v-Triazolines. Part 12.[1] Synthesis of 5-Amino-1-aryl-4-methylene-4,5-dihydro-*v*-triazoles

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A series of 5-amino-4-aminomethyl-1-aryl-4,5-dihydro-*v*-triazoles was synthesized. On reaction with methyl iodide or methyl trifluoromethanesulphonate the corresponding 4-(quaternary)ammoniomethyl salts were obtained. These derivatives, on treatment with several bases under various conditions, underwent a β-elimination yielding 5-amino-1-aryl-4-methylene-4,5-dihydro-*v*-triazoles. In the presence of methoxide the methylene derivatives afforded 1-aryl-4-methoxymethyl-*v*-triazoles *via* nucleophilic addition and elimination of amine. On reaction with non-nucleophilic bases the methylene compounds were isomerized to 5-amino-1-aryl-4-methyl-*v*-triazoles.

In a previous paper [2] we described the reactions with bases of some 1-aryl-4-alkyl- and -aryl-thiomethyl-5-amino-4,5-dihydro-*v*-triazoles. It has been shown that these compounds undergo amine and/or thiol elimination in a competitive reaction yielding 1-aryl-4-alkyl- or -aryl-thiomethyl-*v*-triazoles and/or 5-amino-1-aryl-4-methylene-4,5-dihydro-*v*-triazoles. These compounds were isolated in only one case, fast isomerization to the corresponding 5-amino-1-aryl-4-methyl-*v*-triazoles occurring under the reaction conditions. This reaction scheme was not, therefore, considered a good method for the preparation of 5-amino-1-aryl-4-methylene-4,5-dihydro-*v*-triazoles.

We were interested in the preparation of these compounds, a practically unknown class of triazoline derivatives, in order to understand better the behaviour of the exocyclic double bond towards nucleophiles, bases, and electrophiles. Also, the compounds could be useful in some instances as an alternative starting material for the preparation of the isomeric 1-aryl-4-methyl-5-amino-*v*-triazoles.

We report here the reactions with bases of the quaternary ammonium compounds (3a—i), obtained from the triazolines (1a—g).

4,5-Dihydro-v-triazoles (1a—g). Several members of this class of compounds have been previously described.[3] The new compounds were easily obtained through the known direct reaction of propenal with two moles of secondary amine and the appropriate arylazide. Their properties are listed in Table 1.

The structures of compounds (1a, c, and d) have been confirmed by ^{1}H n.m.r. and their configuration is invariably *trans*, as demonstrated by $J_{4,5}$ 3—3.5 Hz.[3,4]

It is known [3] that the 4,5-dihydro-*v*-triazoles of general type (1) easily undergo elemination of the 5-amino-substituent forming the corresponding triazoles (2) upon treatment with base. The alternative orientation (elimination of the amine residue from the side chain), which would parallel the behaviour of the above 4-alkyl or -aryl-thiomethyl derivatives,[2] is unknown for compounds (1) in which the two potential leaving groups are the same. Obviously, elimination leading to the aromatic product is preferred and the elimination from the side chain becomes competitive only when the substituent is a better leaving group than the amino-group. This better-leaving ability is present in the quaternization products (3).

Quaternary Ammonium Compounds (3a—i).—The quaternization reaction of the triazolines (1a—g) to the corresponding ammonium salts (3a—i) was smoothly accomplished by reaction with a slight excess of methyl iodide or methyl trifluoromethanesulphonate in polar solvents and preferably at room temperature.

This reaction afforded the best results under mild conditions, according to the known [5] thermal lability of the substrates. An excess of the reagent could not be employed due to formation of products derived from quaternization at both amino-groups.

Methyl trifluoromethanesulphonate was found to be superior in the case of the less reactive morpholine derivative which reacted only slowly and at higher temperature with methyl iodide.†

