SYNTHESIS AND STABILITY OF 5-, 7- AND 8-SUBSTITUTED BENZO-1,2,3,5-TETRAZEPIN-4-ONES

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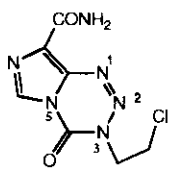
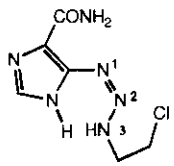
Abstract- In order to determine the effect of substituents on the stability of benzo-fused 1,2,3,5-tetrazepin-4-ones, 5-, 7- and 8-substituted derivatives (**6a-d**), and (**10**) were synthesized. The stability of the tetrazepinones increased with the electron withdrawing character of the substituents at the benzene ring. Bulky groups at the 5 position destabilize the tetrazepinone ring. The unstable tetrazepinones (**6b**, **10** and **14**) decomposed in chloroform at room temperature to benzotriazole derivatives (**11**, **12** and **15**). X-Ray diffraction of nitrobenzotetrazepinone (**6d**) showed that despite the elctron withdrawing effect of the nitro group *para* to the triazene chain, N3 exhibited a significant pyramidal character. In **6d**, the 1,2,3,5-tetrazepinone cycle has an almost perfect seven-membered ring boat shape.

The discovery of the antitumour activity of imidazo-1,2,3,5-tetrazin-4-one (**A**)[1] (mitozolomide) has stimulated interest in designing and synthesizing compounds containing the N=N-N(alkyl)CO moiety.[2-4] Because mitozolomide can be hydrolyzed to the active monoalkyltriazene[5] (**B**), it does not need metabolic activation to show cytotoxicity. We have already reported the synthesis of bi-cyclic compound **C**[4] featuring the novel 1,2,3,5-tetrazepin-4-one ring. This system contains the potential pro-monoalkyltriazene N=N-N-(alkyl)-CO-N moiety which is essential for the antitumour activity of mitozolomide.[5,6]



A



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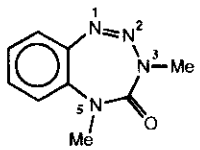
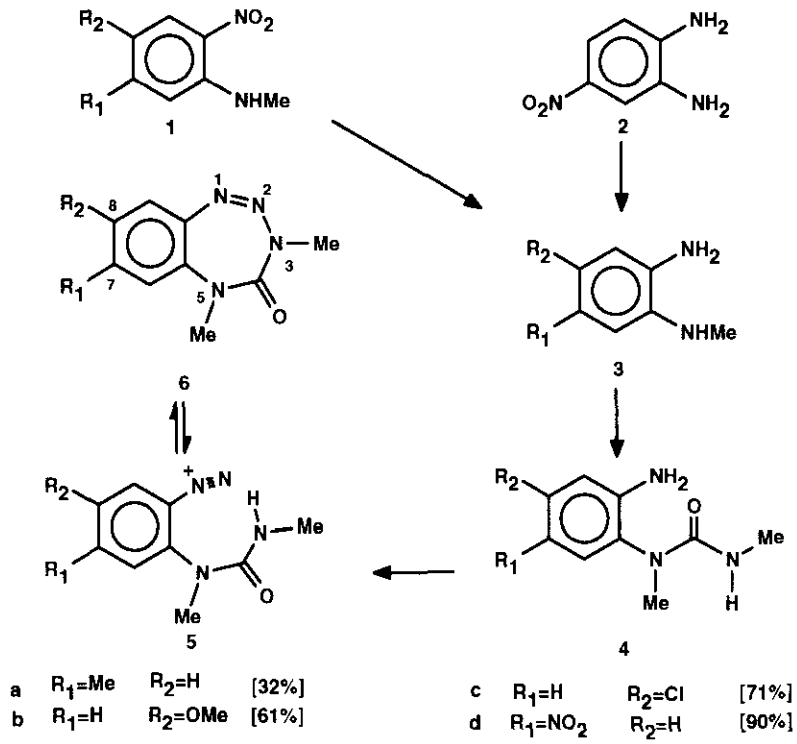


C

We now report the synthesis of bi-cyclic tetrazepinones (**6**) bearing substituents on the benzene ring and on N-5. Our goal was to determine the effect of these substituents on the stability of the benzo-fused

seven-membered ring.

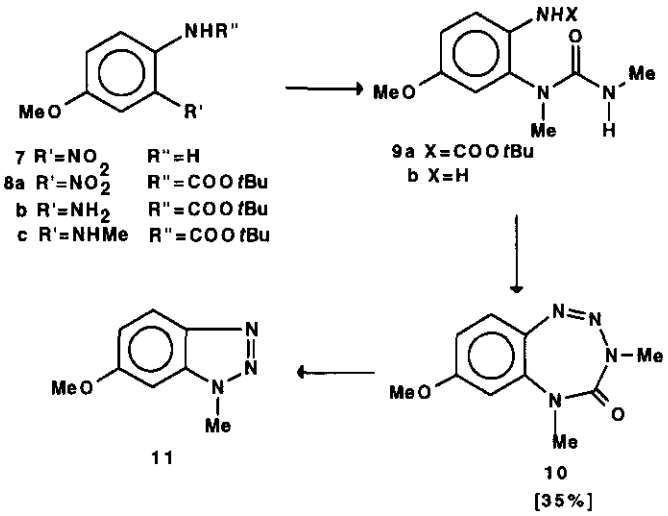
The synthesis of **6a-c**, proceeded according to Scheme 1. *N*-Methyl-2-nitroanilines (**1a-c**), obtained from the treatment of the corresponding 2-nitroanilines with sodium hydride followed by addition of methyl iodide, were hydrogenated catalytically to diamines (**3a-c**). Selective carbamoylation[4] at the *N*-methylamino group by reaction with methyl isocyanate gave ureas (**4a-c**). Diazotization of the resulting ureas with a sodium nitrite solution containing $Na^{15}NO_2$, when labelling was required,[4,7-10] and adjustment of the pH to 8, provided the tetrazepinones (**6a-c**) in the yields given in Scheme 1.



Scheme 1

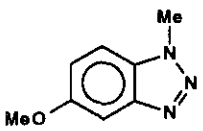
Similarly, 5-nitro-1-(*N*-methyl)-1,2-phenylenediamine (**3d**), obtained from the direct methylation of **2** with methyl iodide under basic condition, was carbamoylated to give aminourea (**4d**) which was converted to **6d** in almost quantitative yield. Tetrazepinone (**6d**) was isolated at pH 6. The synthesis of tetrazepinone (**10**) bearing a methoxy group *para* to the triazene moiety, proceeded according to Scheme 2. 2-Nitro-4-methoxyaniline (**7**) was treated with NaH and di-*tert*-butyl dicarbonate to give urethane (**8a**), the nitro group of which was catalytically reduced to the corresponding amine (**8b**). The latter was methylated to yield **8c**, which was treated with methyl isocyanate to provide urea (**9a**). Deprotection of **9a** in trifluoroacetic acid, followed by neutralization, gave amine (**9b**). Diazotization and adjustment of the pH to 8 gave tetrazepinone (**10**) in 35 % yield (crude) as a brown powder that decomposed slowly at room temperature. The major product isolated from the decomposition of **10**, after one week standing at

room temperature, was found to be benzotriazole (**11**), the structure of which was confirmed by ^{1}H NMR and MS data.



