v-Triazolines. Part XIV (1). 1-Aryl-5-dialkylaminomethyl-4-methylene-4,5-dihydro-v-triazoles

Donato Pocar, Luisa Maria Rossi and Pasqualina Trimarco*

Istituto di Chimica Organica della Facoltà di Farmacia, Università di Milano,
Viale Abruzzi 42, 20131 Milano, Italy

Received May 8, 1979

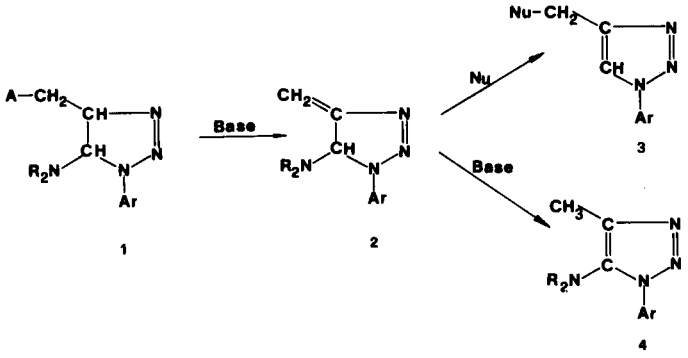
The cycloaddition of arylazides to 1-methyl- and 1-benzyl-2,5-dihydropyrrole affords pyrrolo[3,4-*d*]-*v*-triazole derivatives which react with methyl iodide, yielding the corresponding quaternary ammonium salts. On base-catalyzed elimination 1-aryl-5-dialkyl-aminomethyl-4-methylene-4,5-dihydro-*v*-triazoles are formed. Their structure and behaviour toward methoxide and secondary amines are discussed.

J. Heterocyclic Chem., **17**, 267 (1980).

Very little information has been reported on the preparation and the chemistry of 4-alkylidene-1-aryl-4,5-dihydro-*v*-triazoles.

Recently (2), we reported the isolation of 5-dimethylamino-4-methylene-1-(4-nitrophenyl)-4,5-dihydro-*v*-triazole **2** (Scheme 1) which is formed through base-catalyzed elimination of thiophenoxide from 5-dimethylamino-1-(4-nitrophenyl)-4-phenylthiomethyl-4,5-dihydro-*v*-triazole (**1**, A = C_6H_5-S-). Some other members of this class of compounds have been obtained through β-elimination from 5-amino-4-ammoniomethyl-1-aryl-4,5-dihydro-*v*-triazole salts (3) (**1**, A = $\overset{+}{N}R_3$). These methylene derivatives **2** are reactive toward several nucleophiles owing to the presence of an activated double bond, undergoing an addition-elimination process to **3**.

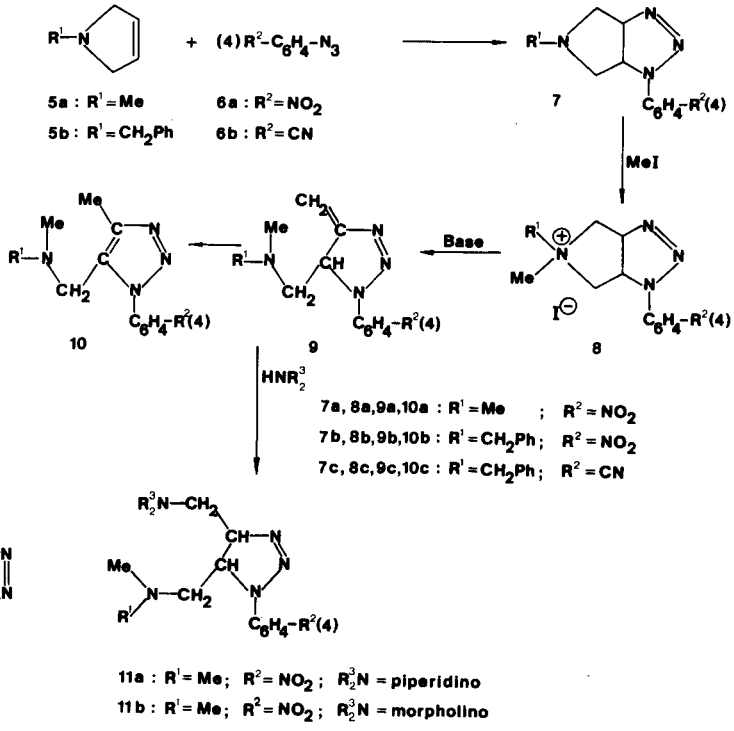
Moreover, by virtue of being monosubstituted in position 5, these compounds were found to be aromatizable to **4** under base catalysis.



