v-Triazolines. Part I. Synthesis and Properties of 5-Amino-4-(α-aminoethyl)-1-aryl-4,5-dihydro-*v*-triazoles

By **Donato Pocar,* Riccardo Stradi,** and **Luisa Maria Rossi,** Istituto di Chimica Organica, Facoltà di Farmacia, 09100 Cagliari, Italy

5-Amino-4-(α-aminoethyl)-1-aryl-*v*-triazolines have been obtained by treating but-1-ene-1,3-diamines with aryl azides. Mixtures of two diastereoisomeric triazolines were always formed. The diastereoisomers were separated in some cases and, on the basis of their n.m.r. spectra, configurations were assigned to the members of each diastereoisomeric pair. These triazolines were rapidly attacked by strong alkali, yielding the corresponding triazoles. The members of a pair of diastereoisomeric triazolines suffer deamination at different rates.

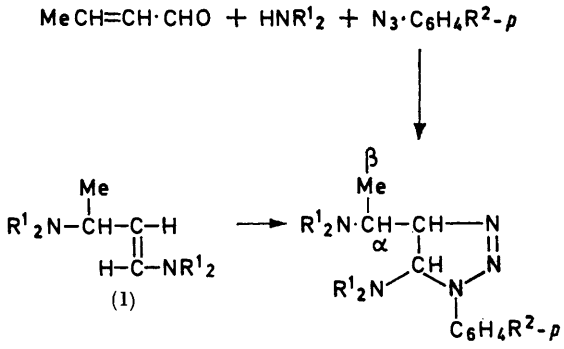
We have previously reported that 5-amino-*v*-triazolines can be easily obtained directly from a mixture containing a carbonyl compound, an amine, and an aryl azide.[1] This method allows the synthesis of 5-aminotriazolines derived from labile enamines. We have now extended the reaction to derivatives of crotonaldehyde. It is known that crotonaldehyde reacts with secondary amines yielding but-1-ene-1,3-diamines.[2] These compounds can generally be isolated, but are sometimes difficult to obtain in high purity owing to their thermal lability. Little attention has been devoted to the enaminic reactivity of the but-1-ene-1,3-diamines. Only the reactions of 1,3-bis(dimethylamino)but-1-ene with sulphenes [3] and with keten [4] have been reported.

By treating crotonaldehyde with dimethylamine 1,3-bis(dimethylamino)but-1-ene (1; R = Me) was readily obtained.[5] The product had the *trans*-configuration, as shown by its n.m.r. spectrum (neat) in which the H-1 signal appeared as a doublet at δ 5·84 p.p.m. (J 13·8 Hz). Enamine (1; R = Me) reacted with 4-nitrophenyl azide yielding the triazoline (2). The same compound (2) was also obtained, in high yield, without isolation of the enamine, from a mixture of crotonaldehyde, 4-nitrophenyl azide, and dimethylamine. Triazolines (3)—(7) were prepared similarly.

T.l.c. and n.m.r. spectroscopy showed that the triazoline (2) was an approximately equimolar mixture of two isomeric triazolines (2a and b). These were separated by fractional crystallization. A similar situation was found for the triazolines (3)—(7). Both isomers of

[1] R. Stradi and D. Pocar, *Gazzetta*, 1969, **99**, 1131.
[2] C. Mannich, K. Handke, and K. Roth, *Ber.*, 1936, **69**, 2112.
[3] L. A. Paquette and M. Rosen, *Tetrahedron Letters*, 1966, 311; *ibid.*, 1967, 703; *J. Amer. Chem. Soc.*, 1967, **89**, 4102; L. A. Paquette, M. Rosen, and H. Stucki, *J. Org. Chem.*, 1968, **33**, 3021.
[4] R. H. Hasek, P. G. Gott, and J. C. Martin, *J. Org. Chem.*, 1966, **31**, 1931.
[5] Z. Arnold, *Coll. Czech. Chem. Comm.*, 1960, **25**, 1308.

triazolines (3) and (4) were separated; in the case of triazolines (6) and (7) only the less soluble isomer was isolated. No attempt was made to separate the isomers of the triazoline (5). The Table shows the n.m.r. data of the isomeric triazolines. For the isomers (b) the