Scheme 2

The structures of compounds (**6a-d**) and (**10**) were assigned on the basis of ^{1}H, ^{13}C, ^{15}N NMR spectra and elemental analysis. The presence of the diazonium species (**5**) was confirmed by ^{15}N NMR, which showed a peak at around -60 ppm[11,12] for the N-2 label following diazotization at acidic pH. The N-2 label of **6a-d** and **10** which we were able to extract from the solution only at neutral or basic pHs appeared in the 63-80 ppm range (downfield from nitromethane). A detailed analysis of the natural abundance ^{15}N NMR of the 3,5-dimethylbenzotetrazepinones reported elsewhere.[26] In the ^{1}H NMR spectra, the two ureido methyl groups of the tetrazepinones appeared at around 3.25 ppm (NMeCO) and 3.40 ppm (N=NNMe). In the ^{13}C NMR spectra, they appeared at around 35 ppm and 37 ppm respectively. Satisfactory NMR spectra were obtained for the unstable tetrazepinone (**10**) when taken with freshly prepared samples.



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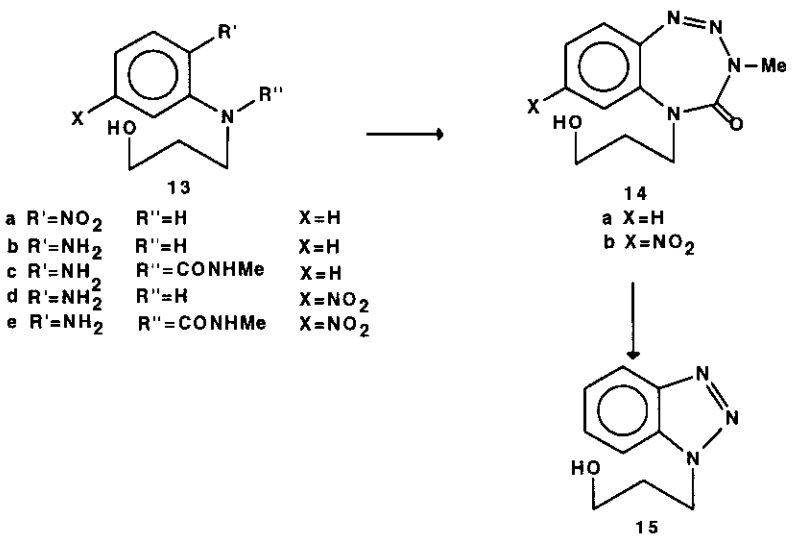
The X-Ray structure of **6d**, which was the most stable tetrazepinone of this series, shows that its fused 1,2,3,5-tetrazepinone ring has an almost perfect seven-membered ring boat shape (Figure 1). Although the nitro group is *para* to the triazene chain, it does not seem to affect greatly the pyramidality of N-3 in the solid. The bond distance N(2)-N(3) (1.446 (7) Å) suggests a single bond character of this linkage, and the pyramidality of bonding about N-3 suggests a somewhat sp^3 character for this nitrogen. These

results contrast with those reported for open-chain benzo- or imidazotriazenes[13,14] and mitozolomide **A**[15] in which bond lengths of N(2)-N(3) (1.305 Å, 1.309 Å, 1.374 Å), and the planarity of bonding around N-3, indicate its considerable sp^2 character. These results suggest that the triazene chain in tetrazepinones is only weakly conjugated with the phenyl ring or that the lone pair of N-3 is only delocalized to a minor extent.



Scheme 3

Tetrazepinones (**6a**, **b**, and **10**) bearing an electron donating group decomposed in chloroform, as confirmed by their ^{15}N NMR spectra which showed an additional peak at around -5 ppm for the ^{15}N label. We were able to isolate benzotriazole (**12**) from the decomposition of **6b**. Its structure was assigned on the basis of ^{1}H NMR and elemental analysis. Tetrazepinones (**6c** or **6d**) bearing electron withdrawing groups and the unsubstituted structure **C** were stable at room temperature both in the solid and in solution.

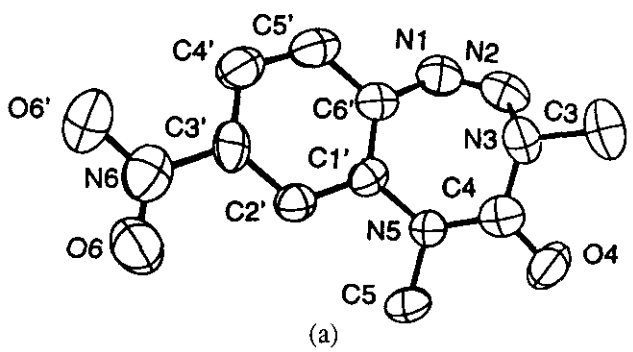
Having established that electron withdrawing groups stabilized the tetrazepinones, we proceeded to attach larger groups at N-5 in an effort to mimic nucleosides. It is now known that analogues in which the sugar moiety is replaced by 2-hydroxyethoxymethyl groups,[16,17] aliphatic alcohols and carbocyclic systems[18,19] can be potent antiviral drugs.

The synthesis of compound (**14a**), as shown in Scheme 3, proceeded according to Scheme 1. 2-Chloronitrobenzene was allowed to react with 3-aminopropanol to give **13a**, which was catalytically hydrogenetated to **13b**. The latter compound was treated with methyl isocyanate to give aminourea (**13c**) which was diazotized with [5 % ^{15}N] $NaNO_2$ to provide the corresponding diazonium salt specifically labelled at *N*-2. Adjustment of the pH to 8, followed by multiple extractions, gave **14a** as a clear oil that decomposed over a period of a few hours at room temperature, as observed by the appearance of an

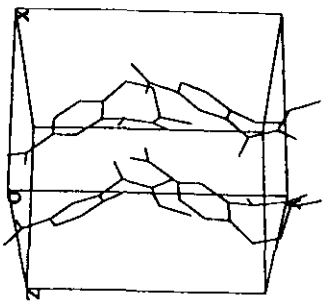
additional peak at around -5 ppm in its ^{15}N NMR spectrum, characteristic of *N*-2 in benzotriazole derivatives (Figure 2a-b). The decomposition product was isolated and assigned the benzotriazole structure (**15**) on the basis of NMR and high resolution MS data.