Scheme 1

It was of interest to us to prepare some examples of 4-methylene-4,5-dihydro-*v*-triazoles without the amino residue directly linked to position 5, since the only described members of this class of compounds, namely 5,5-dimethyl-4-isopropylidene-4,5-dihydro-triazoles (4), are not aromatizable and their behaviour toward bases was not investigated.

We now report our results on the reactions with bases of compounds **8** (Scheme 2).



Scheme 2

By reacting 1-methyl- and 1-benzyl-2,5-dihydropyrrole **5a,b** with 4-nitro- and 4-cyanophenylazide **6a,b**, the corresponding cycloadducts **7a-c** were formed in fair yield.

Their structure was confirmed by analytical and spectral data (Table).

The quaternarization of compounds **7a-c** was easily accomplished by allowing a solution of the starting compounds to react with excess methyl iodide at room temperature. The corresponding quaternary ammonium iodides **8a-c** were obtained as sparingly soluble com-

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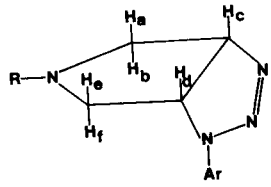
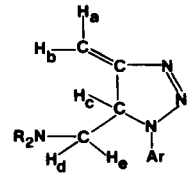
Table

Nmr Data of Compounds **7** and **9**





Compound No.	H_a	H_b	H_c	H_d	H_e	H_f	J_{ab}	J_{ac}	J_{bc}	J_{cd}	J_{de}	J_{df}	J_{ef}	Me or CH_2	Aromatic
7a	2.58	3.42	5.21	4.39	2.42	3.14	10.3	6.7	1.2	10	5	∿0	10	2.30	7.10-8.30
7b	2.65	3.37	5.18	4.35	2.54	3.09	10.1	7	1.3	10.3	5.1	∿0	10	3.65	7.05-8.25
7c	2.64	3.41	5.20	4.34	2.52	3.09	10.2	7	1.3	10	4.9	∿0	10	3.63	7.20-7.80

Note: Assignments were made on the basis that H_c should be more deshielded by the N=N grouping than H_d. Other assignments are confirmed in accordance with coupling constants and confirm the known (5) greater deshielding of *endo*-protons. Coupling constants observed are in agreement with molecular models.

	H_a	H_b	H_c	H_d	H_e	J_{ab}	J_{ac}	J_{bc}	J_{cd}	J_{ce}	J_{de}	Me	CH_2	Aromatic
9a	5.77	5.30	4.50	∿2.75	∿2.40	1.5	3.2	3.0	4.5	6	13.5	2.30	—	7.36-8.25
9b	5.89	5.43	4.52	∿2.90	∿2.50	1.2	3.4	3.0	4	6	13	2.32	3.52	7.10-8.20
9c	5.85	5.40	4.51	∿2.88	∿2.53	1.2	3.6	3.2	5	6	13	2.32	3.55	7.15-7.95

Note: Assignments of H_a and H_b were tentatively made by analogy with compounds **2**.

pounds. The site of quaternarization is clearly indicated by the strong downfield shift in the ^1H nmr spectrum of the signals associated with both methylene groups; this excludes a quaternarization at the triazoline nitrogen (6).

The elimination reaction on the quaternary ammonium salts **8a-c** was performed using 1% sodium hydroxide in methanol or a 4:1 mixture of ethanol and triethylamine shaken with moist potassium hydroxide.

