v-Triazolines. Part III.[1] *cis-trans* Equilibrium of 1-Aryl-4,5-dihydro-*v*-triazoles

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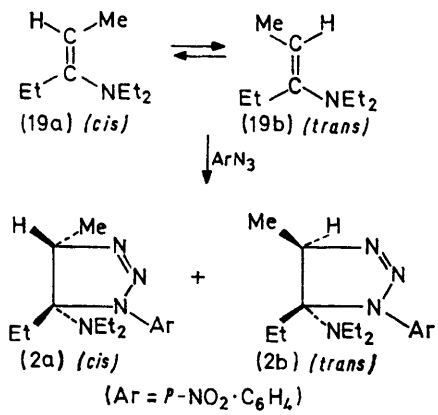
The stereochemical features of the reaction between 4-nitrophenyl azide and some enamines deriving from straight-chain aliphatic ketones or aryl alkyl ketones have been studied. Under kinetically controlled conditions the *cis–trans* equilibrium mixture of the enamine reacts with the azide, yielding exclusively the *trans*-triazoline. At higher temperature or in the presence of acidic catalysts, the *trans*-triazoline epimerizes, thus affording a *cis–trans* equilibrium mixture. The factors which affect the equilibrium position and the epimerization rate are discussed and a probable epimerization mechanism is suggested.

ALTHOUGH a number of 1-aryl-5-amino-*v*-triazolines have been described little is known of their stereochemistry. Thus Munk and Kim [2] have studied the 5-aminotriazolines deriving from the addition of an aromatic azide to an aldehyde enamine and on the basis of the n.m.r. spectra have suggested a *trans*-structure for the triazolines obtained. More recently the *cis*- and *trans*-forms of the 5-amino-*v*-triazolines bearing secondary amine groups [3] have been detected.

The stereochemical aspects of the reaction between 4-nitrophenyl azide and some enamines of straight-chain aliphatic ketones or aryl alkyl ketones are here considered.

3-Diethylaminopent-2-ene (19), obtained by treating diethyl ketone with diethylamine,[4] readily reacts in boiling chloroform with 4-nitrophenyl azide, to yield the corresponding 1-(4-nitrophenyl)-4-methyl-5-ethyl-5-diethylamino-*v*-triazoline (2). The product isolated is a mixture of two stereoisomeric triazolines (2a) and (2b), as evidenced by their corresponding n.m.r. spectra. Clearly, (2a) and (2b) are the *cis*- and *trans*-isomers, respectively.†



The question of the *cis–trans* isomerism of the enamine (19) has already been studied.[5] It has been shown that (19) is an equilibrium mixture of two isomers, (19a) and (19b). At equilibrium (19b) represents 86% of the mixture. The ratio of (2a) to (2b) is *ca.* 45 : 55, as shown by the relative intensities of the n.m.r. signals ($CDCl_3$: δ 0·42—1·33 p.p.m., 9H, 6 partially overlapped triplets, Me groups of the Et residues; δ 1·53 and 1·61 p.p.m., 3H, 2 doublets, Me groups at C-4 of the *cis*- and *trans*-triazolines, respectively: δ 1·82—3·09 p.p.m., 6H, overlapped quartets, methylene groups of the Et residues; δ 4·21 and 4·54 p.p.m., 1H, 2 quartets, H on C-4 of the *cis*- and *trans*-triazolines, respectively).

By treating 4-nitrophenyl azide with the enamine (19) under more controlled conditions, in anhydrous benzene at room temperature, and by isolating the reaction product immediately after completion of the reaction (which is easily followed by n.m.r. spectroscopy) only one triazoline is obtained. However, this triazoline is quickly converted into an equilibrium mixture containing *ca.* 55% of the starting product and 45% of its stereoisomer. In this way a mixture identical to that directly formed by treating 4-nitrophenyl azide with the enamine (19) in chloroform at higher temperature is formed.