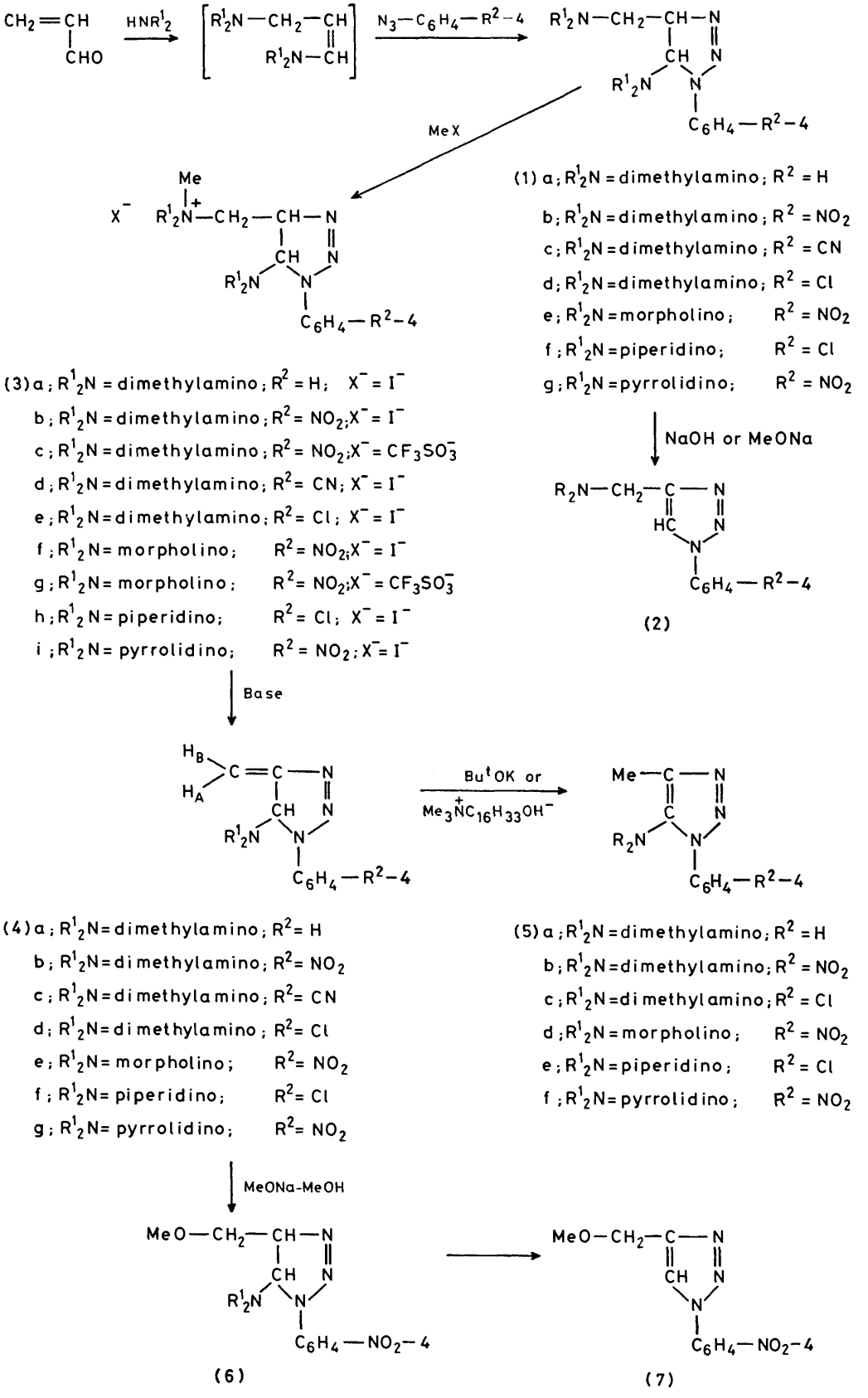
The site of the quaternization was demonstrated by comparing the ^{1}H n.m.r. spectra of the triazolines (1)

TABLE 1

Preparation and properties of the triazolines (1)

	^{1}H N.m.r. ($CDCl_3$)			Reaction	Cryst.	M.p.	Yield	Found (%) [Reqd. (%)]		
	δ_{H-4}	δ_{H-5}	$J_{4,5}$ (Hz)	time (h)	solvent	(°C)	(%)	C	H	N
(1a)	4.42	4.47	3	2	Hexane	97—100	35	63.2 [63.15]	8.35 [8.55]	28.55 [28.3]
(1c)	4.38	4.57	3	2	Di-isopropyl ether	83—68	85	62.0 [61.75]	7.25 [7.4]	30.6 [30.85]
(1d)	4.56	4.83	3.5	5	Pentane	44—46	75	55.8 [55.4]	7.05 [7.15]	24.50 [24.85]

† Starting from 1-(4-nitrophenyl)-4-(*N*-methylanilino)methyl-5-(*N*-methylanilino)-4,5-dihydro-*v*-triazoles we could not obtain the quaternized derivative. This substrate did not react with methyl iodide and on reaction with methyl trifluoromethanesulphonate 1(-4-nitrophenyl)-*v*-triazole was obtained as the sole important product and in fair yield. This result can be explained assuming a retro-Mannich reaction, which has been already observed when the above triazoline was treated with acids.[3]