(2) $R^1 = Me$, $R^2 = NO_2$
(3) $R^1_2 = [CH_2]_4$, $R^2 = NO_2$
(4) $R^1_2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^2 = NO_2$
(5) $R^1_2 = [CH_2]_2{\cdot}NMe{\cdot}[CH_2]_2$, $R^2 = NO_2$
(6) $R^1_2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^2 = Cl$
(7) $R^1_2 = [CH_2]_5$, $R^2 = Cl$

signals associated with H-4 are partially overlapped by the signals of the amine residues. Accordingly, only approximate values can be given. For isomers (a) the H-4 signals are undetectable. Since these compounds show asymmetry at C-4, C-5, and C-α, four diastereoisomeric triazolines are theoretically possible. However, only the isomers in which H-4 and H-5 are *trans* are formed ($J_{4,5}$ is never greater than 4 Hz).[6] Thus, only two diastereoisomers (each comprising an enantiomeric pair) are to be considered; their configurations are 4*SR*,5*RS*,α*RS* (8a) and 4*SR*,5*RS*,α*SR* (8b).

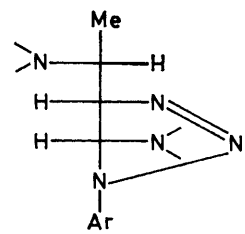
The Table shows that (i) in the isomers (a) the methyl doublet is always at lower field than the corresponding signal for the isomers (b); (ii) the H-4 signal is always at higher field for the *a*-isomers; and (iii) the coupling constant $J_{4,\alpha}$ is always greater for isomers (a) (8·5—9·9 Hz) than for isomers (b) (4·5—5 Hz). These time-averaged coupling constants suggest that in isomers (a) the population of high-J rotamers is greater than in isomers (b).

N.m.r. data * for the triazolines (2)—(4), (6), and (7)

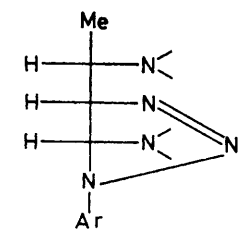
Triazoline	H-β	H-α	H-4	H-5	$J_{4,\alpha}$	$J_{\alpha\beta}$	$J_{4,5}$
(2a)	1·17	2·2	4·30	4·84	9·9	6·5	3·0
(2b)	0·99	2·77	4·50	4·82	5·0	6·5	3·8
(3a)	1·14		4·55	5·24	8·5	6·5	3·0
(3b)	0·78	2·85	4·77	5·37	4·5	6·5	3·0
(4a)	1·30		4·64	5·03	9·0	6·5	3·0
(4b)	1·06	2·75	4·68	4·88	5·0	6·5	3·0
(6a)	1·23		4·41	4·84	9·0	6·5	3·0
(6b)	0·99	2·80	4·54	4·78	5·0	6·8	3·8
(7a)	1·34		4·48	4·90	8·5	6·5	3·0
(7b)	1·05	2·80	4·55	4·79	5·0	6·5	4·0

* δ in p.p.m. from internal tetramethylsilane; J in Hz.

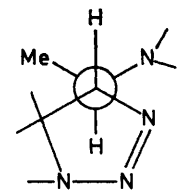
Molecular models indicate that the preferred conformations of the molecules should be (9a and b). These conformations are considered more favourable because they allow free rotation of all groups, particularly of the bulky amine residues. This free rotation is suggested by the lack of changes in the n.m.r. spectra with increasing temperature. On this basis it seems reasonable to assign the 4*SR*, 5*RS*,α*RS*-configuration to triazolines (a) [$J_{4,\alpha}$ (average) = 8—9 Hz; greater contribution of *trans*-rotamer] and the 4*SR*,5*RS*,α*SR*-configuration to triazolines (b) [$J_{4,\alpha}$ (average) = 4·5—5 Hz; greater contribution of gauche rotamer). This assignment is supported by the chemical shifts of the methyl group and H-α. In the 4*SR*,5*RS*,α*RS*-form H-α is more shielded by the triazoline ring, while the methyl group is not subjected to this shielding effect; in the 4*SR*,5*RS*,α*SR*-form the reverse is true: the methyl group is shielded whereas H-α is not. A similar argument explains the slight difference in the chemical shift of H-4, which appears more shielded by the group on C-α in the 4*SR*,5*RS*,α*RS*-isomer than in the 4*SR*,5*RS*,α*SR*-isomer.