Both bases afforded a mixture of the expected 4-methylene derivatives **9a-c** and of the corresponding isomerization products **10a-c** which were isolated through column chromatography. The isomerization of **9** to **10** appears to be a base-catalyzed process likely occurring *via* an allyl-type carbanion intermediate, which is originated through proton abstraction from C-5 (7). The isomerization was very rapid in the presence of methoxide resulting in a very low **9:10** ratio in the reaction mixture, whereas with triethylamine/potassium hydroxide, a satisfactory yield of compounds **9a-c** could be obtained.

The structure of compounds **9** and of the corresponding isomerization products **10** was inferred from analytical and spectral data. The alternative 5-methylene structure for compounds **9** could be ruled out through a comparison of the uv spectra of **9c** and 1-(4-cyanophenyl)-5-dimethylamino-4-methylene-4,5-dihydro-*v*-triazole (3), which show a very similar absorption (λ = 354 nm, ϵ = 15700 and λ = 346 nm, ϵ = 15500, respectively), indicating the presence of the same $CH_2=\overset{|}{C}\text{-}N=N\text{-}$ chromophore.

The formation of 4-methylene derivatives and not of the isomeric 5-methylene compounds is in good agreement with the known steric requirements of the Hofmann-type elimination (8) and with the general fact that in the 4,5-dihydrotriazole ring the more acidic hydrogen atom is linked to C-4.

Moreover, the difficulty of amine elimination from the more hindered and less acidic position 5 was confirmed by the failure of some attempts to obtain 5-methylene-4,5-dihydro-*v*-triazole derivatives. By reacting 4-nitrophenylazide with allyl-dimethylamine and allyl-diethylamine, the expected 5-dimethylaminomethyl- and 5-diethylaminomethyl-1-(4-nitrophenyl)-4,5-dihydro-*v*-triazoles were obtained (9). The corresponding quaternarization products were easily prepared by reaction with methyl iodide (10). However, no elimination products could be obtained under the mild reaction conditions described for compounds **8** and only degradation products were formed when the elimination was attempted under more strenuous conditions.

On reaction with methoxide compounds **9** were found to behave differently from compounds **2**, yielding only the isomerization products **10**. Products deriving from the addition to the double bond were not detected. Under the same conditions compounds **2** afforded mainly the corresponding 1-aryl-4-methoxymethyl-*v*-triazoles (**3**, Nu = MeO) together with only a small amount of isomerization product **4**.

Since the activation of the methylene double bond

should be very similar in the two cases, the preferred isomerization of compounds **9** should be explained through the relatively easier deprotonation of C-5, both for electronic and steric grounds.

This view was confirmed by the fact that good nucleophiles, but relatively weak bases, as piperidine and morpholine could be added at room temperature and in high yield to the activated double bond of **5a**, affording the *trans*-4,5-dihydro-*v*-triazoles **11a,b**. In this case only a small amount of the aromatized compound **10a** was identified in the reaction mixture.

EXPERIMENTAL

All melting points are uncorrected. The nmr spectra were recorded at 60 MHz using Varian A-60 and EM-360 A spectrometers. Chemical shifts are given in ppm relative to internal TMS. The uv spectra were recorded with a Beckman 24 spectrometer in chloroform solution. Tlc was run on silica gel GF 254 with benzene-ethyl acetate (20-60%) as eluent.

5-alkyl-1-aryl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*d*]-*v*-triazoles (**7a-c**).

The 1-alkyl-2,5-dihydropyrrole **5** (50 mmoles) and the arylazide **6** (50 mmoles) were mixed and diluted with anhydrous acetonitrile (5-10 ml.). The solution was left at room temperature until complete reaction (tlc). The precipitate obtained was filtered and recrystallized from isopropyl ether.

Compound **7a**.

This compound had m.p. 153° dec., yield 80%.

