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**1*H*,6*H*-TRIAZOLO[4,5-*e*]BENZOTRIAZOLE-3-OXIDES AND 5,5'-(*Z*)-
DIAZENE-1,2-DIYLBIS(2-METHYL-2*H*-1,2,3-BENZOTRIAZOLE)
DERIVED FROM CHLORONITROBENZOTRIAZOLES AND
HYDRAZINE**

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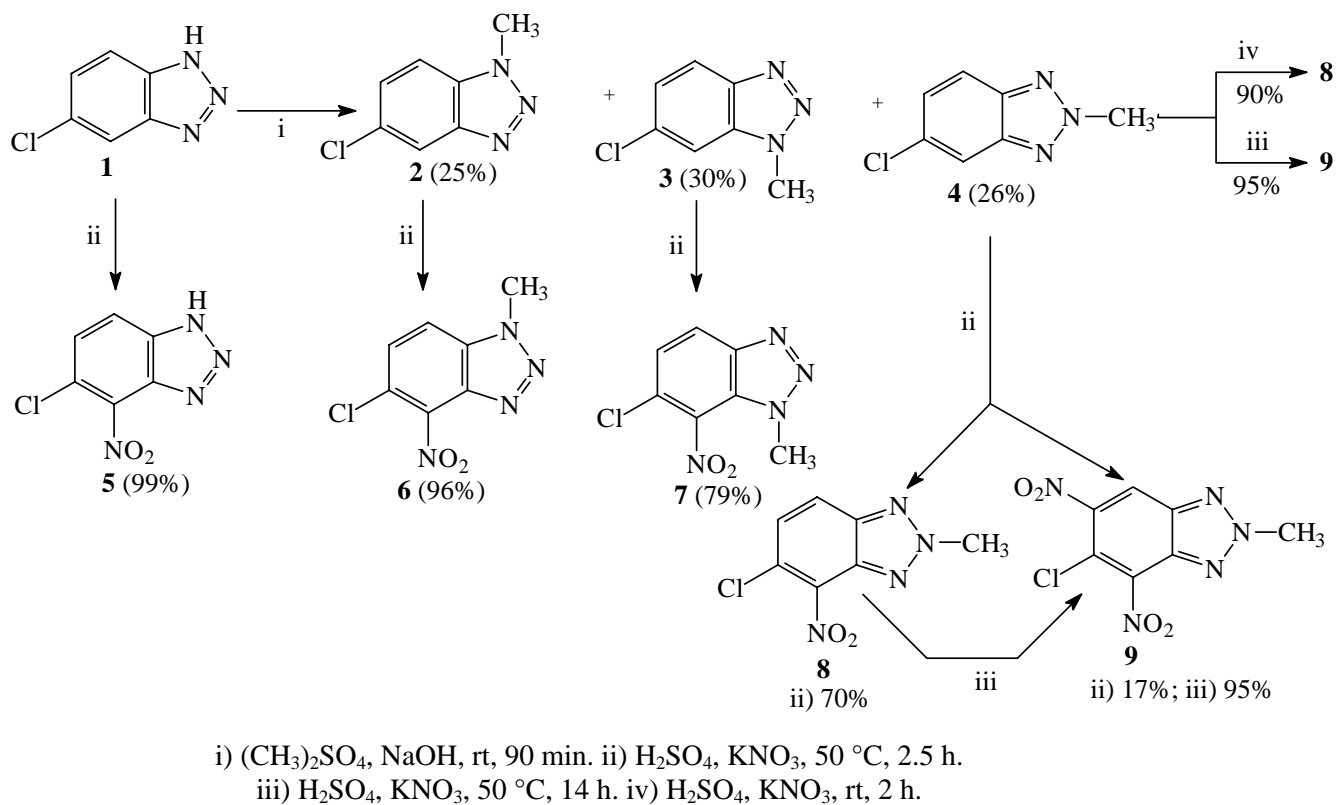
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Abstract – Nitration of 5-chlorobenzotriazole (**1**) and its *N*-methyl derivatives (**2** and **3**) produced 5-chloro-4-nitrobenzotriazole (**5**), 5-chloro-1-methyl-4-nitrobenzotriazole (**6**) and 6-chloro-1-methyl-7-nitrobenzotriazole (**7**) respectively. Nitration of 5-chloro-2-methylbenzotriazole (**4**) gave either 5-chloro-2-methyl-4-nitrobenzotriazole (**8**) or 5-chloro-2-methyl-4,6-dinitrobenzotriazole (**9**). Introduction of the nitro group activated chlorine atom that underwent nucleophilic displacement by hydrazine to give rise to a new tricyclic system 1*H*,6*H*-triazolo[4,5-*e*]benzotriazole-3-oxide compounds (**10** and **11**) in the case of **5** and **6**. From **9** no linear or angular tricyclic triazolobenzotriazole was obtained but instead the 5,5'-(*Z*)-diazene-1,2-diylbis(2-methyl-2*H*-1,2,3-benzotriazole) (**18**).

