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# Structural and Dynamic Behaviour of Heterocycles Derived from Ethylenediamines with Formaldehyde: 1,3,5-Triazinanes and Bis(imidazolidinyl)methanes

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**Abstract:** Formaldehyde is a simple chemical compound that is used as a building block in obtaining a wide range of products. The versatility of formaldehyde in chemical synthesis becomes evident when it is reacted with *N*-alkylethylenediamines. Therefore, this paper reports the structure and reactivity of a series of compounds derived from easily accessible molecules, such as formaldehyde, sodium hydrosulphide, and *N*-alkylethylenediamines. The 1,3,5-triazines (***1a-1d***) and bis(3-alkyl-imidazolidin-1-yl)methanes (***2a-2d***) were obtained by simple reaction conditions. Additionally, different proportions of sodium hydrosulphide and formaldehyde were used with *N*-benzylamine to obtain *N*-benzyltriazinane (***3***), *N*-benzylthiadiazinane (***4***) and *N*-benzyldithiazinane (***5***). All these compounds were characterized by analytical, spectroscopic, and spectrometric techniques, such as melting point, solubility, one-dimensional and two-dimensional nuclear magnetic resonance ($^{13}$C, $^{1}$H, $^{15}$N, COSY, HETCOR, NOESY, COLOC), elemental analysis, high- and low-resolution mass spectrometry, among others. The structures of compounds **4** and **5** were obtained by single-crystal X-ray diffraction. The results show that small variations in the stoichiometry and the reaction conditions significantly influence the products obtained.

**Keywords:** formaldehyde; triazinane; imidazolidine; ethylendiamine; bis(imidazolidinyl)methane



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## 1. Introduction

On the one hand, imidazolidines are of commercial interest due to their multiple biological activities related to ring substitution [1,2]. Bis(imidazolidinyl)methanes are derived from these heterocycles and have shown excellent antimicrobial, antiparasitic, and antitumor activity [3]. These properties could be related to its hydrophobic nature, which increases the bioavailability of its biologically active precursors (carbonyl and ethylenediamine) [4]. In addition, microbiological studies have shown a high activity of these derivatives against fungi, aerobic bacteria and anaerobic bacteria in the degradation of petroleum derivatives [5]. Artificial neural networks used in pharmacology identify them as potential new drugs against Chagas disease [6]. Some authors have even used them in the design of lithium carbanions and in the reduction with borane [7,8]. Therefore, new green synthesis techniques have been implemented to obtain them [9].

On the other hand, 1,3,5-triazinanes are exceptionally important because they have three nitrogen atoms with different degrees of hybridization and are good hydrogen-bond acceptors, which is why they are widely used by the pharmaceutical and biotechnological industries [10]. In the literature, 2,4,6-trichloro-1,3,5-triazine, also named as cyanuric chloride, and 1,3,5-trichloro-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione, also named as trichloroisocyanuric acid, symclosene or chloreal, are known [11,12]. Both commercial compounds

are produced on an industrial scale and are economically accessible. The first is used in agricultural pesticides and photoactive compounds, while the second is used in the treatment and disinfection of swimming pools and food surfaces [13,14]. Additionally, it has been reported that 1,3,5-triazinanes have a wide variety of applications, such as in anticorrosives [15–17], explosives [18,19], precursors in the synthesis of insecticides [20] and organic compounds [21,22]. For example, in the synthesis of heterocycles, they are easy to prepare and low-cost substances, allowing other compounds of biological or technological interest to be obtained [23].

*N*-alkylethylenediamines react with formaldehyde to obtain different products (imidazolidines, 1,3,5-triazinanes or bis(imidazolidinyl)methanes), which depend on the nature of the reagents, the stoichiometry of the reaction, the solvent used, as well as the time and temperature of the reaction. In this work, a clear competition between 1,3,5-triazinanes and bis(imidazolidinyl)methanes was observed, testing various reaction conditions during the synthesis of the products. Due to the above and considering the chemical and biological importance of these compounds, there was an interest in understanding the structural and dynamic behaviour of the new heterocycles derived from *N*-alkylethylenediamines.