Table 1. Selected Bond Lengths (Å) and Angles (degree) of **6d**

Bond Length (Å)			
O (4) - C (4)	1.228 (9)	N (5) - C (5)	1.466 (6)
O (6) - N (6)	1.205 (7)	N (5) - C (1')	1.407 (9)
O (6') - N (6)	1.227 (8)	N (6) - C (3')	1.473 (10)
N (1) - N (2)	1.253 (10)	C (1') - C (2')	1.383 (10)
N (1) - C (6')	1.409 (9)	C (1') - C (6')	1.399 (8)
N (2) - N (3)	1.446 (7)	C (2') - C (3')	1.389 (9)
N (3) - C (3)	1.489 (9)	C (3') - C (4')	1.374 (9)
N (3) - C (4)	1.419 (8)	C (4') - C (5')	1.375 (11)
N (5) - C (4)	1.361 (10)	C (5') - C (6')	1.384 (10)
Bond Angle (o)			
N (2) - N (1) - C (6')	122.5 (5)	N (3) - C (4) - N (5)	116.2 (6)
N (1) - N (2) - N (3)	117.4 (5)	N (5) - C (1') - C (2')	119.9 (5)
N (2) - N (3) - C (3)	108.0 (5)	N (5) - C (1') - C (6')	120.3 (6)
N (2) - N (3) -C (4)	114.5 (5)	C (2') - C (1') - C (6')	119.6 (6)
C (3) - N (3) - C (4)	114.3 (6)	C (1') - C (2') - C (3')	117.7 (5)
C (4) - N (5) - C (5)	115.3 (5)	N (6) - C (3') - C (2')	117.0 (5)
C (4) - N (5) - C (1')	121.5 (5)	N (6) - C (3') - C (4')	119.0 (6)
C (5) - N (5) - C (1')	119.0 (6)	C (2') - C (3') - C (4')	124.1 (6)
O (6) - N (6) - O (6')	123.6 (7)	C (3') - C (4') - C (5')	116.9 (6)
O (6) - N (6) - C (3')	119.0(6)	C (4') - C (5') - C (6')	121.4 (5)
O (6') - N (6) - C (3')	117.5 (5)	N (1) - C (6') - C (1')	124.2 (6)
O (4) - C (4) - N (3)	120.5 (7)	N (1) - C (6') - C (5')	115.2 (5)
O (4) - C (4) - N (5)	123.3 (6)	C (1') - C (6') - C (5')	120.1 (7)



(a)



(b)

Figure 1. (a) ORTEP[24] view of the X-Ray structure for **6d** (50 % probability ellipsoid). For clarity, hydrogen atoms have been omitted; (b) Stereoview of the contents of the unit cell of **6d**.

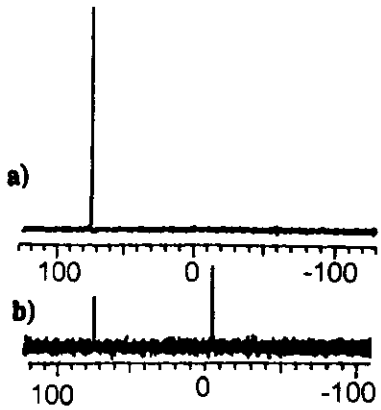
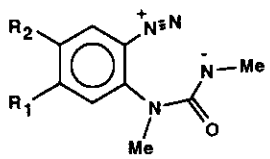


Figure 2. a)^{15}N NMR of the N-2 label of freshly prepared tetrazepinone (**14a**) in $CDCl_3$ (decoupled)
b)^{15}N NMR of tetrazepinone (**14a**) after standing (dry) at room temperature overnight. (Another peak appeared in the -5 ppm region, indicating decomposition to benzotriazole (**15**)).

Since a nitro group on the benzene ring stabilizes the tetrazepinone ring systems, we therefore synthesized **14b** in a similar manner. 4-Nitro-1,2-phenylenediamine was treated with 3-bromopropanol to give **4d** which was carbamoylated with methyl isocyanate to provide **13e**. The diazotization of the latter aminourea followed by adjustment of the pH to 6 gave tetrazepinone (**14b**) as a pale yellow oil, which was stable at room temperature. In contrast to **5a**, tetrazepinone (**5b**) could be kept at room temperature for 5 days without decomposing. Attachment of a cyclopentyl group to N-5 by similar method resulted in the formation of highly unstable tetrazepinones.[25]



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Previous X-Ray crystallographic data indicated that the torsion angle between the N1-H bond and the plane of the aromatic ring in *N*-(2-aminophenyl)-*N'*-methylurea was 58.92°.[28a-b] Owing to steric hindrance, we believe that bulky groups at the tetrazepinone N5 as in **14** may assume a much larger torsion angle with the plane of the phenyl ring. This may force the tetrazepinone ureido portion to adopt an orientation that may cause an elongation of the N2N3 bond and thereby destabilize the tetrazepinone ring. Ring opening in solution would generate a zwitterion of type (**16**) that can undergo rapid cyclization to benzotriazole derivatives and subsequent loss of methyl isocyanate. Similarly, due the stabilizing effect exerted by the para methoxy group on the diazonium ion in species (**16**), the electron-rich tetrazepinone (**10**) may preferentially exist as an acyclic diazonium urea and this may explain its rapid conversion to the corresponding benzotriazole in solution and in the solid. In **6b**, the methoxy

group which is para to N5 may enchance electron donating character of the latter and thereby accelerate its addition to the neighboring diazonium ion to give **12**. Inversely, electron withdrawing substituents (e.g. Cl, NO_2) which destabilize the diazonium ion and decrease the electron donating character of N5 stabilize tetrazepinones. Detailed studies on the mechanisms of tetrazepinone decomposition *via* their cyclic/acyclic equilibria are now available.[26,27]

In summary, this study demonstrates that the 1,2,3,5-tetrazepin-4-one ring is stabilized by electron withdrawing groups on the phenyl ring, and destabilized by electron donating groups and large substituents at N-5. Electron delocalization in the triazene moiety may contribute only little to the stability of the tetrazepinone ring system. The unstable tetrazepinones decompose to benzotriazole derivatives at room temperature.

EXPERIMENTAL

Melting points were measured on a Gallenkamp block and are uncorrected. Thin-layer and flash chromatography were performed on silica gel 60 F_{254} aluminum plates and Merck Silica Gel 60 (230-400 mesh) respectively. ^{1}H NMR spectra were recorded on a Varian XL-200 at 200 MHz. ^{13}C NMR spectra were obtained at 75.40 MHz on a Varian XL-300. All ^{1}H NMR spectra were run either in $CDCl_3$ or in DMSO-d_6. Chemical shifts are reported downfield from tetramethylsilane (TMS) and all coupling constants are in Hz. Low resolution chemical ionization (CI) MS spectra were recorded on a Kratos MS25RFA, double focusing mass spectrometer in the direct inlet mode. All compounds were shown to be homogeneous by TLC and high-field NMR. Unless otherwise stated, all reaction extracts were dried over anhydrous potassium carbonate. The 2-nitroanilines were purchased from Aldrich Chemical Company.

^{15}N NMR spectra were recorded on a Varian XL-300 at 30.40 MHz and chemical shifts are reported up- and downfield from nitromethane, which was used as the external standard. The 90 ^{o} pulse width was 18 μs and the pulse interval was set at 3s. The temperature of the probe was maintained at 0 ^{o}C for the spectra of diazonium salts and at 20 ^{o}C for the natural abundance spectra. Spectra were obtained after 100 scans for the ^{15}N enriched compounds when sample concentrations were around 0.10 M in $CDCl_3$ (gated coupled) and after about 9000 scans for natural abundance spectra at concentrations around 0.5 M. All reactions were monitored by thin layer chromatography (TLC).