Benzotriazole continues to receive a deal of interest for its versatility as synthetic auxiliary.^{1,2} However, little attention has been paid for the reactions of electrophilic substitution on the benzene counterpart unless these compounds were necessary as intermediates in building block of heterocyclic systems. This is our case that for years we pursued the goal to obtain novel triazoloquinolines, triazoloquinoxalines of pharmaceutical interest³⁻¹¹ and to study the chemistry of benzotriazole¹²⁻¹⁸ and its derivatives endowed with pharmacological activities.¹⁹⁻²⁷

It is well known that electrophilic substitution reactions (halogenation and nitration) on benzotriazole and its *N*-alkyl derivatives have not been widely used because the triazole acts as a deactivating group on the benzene ring and orientation is largely influenced by both the nature and position of the substituents giving rise to 4- or 5- ring substituted benzotriazoles. Thus, the standard methods of synthesis involve cyclization of substituted 1,2-diaminobenzenes by means of nitrous acid. In the past some of us adopted

this procedure to prepare several unambiguous 5-monosubstituted or 5,7(4,6)-disubstituted *N*-(*N*3)-alkylbenzotriazole isomers.¹² Successively, when 5-nitrobenzotriazole became commercially unavailable, we had to re-examine the nitration reaction of benzotriazole as reported by Fries *et al.*²⁸ and Miller and Wagner²⁹ and we discovered that the 4-nitro isomer was mainly formed (58% yield) but it was accompanied by the 15% yield of the 5-nitro ones. This result is described now for the first time and seems in accordance with the observations of Kamel *et al.*³⁰ for the case of the nitration of 2-methylbenzotriazole which led to a similar mixture of 2-methyl-4-nitro- and 2-methyl-5-nitrobenzotriazoles. The situation can be different when an appropriate substituent is already present in the benzene moiety. This is the case we have examined in the present paper in which all previously known 5-chloro-1*H*-benzotriazole (**1**) and its three *N*-methyl derivative isomers (**2**, **3** and **4**)¹² underwent nitration according to Scheme 1.



Scheme 1

These new *ortho*-chloronitrobenzotriazoles (**5**, **6**, **7**, **8**) were then submitted to nucleophilic displacement of chlorine by hydrazine hydrate in order to prepare 1*H*,6*H*(7*H*)(8*H*)-triazolo[4,5-*e*]benzotriazole-3-oxides (**10**, **11**, **12** and **13**) of Scheme 2 for pharmacological studies.

N-Methyl isomers (**2**, **3** and **4**) of 5-chloro-1*H*-benzotriazole (**1**) were prepared as previously described on alkylation with dimethyl sulfate in alkaline medium with an overall yield of 76% of pure isomers.¹² Compounds (**1**, **2** and **3**) separately underwent mononitration at position C-4 in excellent yields carrying

out the reaction in sulfuric acid and potassium nitrate at 50°C for 2.5 h. Under the same conditions from compound (**4**) we isolated both 5-chloro-2-methyl-4-nitrobenzotriazole (**8**) and 5-chloro-2-methyl-4,6-dinitrobenzotriazole (**9**) in the ratio of about 4:1. When the reaction was carried out at room temperature, the sole compound (**8**) was isolated in 90% yield, whereas operating at 50°C for 14 h compound (**9**) was formed in 95% yield. The latter was straightforward obtained from **8** in an identical yield under the same conditions. An explanation for mononitration in the case of compounds (**1**, **2** and **3**) may be due to the concomitant *ortho* directing effect of both chlorine atom and triazole group.

