data of both isomers

Table 2. Content (%) of I′ in the equilibrium mixtures of I′ and I″ in deuteriochloroform (4 % w/v-concentration) as determined from NMR spectra.

	1-Methyl-Δ^2-1,2,3-triazoline					1-Benzyl-Δ^2-1,2,3-triazoline				
Solvent	a	b	c	d	h	k	l	m	n	q
Deuterio-chloroform	68	85	100	100	78	70	90	100	100	80

(I′ and I″) are given. The δ-values of the methyl groups at C-4 fall into two groups, namely at 1.41 – 1.57 or at 1.05 – 1.21. They can be oriented either *cis* or *trans* relative to the hydroxy group at C-5. The compounds with bulky substituents at C-5 (Ic, d, m, and n) exist in only one form in chloroform solution (Table 2), and this is undoubtedly the I′-isomer in which the bulky group at C-5 is *trans* to the methyl group at C-4. The signals of the C-4-methyl groups in compounds (I″h) and (I″q) and of one of the two methyl groups in (Ij) and (Ir) are found at unusually high field. Since these compounds have a phenyl group at C-5 the upfield shift must be due to shielding by ring currents in the phenyl group. Consequently, the phenyl and the methyl groups are *cis* oriented in (I″h) and (I″q).

From the spectra of the above mentioned compounds it may be concluded that the methyl groups with δ-values of about 1.48, are positioned *cis* to the hydroxy group at C-5, whereas *trans* methyl groups give rise to signals at *ca.* 1.13. Similar conclusions have been arrived at by Huisgen and Szeimies [6] in the case of 5-alkoxy-Δ^2-1,2,3-triazolines. Furthermore, in agreement with the finding of Demarco *et al.*[7] it is observed that the chloroform-pyridine solvent shifts are larger (*ca.* −0.22) for the *cis* than for the *trans* methyl groups (only −0.06 to −0.15) (Tables 3 and 4). By using these δ-values and solvent shifts, structures were assigned to the remaining pairs of diastereomers (Ia, b, k, and l) as shown in Tables 3 and 4. The assignments are confirmed by the

Table 3. NMR spectra of 1-methyl-5-hydroxy-Δ^2-1,2,3-triazolines. The spectra have been recorded in deuteriochloroform and pyridine as 4 % w/v solutions. The general effect of dilution is a small downfield shift; thus the signals of Ia are shifted 0.01 – 0.05 ppm downfield on dilution four times (to 1 %). In Table 3 and 4 are given δ-values in deuteriochloroform as well as solvent shifts, $\Delta = \delta_{CDCl_3} - \delta_{pyridine}$. In a few cases solvent shifts in benzene are also given; these are shown in parentheses (Δ) = $\delta_{CDCl_3} - \delta_{benzene}$.

	R_b^4	R_a^4	R^5	Me[1]		Me-groups in 4-position *cis*		Me-groups in 4-position *trans*		H in 4-position *cis*		H in 4-position *trans*		Other signals
				δ	Δ	δ	Δ	δ	Δ	δ	Δ	δ	Δ	
I'a				3.27s	−0.10	1.44d	−0.20					3.63q	−0.20	1.47(s,−0,11,3H)
	H	Me	Me											
I''a				3.27s				1.05d	−0.06	4.22q	−0.39			1.38(s,−0,12,3H)
I'b				3.24s	−0.09	1.44d	−0.22					3.78q	−0.20	ca. 0.9("t",3H) *ca.* 1.83("q",2H)
	H	Me	Et											
I''b				3.24s				1.05d		4.24q				
I'c	H	Me	i-Pr	3.24s	−0.07	1.44d	−0.22					3.84q	−0.23	1.03(d,−0,11,3H)0.83(d,−0,04,3H) 2.19(sept.,−0,14,1H)
I'd	H	Me	*t*-Bu	3.37s	−0.06	1.41d	−0.22					4.10q	−0.23	1.02(s,−0,10,9H)
I''e	H	$-(CH_2)_4-$		3.28s	−0.10					4.11dd	−0.38			0−2.5(m,8H)
If	Me	Me	i-Pr	3.26s	−0.09	1.52s	−0.21	1.13s	−0.10					1.07(d,3H)1.18(d,3H)2.18(sept,1H)
Ig	Me	Me	*t*-Bu	3.34s	−0.08	1.57s	−0.20	1.20s	−0.10					1.17(s,9H)
I'h				3.22s	−0.10	1.48d	−0.18					3.92q	−0.21	}
	H	Me	Ph											7.2−7.7(m)
I''h				3.30s				0.67d	−0.11	4.48q	−0.39			}
I'i				3.19s	−0.05							3.76q	−0.23	0.8−1.3(m,3H) 1.6−2.2(m,2H)
	H	Et	Ph											}
I''i				3.29s										7.2−7.7(m,5H)
Ij	Me	Me	Ph	3.26s	−0.06	1.54s	−0.25	0.63s	−0.14					7.42("s",5H)

$J_{H^4Me^4} = 7.0 - 7.4$ cps. *cis* and *trans* refer to position relative to the hydroxy group at C-5. (Δ) values for H^4, Me^4, and Me^5 in I'a are +0.30, +0.11, and +0.40. In I''a they are +0.08, +0.26, and +0.31. Ia is, however, very sparingly soluble in benzene.