To the triazoline which is isolated under controlled conditions is assigned the *trans*-structure (2b) since its hydrogen atom at C-4 resonates at lower field than in the corresponding isomeric triazoline (Δδ = 0·33 p.p.m. in $CDCl_3$).‡ 3-(*N*-Methylanilino)pent-2-ene (20) behaves

MeC:CEt·NMePh (20)

very similarly. On reaction with 4-nitrophenyl azide in refluxing chloroform this enamine affords a mixture of two isomeric triazolines, (10a) and (10b), while in benzene at room temperature only the *trans*-isomer (10b) is obtained. The enamine (20) is an equilibrium mixture in which the *trans*-form represents *ca.* 20%.[5] The (10a) to (10b) ratio in the mixture obtained at higher temperature is 1 : 3. In this case too, the pure *trans*-triazolines equilibrates in solution with the *cis*-one.

Several other triazolines show the same behaviour as compounds (2) and (10). The Table shows all the

† By *cis*-isomer is meant the triazoline in which the hydrogen atom at C-4 and the ethyl group are *cis*.

‡ Here and in the subsequent cases the *trans*-structure will be assigned to the triazoline whose hydrogen on C-4 resonates at lower field. The correctness of this assignment has been demonstrated (results to be published).

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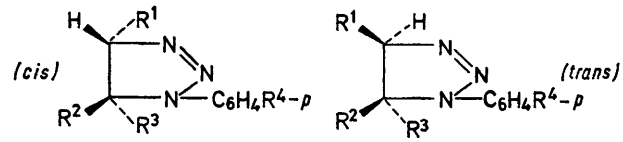
[2] M. E. Munk and Y. K. Kim, *J. Amer. Chem. Soc.*, 1964, **86**, 2213.

[3] C. Pedersen and C. E. Olsen, 2me Congrés Internat. de Chimie Hétérocyclique, Montpellier, 1969; C. E. Olsen, Thesis, Technical University of Denmark, Lyngby, 1969.

[4] W. A. White and H. Weingarten, *J. Org. Chem.*, 1967, **32**, 213.

[5] R. Stradi and D. Pocar, *Chimica e Industria*, 1971, **53**, 265.

TABLE

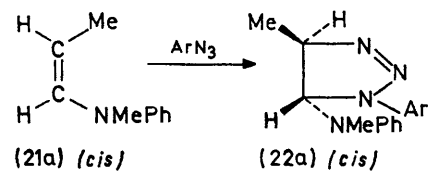


No.	R^1	R^2	R^3	R^4	*cis* * δ(Me)	*cis* * δ(H-4)	*trans* * δ(Me)	*trans* * δ(H-4)	Equil. *cis*/*trans*	React. time	M.p.‡
(1)	Me	Et	NMe_2	NO_2	1·47	4·17	1·48	4·57	28/72	30 min	116°
(2)	Me	Et	NEt_2	NO_2	1·53	4·21	1·61	4·54	45/55	30 min	68
(3)	Me	Et	NPr^i_2	NO_2	1·55	4·20	1·60	4·55	45/55	30 min	99
(4)	Me	Et	Pyrrolidino	NO_2		4·10		4·56	60/40	1 min	90
(5)	Me	Et	Piperidino	NO_2		4·17		4·62	20/80	35 min	128
(6)	Me	Et	Piperidino	Cl		4·02		4·48	20/80	26 h	68
(7)	Me	Et	Morpholino	NO_2	1·63	4·20	1·60	4·65	20/80	30 min	167
(8)	Me	Et	Morpholino	Cl	1·58	4·10	1·52	4·56	20/80	26 h	89
(9)	Me	Et	$NMeC_6H_{11}$	NO_2		4·04		4·64	25/75	30 min	138
(10)	Me	Et	NMePh	NO_2	1·67	4·30	1·49	4·91	25/75	48 h	143
(11)	Et	Pr^n	NEt_2	NO_2		3·96		4·24	45/55	30 min	112
(12)	Pr^i	Bu^t	NMe_2	NO_2		3·70		4·01	85/15	85 min	108
(13)	Me	Ph	NEt_2	NO_2	1·60	3·94		4·80	45/55	10 min	127
(14)	Me	Ph	Pyrrolidino	NO_2	1·48	3·85	0·68	4·66	55/45	2 min	138
(15)	Me	Ph	Morpholino	NO_2	1·55	3·98	0·76	4·69	20/80	40 min	164
(16)	Ph	Me	NEt_2	NO_2			1·25	5·58	0/100 †	30 min	135
(17)	Ph	Me	Pyrrolidino	NO_2			1·25	5·58	0/100 †	30 min	119
(18)	Ph	Me	Morpholino	NO_2			1·23	5·71	0/100	2 h	170