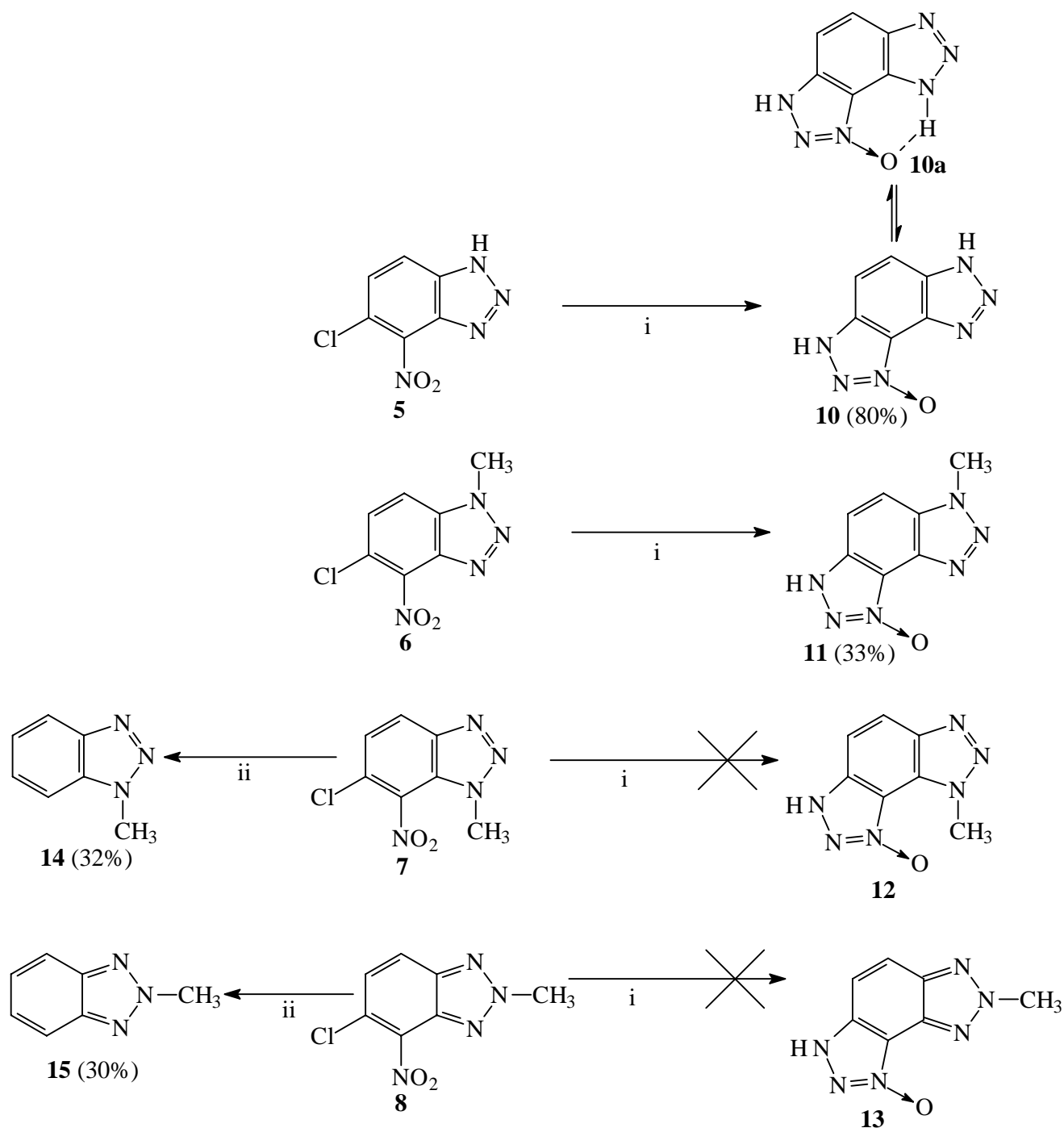
In the case of nitration of the isomer (**4**) it is noteworthy to observe the formation of a mixture of compounds (**8**) and (**9**) in the ratio of 4:1 respectively. However, it must be also pointed out that this reaction undergoes kinetic versus thermodynamic control showing a certain analogy with the reactivity of naphthalene, as previous observed by Kamel *et al.*,³⁰ although in this case it was very selective since the triazole ring can't be nitrated.

Thus, at room temperature for 2 h compound (**4**) was transformed into **8** in 90% yield, whereas at 50°C for 14 h the dinitro compound (**9**) was formed in 95% yield. It seems reasonable to think that this behavior is strongly favoured by the concomitant *ortho meta* directing effects of both chlorine/triazole and nitro groups respectively. In addition it must be noted that our attempt at nitrating of the mononitro isomers (**6** and **7**), under the same conditions as above, was not successful and the starting compounds were fully recovered. This would account for the influence of the different position of the substituent on triazole ring.

At this stage it was interesting to study the activating effects of nitro group towards the nucleophilic displacement of chlorine atom by hydrazine hydrate for a ring closure into a triazole N-oxide. Therefore, we have submitted the mononitro compounds (**5-8**) to reaction with an excess of hydrazine hydrate according to the conditions depicted in Scheme 2, previously experienced by us in the case of chloro-nitroquinolines.⁹⁻¹¹

This procedure was only partially successful for we were able to isolate the 1*H*,6*H*-triazolo[4,5-*e*]benzotriazole-3-oxides (**10**) (80 %) and (**11**) (33 %) but none of the expected (**12**) and (**13**). In the attempt to obtain also the derivatives (**12**) and (**13**) we repeated the same reaction on compounds (**7**) and (**8**) in a sealed steel vessel at 70°C for 90 h. Unfortunately, only the previously described³¹ 1-methylbenzotriazole (**14**) (32 %) and 2-methylbenzotriazole (**15**) (30 %) were respectively isolated.