Table 4. NMR data of 1-benzyl-5-hydroxy-Δ^2-1,2,3-triazolines (4 % w/v, magnet temperature).

	R_b^4	R_a^4	R^5	Benzylic protons A δ	Δ	B δ	Δ	Me-groups in 4-position *cis* δ	Δ	*trans* δ	Δ	H in 4-position *cis* δ	Δ	*trans* δ	Δ	Other signals
I'k				4.62	−0.26	4.99	−0.17	1.48d	−0.19					3.73q	−0.21	1.34(s,−0,19,3H)
	H	Me	Me													
I''k				4.71	−0.22	4.98	−0.18			1.08d	−0.08	4.28q	−0.39			1.28(s,−0.20,3H)
I'l				4.60	−0.22	4.92	−0.16	1.48d	−0.21					3.86q	−0.22	0.6−1.2(m)1,5−2.0(m)
	H	Me	Et													
I''l				4.68		4.98				1.10d	−0.07	4.31q				
I'm	H	Me	i-Pr	4.60	−0.17	4.82	−0.15	1.47d	−0.23					3.93q	−0.21	0.69 0.99(d,3H)2.14(sept,1H)
I'n	H	Me	*t*-Bu	4.64	−0.25	4.90	−0.02	1.42d	−0.25					4.21q	−0.25	0.96(s,9H)
I''o	H	$-(CH_2)_4-$		4.68	−0.23	5.00	−0.18					4.15dd	−0.40			0−2.7(m,8H)
Ip	Me	Me	i-Pr	4.63	−0.27	4.83	−0.16	1.55s	−0.23	1.21	−0.09					0.99 1.09(d,3H)2.18(sept,1H)
I'q				4.69	−0.25	4.54	−0.08	1.47d	−0.17					4.02q	−0.22	
	H	Me	Ph													
I''q										0.72d	−0.11	4.22q				
Ir	Me	Me	Ph	4.70	−0.28	4.55	−0.11	1.55s	−0.28	0.68s	−0.15					
Is[2]	H	H	Me	4.70	−0.23	4.98	−0.20					4.26	−0.42	3.78	−0.29	1.43(s,−0.15,3H)
It[2]	H	H	Ph	4.63	−0.30	4.63	−0.07					4.49	−0.41	4.08	−0.27	

$J_{H^4Me^4} = 7.2-7.5$ cps. $|J_{AB}| = 15-16$ cps. δ_A and δ_B have been calculated from the equation $\delta_A - \delta_B = \sqrt{(\nu_4-\nu_1)(\nu_3-\nu_2)}$.
The aromatic protons lie within the range 7.2−7.6 ppm usually as multiplets.
cis and *trans* refer to position relative to the hydroxy group at C-5. (Δ) values for H^4, Me^4, and Me^5 are the following: I'k: +0.31, +0.09, +0.26; I''k: +0.02, +0.02, +0.26, +0.20, and −0.01 and +0.16 for the *cis* and *trans* methyl groups of Ip, respectively.

δ-values of H-4. These fall into two ranges, namely 3.6 – 4.0 (except for the two *tert*-butyl derivatives (I'd) and (I'n)) when H-4 is *trans* to the hydroxy group (I'-isomers) and 4.1 – 4.5 when H-4 is *cis* oriented (I''-isomers). The two cyclohexane derivatives, (Ie) and (Io), must necessarily possess the I''-form; in agreement herewith their H-4-protons give signals at δ 4.11 and 4.15, respectively.

Because of restricted solubility it has not been possible to utilize benzene induced solvent shifts in general for the assignment of structures. Spectra of (Ia), (Ik), and (Ip) in benzene solution, however, show that hydrogen atoms or methyl groups, which are *trans* to the hydroxy group, are shielded much more than the corresponding *cis* oriented groups. This is consistent with the association of a molecule of benzene to the triazoline opposite to the hydroxy group.[8–10]

The diastereotopic benzylic protons in compounds (Ik to p) give signals which fall into two ranges, the A-protons at 4.6 – 4.7 δ and the B-protons at 4.8 – 5.0 (Table 4). The pyridine induced solvent shifts (Δ-values) are quite constant for the A-protons, but vary considerably for the B-protons. In compounds (Iq and r) the B-protons give signals at rather high field, probably due to shielding by the phenyl groups at C-5.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded on Varian A-60 or HA-100 spectrometers. Unless otherwise stated deuteriochloroform was used as solvent. Chemical shifts are given in ppm (δ-values) relative to tetramethylsilane.

tert-Butyl alcohol. A FLUKA *purissimum* grade was used without further purification.

Methyl azide, prepared according to the literature,[11] was used as an approximately 20 % w/v solution in *tert*-butyl alcohol. The solution was dried with molecular sieve 4A.