(1) a; R^1_2N = dimethylamino; R^2 = H
b; R^1_2N = dimethylamino; R^2 = NO_2
c; R^1_2N = dimethylamino; R^2 = CN
d; R^1_2N = dimethylamino; R^2 = Cl
e; R^1_2N = morpholino; R^2 = NO_2
f; R^1_2N = piperidino; R^2 = Cl
g; R^1_2N = pyrrolidino; R^2 = NO_2

(2)

(3) a; R^1_2N = dimethylamino; R^2 = H; X^- = I^-
b; R^1_2N = dimethylamino; R^2 = NO_2; X^- = I^-
c; R^1_2N = dimethylamino; R^2 = NO_2; X^- = $CF_3SO_3^-$
d; R^1_2N = dimethylamino; R^2 = CN; X^- = I^-
e; R^1_2N = dimethylamino; R^2 = Cl; X^- = I^-
f; R^1_2N = morpholino; R^2 = NO_2; X^- = I^-
g; R^1_2N = morpholino; R^2 = NO_2; X^- = $CF_3SO_3^-$
h; R^1_2N = piperidino; R^2 = Cl; X^- = I^-
i; R^1_2N = pyrrolidino; R^2 = NO_2; X^- = I^-

(4) a; R^1_2N = dimethylamino; R^2 = H
b; R^1_2N = dimethylamino; R^2 = NO_2
c; R^1_2N = dimethylamino; R^2 = CN
d; R^1_2N = dimethylamino; R^2 = Cl
e; R^1_2N = morpholino; R^2 = NO_2
f; R^1_2N = piperidino; R^2 = Cl
g; R^1_2N = pyrrolidino; R^2 = NO_2

(5) a; R^1_2N = dimethylamino; R^2 = H
b; R^1_2N = dimethylamino; R^2 = NO_2
c; R^1_2N = dimethylamino; R^2 = Cl
d; R^1_2N = morpholino; R^2 = NO_2
e; R^1_2N = piperidino; R^2 = Cl
f; R^1_2N = pyrrolidino; R^2 = NO_2

(6)

(7)

SCHEME

TABLE 2

Preparation and properties of the quaternary ammonium compounds (3)

	^{1}H N.m.r. [a] δMe-N$^+$	Reaction solvent	Reaction time (h)	Cryst. solvent	M.p. [b] (°C)	Yield (%)	Found (%) [Reqd. (%)] C	H	N
(3a)	3.34	MeCN	0.5	MeCN	165—170	60	43.3 [43.2]	5.9 [6.2]	17.65 [18.0]
(3b)	3.42	THF	0.25	MeCN	148	75	38.45 [38.7]	5.1 [5.35]	19.05 [19.35]
(3c)	3.29	MeCN	4	EtOH	115—133	90	39.5 [39.75]	5.0 [4.45]	18.2 [18.5]
(3d)	3.39	MeCN	2	MeCN	144—150	70	43.4 [43.5]	5.55 [5.6]	19.8 [20.3]
(3e)	3.37	MeCN	2	MeCN	154—157	80	39.5 [39.65]	5.4 [5.45]	16.2 [16.5]
(3f)	3.27	MeCN	4 [c]	MeCN	195	65	41.35 [41.7]	5.15 [5.2]	15.85 [16.2]
(3g)	3.42	MeCN	3	EtOH	163—166	95	42.5 [42.2]	5.0 [5.0]	15.7 [15.55]
(3h)	3.44	MeCN	12	MeCN	153—173	90	48.6 [49.0]	6.6 [6.35]	14.0 [14.3]
(3i)	3.41	MeCN	16	MeCN [d]	145—150	80	44.65 [44.45]	5.45 [5.55]	17.15 [17.3]

[a] Solvent [$^2H_6$]DMSO or $CDCl_3$–[$^2H_6$]DMSO; owing to insolubility generally poor spectra were obtained. [b] In some cases melting range with decomposition. [c] Reflux. [d] Purified by extraction with warm solvent.