An explanation of the different reactivity of **7** and **8** in comparison with that of **5** and **6** may be due to the position of the methyl group on the N3 or N2 of triazole ring in **7**, **8** where, owing to the resonance forms, the presence of a positive charge on these nitrogen atoms is counterbalanced by a further negative charge on the nitro group which decreases its withdrawing effect.



i) $\text{H}_2\text{N-NH}_2$, $\text{CH}_3\text{CH}_2\text{OH}$, reflux, 30 h. ii) $\text{H}_2\text{N-NH}_2$, $\text{CH}_3\text{CH}_2\text{OH}$ (sealed steel vessel), 70°C , 90 h.

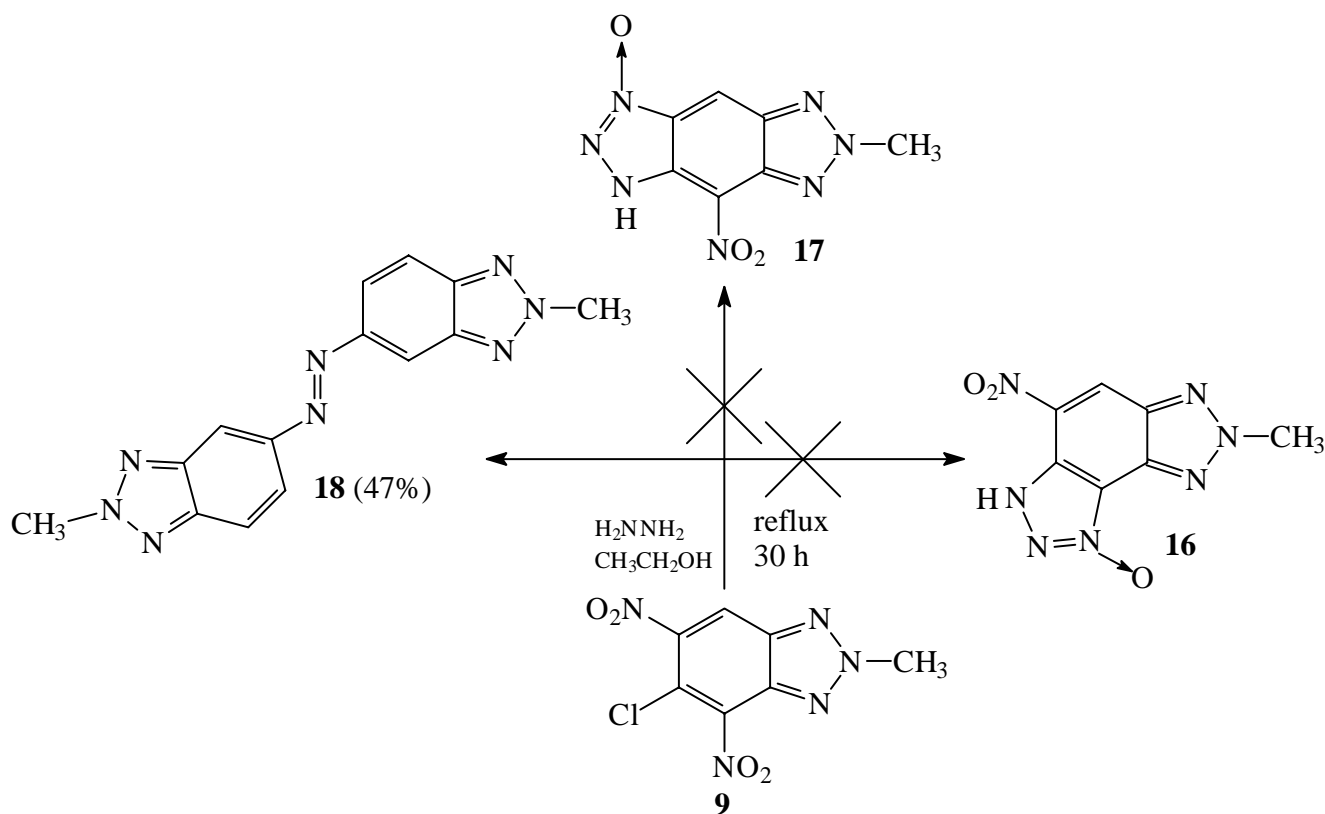
Scheme 2

In this way chlorine atom at position C-5 resulted more stable towards the nucleophile. In addition, in the case of **7**, steric hindrance of N3-methyl group might play a negative effect for the substitution reaction. In the light of this result we have to think that because this type of reaction does not take place even under more drastic conditions the hydrazine would behave as strongly reducing agent to cause displacement of

both chlorine and nitro group up to give rise to the above mentioned 1-methylbenzotriazole (**14**) and 2-methylbenzotriazole (**15**).

