Chemical, Physicochemical and Crystallographical Studies in the 1,2,4-Triazole Series (1)

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The structure of the condensation product of 1,2,4-triazole and morpholinochloroethane was determined by comparison of its chemical, physicochemical and crystallographical characteristics with those of two isomeric compounds prepared by an univocal synthesis.

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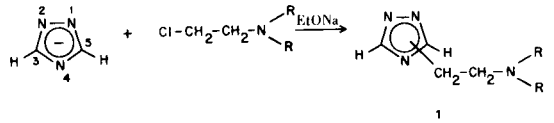
In a chemical and pharmacological study of structural histamine-like substances, we prepared several dialkylaminoethyl-1,2,4-triazoles (3).

As the synthetic methods produced, *a priori*, two isomers in several instances, we were faced with an important problem of structure both in the chemical field and from the point of view of its consequences on pharmacodynamic activity. Thus, it appeared necessary to study this question systematically by means of chemical, physicochemical and strictly physical methods. An easy method of preparation of 2-dialkylaminoethyl-1,2,4-triazoles involves the reaction of dialkylaminochloroethanes with 1,2,4-triazole sodium salt. This technique does not permit the determination of the position of the substituent on the triazole nucleus. 1,2,4-Triazole may exist at room temperature in two tautomeric forms.

1*H*-1,2,4-Triazole 4*H*-1,2,4-Triazole

Thus, considering the aromatic character of 1,2,4-triazole, the substitution reaction of the aminochloroalkane can be illustrated in the following scheme which does not allow prediction of where the substitution by the dialkylaminoethyl group will take place (1 or 4 on the nucleus).



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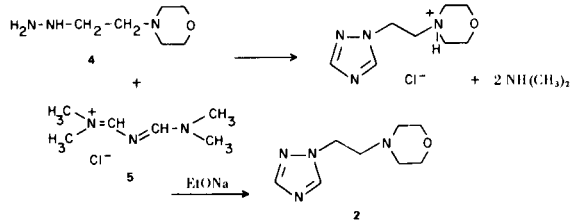
In every case, we only isolated one product whose substitution position remained to be determined. It was essential to specify the structure of the compounds obtained since the literature showed us examples, for the triazole series, of isomeric forms with very different and sometimes antagonistic pharmacological properties (4). Thus, 1-phenyl-1,2,4-triazole is active as a tranquillizer, whereas 4-phenyl-1,2,4-triazole has anticonvulsive properties (5).

To determine unambiguously the substitution site, we studied the characteristics of one particular compound, the 1- (or 4-) (2-morpholinoethyl)-1,2,4-triazole (**1**). We used an univocal method of synthesis for 1-(2-morpholinoethyl)-1,2,4-triazole (**2**) and a different univocal method of synthesis for 4-(2-morpholinoethyl)-1,2,4-triazole (**3**), these compounds being employed as reference substances for comparative studies.

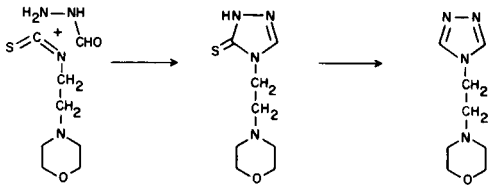
The condensation of diformamide to synthetise 1-(2-morpholinoethyl)-1,2,4-triazole (**2**) with morpholinoethylhydrazine seemed the easiest way. However, the difficulty of preparation (6) of this first compound led us to replace it by the 3-dimethylamino-2-azaprop-2-enylidenedimethyl-



4 2

ammonium chloride. After cyclisation, we obtained the triazole derivative for which the morpholinoethyl chain was at position 1 on the nucleus.

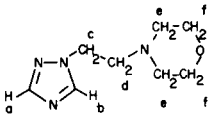
The method chosen for the synthesis of 4-(2-morpholinoethyl)-1,2,4-triazole (**3**) implied the use of 2-morpholinoethylisothiocyanate (**6**), a new compound, whose cyclising condensation with formylhydrazine gave the triazolinethione (**7**) directly. The hydrogenolysis of the thione group led to 4-(2-morpholinoethyl)-1,2,4-triazole (**3**).