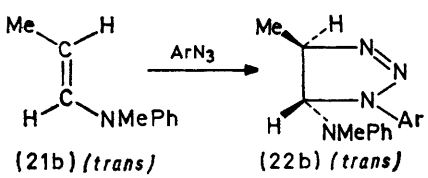
* In $CDCl_3$, 7%. † A weak signal at *ca.* δ 5 p.p.m. which might be assigned to 4-H (*cis*). ‡ Of the *trans*-form.

products prepared, together with the corresponding n.m.r. and experimental data.

The experimental results can be explained as follows. Under controlled conditions both isomers *cis* and *trans* of the enamines (19) and (20) are completely consumed affording exclusively the *trans*-triazoline. This means that the *trans*-enamines react with the aryl azide faster than the *cis*-isomers. The greater reactivity of the type b enamines is confirmed by 1-(*N*-methylanilino)-propene (21) which can be prepared both as the pure *trans*-form (21b) and as the pure *cis*-form (21a).[6] With 4-nitrophenyl azide, both enamines yield the corresponding *trans*- and *cis*-triazolines, (22b) and (22a), the formation of the *trans*-triazoline being *ca.* 10 times faster than the formation of the *cis* one.



(21a) *(cis)* (22a) *(cis)*



(21b) *(trans)* (22b) *(trans)*

(Ar = *p*-NO_2·C_6H_4)

When the enamines (19) and (20) are allowed to react at reflux temperature, a mixture of the *cis*- and *trans*-triazolines is obtained. This fact could be explained by assuming that at higher temperature the rate of the addition to the *cis*-enamines is increased. However, an isomerization of the *trans*-triazoline into its *cis*-isomer as an equilibrium process seems more logical, since the pure *trans*-isomer, under the same conditions which, in the case of the reaction between enamine and azide lead to a *cis*–*trans* mixture, yields the same mixture, exactly in the same *cis*–*trans* ratio.

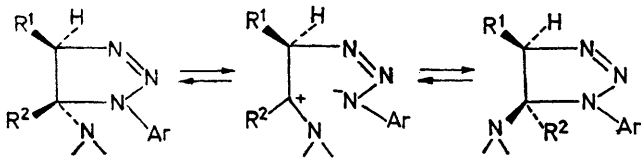
The position of the *cis*–*trans* equilibrium is not greatly influenced by the solvent and/or the temperature. When R^1 and R^2 are relatively small, the relative amounts of the two isomeric triazolines are of the same order of magnitude. However, when C-4 and C-5 bear bulky alkyl groups, as in the case of the triazoline (12), the *cis*-structure (12a) becomes more stable than the *trans* one (12b) because in the former the two bulky alkyl groups are farther apart. When R^1 is a bulky group and R^2 is a small one the effect of the interaction between R^1 and the amine group, which represent the two more space-filling substituents, is overwhelming. As a consequence the triazolines (14)—(18) (R^1 = Ph, R^2 = Me) exist as the *trans*-forms.

The equilibration rate of the *trans*-isomer with the *cis* one appears to depend upon three main factors: the temperature, the presence of an acidic catalyst, and the amine group. For example a 0·33M benzene solution of the triazoline (4b) equilibrates after *ca.* 10 min at 80°, but only after more than 3 h at room temperature. The same equilibrium, at room temperature, is attained through a practically instantaneous reaction by addition of a trace of trichloroacetic acid to the above benzene solution. The effect of the amine residue is evidenced by equilibrating in benzene at 80° a series of *trans*-4-methyl-5-ethyl-5-amino-*v*-triazolines (1), (2), (4), (7), and (10). The following order is observed: pyrrolidino > dimethylamino ≈ diethylamino ≫ morpholino > *N*-methylanilino. The equilibration rate also de-

[6] M. Rivière and A. Lattes, *Bull. Soc. chim. France*, 1967, 2559.

pends on the aryl group in position 1, as evidenced by the 4-chlorophenyltriazolines which equilibrate slower than the corresponding 4-nitrophenyl analogues.