## 2. Materials and Methods

### *2.1. General Experimental Details*

The reagents used in this investigation were purchased from Sigma-Aldrich Chemical, Fluka Chemika or Strem Chemical. Reactive-grade solvents, such as toluene, methylene chloride, chloroform and tetrahydrofuran were previously dried according to the procedures already established in the literature. NMR spectra in one and two dimensions were determined in the following equipment: Jeol GSX-DELTA 270 MHz [$^{1}$H: 270.17 MHz, $^{13}$C: 67.94 MHz, $^{15}$N: 27.39 MHz], Jeol Eclipse GSX-DELTA 400 [$^{1}$H: 399.78 MHz, $^{13}$C: 100.53 MHz, $^{15}$N: 40.52 MHz] and BRUKER-AVANCE 300 [$^{1}$H: 300.13 MHz, $^{13}$C: 75.47 MHz, $^{15}$N: 30.42 MHz]. The $^{1}$H and $^{13}$C spectra were acquired with reference to $Si(CH_3)_4$ and the $^{15}$N spectra with reference to $CH_3NO_2$ in 5 mm diameter resonance tubes. Chemical shifts are expressed in parts per million (ppm) and were obtained at room temperature.

Melting points were measured in capillary tubes sealed in Gallemkamp Mel-Temp II Laboratory Devices equipment. The elemental analyses were performed on FLASH(EA) 1112 Series, Thermo Finnigan equipment. Mass spectra were acquired in HP-5989A MS Engine Hewlett-Packard equipment coupled to a gas chromatograph 5890 series II by direct insertion to 20 eV or by high resolution using Agilent Technologies LC/MCD TOF equipment with ESI and APCI ionization sources.

Crystallographic data were collected in Nonius Kappa CCD equipment with an area detector using monochromatic molybdenum $K_\alpha$ radiation (0.71073 Å), and intensities were measured using scans in φ and ω. The structures were solved using direct methods with SHELX-97, Sir 2002 and 2004. The refinement of all structures ($F^2$ based on all data) was done with the least-squares technique of the complete matrix with Crystals-1287d-2009. All atoms except hydrogen were refined anisotropically.

### *2.2. Synthesis of 1,3,5-Triazinanes (**1a**-**1d**)*

#### 2.2.1. Synthesis of 2,2′,2″-(1,3,5-Triazinane-1,3,5-triyl)tris(*N*-methylethylenamine) (***1a***)

In a round-bottom flask provided with a magnetic stirrer, *N*-methylethylenediamine (5 mL, 53.9 mmol) was dissolved in tetrahydrofuran (50 mL), then placed at –78 °C in a dry ice–acetone bath, and aqueous formaldehyde (4.4 mL, 59.3 mmol) previously cooled in an ice bath was slowly added. The reaction mixture was stirred for 30 min at 5 °C and 24 h at room temperature, then tetrahydrofuran was evaporated. The reaction mixture was solubilized with methylene chloride, purified with activated carbon, and dried with sodium sulphate. After filtering and evaporating the solvent, the mixture of compounds ***1a*** and ***2a*** was obtained as a colourless liquid in a ratio of 40:60, respectively. Product ***1a*** was identified by comparison with the NMR data of pure compound ***2a*** obtained later. Compound ***1a***: $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 3.29 (s, 6H, H2, H4, H6), 2.96 (t, 6H, $J$ = 7.0 Hz, H8), 2.50 (t, 6H,

*J* = 7.0 Hz, H7), 3.40 (s br, 3H, H9), 2.25 (s, 9H, H10). $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 72.3 (C2, C4, C6), 54.2 (C7), 45.7 (C8), 39.5 (C10). $^{15}$N NMR (41 MHz, $CDCl_3$) δ: −327.1 (N9), −340.0 (N1, N3, N5).

2.2.2. Synthesis of 2,2′,2″-(1,3,5-Triazinane-1,3,5-triyl)tris(*N*-ethylethylenamine) (***1b***)

Compound ***1b*** was obtained in the same manner as compound ***1a*** from *N*-ethylethylen ediamine (5 mL, 46.5 mmol) and aqueous formaldehyde (3.8 mL, 51.2 mmol). The mixture of compounds ***1b*** and ***2b*** was obtained as a slightly yellow liquid in a ratio of 45:55, respectively. Product ***1b*** was identified by comparison with the NMR data of pure compound ***2b*** obtained later. Compound ***1b***: $^{1}$H NMR (400 MHz, $CDCl_3$) δ: 3.24 (s, 6H, H2, H4, H6), 2.95 (s br, 3H, H9), 2.86 (t, 6H, *J* = 7.0 Hz, H8), 2.42 (t, 6H, *J* = 7.0 Hz, H7), 2.31 (q, 6H, *J* = 7.3 Hz, H10), 0.92 (t, 9H, *J* = 7.3 Hz, H11). (101 MHz, $CDCl_3$) δ: 70.3 (C2, C4, C6), 51.9 (C7), 47.5 (C10), 45.2 (C8), 14.1 (C11). $^{15}$N NMR (41 MHz, $CDCl_3$) δ: −326.1 (N9), −341.2 (N1, N3, N5).