Confirmation of the role played by the electronreleasing effects of the methyl group on triazole nitrogen may come from the great difference in the yields recorded in the formation of **10** (80%) against that of **11** (33%) and in no formation of **12** and **13**.

We have also examined the reaction of **9** with hydrazine hydrate in refluxing ethanol since from this compound it would be reasonable to expect either a linear or angular ring closure to give **17** and/or **16**. Interestingly, the only compound isolated was the azocompound (**18**) in 47% yield (Scheme 3) that seems to exclude any chance of formation of a tricyclic system.



Scheme 3

No apparent reason out of a susceptibility of the nitro groups to the reducing conditions as experienced in the above cases of **7** and **8** accounts for the formation of **18**, that is supported by its analytical data and NMR spectra, *via* the suggested mechanism of Figure 1.

In our opinion the strongly activated chlorine atom would force the reaction of 2 moles of **9** with one mole of hydrazine to form the intermediate (**19**). Then the excess of base would displace the adjacent nitro groups in analogy with other described cases of dinitrobenzenes.³² Successive oxidation of hydrazo

to azo compound should be favoured by *ortho* quinonoid form of the benzotriazole moiety. All the structures of the described compounds were proved by the analytical data and $^1\text{H-NMR}$ spectra.

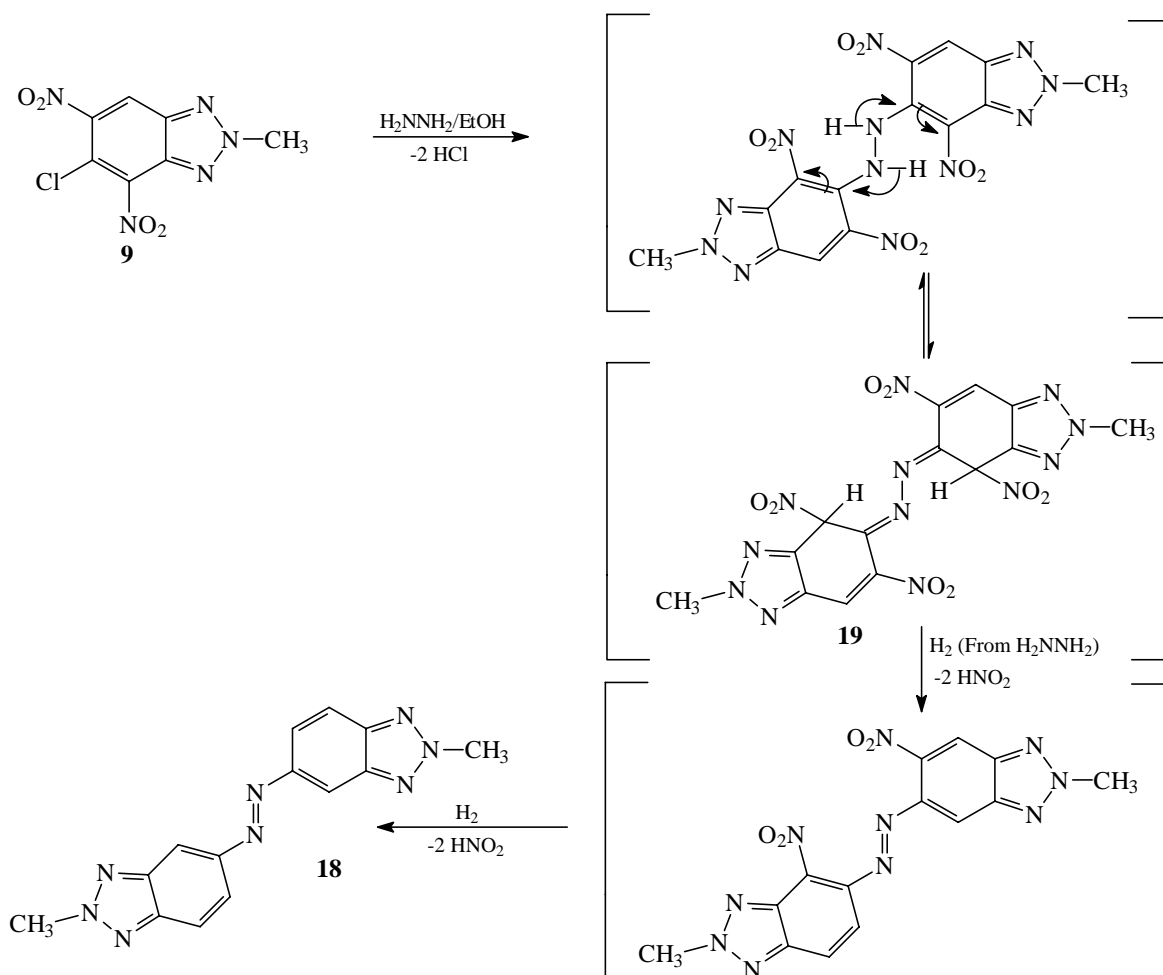


Figure 1

In particular the UV spectra were recorded to observe whatsoever influence of the nitro group on the starting 5-chlorobenzotriazoles. Compounds (**6**) and (**7**) exhibited very similar chromophores. The longest wavelength peaks appears between 270-280 nm while a second lowest peak appears between 250-240 nm. In the 2-methyl isomer (**8**) two very close maxima were recorded at 278, 272 nm. In comparison with the reported spectra of their precursors (**2**, **3** and **4**)¹² it must be noted that the extinction coefficients of the maxima at shortest wavelength (250-240 nm) in (**6**) and (**7**) resulted much lower than those at higher wavelength, where in compound (**8**) this difference could not be noted. From these data it is clear that the influence of the nitro group on the chromophore produced a very little hypsochromic effect. In the tricyclic compounds (**10**) and (**11**) does not seem to be present any characteristic difference. However, compound (**11**) in very concentrated solution exhibited a certain analogy with the spectra of