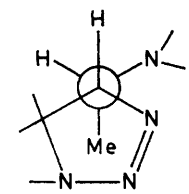
(8a) 4*SR*,5*RS*,α*RS*



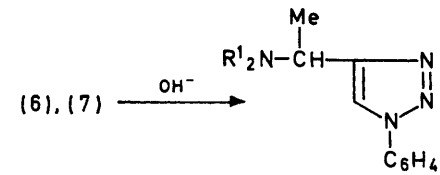
(8b) 4*SR*,5*RS*,α*SR*



(9a) 4*SR*,5*RS*,α*RS*



(9b) 4*SR*,5*RS*,α*SR*



(10) $R^1_2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$
(11) $R^1_2 = [CH_2]_5$

Strong bases readily react with the foregoing 5-aminotriazolines, as expected for triazolines derived from aldehyde enamines.[7] This reaction probably occurs through deprotonation at C-4, followed by elimination of the amine residue at C-5. From the 4-nitrophenyltriazolines only low yields of the corresponding triazoles were obtained; in contrast the 4-chlorophenyl derivatives (6) and (7) afforded the triazoles (10) and (11) in 80—85% yield. The reaction with bases proceeded faster with diastereoisomers (b). For example, a

[6] R. Sustmann, R. Huisgen, and H. Huber, *Chem. Ber.*, 1967, **100**, 1802.

[7] N. E. Munk and Y. K. Kim, *J. Amer. Chem. Soc.*, 1964, **86**, 2213; P. Ferruti, D. Pocar, and G. Bianchetti, *Gazzetta*, 1967, **97**, 109.

mixture of isomers (6a and b) (1 : 1) was treated with sodium hydroxide in ethanol. Samples were taken every 15 min and the amounts of unchanged triazolines were measured by n.m.r. spectroscopy. After about 15 min isomer (6b) had reacted to the extent of about 60%, whereas only about 20% of isomer (6a) had been converted into the triazole. After 30 min only traces of (6b) were detectable, and half of the original amount of (6a) was still present after 1 h. This greater reactivity isomer (b) is probably due to steric hindrance of H-4, which is less in the 4*SR*,5*RS*,α*SR*- than in the 4*SR*,5*RS*,-α*RS*-isomer. On the other hand, the 4*SR*,5*RS*,α*SR*-structure appears to be more crowded, and this should assist the amine elimination and the formation of the aromatic structure.

This difference in reactivity was used for separation of the isomeric triazolines (4a and b). The latter was obtained by fractional crystallization. By briefly boiling the mixture of isomers with alcoholic sodium hydroxide isomer (4b) was almost completely consumed, thus allowing recovery of isomer (4a) almost free from (4b).

EXPERIMENTAL

N.m.r. spectra were recorded with a Jeol JNM–C–60 HL spectrometer (60 MHz) for solutions in [^{2}H]chloroform with tetramethylsilane as internal standard.

5-*Dimethylamino*-4-(α-*dimethylaminoethyl*)-4,5-*dihydro*-1-(4-*nitrophenyl*)-v-*triazole* (2).—(*a*) 1,3-Bis(dimethylamino)-but-1-ene [5] (1) (25 mmol) in benzene or chloroform (10 ml) was treated with 4-nitrophenyl azide (25 mmol) in the same solvent (20 ml). The mixture was set aside for 24 h, then concentrated to half its volume and diluted with light petroleum ether. Cooling (0 to −10°) precipitated the triazoline (2) almost quantitatively.

(*b*) A solution of 4-nitrophenyl azide (50 mmol) in chloroform (30 ml) was treated with crotonaldehyde (50 mmol) and the mixture was cooled in ice. Dimethylamine (100 mmol) in chloroform (20 ml) was then added. The mixture was left at room temperature for 24 h, then the solvent was distilled off under reduced pressure and the residue was treated with light petroleum and cooled at −10° until the product was completely precipitated (yield 90%). The crude triazoline [an almost equimolecular mixture of (2a) and (2b) (n.m.r.)] was recrystallized four times from ethanol to give isomer (2a) as pale yellow crystals, m.p. 145—146°. The mother liquor was evaporated and the residue was dissolved in boiling n-heptane. The solution was cooled and the precipitate separated. Cooling at −10° gave a second crop, comprising *ca.* 70% isomer (2b). The filtrate was evaporated to dryness and the residue was recrystallized from n-heptane yielding pure (2b) as pale yellow crystals, m.p. 85—86°.