Anal. Calcd. for $C_{11}H_{13}N_5O_2$: C, 53.45; H, 5.30; N, 28.35. Found: C, 53.75; H, 5.15; N, 28.60.

Compound **7b**.

This compound had m.p. 150° dec., yield 70%.

Anal. Calcd. for $C_{17}H_{17}N_5O_2$: C, 63.15; H, 5.30; N, 21.65. Found: C, 63.45; H, 5.15; N, 21.45.

Compound **7c**.

This compound had m.p. 125-126° dec., yield 35%.

Anal. Calcd. for $C_{18}H_{17}N_5$: C, 71.25; H, 5.65; N, 23.10. Found: C, 71.20; H, 5.60; N, 23.10.

1-Aryl-5,5-dialkyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*d*]-*v*-triazolium iodides (**8a-c**).

Compound **7** (20 mmoles) was dissolved in anhydrous acetonitrile (250 ml.) and methyl iodide (30 mmoles) was added. The solution was left at room temperature for 24 hours. The precipitate of the ammonium salt was filtered and washed with anhydrous chloroform or diethyl ether. An analytical sample was purified by repeated washing with chloroform.

Compound **8a**.

This compound had m.p. 187° dec., yield 75%.

Anal. Calcd. for $C_{12}H_{16}IN_5O_2$: C, 36.95; H, 4.15; N, 17.95. Found: C, 36.90; H, 4.15; N, 18.15.

Compound **8b**.

This compound had m.p. 97-100° dec., yield 95%.

Anal. Calcd. for $C_{18}H_{20}IN_5O_2$: C, 46.45; H, 4.35; N, 15.05. Found: C, 46.47; H, 4.35; N, 15.25.

Compound **8c**.

This compound had m.p. 180-184° dec., yield 65%.

Anal. Calcd. for $C_{19}H_{20}IN_5$: C, 51.20; H, 4.55; N, 15.75. Found: C, 51.40; H, 4.50; N, 15.95.

Reaction of **8a-c** with Sodium Methoxide.

Compound **8** (5 mmoles) was reacted at room temperature in methanol (30 ml.) containing sodium methoxide (10 mmoles). The reaction mixture was stirred for several hours (2-5) and followed by tlc. During the first reaction period both products **9** and **10** were evidenced besides the unreacted starting compound. After complete reaction of the starting material only trace amounts of **9** were still present and the main product was compound **10**. The reaction mixture was evaporated, taken up with water, extracted with ether, dried over sodium sulfate and evaporated. The residue was recrystallized from isopropyl ether or ethanol.

Compound **10a**.

This compound had m.p. 107-109°, yield 40%; nmr (deuteriochloroform): δ 2.27 (6H, s, $N(CH_3)_2$), 2.40 (3H, s, CH_3), 3.41 (2H, s, CH_2), 8.05-8.50 (4H, m, arom.).

Anal. Calcd. for $C_{12}H_{15}N_5O_2$: C, 55.15; H, 5.80; N, 26.80. Found: C, 54.80; H, 5.60; N, 26.50.

Compound **10b**.

This compound had m.p. 93-95°, yield 60%; nmr (deuteriochloroform): δ 1.94 (3H, s, NCH_3), 2.28 (3H, s, CH_3), 3.22 and 3.34 (4H, 2s, CH_2NCH_2), 7.0-7.35 (5H, m, C_6H_5), 7.73-8.15 (4H, m, arom.).

Anal. Calcd. for $C_{18}H_{19}N_5O_2$: C, 64.10; H, 5.65; N, 20.75. Found: C, 63.65; H, 5.50; N, 20.40.

Compound **10c**.

This compound had m.p. 91-92°, yield 50%; nmr (deuteriochloroform): δ 2.17 and 2.45 (3 + 3H, 2s, $2CH_3$), 3.54 (4H, s, CH_2-N-CH_2), 7.28 (5H, m, C_6H_5), 7.68-8.24 (4H, m, arom.).

Anal. Calcd. for $C_{19}H_{19}N_5$: C, 71.90; H, 5.60; N, 22.10. Found: C, 71.85; H, 6.00; N, 22.10.