naphthotriazole previously reported.¹² The azo compound (**18**) did show a maximum at 274 nm as recorded in the above reported other cases while we could observe a hyperchromic effect on the peak at 232 nm.

In conclusion, from our experiments it emerges an easy and quite convenient synthesis of benzo[1,2-*d*:3,4-*d'*]bis-1,2,3-triazolo 1-oxides (**10** and **11**) as well as that of 5,5'-(*Z*)-diazene-1,2-diylbis(2-methyl-2*H*-1,2,3-benzotriazole) (**18**) starting from the commercially available 5-chlorobenzotriazole.

EXPERIMENTAL

Melting points are uncorrected and were taken in open capillaries in a Digital Electrothermal IA9100 melting point apparatus. ¹H-NMR spectra were recorded at 200 MHz using a Varian XL-200 spectrometer. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane as internal standard. MS spectra were performed on a combined HP 5790 (GC)-HP 5970 (MS) apparatus or with a combined Liquid Chromatograph-Agilent 1100 series Mass Selective Detector (MSD). Column chromatography was performed using 70-230 mesh (Merck silica gel 60). The progress of the reactions and the purity of the final compounds were monitored by TLC using Merck F-254 commercial plates. Light petroleum refers to the fraction with bp 40-60°C.

Nitration of 1*H*-benzotriazole

To a solution of benzotriazole (20 g, 168 mmol) in sulfuric acid (97-98 %) (68 mL), externally cooled with an iced bath, conc. nitric acid (17 mL, *d*=1.51) was slowly added taking care that the temperature did not exceed 30°C. Then the mixture was allowed to reach rt and stirred for an additional hour. Finally the reaction mixture was poured onto water and crushed ice (150 mL) to give a solid that was collected (25.4 g).

Tlc showed two spots. Crystallization of the crude mixture from acetone gave 16 g (58%) of 4-nitrobenzotriazole, mp 230-232°C identical with an authentic specimen described by Fries *et al.*²⁸ and Miller and Wagner.²⁹ From the mother liquors on evaporation it was obtained a mixture of two compounds.

This was then chromatographed on silica gel column eluting with ether to give in the order: 3.1 g of an inseparable mixture of 4- and 5-nitrobenzotriazoles and in the end 4 g (15%) of 5-nitrobenzotriazole, mp 210-211°C identical with an authentic specimen as described by Zincke *et al.*³³

Preparation of 5-chloro-1-methylbenzotriazole (**2**), 6-chloro-1-methylbenzotriazole (**3**) and 5-chloro-2-methylbenzotriazole (**4**)

To commercially available (Aldrich) 5-chlorobenzotriazole (**1**) (5.0 g, 32.6 mmol) dissolved in 2N NaOH (65 mL, 130 mmol) methyl sulfate (8.5 mL, 51 mmol) was added at rt under stirring within 30 min.