The more plausible epimerization mechanism appears to be the ring opening of the triazoline by cleavage of the N(1)–C(5) bond. The subsequent ring closure of the polar intermediate can yield both epimers:



Logically, the greater the electron-donating ability of the amine nitrogen the more stabilized will be the carbonium ion at C_5 and the easier the ring cleavage. This is evidenced by an increase of the epimerization rate with increasing availability of the nitrogen lone-pair. By similar reasoning we can explain the accelerating effect on the reaction rate exerted by the strongly electron-withdrawing 4-nitrophenyl group (see above) which delocalizes the negative charge on the N-atom more effectively than a 4-chlorophenyl residue.

The increase in the reaction rate under the influence of acidic catalysts is explained by assuming, besides the protonation of the amine group, also the protonation of the triazoline system at N-1 or N-3. In both cases the net result is a positive charge on N-1 and this greatly aids the epimerization according to the proposed mechanism.

EXPERIMENTAL

The n.m.r. spectra have been recorded on a Jeol JNM-C-60 HL instrument at 60 MHz with Me_4Si as internal standard.

Enamines.—The *N*-methylanilinoenamines were prepared by the procedure of Hoch;[7] the other enamines were obtained according to the method of White and Weingarten.[4]

Reaction in Chloroform at Boiling Point.—4-Nitrophenyl azide (0·01 ml) in chloroform (10 ml) was added to a solution of the enamine (0·01 mol) in anhydrous $CHCl_3$ (10 ml). The mixture was refluxed for 30 min and then the solvent was distilled off under reduced pressure; the residue was treated with light petroleum. The precipitate was filtered off and washed with light petroleum. The n.m.r. data have been obtained on the crude isomeric mixture.

Reaction in Benzene at Room Temperature.—4-Nitrophenyl azide (0·01 mol) in benzene (10 ml) was added to a solution of the enamine (0·01 mole) in anhydrous benzene (10 ml). The mixture was set aside for the time indicated in the Table after which the reaction product was precipitated by addition of light petroleum. For the more-soluble products it was best to evaporate the solvent under reduced pressure at low temperature and to treat the residue obtained with light petroleum. The adduct was filtered off and washed with anhydrous ethanol. The data corresponding to the synthesized triazolines are shown in the Table.

trans-1-(4-*Nitrophenyl*)-4-*methyl*-5-(N-*methylanilino*)-v-*triazoline* (22b).—The *trans*-enamine (21b)[6] (1 mmol) dissolved in anhydrous benzene (0·5 ml) was allowed to react with 4-nitrophenyl azide (1·1 mmol) in benzene (1 ml). The reaction was followed by n.m.r. spectroscopy (half-transformation time 0·5 h). The solvent was evaporated and the residue was recrystallized from ethanol to give yellow crystals, m.p. 154°;[8] δ ($CDCl_3$) 1·47 (3H, d, *J* 7 Hz, CH_3), 2·41, (3H, s, N–CH_3), 4·55 (1H, octet, *J* 7 Hz and 3 Hz, 4-H), and 5·48 (1H, d, *J* 3 Hz, 5-H).

cis-1-(4-*Nitrophenyl*)-4-*methyl*-5-(N-*methylanilino*)-v-*triazoline* (22a).—The *cis*-enamine (21a)[6] (1 mmol) was allowed to react as described for the *trans*-isomer. The half-transformation time was *ca.* 6 h. The solvent was evaporated and the residue was washed with ethanol to give yellow crystals, m.p. 123°; δ ($CDCl_3$) 1·60 (3H, d, *J* 7 Hz, Me), 2·33 (3H, s, N–Me); 4·45 (1H, octet, *J* 7 Hz and 9 Hz, 4-H), and 5·82 (1H, d, *J* 9 Hz, 5-H).

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[1/1804 *Received*, 4*th October*, 1971]

[7] J. Hoch, *Compt. rend.*, 1935, **200**, 938.
[8] R. Stradi and D. Pocar, *Gazzetta*, 1969, **99**, 1131.