2.2.3. Synthesis of 2,2′,2″-(1,3,5-Triazinane-1,3,5-triyl)tris(*N*-benzylethylenmine) (***1c***)

Compound ***1c*** was obtained in the same manner as compound ***1a*** from *N*-benzylethylen ediamine (5 mL, 32.3 mmol) and aqueous formaldehyde (2.7 mL, 35.5 mmol). The mixture of compounds ***1c*** and ***2c*** was obtained as a colourless liquid in a ratio of 50:50, respectively. Product ***1c*** was identified by comparison with the NMR data of pure compound ***2c*** obtained later. Compound ***1c***: $^{1}$H NMR (400 Mhz, $CDCl_3$) δ: 7.35–7.15 (m, 15H, $H_{ar}$), 3.59 (s, 6H, H10), 3.42 (s, 6H, H2, H4, H6), 3.02 (t, 6H, *J* = 7.1 Hz, H8), 2.62 (t, 6H, *J* = 7.1 Hz, H7), 2.60 (s br, 3H, H9). $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 139.0 ($C_i$), 128.7 ($C_o$), 128.5 ($C_m$), 127.2 ($C_p$), 70.7 (C2, C4, C6), 58.0 (C10), 52.3 (C7), 45.4 (C8). $^{15}$N NMR (41 MHz, $CDCl_3$) δ: −318.8 (N9), −340.9 (N1, N3, N5).

2.2.4. Synthesis of 2,2′,2″-(1,3,5-Triazinane-1,3,5-triyl)tris(*N*,*N*-dimethylethylenamine) (***1d***)

Compound ***1d*** was obtained in the same manner as compound ***1a*** of *N*,*N*-dimethylethy lenediamine (5 mL, 43.5 mmol) and aqueous formaldehyde (3.6 mL, 35.5 mmol). Compound ***1d*** was obtained pure as a slightly yellow liquid (3.2 g, 73%). Compound ***1d***: $^{1}$H NMR (400 Mhz, $CDCl_3$) δ: 3.12 (s, 6H, H2, H4, H6), 2.29 (t, 6H, *J* = 6.8 Hz, H7), 2.12 (t, 6H, *J* = 6.8 Hz, H8), 1.96 (s, 18H, H10). $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 74.7 (C2, C4, C6), 57.5 (C8), 50.4 (C7), 45.6 (C10). $^{15}$N NMR (41 MHz, $CDCl_3$) δ: −355.6 (N9), −334.1 (N1, N3, N5). LRMS (EI, 20 eV), *m*/*z* (%): 301 (2), 242 (5), 201 (9), 158 (8), 142 (38), 130 (27), 101 (68), 72 (22), 58 (100), 42 (12); HRMS (ESI+) *m*/*z* calc. for $(M+H)^+$: 301.3080, found: 301.3074. EA calc. for $C_{15}H_{36}N_6$ $\frac{1}{2}CH_2Cl_2$: C, 54.28; H, 10.87; N, 24.50. found: C, 54.01; H, 10.86; N, 25.01.

*2.3. Synthesis of Bis(3-alkyl-imidazolidin-1-yl)methane (**2a**-**2d**)*

2.3.1. Obtaining Bis(3-methylimidazolidin-1-yl)methane (***2a***)

In a round-bottom flask provided with a magnetic stirrer, *N*-methylethylenediamine (5 mL, 53.9 mmol) was dissolved in tetrahydrofuran (50 mL), then aqueous formaldehyde was added slowly (4.4 mL, 59.3 mmol). The reaction mixture was stirred for 10 min at 5 °C in a water ice bath and maintained at reflux for 6 h in tetrahydrofuran. The solvent was evaporated, and the reaction mixture was solubilized with methylene chloride, purified with activated carbon and dried with sodium sulphate. After filtering and evaporating the solvent, pure compound ***2a*** was obtained as a colourless liquid (4.6 g, 92%). $^{1}$H NMR (400 Mhz, $CDCl_3$) δ: 3.26 (s, 4H, H2), 3.23 (s, 2H, H6), 2.75 (t, 4H, *J* = 6.7 Hz, H5), 2.55 (t, 4H, *J* = 6.7 Hz, H4), 2.19 (s, 6H, H7). $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 77.0 (C6), 76.6 (C2), 54.1 (C4), 51.0 (C5), 40.6 (C7). $^{15}$N NMR (41 MHz, $CDCl_3$) δ: −326.9 (N1), −340.7 (N3). LRMS (EI, 20 eV), *m*/*z* (%): 183 (2), 167 (2), 156 (3), 142 (2), 126 (2), 113 (9), 99 (31), 85 (45), 72 (22), 58 (54), 44 (100). EA calc. for $C_9H_{20}N_4$ $^{1}/_{3}CH_2Cl_2$: C, 52.73; H, 9.80; N, 26.35. found: C, 52.78; H, 10.09; N, 26.47.