6 **7** **3**

Results and Discussion.

The results of the different physicochemical studies of **1**, **2**, and **3** appear in Table I. Ir spectra of the two isomers present a strong analogy; in fact, only one notable difference appears in the 1600-1800 cm^{-1} area. The bands of weak intensity (1640 and 1740 cm^{-1}) corresponding to the C=N bonds of the triazole ring, substituted at N_1 (**2**) are replaced, for 4-substituted triazoles (**3**), by a single absorption band at 1675 cm^{-1}. The C=N bonds are equivalent for this last mentioned compound. The nmr spectrum of **2** in carbon tetrachloride presents, for each carbon-proton of the triazole nucleus, a singlet at δ = 7.70 ppm and δ = 8.08 ppm. The non-equivalence of the protons a and b corresponds to the dissymmetry of the molecule.



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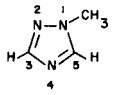
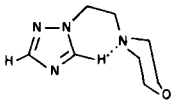
We assigned to the proton b the signal appearing in the lower field, referring to Jacquier's study (7) of 1-methyl-1,2,4-triazole (this author was in favour of the proton 5 deshielding with regard to the proton 3). The possible establishment of a hydrogen-bonding between the proton 5 and the morpholine nitrogen atom is in accordance with this hypothesis.



1-Methyl-1,2,4-triazole



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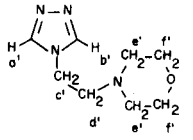
Owing to the apparent symmetry of **3**, we could expect the protons a′ and b′ to be equivalent and to resonate at the same field. The same deshielding was noted for b′



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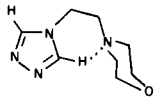

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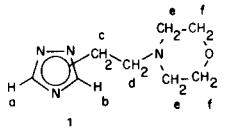
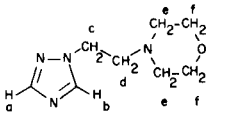
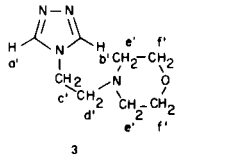
Table I

	B.p. °C Torr	$n_D^{21.6}$	d_{25}^{25}	Nmr (δ in ppm) Carbon tetrachloride	Nmr (δ in ppm) Deuteriobromoform	G.C. retention time s
 **1**	128/0.05	1.5040	1.137	(a) 7.70; s; i = 1 (b) 8.08; s; i = 1 (c) 4.20; t; i = 2; J = 6 Hz (d) 2.70; t; i = 2; J = 6 Hz (e) 2.40; m; i = 4 (f) 3.52; m; i = 4	7.90; s; i = 1 8.24; s; i = 1 4.32; t; i = 2; J = 6 Hz 2.80; t; i = 2; J = 6 Hz 2.45; m; i = 4 3.65; m; i = 4	39
 **2**	128/0.05	1.5040	1.137	(a) 7.70; s; i = 1 (b) 8.08; s; i = 1 (c) 4.20; t; i = 2; J = 6 Hz (d) 2.70; t; i = 2; J = 6 Hz (e) 2.40; m; i = 4 (f) 3.52; m; i = 4	7.90; s; i = 1 8.24; s; i = 1 4.32; t; i = 2; J = 6 Hz 2.80; t; i = 2; J = 6 Hz 2.45; m; i = 4 3.65; m; i = 4	39
 **3**	194/0.05	1.5178	1.158	(a′) 7.70; s; i = 1 (b′) 8.08; s; i = 1 (c′) 4.20; t; i = 2; J = 6 Hz (d′) 2.70; t; i = 2; J = 6 Hz (e′) 2.40; m; i = 4 (f′) 3.52; m; i = 4	8.30; s; i = 2 4.22; t; i = 2; J = 6 Hz 2.72; t; i = 2; J = 6 Hz 2.53; m; i = 4 3.67; m; i = 4	172

(δ = 8.08 ppm) in respect to a' (δ = 7.70 ppm) as for b (δ = 8.08 ppm) in respect to a (δ = 7.70 ppm).