Reaction of **8a-c** with Triethylamine/Potassium Hydroxide.

Compound **8** (1.1 mmoles) was reacted, at room temperature, with ethanol (300 ml.) and triethylamine (75 ml.) which had been previously shaken with moist potassium hydroxide pellets. The mixture was stirred until complete reaction of the starting material (24-72 hours.). A mixture of products **9** and **10** was formed (tlc). The solution was evaporated to dryness and the residue was taken up in water, extracted with ether and the ethereal layer was dried over sodium sulfate and evaporated. The residue was chromatographed on a silica gel column (ethyl acetate:benzene, 2:3), yielding **9** as the first fraction and **10** as the second fraction.

Compound **9a**.

This compound had m.p. 127-128° (from isopropyl ether), yield 25%.

Anal. Calcd. for $C_{12}H_{15}N_5O_2$: C, 55.15; H, 5.80; N, 26.80. Found: C, 54.85; H, 5.85; N, 26.60.

Compound **9b**.

This compound had m.p. 100-101° (from isopropyl ether), yield 35%.

Anal. Calcd. for $C_{18}H_{19}N_5O_2$: C, 64.10; H, 5.65; N, 20.75. Found: C, 64.25; H, 5.90; N, 20.60.

Compound **9c**.

This compound had m.p. 66-67° (from isopropyl ether), yield 60%

Anal. Calcd. for $C_{19}H_{19}N_5$: C, 71.90; H, 5.60; N, 22.10. Found: C, 71.75; H, 5.65; N, 22.15.

Reaction of **9a** with Piperidine and Morpholine.

The methylene triazoline **9a** (0.5 g., 1.9 mmoles) was reacted with piperidine (3 ml.) and morpholine (3 ml.), respectively. The reaction mixture was left at room temperature for 24 hours. After evaporation *in vacuo* the residue was recrystallized yielding **11a** and **11b**, respectively.

Compound **11a**.

This compound had m.p. 124° dec., (from methanol), yield 45%; nmr (deuteriochloroform): δ 1.32-1.58 (6H, m, $(CH_2)_3$), 1.90-2.85 (8H, m, $(-CH_2)_2NCH_2$- and $>NCH_2$), 2.25 (6H, s, $N(CH_3)_2$), 4.07 (1H, 5-line signal, H-5), 4.92 (1H, 5-line signal, H-4, J_{4-5} = 4 Hz), 7.25-8.25 (4H, m, arom.).

Anal. Calcd. for $C_{17}H_{26}N_6O_2$: C, 58.95; H, 7.55; N, 24.25. Found: C, 59.10; H, 7.50; N, 24.40.

Compound **11b**.

This compound had m.p. 132° dec., (from isopropyl ether), yield 50%; nmr (deuteriochloroform): δ 2.20-2.85 (8H, m, $(-CH_2)_2NCH_2-$ and $>N-CH_2$), 2.37 (6H, s, $N(CH_3)_2$), 3.62-3.86 (4H, m, CH_2-OCH_3), 4.20 (1H, 5-line signal, H-5), 5.05 (1H, 5-line signal, H-4, J_{4-5} = 4 Hz), 7.40-8.55 (4H, m, arom.).

Anal. Calcd. for $C_{16}H_{24}N_6O_3$: C, 55.15; H, 6.95; N, 24.10. Found: C, 55.40; H, 6.90; N, 23.80.

Acknowledgement.

The cooperation of Dr. Nunzia Fiammeni for the experimental work is gratefully acknowledged. We thank Dr. Carlo Bugatti for the uv spectra.

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(6) However, further details on the structure of these salts could not be desumed from ^1H nmr spectra which were always of poor quality owing to bad solubility.

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(9) The reaction was performed as described for compounds **7**, reaction time 20-24 days, m.p. 125-127° dec., and 124-125° dec., respectively.

(10) As described for compounds **8**, m.p. 142° dec., and 137-140° dec., respectively.