Benzyl azide was prepared according to Curtius and Ehrhardt.[12]

The ketones were commercially available with the exception of 2,2,4-trimethyl-3-pentanone, which was prepared in analogy with the method of Cook and Percival.[13]

General procedure for the preparation of 1-benzyl- and 1-methyl-5-hydroxy-Δ^2-1,2,3-triazolines. Benzyl azide (0.02 mol) was added to a solution of potassium (1.0 g) in *tert*-butyl alcohol (20 ml). With methyl azide the following procedure was used: a 20 % solution of methyl azide (0.024 mol) in *tert*-butyl alcohol was added to potassium *tert*-butoxide, prepared from 1.0 g of potassium. To the solution of the azide the appropriate ketone (0.02 mol) was added, and the mixture was shaken until a homogeneous solution was obtained. The mixture turned yellow or orange after a short time. The reaction was followed by NMR spectroscopy, and when it was complete the product was isolated by one of the following procedures:

A. If the product crystallized on pouring the reaction mixture into 200 ml of ice-water, it was filtered off, washed with water and pentane, and recrystallized from ethyl acetate-pentane.

B. If the product did not crystallize when the reaction mixture was poured into 200 ml of ice-water it was extracted with methylene chloride. The extract was dried with sodium sulfate (magnesium sulfate should not be used because of its acidic nature) and the solvent was removed *in vacuo* at room temperature. The product usually crystallized on cooling, if not it was dissolved in ether, cooled to – 75°C, and induced to crystallize by scratching. Recrystallization from ethyl acetate-pentane afforded the pure products.

C. Ice (*ca.* 10 g) was added to the reaction mixture; *tert*-butyl alcohol was removed *in vacuo*, and the aqueous phase was extracted with methylene chloride.

D. In some cases extraction of the triazoline from its aqueous solution was very difficult. Procedure C was then used, but the extraction was performed continuously for 20 h. The methylene chloride was renewed after 1 and 7 h.

2-Bromo-2,4,4-trimethyl-3-pentanone. 2,2,4-Trimethyl-3-pentanone (12.8 g) was heated to 40 – 50°C and bromine (5.1 ml) was added dropwise. When the evolution of hydrogen bromide had ceased the reaction mixture was distilled yielding 19.0 g (92 %) of a product with b.p. 70°C (12 – 15 mmHg) (reported [14] 65 – 66°C (13 – 14 mmHg). NMR-spectrum: 1.41 δ (s, 9H) and 1.96 δ (s, 6H).

2-Azido-2,4,4-trimethyl-3-pentanone (III). To a stirred solution of sodium azide (3.9 g) in 30 ml of dimethyl sulfoxide was added 2-bromo-2,4,4-trimethyl-3-pentanone (8.28 g). The temperature rose to *ca*. 40°C and the mixture solidified after 2 min due to separation of sodium bromide. The stirring was continued for 3 h. Ice was then added and the mixture was extracted with ether (50 ml). The ether phase was washed with water and dried with magnesium sulfate. Removal of the ether and distillation of the residue (caution) gave 6.43 g (95 %) of a colourless liquid with b.p. 33°C (2 mmHg). (Found: C 56.89; H 8.94; N 24.95. Calc. for $C_8H_{15}N_3O$: C 56.78; H 8.94; N 24.84.) NMR spectrum: 1.26 δ (s, 9H) and 1.48 δ (s, 6H).

Reaction of 2-azido-2,4,4-trimethyl-3-pentanone (III) with methylmagnesium iodide. Methylmagnesium iodide (3.5 mmol) in ether (6 ml) was added to a solution of (III) (0.508 g, 3 mmol) in 25 ml of ether with stirring. The mixture was stirred at reflux temperature for 1.5 h. A solution of ammonium chloride (0.7 g) and conc. ammonia (0.3 ml) in 2 ml of water was added, and stirring was continued until the precipitated magnesium salt had dissolved. The ether phase was separated, washed with water, and dried over sodium sulfate. Removal of the ether in vacuum left 0.63 g of a mixture of crystals and liquid which was placed in a water bath at 70°C; the liquid was distilled off at 0.01 mmHg. Yield of the azido alcohol (IV); 0.33 g (60 %). (Found: C 57.76; H 10.24; N 22.14. Calc. for $C_9H_{19}N_3O$: C 58.33; H 10.33; N 22.68.) The IR spectrum revealed the azido group at 2110 cm^{-1}. The NMR spectrum showed signals at 1.08 δ (s, 9H), 1.19 (s, 3H), 1.43 (q, 3H), and 1.47 (q, 3H). The two methyl groups geminal to the azido group couple with a coupling constant of 0.4 Hz. IR and NMR spectra revealed that (IV) was slightly contaminated with the starting material (III).

The residue from the distillation consisted of the triazoline (Ig), 0.176 g (32 %), m.p. 117 – 119°C. Recrystallization from ethyl acetate-pentane gave the pure product (Table 1).

Microanalyses were performed by Dr. A. Bernhardt.

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