This fact can be explained by the establishment of hydrogen bonding between the proton b' and the morpholine nitrogen atom. The result was a dissymmetry analogous to the one existing for **2**. The use of deuteriobromoform as a solvent did not change the nmr spectrum of **2** (see Table I).

However, an important solvent effect was noted for **3**. The signals corresponding to the protons a' and b' coalesced even at room temperature. The hydrogen bonding noted above (between proton b' and morpholine nitrogen atom) when carbon tetrachloride was used as a solvent did not appear in a deuteriobromoform medium. The molecule reverted to a symmetric structure, the protons a' and b' becoming equivalent. The nmr spectrum of **1** was strictly identical with that of **2** both in carbon tetrachloride and in deuteriobromoform.

Under the conditions related in the experimental, the gas chromatograms of **2** and **3** are very different, such as a short retention time (39 seconds) and a very sharp peak for **2** and a very much higher retention time (172 seconds) and a wider peak with a trail for **3**. A chromatogram of **1**, under the same conditions, was strictly identical with that of **2**.

The physicochemical measures concerning compounds **1**, **2** and **3** indicated notable differences between isomers **2** and **3** and allowed us to establish the identity of **1**.

It seemed interesting to carry out a similar study on the same compounds, after salt formation. This permitted the

Table II

	M.p. °C (Recrystallisation solvent)	Nmr (δ in ppm) Deuterium oxide (1)
1f	217 (methanol)	(a) 8.78; s; i = 1 (b) 9.66; s; i = 1 (c) 3.93; t; i = 2; J = 6 Hz (d) 3.80; t; i = 2; J = 6 Hz (e) 3.55; m; i = 4 (f) 4.98; m; i = 4
2c	217 (methanol)	(a) 8.70; s; i = 1 (b) 9.54; s; i = 1 (c) 3.93; t; i = 2; J = 6 Hz (d) 3.80; t; i = 2; J = 6 Hz (e) 3.55; m; i = 4 (f) 4.95; m; i = 4
3c	254 (methanol)	(a') 7.48; s; i = 2 (b') 7.48; s; i = 2 (c') 3.98; t; i = 2; J = 6 Hz (d') 3.72; t; i = 2; J = 6 Hz (e') 3.51; m; i = 4 (f') 4.90; m; i = 4

(1) The denomination is the same as for **1**, **2** and **3**.

Table III

Crystal Data

	a (Å)	b (Å)	c (Å)	Space group	Lattice size (Å^3)
1c	10.246 ± 0.005	10.384 ± 0.005	22.691 ± 0.01	Pbca	2414
2c	10.247 ± 0.005	10.386 ± 0.005	22.684 ± 0.01	Pbca	2414
3c	5.9 ± 0.2	11.2 ± 0.2	36.7 ± 0.2	C 222$_1$	2425

examination of these molecules where the hydrogen-bonding CH. . . . N (for the morpholine) examined above could not exist. The results concerning the dihydrochlorides **1c**, **2c** and **3c** are reported in Table II. The nmr spectra examination of **2c** and **3c** in deuterium oxide confirmed the results obtained for **2** and **3** in deuteriobromoform. The protons attached to the C atoms of the triazole nucleus in **2c** were differentiated but were equivalent in **3c** (symmetrical molecule).

The study of the X-ray diffraction spectra of crystals of **1c**, **2c** and **3c** allowed the determination of their exact structure. However, it required much less time if we limited ourselves to a comparative study of **1c** with respect to **2c** and **3c** in order to consider the space group of these crystals and the parameters of their experimental unit cell. Indeed, although the crystalline system is not influenced by the structure of the molecules which compose one crystal, the parameters of the unit cell were strongly influenced by the field of intermolecular forces. This was the method we used. The results are summarized in Table III.