5-Methyl-1-(*N*-methyl)-2-phenylenediamine (3a). A solution of 5-methyl-2-nitroaniline (3 g, 20 mmol) in dimethylformamide (DMF) (50 mL) was treated with NaH (60% oil dispersion) (1 g, 25 mmol). When gas evolution ceased, methyl iodide (1.2 mL, 19 mmol) was added dropwise at 0 ^{o}C and the solution was stirred for 1 h after which it was diluted with cold water (100 mL). *N*-5-Dimethyl-2-nitroaniline (**1a**)

precipitated as yellow crystals which were dried under vacuum (3 g, 92 %); TLC (20 % ethyl acetate in hexane), Rf=0.5; mp. 90 °C; δ_H (200 MHz; $CDCl_3$) 8.03 (1H, d, *J*=9, Ar), 6.58 (1H, s, Ar), 6.43 (1H, d, *J*=9, Ar) 6.10 (1H, br s, N*H*CH_3), 2.98 (3H, d, *J*=5, NHC*H*$_3$), 2.33 (3H, s, ArC*H*$_3$); MS *m/z* (CI, isobutane) 167 (MH^+, 100 %) .

A mixture of **1a** (2.5 g) and 10 % Pd-C (500 mg) in methanol (25 mL) was hydrogenated at 2 atm. Filtration and evaporation gave **3a** as a brown liquid in quantitative yield (2 g), TLC (10 % methanol in methylene dichloride), Rf=0.50; δ_H(200 MHz; $CDCl_3$) 6.60 (1H, d, *J*=8, Ar), 6.45 (2H, overlap of d and s, Ar), 3.20 (3H, br s, NH, NH_2), 2.83 (3H, s, NHC*H*$_3$), 2.25 (3H, s, ArC*H*$_3$). (*N*-Alkyl-1,2-phenylene diamines darken when exposed to light; they must be used immediately after their preparation)

4-Methoxy-1-(*N*-methyl)-1,2-phenylenediamine (3b). As described for **3a**, the 4-methoxy-*N*-methyl-2-nitroaniline (**1b**) was obtained as reddish needles (2 g, 92 %) from the treatment of 4-methoxy-2-nitroaniline (2 g, 12 mmol) with NaH (60% oil dispersion) (0.6 g, 15 mmol) and methyl iodide (0.9, 13 mmol) in DMF (50 mL), mp 120 °C; TLC (80 % hexane in ethyl acetate), Rf=0.5; δ_H(200 MHz; $CDCl_3$) 8.00 (1H, br s, N*H*CH_3), 7.60 (1H, d, *J*=3, Ar), 7.17 (1H, dd, *J*=3, *J*=9, Ar), 6.80 (1H, d, *J*=9, Ar), 6.10 (1H, br s, N*H*CH_3), 3.80 (3H, s, *J*=3, OCH_3), 3.01 (3H, d, *J*=4, NHC*H*$_3$); MS *m/z* (CI, isobutane) 183 (MH^+, 100 %).

A mixture of **1b** (1.9 g) and 10 % Pd-C (350 mg) in methanol (20 mL) was hydrogenated at 2 atm. Filtration and evaporation gave **3b** as a brown liquid in quantitative yield (1.5 g); TLC (10 % methanol in methylene dichloride), Rf=0.8; δ_H(200 MHz; $CDCl_3$) 6.80 (1H, d, *J*=9, Ar), 6.25 (1H, s, Ar), 6.20 (1H, d, *J*=9, Ar), 3.70 (3H, br s, NH, NH_2), 2.70 (3H, s, NHC*H*$_3$).

4-Chloro-1-(*N*-methyl)-1,2-phenylenediamine (3c). The *N*-methyl-2-nitroaniline (**1c**) was obtained from the treatment of 2-chloro-4-nitroaniline (2 g, 12 mmol) with methyl iodide (0.8 mL, 13 mmol) and NaH (60% oil dispersion) (0.6 g, 15 mmol) in DMF (50 mL), as yellow needles (2 g, 90 %), mp 100 °C; TLC (80 % hexane in ethyl acetate), Rf=0.5; δ_H(200 MHz; $CDCl_3$) 9.14 (1H, d, *J*=3, Ar), 8.60 (1H, br s, N*H*CH_3), 8.30 (1H, dd, *J*=3, *J*=10, Ar), 6.92 (d, 1H, *J*=10, Ar), 3.15 (3H, d, *J*=5, NHC*H*$_3$); MS *m/z* (CI, isobutane) 187 (MH^+, 100 %) .

A mixture of **1c** (1.9 g) and 10 % Pd-C (350 mg) in methanol (20 mL) was hydrogenated at 3 atm. Filtration and evaporation gave **3c** as a brown liquid in quantitative yield (1.5 g); TLC (10 % methanol in methylene dichloride), Rf=0.7; δ_H(200 MHz; $CDCl_3$) 6.80 (2H, overlap of d and s, *J*=8, Ar), 6.50 (1H, d, *J*=8, Ar) 3.40 (3H, br s, NH, NH_2), 2.80 (3H, d, *J*=5, NHC*H*$_3$).

5-Nitro-1-(*N*-methyl)-2-phenylenediamine (3d). To a solution of 4-nitro-1,2-phenylenediamine (**2**) (6 g, 39.2 mmol) in DMF (50 mL) was added dropwise methyl iodide (2 mL, 32 mmol) and saturated

sodium carbonate (10 mL). The solution was stirred overnight and the solvent was evaporated under vacuum. The dark-red residue that resulted was chromatographed on silica gel (30% hexane in ethyl acetate) to give **3d** (4 g, 48 %) as a yellow solid; mp 120 °C; TLC (40 % hexane in ethyl acetate), Rf=0.30; δ_H(200 MHz; $CDCl_3$) 7.68 (1H, d, *J*=7, Ar), 7.50 (1H, s, Ar), 6.65 (d, *J*=7, Ar), 3.90 (2H, br s, NH_2), 3.20 (1H, br s, N*H*CH_3), 2.90 (3H, d, *J*=4, NHC*H*$_3$); MS *m/z* (CI, isobutane) 168 (MH^+, 100 %).

***N*-(2-Amino-5-methylphenyl)-*N,N'*-dimethylurea (4a).** A solution of **3a** (2.2 g, 16.2 mmol) in methylene dichloride (100 mL) was treated with methyl isocyanate (1 mL, 17 mmol) at rt. The mixture was kept overnight and evaporated under reduced pressure. Purification by column chromatography (5 % methanol in methylene dichloride) gave **4a** (2 g, 64 %) as a pale brown powder, mp 118 °C; δ_H(200 MHz; $CDCl_3$) 6.95 (1H, d, *J*=8, Ar) 6.85 (1H, s, Ar), 6.72 (1H, d, *J*=8, Ar), 4.25 (1H, br s, CON*H*CH_3), 3.7 (2H, br s, NH_2), 3.15 (3H, s, ArC*H*$_3$NCO), 2.71 (3H, d, *J*=5, CONHC*H*$_3$), 2.2 (3H, s, ArC*H*$_3$); δ_C(75.40 MHz; $CDCl_3$) 158.28 (s), 141.24 (s), 129.87 (d), 128.88 (d), 128.46 (s), 127.42 (s), 116.52 (d), 36.43 (q), 27.43 (q), 20.21 (q).