TABLE 3

Yields of products (4) and/or (5) and/or (7)

Starting compound	Base	Solvent	Reaction [a] temp (°C)	Main product [yield (%)]	Identified by-products
(3d)	Ag_2O	MeOH–H_2O	room temp.	(4c) [75]	
(3e)	Ag_2O	MeOH–H_2O	room temp.	(4d) [80]	
(3f)	Ag_2O	MeOH–H_2O	room temp.	(4e) [45]	(5d) [b]
(3h)	Ag_2O	MeOH–H_2O	room temp.	(4f) [85]	
(3i)	Ag_2O	MeOH–H_2O	room temp.	(4g) [25]	(7), (5f)
(3d)	KOH	Et_3N	70	(4c) [50]	
(3i)	KOH	Et_3N	70	(4g) [25]	(5f)
(3a)	Bu^{t}OK	Bu^{t}OH	80	(5a) [60]	
(3c)	Bu^{t}OK	Bu^{t}OH	80	(5b) [70]	
(3g)	Bu^{t}OK	Bu^{t}OH	80	(5d) [70]	
(3c)	NaOH	MeOH	room temp.	(7) [80]	(5b)
(3g)	NaOH	MeOH	room temp.	(7) [70]	(5d)
(3b)	NaOH	MeOH	room temp. [c]	(4b) [50]	(7), (5b)

[a] Reaction time until complete reaction of the starting compound (t.l.c.). [b] A small amount of the triazoline (1e) was also obtained, probably through the competitive nucleophilic displacement of the methyl group of (3f). [c] Reaction time 0.5 h.

TABLE 4

5-Amino-4-methylenetriazolines (4)

	^{1}H N.m.r. ($CDCl_3$) δ_{H-5}	δ_{H-B}	δ_{H-A}	$J_{A,B}$	$J_{5,A}$	$J_{5,B}$	Cryst. solvent	M.p. [a] (°C)	Found (%) [b] [Reqd. (%)] C	H	N
(4a)	5.22	5.24	5.83	1.3	2.9	2.5		(oil) [c]			
(4b)	5.30	5.41	6.02	1.3	2.8	2.3	MeOH	111—114	53.20 [53.45]	5.0 [5.3]	28.15 [28.35]
(4c)	5.44	5.54	6.14	1.5	2.9	2.9	MeOH	115—119	63.45 [63.4]	5.8 [5.75]	29.7 [30.8]
(4d)	~5.45	~5.45	6.03				Hexane	57—62	56.15 [55.8]	5.55 [5.55]	22.0 [23.45]
(4e)	5.47	5.64	6.24	1.5	2.7	2.3	MeOH	153—155	53.7 [54.0]	4.95 [5.20]	23.9 [24.2]
(4f)	5.36	5.39	5.99	1.2	2.9		MeOH	87—91	60.75 [60.75]	6.1 [6.20]	20.5 [20.24]
(4g)	5.79	5.59	6.16	1.3	2.7	2.5	MeOH or n-pentane	102—106	56.85 [57.15]	5.2 [5.55]	25.25 [25.65]

[a] Decomposition. [b] Generally, probably owing to easy decomposition with elimination of nitrogen, low N values were obtained. [c] Poor analysis obtained.

with those of the corresponding quaternary ammonium derivatives (3). For example, in the spectrum of (3i) only the AB signal associated with the CH_2 group shows a strong downfield shift (δ 3.8) with respect to the corresponding signal in the spectrum of (1g) (δ 2.5). The other signals are affected to a lesser extent. Products (3a—g) are listed in Table 2.

Elimination Reactions.—The quaternary ammonium salts (3a—i) underwent a β-elimination on treatment with base. The ratio of the reaction products was dependent on the kind of base and on the reaction conditions.

In Table 3 are reported the main products, together with the minor products whenever isolated or identified.

The properties of compounds (4) are listed in Table 4.

As shown in the Scheme and discussed below, the results can be rationalized through the common feature that the first step is always formation of the 4-methylene derivative (4) by β-elimination, in some instances followed by nucleophilic addition and/or isomerization to the 1-aryl-5-amino-*v*-triazoles (5).

(a) *Silver oxide.* The reaction was performed using a suspension of silver oxide in aqueous methanol. The quaternary ammonium iodides (3d—f, h, and i) afforded, after a short time at room temperature, fair yields of the expected products (4c—g). This is the best reagent for the preparation of the methylene derivatives.

As shown in Table 3 a small amount of isomerization products was also formed in some instances.

(b) *Triethylamine–potassium hydroxide.* Elimination could also be achieved by reaction of compounds (3) with triethylamine containing a little aqueous potassium hydroxide at a higher temperature. Under these conditions the quaternary ammonium iodides (3d and i) reacted slower than with silver oxide and afforded the expected methylene derivatives (4c and g) in moderate yield.