The following observations can be made. (1) The identity of the orthorombic lattices of **1c** and **2c** take into account the experimental error. (2) The identity of the space groups with the systematic extinctions shows that compound **3c** has an orthorombic unit cell with parameters and space groups which are quite distinct from **1c** and **2c**. These results show that **1c** was identical with **2c** and reveal significative differences with **3c**.

The following observations were also noted. 1) There is a great influence of the configurations of the molecules on their arrangement in the crystalline system. 2) There are almost identical values for the primitive unit cell sizes of firstly, **1c** and **2c**, and secondly, the face centered unit cell of **3c**. 3) The very close densities of **1c**, **2c** and **3c** induced the same number of eight molecules for per unit cell. Thus, the steric hindrance was almost identical for **2c** and **3c** but on the other hand, their spatial arrangement was very different.

The chemical and physical studies described in this

publication enabled us to determine with certainty that the reaction between an aminochloroethane molecule and 1,2,4-triazole led to a compound substituted at the nitrogen atom N_1, under the experimental conditions noted here. Furthermore, we were able to show the different behaviour of 1-(2-morpholinoethyl)-1,2,4-triazole and of 4-(2-morpholinoethyl)-1,2,4-triazole in solution (nmr spectrometry) and in the gaseous phase. These results were corroborated by crystallographic study on the corresponding dihydrochlorides.

EXPERIMENTAL (8)

1-(or 4-)(2-Morpholinoethyl)-1,2,4-triazole (**1**).

Equimolecular proportions of 1,2,4-triazole (6.9 g.) and sodium (2.3 g.), in solution in minimum quantities of absolute ethanol, were both heated until a pink coloration was developed (1 hour). The equimolecular quantity of 2-morpholino-1-chloroethane (15 g.) was then added to this ethanolic sodium derivative solution. Refluxing was maintained for 10 hours, the sodium chloride was then filtered off, the solvent evaporated and the residue distilled under vacuum, b.p. 128° (0.05 torr), 60% yield.

Anal. Calcd. for $C_8H_{14}N_4O$: C, 52.73; H, 7.74; N, 30.75. Found: C, 52.08; H, 7.76; N, 30.66.

The dihydrochloride **1c** had m.p. 217° (methanol).

Anal. Calcd. for $C_8H_{16}Cl_2N_4O$: C, 37.66; H, 6.32; N, 21.96. Found: C, 37.85; H, 6.27; N, 22.34.

1-(2-Morpholinoethyl)-1,2,4-triazole (**2**).

An equimolecular mixture of 3-dimethylamino-2-azapro-2-en-1-ylidene dimethylammonium (9) (6.2 g.) and morpholinoethylhydrazine (5.5 g.) was heated at 100° without a solvent for 1 hour (the end of the reaction was indicated by the cessation of the release of dimethylamine). The neutralization was carried out with sodium ethylate, sodium chloride was collected, ethanol evaporated and the residue distilled under reduced pressure, b.p. 128° (0.05 torr), 50% yield.

Anal. Calcd. for $C_8H_{14}N_4O$: C, 52.73; H, 7.74; N, 30.75. Found: C, 52.31; H, 7.78; N, 30.69.

The dihydrochloride **2c** had m.p. 217° (methanol).

Anal. Calcd. for $C_8H_{16}Cl_2N_4O$: C, 37.66; H, 6.32; N, 21.96. Found: C, 37.54; H, 6.30; N, 21.82.

2-Morpholinoethylisothiocyanate (**6**).

Carbon disulfide (3.8 g.) in dry ether was added dropwise to 6.5 g. of 2-morpholinoethylamine and 10.3 g. of dicyclohexylcarbodiimide in dry ether with agitation at 0°. After the mixture was stirred for 12 hours, the precipitated dicyclohexylthiourea was collected. Evaporation of the solvent left the residue which was distilled off, b.p. 88-90° (0.1 torr), 81% yield, $n_D^{21.2} = 1.5332$; ir: $\nu = 2150\ cm^{-1}$ and $2200\ cm^{-1}$ (characterising isothiocyanate).