***N*-(2-Amino-4-methoxyphenyl)-*N,N'*-dimethylurea (4b).** As described for **4a**, a solution of **3b** (1 g, 7 mmol) and methyl isocyanate (0.4 mL, 7 mmol) in methylene dichloride (50 mL) afforded after purification by column chromatography (5 % methanol in methylene dichloride) **4b** (1.2 g, 86.4 %) as a white powder, mp 135 °C; δ_H(200 MHz; $CDCl_3$) 6.92 (1H, d, *J*=8, Ar), 6.31 (1H, s, Ar), 6.30 (1H, d, *J*=8, Ar), 4.40 (1H, br q, CON*H*CH_3), 3.70 (3H, s, OCH_3), 3.15 (3H, s, ArNC*H*$_3$CO), 2.71 (3H, d, *J*=4.5, CONHC*H*$_3$); δ_C (75.4 MHz; $CDCl_3$) 158.09 (s), 152.95 (s), 137.35 (s), 128.37 (s), 117.5 (d), 115.61 (d), 113.62 (d), 55.80 (q), 35.47 (q), 27.54 (q).

***N*-(2-Amino-4-chlorophenyl)-*N,N'*-dimethylurea (4c).** As described for **4a**, a solution of **3c** (2 g, 14 mmol) and methyl isocyanate (1 mL, 17 mmol) in methylene dichloride (100 mL) gave after purification by column chromatography (5 % methanol in methylene dichloride) **4c** (2.1g, 75 %) as a white powder; mp 150 °C; δ_H(200 MHz; $CDCl_3$) 6.85 (1H, d, *J*=8, Ar), 6.75 (1H, d, *J*=2, Ar), 6.67 (1H, dd, *J*=2, *J*=8), 4.40 (1H, br q, CON*H*CH_3), 4.20 (2H, s, NH_2), 3.15 (3H, s, ArNC*H*$_3$CO), 2.70 (d, 2H, *J*=4 CONHC*H*$_3$); δ_C (75.4 MHz; $CDCl_3$) 159.38 (s), 146.33 (s), 136.00 (s), 131.30 (d), 127.24 (s). 120.14 (d), 117.23 (d), 36.80 (q), 28.85 (q).

***N*-(2-Amino-5-nitrophenyl)-*N,N'*-dimethylurea (4d).** A solution of **3d** (680 mg, 4.12 mmol) in acetonitrile (15 mL) was treated with methyl isocyanate (0.30 mL, 5 mmol) and kept overnight without stirring. The resulting pale yellow precipitate was filtered and dried under vacuum to give **4d** (650 mg, 72 %) as a yellow powder; mp 180-185 °C; δ_H(200 MHz; DMSO-d_6) 8.39 (1H, dd, *J*=3, *J*=9), 8.36 (1H, d,

J=3, Ar), 7.23 (1H, d, *J*=9, Ar), 7.11 (2H, br s, NH_2), 6.30 (1H, br q, *J*=5, *H*NCH_3), 3.40 (3H, s, ArNCH_3CO), 2.99 (3H, d, *J*=5, $CONHCH_3$); δ_C(75.4 MHz; $CDCl_3$) 157.17 (s), 152.60 (s), 135.60 (s), 126.37 (d), 126.14 (s), 125.00 (d), 114.01 (d), 35.12 (q), 26.70 (q).

3,5,7-Trimethyl-*3H*-1,2,3,5-benzotetrazepin-4(*5H*)-one (6a). Urea **4a** (1g, 5.55 mmol) was dissolved in 2N HCl (20 mL) and diazotized with 20 % aqueous [5 %^{15}N] $NaNO_2$ (2 mL); (enrichment was obtained by mixing 20 mg of $Na^{15}NO_2$ with 380 mg of $NaNO_2$). The solution was extracted three times with methylene dichloride. After adjusting its pH to 8, the aqueous layer was re-extracted with hexanes (6x100 mL). The solvent was evaporated to give **6a** (360 mg, 36 %) as a pale brown powder, mp 60 °C; Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.8; H, 5.9; N, 27.4. Found: C, 59.2; H, 5.9; N, 27.2; IR ν_{max} (MeOH)/cm^{-1} 3000 (CH), 1682 (C=O); UV (methanol) λ_{max} /nm (log ε): 240 (4.04) 374 (3.77); δ_H(200 MHz; $CDCl_3$) 7.30 (1H, d, *J*=8, Ar), 7.04 (1H, d, *J*=8, Ar), 6.90 (1H, s, Ar), 3.37 (3H, s, $N{=}NNCH_3$), 3.26 (3H, s, Ar$N(CH_3)CO$), 2.40 (3H, s, ArCH_3); δ_C(75.40 MHz; $CDCl_3$) 160.77 (s), 143.30 (s), 140.46 (s), 139.59 (s), 128.30 (d), 126.56 (d), 121.27 (d), 38.05 (q), 36.25 (q), 22.86 (q). δ^{15}_N(30.40 MHz; $CDCl_3$) 45.10 (N1), 71.2, -5 triazole).

3,5-Dimethyl-8-methoxy-*3H*-1,2,3,5-benzotetrazepin-4(*5H*)-one (6b). Urea **4b** (0.7 g, 3.6 mmol) in 2N HCl (10 mL) was diazotized with 20 % aqueous [5 % ^{15}N] $NaNO_2$ (1.3 mL). The mixture was extracted with three 20 mL portions of methylene dichloride. The pH of the aqueous layer was adjusted to 8 with a saturated aqueous sodium carbonate solution, and the resulting precipitate was extracted with methylene dichloride (5 x 25 mL). The solution was dried over anhydrous potassium carbonate, filtered and evaporated to give **6b** as a brown powder; mp 109 °C. Anal. Calcd for $C_{10}H_{12}N_4O_2$: C, 54.5; H, 5.5; N, 25.4. Found: C, 54.5; H, 5.5; N, 25.3; IR $\nu_{max}(CDCl_3)/cm^{-1}$ 3000 (CH) 1690 (C=O); UV λ_{max} (MeOH)/nm (log ε) 238 (4.24), 302 (3.46); δ_H(200 MHz; $CDCl_3$) 7.05 (overlap of d, 2H, *J*=9, Ar), 7.10 (1H, s, Ar), 3.85 (3H, s, OCH_3), 3.40 (3H, s, $N{=}NNCH_3$), 3.25 (3H, s, Ar$N(CH_3)CO$); δ_C(75.40 MHz; $CDCl_3$) 159.37 (s), 155.34 (s), 141.97 (s), 131.45(s), 120.49 (d), 118.61 (d), 109.60 (d), 55.73 (q), 36.80 (q), 34.94 (q). $\delta^{15}_{N\text{-}2}$(30.40 MHz; $CDCl_3$) 74.6, -5 (triazole).

3,5-Dimethyl-8-chloro-*3H*-1,2,3,5-benzotetrazepin-4(*5H*)-one (6c). As described for **6b**, diazotization of **4c** (1.2 g, 5.61 mmol) with $NaNO_2$ (0.387 g) in 2N HCl (15 mL) afforded **6c** (0.9 g, 71.3 %) as a brown powder, mp 85 °C. Anal. Calcd for $C_9H_9N_4OCl$: C, 48.1; H, 4.0; N, 24.5. Found: C, 48.0; H, 4.0; N, 24.5; IR $\nu_{max}(CDCl_3)/cm^{-1}$ 3000 (CH) 1696 (C=O); UV λ_{max} (MeOH)/nm (log ε) 260 (3.76), 291 (3.28); δ_H(200 MHz; $CDCl_3$) 7.40 (1H, s, Ar), 7.35 (1H, d, *J*=9, Ar), 7.05 (1H, d, *J*=9, Ar), 3.40 (3H, s,

N=NNCH$_3$), 3.25 (3H, s, ArN(C*H*$_3$)CO); δ_C(75.40 MHz; $CDCl_3$) 159.06 (s), 141.95(s), 136.97 (s) 131.08 (d), 129.61 (s), 128.63 (d), 120.96 (d), 36.90 (q), 35.04 (q). $\delta^{15}_{N\text{-}2}$(30.40 MHz; $CDCl_3$) 75.30.