(c) *Sodium hydroxide–methanol.* On reaction of (3c and g) with 1% w/v sodium hydroxide–methanol for several hours a mixture of the corresponding 4-methoxymethyl-1-(4-nitrophenyl)-*v*-triazole (7) (main product) and 5-amino-4-methyl-*v*-triazoles (5b and d) was produced. The formation of the triazole (7) occurs through elimination forming the methylene-*v*-triazolines (4b and e) which undergo subsequent addition of methoxide. The intermediate 5-amino-4-methoxymethyl derivatives (6) are deaminated in the basic medium leading to the triazole (7).* As a secondary reaction path a small amount of compounds (4b and c) was isomerized to (5b and d).

The course of the reaction was confirmed by reaction of (3b) with sodium hydroxide in methanol at room temperature and isolation of the products after a short time. Besides some unchanged starting material, a mixture of (4b), (5b), and (7) was obtained which, on further reaction for a longer time, yielded the expected products (7) and (5b).

Reaction with Potassium t-Butoxide in t-Butyl Alcohol.—In agreement with the above results, a non-nucleophilic and stronger base should favour isomerization of the elimination products to the aromatic 5-aminotriazoles (5). This was confirmed by refluxing the quaternary ammonium salts (3a, c, and g) with potassium t-butoxide in t-butyl alcohol. Only the corresponding triazole derivatives (5a, b, and d) were formed in high yield.

Isomerization of (4b, d—g).—The isomerization reaction of the isolated methylene compounds (4b, d—g) to the tautomeric 5-amino-4-methyl-*v*-triazoles (5b—f) was accomplished by reaction with strong bases devoid of nucleophilic character. Good results were obtained with potassium t-butoxide (for compounds 4b, d—g) and cetyltrimethylammonium hydroxide for compounds (4e and f). An isomerization *via* an allyl carbanion intermediate is postulated.[6] The new compounds of this class are listed in Table 5.

TABLE 5

5-Amino-1-aryl-4-methyl-*v*-triazoles (5)

	^{1}H N.m.r. δ_{Me}	M.p. (°C)	Cryst. solvent	Found (%) [Reqd. (%)] C	H	N
(5a)	2.42	65—66	n-Pentane	65.0 [65.3]	7.1 [6.95]	27.4 [27.7]
(5c)	2.40	124—128	Chloroform–n-pentane	60.45 [60.75]	6.0 [6.2]	19.8 [20.25]
(5e)	2.45	103—105	Chloroform–n-pentane	55.9 [55.8]	5.6 [5.35]	23.3 [23.65]

^{1}H *N.m.r. Spectra of* (4a—g).—The CH_2=C-CH< system of the 4,5-dihydro-*v*-triazoles (4) is associated in the ^{1}H n.m.r. spectra with an ABX pattern.† The signal associated with H-5 can be identified since it is more influenced by protonation than the others. It is always found at higher field than the signals associated with the methylene group, except in the case of the pyrrolidine derivative which characteristically[7] shows a strong downfield shift. The signals associated with the methylene protons were assigned on the basis of the results of lanthanide induced shifts with $Eu(fod)_3$ on the pyrrolidine compound (4g). These results do not agree with the attributions made for compound (4b), on the ground of the values of the *cisoid* and *transoid* coupling constants.[2]

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded with Varian A-60 and 360 A spectrometers at 60 MHz (Me_4Si as internal standard); silica gel (Merck) was employed for column chromatography; t.l.c. was run on silica gel GF 254 (Merck) with benzene–ethyl acetate (1 : 9—3 : 2) as eluant.

Triazolines (1).—The triazolines (1b and e—g) are known compounds;[3] the *triazolines* (1a, c, and d) were prepared as described and were purified by recrystallization (Table 1).

Quaternary Ammonium Iodides (3a, b, d—f, h, *and* i).—To a solution of the triazoline (1) in the minimum amount of the appropriate solvent was added a moderate excess (10—50%) of methyl iodide. The reaction mixture was stirred and left for the time indicated (Table 2) at room temperature. Only in the case of the triazoline (3d) was the reaction performed under reflux. The completion of the reaction was determined by t.l.c. Isolation of the quaternary ammonium iodides was achieved by evaporation of the reaction solution, or by filtration of the crystalline product which directly separated out from the reaction mixture. The *products* were purified as indicated in Table 2.

Quaternary Ammonium Trifluoromethanesulphonates (3c *and* g).—The starting triazoline was dissolved in the minimum amount of acetonitrile and treated with a 10% excess of methyl trifluoromethanesulphonate at room

* The intermediates (6) were not isolated and therefore an S_N2' mechanism cannot be excluded. Further studies on the reactions between methylene triazolines and nucleophiles will hopefully clarify this point and will be published elsewhere.