4,5-*Dihydro*-1-(4-*nitrophenyl*)-5-*pyrrolidino*-4-(α-*pyrrolidinoethyl*)-v-*triazole* (3).—To a solution of pyrrolidine (50 mmol) in chloroform (10 ml) was added a solution of 4-nitrophenyl azide (25 mmol) and crotonaldehyde (25 mmol) in chloroform (20 ml). After 6 h at room temperature the mixture was diluted with light petroleum and the precipitate was filtered off. The product (3) was obtained in 54% yield, m.p. *ca.* 150°. Recrystallization from ethanol yielded the pure isomer (3a) as yellow crystals, m.p. 158°. The mother liquor was cooled to −15° during 24 h. A precipitate comprising isomer (3b) together with a minor amount of (3a) was obtained. The mother liquor was evaporated and the residue was treated with light petroleum. The precipitate was filtered off and recrystallized from ethanol to give pure isomer (3b), m.p. 96°.

4,5-*Dihydro*-5-*morpholino*-4-(α-*morpholinoethyl*)-1-(4-*nitrophenyl*)-v-*triazole* (4).—By the method described for compounds (3), a mixture of isomers (4a) and (4b) was obtained in 68% yield, m.p. *ca.* 160°. Recrystallization from ethanol yielded a precipitate enriched in (4a). The mother liquor was cooled to −10°, yielding a second crop, which on recrystallization from ethanol gave almost pure triazoline (4b), m.p. 172°. The first precipitate was dissolved in boiling ethanolic 1% sodium hydroxide. After 10 min the solution was cooled and filtered to yield almost pure isomer (4a), m.p. 186° (from ethanol).

4,5-*Dihydro*-5-(4-*methylpiperazin*-1-*yl*)-4-[α-(4-*methylpiperazin*-1-*yl*)*ethyl*]-1-(4-*nitrophenyl*)-v-*triazole* (5).—The reaction was carried out as described for compounds (3), for 24 h at room temperature. The product was precipitated from the reaction mixture with di-isopropyl ether; it contained both isomers, m.p. *ca.* 157°, and was recrystallized from di-isopropyl ether (yield 50%).

1-(4-*Chlorophenyl*)-4,5-*dihydro*-5-*morpholino*-4-(α-*morpholinoethyl*)-v-*triazole* (6).—The reaction was carried out as described for triazoline (3) (5 h under reflux). The cooled mixture was diluted with di-isopropyl ether and the precipitate (57%) was filtered off; m.p. 135°. Recrystallization from ethanol yielded pure isomer (6a), m.p. 175°. The mother liquor was evaporated and the residue was recrystallized twice from di-isopropyl ether. The product comprised *ca.* 75% of isomer (6b), m.p. 125°.

1-(4-*Chlorophenyl*)-4,5-*dihydro*-5-*piperidino*-4-(α-*piperidinoethyl*)-v-*triazole* (7).—The reaction was carried out as described for triazoline (6). The product was isolated by evaporating the mixture and adding light petroleum to the residue. The mixture of (7a) and (7b) (55%) melted at *ca.* 75°. Recrystallization from di-isopropyl ether yielded pure isomer (7b), m.p. 138°.

1-(4-*Chlorophenyl*)-4-(α-*morpholinoethyl*)-v-*triazole* (10).—The morpholinotriazoline (6) (10 mmol) was dissolved in ethanolic 1% sodium hydroxide (50 ml) and refluxed for about 2 h. The solvent was evaporated off under reduced pressure and water was added to the residue. The product was filtered off and recrystallized from di-isopropyl ether to give the triazole (10) (80%), m.p. 115°, δ 1·48 (3H, d, Me), 3·84 (1H, q, H-α), and 7·72 (1H, s, H-5) p.p.m.

1-(4-*Chlorophenyl*)-4-(α-*piperidinoethyl*)-v-*triazole* (11).—The piperidinotriazoline (7) (10 mmol) was similarly treated with alkali. After 1·5 h under reflux the mixture was evaporated under reduced pressure and the residue was treated with water. The product was filtered off and recrystallized from di-isopropyl ether to give the triazole (11) (85%), m.p. 90—91°, δ 1·51 (3H, d, Me), 3·97 (1H, q, H-α), and 7·81 (1H, s, H-5) p.p.m.

We thank the Italian C.N.R. for financial aid.

[1/1186 *Received*, 9*th July*, 1971]