3,5-Dimethyl-7-nitro-*3H*-1,2,3,5-benzotetrazepin-4(*5H*)-one (6d). A solution of **4d** (1.2 g, 5.35 mmol) in 2N HCl (15 mL) was treated with 20 % aqueous [5 % ^{15}N] $NaNO_2$ (2 mL). The pH of the aqueous layer was adjusted to 6 and the resulting precipitate was extracted with methylene dichloride (6 x 20 mL). The solvent was dried over anhydrous sodium carbonate and evaporated to give **6d** (1.13 g, 90 %) as a pale yellow powder which was recrystallized from methylene dichloride: yellow needles, mp 119 °C. Anal. Calcd for $C_9H_9N_5O_3$: C, 46.0; H, 3.9; N, 29.8. Found: C, 46.1; H, 3.7; N, 29.6; IR $\nu_{max}(CDCl_3)/cm^{-1}$ 3000 (CH) 1702 (C=O); UV λ_{max} (MeOH)/nm 248 (4.01) 316 (3.63); δ_H(200 MHz; $CDCl_3$) 8.20 (1H, d, *J*=8, Ar), 8.00 (1H, s, Ar), 7.80 (1H, d, *J*=8, Ar), 3.40 (3H, s, N=NNCH$_3$), 3.25 (3H, s, ArN(C*H*$_3$)CO); δ_C(75.4 MHz; $CDCl_3$) 158.80 (s), 146.50 (s), 144.50 (s), 139.50 (s), 128 (d), 118.50 (d), 114.8 (d), 36.70 (q), 34.50 (q). $\delta^{15}_{N\text{-}2}$(30.40 MHz; $CDCl_3$) 80.40.

4-Methoxy-2-nitro-*N*-*tert*-butoxycarbonylaniline (8a). To a solution of 4-methoxy-2-nitroaniline **7** (4 g, 24 mmol) in THF (25 mL) was added NaH (50% oil dispersion) (1 g, 25 mmol) in portions . When the gas evolution ceased, di-*tert*-butyl dicarbonate (7.2 g, 34 mmol) was added in portions. The solution was then diluted with dioxane (100 mL) and heated at reflux overnight. Excess NaH was quenched with cold methanol. The solvent was removed and the residue suspended in methylene dichloride. After extraction with water, the methylene dichloride layer was dried over $MgSO_4$ and evaporated under reduced pressure. The resulting yellow residue was chromatographed on a silica gel column (30 % ethyl acetate in hexane) to give **8a** as a yellow oil that solidified on standing (4 g, 50 %), mp 66 °C. IR $\nu_{max}(CDCl_3)/cm^{-1}$ 3400 (NH), 3000 (CH), 1727 (C=O) cm^{-1}; δ_H(200 MHz; $CDCl_3$) 9.40 (1H, s, *H*NCOO-tBu), 8.41 (1H, d, *J*=9, Ar), 7.61 (1H, dd, *J*=3, *J*= 9, Ar), 7.20 (1H, dd, *J*=3, *J*= 9, Ar), 3.87 (3H, s, OCH_3), 1.51 (9H, s, tBu).

1-(*N*-Methyl)-2-(*N*-*tert*-butoxycarbonyl)-4-methoxy-1,2-phenylenediamine (8c). A mixture of **8a** (4 g) and 10 % Pd-C (500 mg) in methanol (20 mL) was hydrogenated at 3 atm. Filtration and evaporation gave **8b** as a brown oil in quantitative yield (3.5 g); IR $\nu_{max}(CDCl_3)/cm^{-1}$ 3400 (NH, NH_2), 3000 (CH), 1716 (C=O); δ_H(200 MHz; $CDCl_3$) 7.05 (1H, d, *J*=10, Ar), 6.30 (2H, overlap of s and d, Ar), 6.00 (1H, br s, N*H*COOtBu), 4.00 (5H, overlap of d and s, OCH_3, NH_2), 1.45 (9H, s, tBu). To a solution of this oil (3 g, 12.6 mmol) in acetonitrile (25 mL) was added in one portion methyl iodide (0.8 g, 13 mmol) and saturated aqueous sodium carbonate (3.3 mL). After 16 h, the solvent was evaporated and the resulting

yellow residue purified on silica gel (30 % ethyl acetate in hexane) to give amine **(8c)** (1.5 g, 47 %) as a pale yellow powder, mp 83 °C. IR $\nu_{max}(CDCl_3)/cm^{-1}$ 3025 (CH), 3400 (NH), 1716 (C=O); δ_H(200 MHz; $CDCl_3$) 7.05 (1H, d, *J*=9, Ar), 6.20 (2H, overlap of d and s, Ar), 5.80 (1H, br s, N*H*COOtBu), 4.20 (1H, br s, N*H*CH_3) 3.80 (3H, s, OCH_3), 2.80 (3H, s, NHC*H*$_3$), 1.45 (9H, s, tBu).

***N*-(2-Amino-5-methoxyphenyl)-*N,N'*-dimethylurea (9b).** Amine **8c** (1 g, 4.2 mmol) was treated overnight with methyl isocyanate (0.3 mL, 5.6 mmol) in methylene dichloride (50 mL). The solvent was evaporated to give **9a** as a clear oil in quantitative yield (1.3 g). δ_H(200 MHz; $CDCl_3$) 8.01 (1H, d, *J*=9, Ar), 6.85 (1H, dd, *J*=3, *J*=9, Ar) 6.68 (1H, dd, *J*=3, *J*=9, Ar), 6.57 (1H, s, N*H*COOtBu), 3.76 (3H, s, OCH_3) 2.86 (3H, s, ArNCH$_3$CO), 2.73 (3H, d, J=4, CONHC*H*$_3$) 1.50 (9H, s, tBu). A solution of **9a** (1 g) in trifluoacetic acid (10 mL) was heated to 45 °C for 10 min then was cooled to 0 °C and neutralized with aqueous sodium carbonate. Extraction with methylene dichloride and evaporation of the solvent gave **9b** (500 mg, 74 %) as a brown powder, mp 120 °C. IR $\nu_{max}(CDCl_3)/cm^{-1}$ 3400-3200 (NH, NH_2), 1649 (C=O); δ_H(200 MHz; $CDCl_3$) 6.80 (2H, overlap of d, Ar), 6.60 (1H, s, Ar) 6.40 (1H, br s, CON*H*CH_3), 3.72 (3H, s, OCH_3), 3.17 (3H, s, ArN(CH_3)CO, 2.71 (3H, d, *J*=5, CONHC*H*$_3$); δ_C(75.4 MHz; $CDCl_3$) 152.94 (s), 137.35 (s), 128.37 (s), 117.59 (d), 115.61 (d), 113.62 (d), 55.80 (q), 35.47 (q), 27.54 (q); *m/z* (CI, isobutane) 210 (MH^+, 100 %), 178 (MH^+-MeOH, 11), 153 (MH^+-MeNCO, 65).