† Because of overlapping of the signals a complete analysis of the spectra is not always possible.

temperature until reaction was complete (t.l.c.). The solvent was evaporated off and the oily residue crystallized by addition of ethanol. Recrystallization from ethanol yielded the *compounds* (3c and g).

Reaction of (3d—f, h, *and* i) *with* Ag_2O.—To a magnetically stirred suspension of the iodide (3) (10 mmol) in methanol–water (9 : 1) (50 ml) was added silver oxide (11 mmol); stirring was continued until complete reaction of the starting compound had occurred (2—3 h; t.l.c.). The precipitate was filtered off and the clear filtrate reduced in volume by evaporation. In most cases the methylene triazoline (4) crystallized out directly. After filtration a second crop of product was obtained by evaporation of the mother-liquor to dryness. The *products* were purified by recrystallization (Table 4) or by column chromatography. Yields are reported in Table 3.

Reaction of (3d *and* i) *with Potassium Hydroxide–Triethylamine*.—The starting ammonium iodide (10 mmol) was dissolved in the minimum amount of triethylamine containing a small amount of potassium hydroxide (*ca.* 50 ml). The reaction mixture was stirred in a water-bath (70 °C) for 2 h. A mixture of the starting iodide and of the elimination product separated out and was recovered by filtration. The *methylene triazoline* was isolated by extraction with a large volume of pentane or by column chromatography using ethyl acetate as eluant.

Reaction of (3e *and* g) *with Sodium Hydroxide–Methanol*.—The quaternary ammonium salt (1 mmol) was treated with 1% sodium hydroxide in methanol (2 mmol). After completion of the reaction the mixture was evaporated. Water was added to the residue and the mixture filtered. The crude solid was washed with water until neutral. The products were identified by t.l.c. and the main *product* (7) was isolated and purified by column chromatography.

Reaction of (3b) *with Sodium Hydroxide–Methanol*.—The compound (3b) (1 mmol) was dissolved in methanol (150 ml) and sodium hydroxide–methanol (1% w/v; 2 mmol) was added. The mixture was stirred for 0.5 h then evaporated under reduced pressure at room temperature. The residue was taken up with water, the mixture filtered, and the solid dried *in vacuo*. The products (4b), (5b), and (7) were identified by t.l.c. and the *methylene triazoline* (4b) was isolated by column chromatography. The pure (4b) melted at 111—114 °C (with slow decomposition).*

A small amount of the basic reaction solution was left standing for 5.5 h. Thereafter only compounds (7) and (5b) could by identified by t.l.c.

Reaction of (3a, c, *and* g) *with Potassium t-Butoxide in t-Butyl Alcohol*.—The ammonium salt (3a, c, or g) (1.0 mmol) was dissolved in warm t-butyl alcohol (50—150 ml). A solution of potassium t-butoxide in t-butyl alcohol (1.5% w/v; 2 mmol) was then added. The mixture was refluxed for 8 h until no starting material was present (t.l.c.). The solution was evaporated and the residue taken up with water and neutralized with hydrochloric acid. The product was extracted with chloroform and the solution dried (Na_2SO_4) and evaporated. The residue was purified by recrystallization to yield the *triazoles* (5a, b, and d).

Isomerization of (4b *and* d—g).—(a) *With potassium t-butoxide–t-butyl alcohol*. The methylene triazoline (4) (2 mmol) was dissolved in the minimum amount of t-butyl alcohol (*ca.* 5—10 ml) and potassium t-butoxide (1 mmol) was added. The reaction mixture was kept at 70 °C until reaction was complete (t.l.c.). The reaction mixture was evaporated and the residue taken up in chloroform. The mixture was filtered and the filtrate washed with water, dried, and the product precipitated by addition of pentane. If necessary the *products* were purified by column chromatography on silica gel (ethyl acetate as eluant). For (5b—f) yields of 90, 50, 30, 50, and 70%, respectively, were obtained.

(*b*) *With cetyltrimethylammonium hydroxide*. The reaction was performed essentially as above by adding to the solution of (4e, f) in t-butyl alcohol a methanolic solution of cetyltrimethylammonium hydroxide (1 mmol). Yields of 35 and 50% of (5d) and (5e), respectively, were obtained.

[9/063 *Received*, 15*th January*, 1979]

* The m.p. of this compound was previously incorrectly indicated as 78 °C.[2]

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