Stirring was continued for an additional 90 min. After then, the crude precipitate formed was purified by silica gel column chromatography eluting with a mixture of ether/light petroleum in the ratio 8:2. In this way we obtained in the order:

compound (**4**) (26 %) as a solid, mp 55-57 °C (ether) [lit.,¹² 55.5-57.5 °C]; ¹H-NMR (CDCl₃): δ 7.84 (d, 1H, *J* = 1.6 Hz, H-4), 7.79 (d, 1H, *J* = 9.0 Hz, H-7), 7.33 (dd, 1H, *J* = 9.0, 1.6 Hz, H-6), 4.50 (s, 3H, CH₃); MS *M/Z* 167, 169 (M⁺);

compound (**3**) (30 %) as a solid, mp 121-123 °C (ether) [lit.,¹² 121-123 °C]; ¹H-NMR (CDCl₃): δ 7.97 (d, 1H, *J* = 8.8 Hz, H-7), 7.54 (d, 1H, *J* = 1.6 Hz, H-4), 7.34 (dd, 1H, *J* = 8.8, 1.6 Hz, H-6), 4.28 (s, 3H, CH₃); MS *M/Z* 167, 169 (M⁺);

compound (**2**) (25 %) as a solid, mp 90-92 °C (ether) [lit.,¹² 97-99 °C]; ¹H-NMR (CDCl₃): δ 8.02 (d, 1H, *J* = 1.4 Hz, H-4), 7.47-7.45 (m, 2H, H-6 + H-7), 4.30 (s, 3H, CH₃); MS *M/Z* 167, 169 (M⁺).

Assignment of the exact structure for the isomers (**2-4**) came by application of nuclear Overhauser effect (nOe) procedure.

Nitration of the 5-chlorobenzotriazole (**1**) and its N-methyl derivatives (**2-4**)

ii (Scheme 1). KNO₃ (3.0 g, 30 mmol) in 15 mL of sulfuric acid (97-98 %) was dropwise added at rt to a stirred solution of the appropriate benzotriazole (**1-4**) (9 mmol) in 15 mL of sulfuric acid (97-98 %). Then, the reaction was heated at 50 °C and the stirring continued for additional 2.5 h. On cooling, the reaction mixture was poured into ice (100 mL) and the crude precipitate obtained was washed with water, and collected by filtration to afford the corresponding derivatives (**5-7**). In the case of compound (**4**) it was obtained a mixture of nitro derivatives (**8/9**) which was purified by flash chromatography on silica gel using ether as eluent. Yields, melting points, analytical and spectroscopical data are reported below.

5-Chloro-4-nitrobenzotriazole (5) (from **1**) (99 % yield); mp 215-217 °C (acetone); UV(EtOH): 286 nm; ¹H-NMR (CDCl₃+DMSO-d₆): δ 16.50 (br s, 1H, NH), 8.24 (d, 1H, *J* = 8.6 Hz, H-7), 7.60 (d, 1H, *J* = 8.6 Hz, H-6); MS *M/Z* 198, 200 (M⁺); Anal. Calcd for C₆H₃N₄O₂Cl: C, 36.29; H, 1.52; N, 28.22. Found C, 36.03; H, 1.65; N, 27.92.

5-Chloro-1-methyl-4-nitrobenzotriazole (6) (from **2**) (96 % yield); mp 125-127 °C (ether); UV(EtOH): 274, 255, 250sh nm; ¹H-NMR (CDCl₃): δ 7.70-7.57 (m, 2H, H-6 + H-7), 4.38 (s, 3H, CH₃); MS *M/Z* 212, 214 (M⁺); Anal. Calcd for C₇H₅N₄O₂Cl: C, 39.55; H, 2.37; N, 26.35. Found C, 39.89; H, 2.21; N, 26.01.

6-Chloro-1-methyl-4-nitrobenzotriazole (7) (from **3**) (79 % yield); mp 91-93 °C (ether); UV(EtOH): 279, 253, 243 nm; ¹H-NMR (CDCl₃): δ 8.16 (d, 1H, *J* = 8.8 Hz, H-7), 7.49 (d, 1H, *J* = 8.8 Hz, H-6), 4.26 (s, 3H, CH₃); MS *M/Z* 212, 214 (M⁺); Anal. Calcd for C₇H₅N₄O₂Cl: C, 39.55; H, 2.37; N, 26.35. Found C, 39.30; H, 2.50; N, 26.12.

5-Chloro-2-methyl-4-nitrobenzotriazole (8) (from **4**) (70 % yield); mp 161-163 °C (ether); UV(EtOH):

278, 272 nm; $^1\text{H-NMR}$ (CDCl_3): δ 8.01 (d, 1H, $J = 9.0$ Hz, H-7), 7.48 (d, 1H, $J = 9.0$ Hz, H-6), 4.58 (s, 3H, CH_3); MS M/Z 212, 214 (M^+); Anal. Calcd for $\text{C}_7\text{H}_5\text{N}_4\text{O}_2\text{Cl}$: C, 39.55; H, 2.37; N, 26.35. Found C, 40.02; H, 2.07; N, 26.30.