3,5-Dimethyl-7-methoxy-*3H*-1,2,3,5-benzotetrazepin-4(*5H*)-one (10). As described for **5b**, urea **9b** (0.45 g) in 5N HCl (7 mL) was diazotized with 15 % aqueous [5 % ^{15}N] $NaNO_2$ (1.2 mL) to give **10** (151 mg, 36 %) as a brown powder, mp 61 °C (effervescence). Anal. Calcd for $C_{10}H_{12}N_4O_2$: C, 54.5 H, 5.5; N, 25.4. Found: C, 53.6; H, 5.3; N, 23.9.; (the compound decomposed slowly at rt, therefore no satisfactory elemental analysis was obtained); δ_H(200 MHz; $CDCl_3$) 7.37 (1H, d, *J*=9, Ar), 6.75 (1H, dd, *J*=3, *J*=9, Ar), 6.55 (1H, d, *J*=3, Ar), 3.8 (3H, s, OCH_3), 3.35 (3H, s, N=NNCH$_3$) 3.25 (3H, s, ArN(C*H*$_3$)CO); δ_C(75.40 MHz; $CDCl_3$) 161.7 (s), 140.14 (s), 135.28 (s), 129.20 (d), 110.19 (d), 104.92 (d), 57.80 (q), 36.82 (q), 35.13 (q). $\delta^{15}N$-2(30.40 MHz; $CDCl_3$) 63.00.

1-Methyl-*1H*-6-methoxybenzotriazole (11). The brown oil obtained from the decomposition of solid **10** (250 mg) after two weeks, was purified on silica gel (50 % hexane in ethyl acetate) to give **11** (150 mg) as a yellow crystalline solid; mp 84 °C; δ_H(200 MHz; $CDCl_3$) 7.88 (1H, d, *J*=9, Ar), 7.00 (1H, d, *J*=9, Ar), 6.76 (1H, s, Ar), 4.20 (3H, s, OMe), 3.90 (3H, s, NMe); MS, *m/z* (EI) 163 (M^+, 51 %), 135 (M^+-N_2, 26), 120 (M^+-CH_3N_2, 100).

1-Methyl-*1H*-5-methoxybenzotriazole (12). The NMR solution of **6b** (3 mL, 0.75 M) was purified on a silica gel column (50 % ethyl acetate in hexane) to give benzotriazole (**12**) as a white crystalline solid (300 mg), mp 125 °C. Anal. Calcd for $C_8H_9N_3O$: C, 58.9; H 5.8; N, 25.7. Found: C, 58.4; H, 5.5; N, 25.5; δ_H(200 MHz; $CDCl_3$) 7.36 (d, overlap of d and s, 2H, *J*=9, Ar), 7.15 (d, 1H, *J*=9, Ar), 4.20 (s, 3H, OMe), 3.80 (3H, s, NMe).

***N*-(3'-Hydroxypropyl)-2-nitroaniline (13a).** A solution of 2-chloronitrobenzene (2 g, 12.7 mmol) in 3-aminopropanol (10 mL) was heated to 180 °C for 5 min after which it was cooled and concentrated under vacuum. The resulting dark-red residue was purified on silica gel (50 % hexane in ethyl acetate) to give **13a** (2 g, 81 %) as a red oil. δ_H(200 MHz; $CDCl_3$) 8.14 (2H, overlap of br s and d, *J*=9, Ar, NH), 7.40 (1H, *J*=9, Ar), 6.90 (1H, d, *J*=9, Ar), 6.65 (1H, t, *J*=9, Ar), 3.80 (2H, t, *J*=6, $NCH_2CH_2CH_2$), 3.42 (2H, t, *J*=6, $NCH_2CH_2CH_2$), 1.97 (quintet, 2H, *J*=6, $NCH_2CH_2CH_2$), 1.68 (1H, br s, OH); MS *m/z* (CI, isobutane) 197 (MH^+, 100 %), 151 (MH^+-NO_2, 11).

***N*-(2-Aminophenyl)-*N*-(3'-hydroxypropyl)-*N'*-methylurea (13c).** A solution of amine **13a** (1.5 g) and 10 % Pd-C (500 mg) in methanol (10 mL) was hydrogenated at 2 atm. Filtration and evaporation gave **13b** as a violet oil in quantitative yield (1 g). δ_H(200 MHz; $CDCl_3$) 6.80-6.50 (4H, m, Ar), 3.80 (t, 2H, *J*=6, $NCH_2CH_2CH_2$), 3.26 (5H, overlap of t and br s, *J*=6, $NCH_2CH_2CH_2$, NH, NH_2), 1.90 (2H, overlap of quintet and s, $NCH_2CH_2CH_2$, OH). (*N*-Alkylphenylenediamines darken when exposed to light. They must be used immediately after their isolation). A solution of diamine (**13b**) (1 g, 6 mmol) and methyl isocyanate (0.4 mL, 7 mmol) was left standing overnight at rt. The solvent was evaporated and the resulting brown residue purified on a silica gel column (5 % methanol in methylene dichloride) to give urea (**13c**) (1g , 75 %) as a white powder, mp 118 °C. δ_H(200 MHz; $CDCl_3$) 7.20 (1H, t, *J*=9, Ar), 7.0 (1H, d, *J*=9, Ar), 6.80 (2H, overlap of t, Ar), 4.40 (1H, br q, $CONHCH_3$), 3.9 (2H, br s, NH_2), 3.80-3.65 (4H, br m, $NCH_2CH_2CH_2$), 2.70 (3H, d, *J*=6, $CONHCH_3$) 1.60 (3H, br m, $NCH_2CH_2CH_2$, OH); MS *m/z* (EI) 223 (M^+, 42 %), 166 (M^+-MeNCO, 15), 121 (M^+-MeNCO-CH_2CH_2OH, 100).

3-Methyl-5-(3'-hydroxypropyl)-1,2,3,5-benzotetrazepin-4(5*H*)-one (14a). Urea (**13c**) (1 g, 5.55 mmol) was dissolved in 2N HCl (20 mL) and diazotized with 2 mL of aqueous 20 % [5 % ^{15}N] $NaNO_2$. After 30 min, the solution was extracted three times with methylene dichloride, after which its pH was adjusted to 8. The aqueous layer was extracted six times with three 50 mL portions of methylene dichloride. The solvent was evaporated to give 300 mg (28 %, crude) of **14a** as a clear oil. The resulting compound started effervescing on standing. It was consequently kept in solution for subsequent analysis.

δ_H(200 MHz; $CDCl_3$) 7.36 (2H, d, *J*=8, Ar), 7.20 (2H, overlap of d and t, Ar) 3.90 (2H, t, *J*=7, $NCH_2CH_2CH_2$), 3.50 (2H, br t, $NCH_2CH_2CH_2$), 3.30 (3H, s, N=NNCH_3) 2.65 (br s, 1H, OH), 1.75 (2H, quintet, *J*=7, $NCH_2CH_2CH_2$); δ_C(75.4 MHz; $CDCl_3$) 160.34 (s), 143.90 (s), 138.26 (s), 132.50 (d), 128.30 (d), 126.14 (d), 122.51 (d), 60.58 (t), 45.80 (t), 38.01 (t), 32.24 (t); δ_N(30.4 MHz; $CDCl_3$) 68.5 (q, *J*=2.9, N2 label). (If the compound was left standing overnight at rt, another peak at -5.2 ppm was observed).