4-(2-Morpholinoethyl)-2-Δ-1,2,4-triazoline-5-thione (**7**).

An equimolecular mixture of an ethanolic solution of **6** (13.9 g.) and formylhydrazine (4.85 g.) was heated at reflux for 12 hours. After evaporation of the solvent, the oily residue solidified, m.p. 142° (ethanol), 98% yield.

Anal. Calcd. for $C_8H_{14}N_4OS$: C, 44.84; H, 6.59; N, 26.15. Found: C, 44.77; H, 6.67; N, 25.93.

4-(2-Morpholinoethyl)-1,2,4-triazole (**3**).

The triazolinethione (**7**) (1 g.) in alcoholic solution (60 ml.) was catalytically hydrogenolyzed under pressure (60 bars) at 60° in presence of Raney nickel for 12 hours. The oily residue was distilled after elimination of the solvent, b.p. 194° (0.05 torr), 96% yield.

Anal. Calcd. for $C_8H_{14}N_4O$: C, 52.73; H, 7.74; N, 30.75. Found: C, 52.44; H, 7.71; N, 30.70.

The dihydrochloride **3c** had m.p. 254° (methanol).

Anal. Calcd. for $C_8H_{16}Cl_2N_4O$: C, 37.66; H, 6.32; N, 21.96. Found: C, 37.28; H, 6.27; N, 21.83.

REFERENCES AND NOTES

(1) Work carried out with the support of I.N.S.E.R.M., Contract No. 72.5.113 (9).

(2) Research worker at the I.N.S.E.R.M., present address: Unité U16, Place de Verdun, 59045 Lille Cedex (France).

(3) J. P. Hénichart, R. Houssin, C. Lespagnol, J. C. Cazin, M. Cazin and F. Rousseau, *Chim. Ther.*, **8**, 358 (1973).

(4) C. Ainsworth, N. R. Easton, M. Livezey and D. E. Morrison, *J. Med. Pharm. Chem.*, **5**, 383 (1962).

(5) W. R. Gibson, E. E. Swanson and D. B. Meyers, *J. Am. Pharm. Ass.*, 47, 778 (1958).

(6) E. Allenstein and V. Beryl, *Chem. Ber.*, **100**, 3551 (1967).

(7) R. Jacquier, M. L. Roumestant and P. Viallefont, *Bull. Soc. Chim. France*, 2630 (1967).

(8) Infrared spectra were recorded with a Perkin-Elmer 177 infrared spectrometer, using a potassium bromide pellet for the crystallised sample and sodium chloride windows for liquid samples. Nmr spectra were obtained with a JEOL JNM-MH-60, using tetramethylsilane as the internal standard for carbon tetrachloride and deuteriobromoform, 3-trimethylsilylpropanesulfonate sodium salt for deuterium oxide. The refractive indices were measured with a Carl Zeiss Abbe refractometer. Combustion analyses were performed on a Perkin-Elmer CHN 240. Gas chromatographic analyses were obtained on a Hewlett-Packard 5 700 A catharometer apparatus (with Hewlett-Packard 3373 B integrator) with the following equipment: silicon gum rubber OV_1 column; column and detector temperature, 250°; carrier gas, He (flow 43 ml./minute). The injected solution was a 10^{-2} chloroform solution. Transparent colorless monocrystals were obtained by slow cooling of a saturated methanolic solution, the degree of perfection for **1c** and **2c** being superior to that of **3c**. The selected samples (average size, 0.5 mm) were placed in Lindeman capillary tubes, because of their hygroscopic nature. They were examined on a Philips PW 100 automatic diffractometer for **1c** and **2c**, and using the Weissenberg method (Nonius chamber) for **3c**.

(9) H. Gold, *Angew. Chem.*, 72, 956 (1960).