5-Chloro-2-methyl-4,6-dinitrobenzotriazole (9) (from **4**) (17 % yield); mp 123-125 °C (ether); UV(EtOH): 279, 226 nm; $^1\text{H-NMR}$ (CDCl_3): δ 8.60 (s, 1H, H-7), 4.66 (s, 3H, CH_3); MS M/Z 257, 259 (M^+); Anal. Calcd for $\text{C}_7\text{H}_4\text{N}_5\text{O}_4\text{Cl}$: C, 32.64; H, 1.57; N, 27.19. Found C, 33.01; H, 1.40; N, 26.92.

iii- Compounds (**4**) or (**8**) were submitted to nitration under the same conditions as in *ii*, but heating was prolonged for an additional 11.5 h, to afford the derivative (**9**) pure and in very high yield (95 %).

iv- When compounds (**4**) was submitted to nitration under the same conditions as in *ii*, but the reaction was carried out for 2 h at rt, afforded the derivative (**8**) pure in high yield (90 %).

Reaction of chloro-methyl-nitrobenzotriazoles (**5** - **9**) with hydrazine.

Method i (Scheme 2). A mixture of an opportune nitro derivative (**5**, **6**, or **9**) (2.5 mmol) and a large excess of 98 % hydrazine monohydrate (5.25 mL, 108 mmol) in ethanol (25 mL), was refluxed under stirring for 30 h. The reaction mixture was allowed to reach rt, then the solvent and the excess of hydrazine were removed *in vacuo* to give a crude precipitate which was taken up with acetone (25 mL) and stirred for an additional 30 min. A pure solid was obtained, filtered off and washed with acetone to give **10**, **11** and **18** respectively. Yields, melting points, analytical and spectroscopical data are reported below.

1H,6H-Triazolo[4,5-*e*]benzotriazole-3-oxide (10) (from **5**) (80 % yield); mp > 300 °C (ethanol); UV(EtOH): 274 nm; $^1\text{H-NMR}$ (DMSO-d_6): δ 16.40-16.10 (br s, 2H, 2 NH), 7.97 (d, 1H, $J = 9.2$ Hz, H-5), 7.80 (d, 1H, $J = 9.2$ Hz, H-6); LC/MS: 177 (M+H); Anal. Calcd for $\text{C}_6\text{H}_4\text{N}_6\text{O}$: C, 40.91; H, 2.29; N, 47.71. Found C, 40.59; H, 2.44; N, 47.98.

6-Methyl-1H,6H-triazolo[4,5-*e*]benzotriazole-3-oxide (11) (from **6**) (33 % yield); mp 280-282 °C (ethanol); UV(EtOH): 278sh, 250, 264sh, 230sh, 213 nm; $^1\text{H-NMR}$ (DMSO-d_6): δ 14.28 (s, 1H, NH), 8.08 (d, 1H, $J = 8.8$ Hz, H-5), 7.84 (d, 1H, $J = 8.8$ Hz, H-6), 4.43 (s, 3H, CH_3); LC/MS: 191 (M+H); Anal. Calcd for $\text{C}_7\text{H}_6\text{N}_6\text{O}$: C, 44.21; H, 3.18; N, 44.19. Found C, 40.01; H, 3.34; N, 43.90.

5,5'-(Z)-Diazene-1,2-diylbis(2-methyl-2H-1,2,3-benzotriazole) (18) (from **9**) (47 % yield); mp 186-187 °C (acetone); UV(EtOH): 274, 238sh, 231 nm; $^1\text{H-NMR}$ (DMSO-d_6): δ 8.87 (d, 2H, $J = 2.2$ Hz, H-4 + H-4'), 8.24 (dd, 2H, $J = 9.2$ e 2.2 Hz, H-6 + H-6'), 7.98 (d, 2H, $J = 9.2$ Hz, H-7 + H-7'), 4.61 (s, 6H, 2 CH_3); MS M/Z 292 (10 %) (M^+), 146 (100 %) ($1/2 \text{M}^+$); Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_8$: C, 57.53; H, 4.14; N, 38.34. Found C, 57.78; H, 4.31; N, 38.09.

ii- A mixture of nitro derivative (**7** - **8**) (2.5 mmol) and a large excess of 98 % hydrazine monohydrate (5.25 mL, 108 mmol) in ethanol (100 mL) was heated in a sealed steel vessel at 70°C for 90 h. On cooling, after removal of the solvent and the excess of hydrazine under reduced pressure a crude solid was obtained. Chromatography on silica gel column eluting with a mixture of light petroleum/ethyl acetate (6:4 ratio) gave 1-methylbenzotriazole (**14**) (32 % yield) from **7** and 2-methylbenzotriazole (**15**) (30 % yield) from **8** respectively which were identical with the authentic specimens previously described.³¹

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