1-(3'-Hydroxypropyl)-*1H*-benzotriazole (15). The dark chloroform solution of **14a** (250 mg) which resulted from the NMR experiment (overnight at rt) was evaporated and the resulting dark oily residue purified on a silica gel column (5 % hexane in ethyl acetate) to give 150 mg of **15a**; δ_H(200 MHz; $CDCl_3$) 8.00 (1H, d, *J*=8, Ar), 7.60 (1H, d, *J*=8, Ar), 7.40 (1H, t, *J*=8, Ar), 7.30 (1H, t, *J*=8, Ar), 4.80 (2H, t, *J*=7, $NCH_2CH_2CH_2$), 3.60 (2H, br t, $NCH_2CH_2CH_2$), 3.05 (1H, br s, OH), 2.20 (2H, quintet, *J*=7, $NCH_2CH_2CH_2$); δ_N(30.4 MHz; $CDCl_3$) -5.2 (N2); MS *m/z* (EI) 177 (M^+, 12.7 %), 91 (M^+-$HOCH_2CHCH_2$ -N_2, 100); HRMS Calcd for $C_9H_{11}N_3O$: 177.09021. Found: M^+ 177.09080.

***N*-(3'-Hydroxypropyl)-5-nitro-1,2-phenylenediamine (13d).** 4-Nitro-1,2-phenylenediamine (2 g, 12.7 mmol) and 3-bromopropanol (1.7 mL) in a 1:1 MeOH/DMF mixture (25 mL) were heated at reflux overnight. The solvents were evaporated under vacuum and the resulting dark-red residue chromatographed on silica gel (30 % hexane in ethyl acetate) to give **13d** (1 g, 36 %) as a red powder, mp 89 °C; δ_H(200 MHz; $CDCl_3$) 7.66 (1H, dd, *J*=2.5, *J*=9, Ar), 7.44 (1H, d, *J*=2.5, Ar), 6.64 (1H, d, *J*=9, Ar), 3.85 (2H, t, *J*=6, $NCH_2CH_2CH_2$), 3.60-3.30 (4H, br s, NH_2, NH, OH), 3.30 (2H, t, *J*=6.02, $NCH_2CH_2CH_2$), 1.90 (2H, quintet, *J*=6, $NCH_2CH_2CH_2$).

***N*-(5-Nitro-2-amino-1-phenyl)-*N*-3-hydroxypropyl)-*N'*-methylurea (13e).** A solution of **13d** (400 mg, 1.9 mmol) and methyl isocyanate (0.12 mL, 2.2 mmol) in acetonitrile (20 mL) was kept overnight, concentrated under vacuum and diluted with water (10 mL). The precipitate that formed was collected to give **13e** (400 mg, 78 %) as a yellow powder which was dried under vacuum at room temperature, mp 135-137 °C ; δ_H(200 MHz; $CDCl_3$) 8.10 (1H, dd, *J*=2.5, *J*=9, Ar), 7.90 (1H, d, *J*=2.5, Ar), 6.9 (1H, d, *J*=9, Ar), 4.25 (1H, br q, CONHCH$_3$), 3.80-3.60 (4H, overlap of m, $NCH_2CH_2CH_2$), 2.70 (5H, overlap of d and s, CONHCH_3, NH_2), 1.80 (3H, br m, OH, $NCH_2CH_2CH_2$); MS *m/z* (EI) 268 (M^+, 20.6 %), 211 (M^+-MeNCO, 19.1), 166 (M^+-MeNCO-CH_2CH_2OH, 100).

3-Methyl-5-(3'-hydroxypropyl)-7-nitro-*3H*-1,2,3,5-benzotetrazepin-4(*5H*)-one (14b). As described for **14a**, the diazotization of **13e** (400 mg) with $NaNO_2$ or $Na^{15}NO_2$ in 2N HCl (10 mL) gave **14b** as a

yellow oil, (300 mg, 72 %). δ_H(200 MHz; $CDCl_3$) 8.10 (1H, overlap of s and d, *J*=9, Ar), 7.98 (d, 1H, *J*=9, Ar), 4.00 (t, 2H, *J*=6, $NCH_2CH_2CH_2$), 3.60 (br m, 2H, $NCH_2CH_2CH_2$), 3.40 (3H, s, $N{=}NNCH_3$), 2.19 (1H, br s, OH, D_2O exchangeable), 1.80 (2H, quintet, *J*=6, $NCH_2CH_2CH_2$); δ_C(75.4 MHz; $CDCl_3$) 158.02 (s), 148.57 (s), 145.99 (s), 138 (s) 128 (d), 119.4 (d) 117.01 (d), 59.20 (t), 44.77 (t) 36.90 (q), 30.81 (t); δ_H(30.4 MHz; $CDCl_3$) 78.8 (q, *J*=2.8, N-2); MS *m/z* (CI, NH_3) 280 (MH^+, 67.3 %), 252 (MH^+-N_2, 100), 223 (MH^+-MeNCO, 67). HRMS Calcd for $C_{11}H_{14}O_4N_5$ $[M + H]^+$: 280.10458. Found: 280.10459

X-Ray Crystallography.- Crystals of compound (**6d**) were obtained from slow evaporation of methylene dichloride.

Crystal data.- $C_9H_9N_5O_3$, M = 235.20. Orthorhombic, a = 8.0120 (8), b = 10.9621 (9), c = 11.9290 (10), V=1047.70 (16) $Å^3$ (by least-squares refinement on diffractometer angles for 26 automatically centred reflections with 2θ angle in the range or 90-100°) space group P n 2_1 a, Z=4, Dx =1.491 $g.ml^{-1}$. Small yellow needles. Crystal dimensions: 0.25 x 0.20 x 0.20 mm, μ (Cu-Kα)=0.94 mm^{-1}.

Data Collection and Processing.- Enraf-Nonius CAD4 θ/2θ mode, scan speed 4°/min, Cu-K_α radiation, temperature: 25 °C; 2797 reflections measured 569 were unique giving 552 with $I>2.5\sigma(I)$. No correction was made for absorption.

Structure Analysis and Refinement.- All non-hydrogen atom positions from direct methods.[20] All hydrogen-atom positions from a Fourier difference map. All positional and thermal parameters (anisotropic) and an extinction parameter were refined by full-matrix least square. Final R and Rw were 0.033, and 0.022 for 552 observed reflections and 154 variable parameters. The weighting scheme was based on counting statistics. The maximum and minimum peaks on the final difference Fourier map were to 0.110 and -0.140 eA^{-3}, respectively. Neutral atom scattering factors were taken from Cromer and Waber.[21,22] Anomalous dispersion effects were included in Fcalc; the values for Δf' and Δf" were those of Cromer.[23] Figures were drawn with ORTEPII.[24]

ACKNOWLEDGMENT

We thank the Natural Sciences and Engineering Research Council of Canada and Fonds FCAR, Province de Quebec, for financial support, Dr Françoise Sauriol for assistance and advices in running NMR spectra, Dr Rosemary Hynes for X-Ray structure analysis and Mr. Nadim Saadé for running mass spectra.

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Received, 5th January, 1998