2.3.2. Obtaining Bis(3-ethylimidazolidin-1-yl)methane (***2b***)

Compound ***2b*** was obtained following the same procedure as compound ***2a*** from *N*-ethylethylenediamine (5 mL, 46.5 mmol) and aqueous formaldehyde (3.8 mL, 51.2 mmol). After filtering and evaporating the solvent, pure compound ***2b*** was obtained as a colourless liquid (4.5 g, 91%). $^{1}$H NMR (400 Mhz, $CDCl_3$) δ: 3.09 (s, 4H, H2), 3.01 (s, 2H, H6), 2.53 (t, 4H, *J* = 6.6 Hz, H5), 2.36 (t, 4H, *J* = 6.6 Hz, H4), 2.14 (q, 4H, *J* = 7.2 Hz, H7), 0.73 (t, 6H, *J* = 7.2 Hz, H8). $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 76.4 (C6), 74.6 (C2), 51.7 (C4), 50.3 (C5), 48.5 (C7), 13.7 (C8). $^{15}$N NMR (41 MHz, $CDCl_3$) δ: −327.2 (N1), −328.8 (N3). LRMS (EI, 20 eV), *m*/*z* (%): 211 (16), 197 (1), 154 (1), 127 (2), 113 (100), 99 (7), 84 (3), 72 (8), 58 (2), 56 (3), 42 (2). EA calc. $C_{11}H_{24}N_4$ 1/9 $CH_2Cl_2$: C, 60.18; H, 11.01; N, 25.26. found: C, 60.51; H, 10.86; N, 24.86.

2.3.3. Obtaining Bis(3-benzylimidazolidin-1-yl)methane (***2c***)

Compound ***2c*** was obtained following the same procedure as compound ***2a*** from *N*-benzylethylenediamine (5 mL, 32.3 mmol) and aqueous formaldehyde (2.7 mL, 35.5 mmol). After filtering and evaporating the solvent, pure compound ***2c*** was obtained as a colourless liquid (4.8 g, 88%). $^{1}$H NMR (400 Mhz, $CDCl_3$) δ: 7.35–7.15 (m, 15H, $H_{ar}$), 3.60 (s, 4H, H7), 3.42 (s, 4H, H2), 3.33 (s, 2H, H6), 2.86 (t, 4H, *J* = 7.2 Hz, H5), 2.70 (t, 4H, *J* = 7.2 Hz, H4). $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 139.1 ($C_i$), 128.7 ($C_o$), 128.4 ($C_m$), 127.1 ($C_p$), 76.7 (C6), 75.2 (C2), 59.1 (C7), 52.3 (C4), 50.7 (C5). $^{15}$N NMR (41 MHz, $CDCl_3$) δ: −327.6 (N1), −327.9 (N3). LRMS (EI, 20 eV), *m*/*z* (%): 335 (3), 292 (2), 251 (2), 220 (13), 205 (42), 175 (91), 161 (54), 146 (6), 132 (16), 119 (10), 99 (16), 91 (100), 83 (37), 72 (14), 57 (18), 42 (37). EA calc. $C_{21}H_{28}N_4$: C (74.96), H (8.39), N (16.65). found: C (74.68), H (8.30), N (16.73).

2.3.4. Obtaining Bis(3-phenylimidazolidin-1-yl)methane (***2d***)

Compound ***2d*** was obtained following the same procedure as compound ***2a*** from *N*-phenylethylenediamine (5 mL, 37.6 mmol) and aqueous formaldehyde (3.1 mL, 41.4 mmol). After filtering and evaporating the solvent, pure compound ***2d*** was obtained as a white solid (4.8 g, 82%, Mp 142 °C). $^{1}$H NMR (400 Mhz, $CDCl_3$) δ: 7.25 (dd, 4H, $JH_m$-$H_p$ = 7.3 Hz, $JH_m$-$H_o$ = 7.8 Hz, $H_m$), 6.72 (t, 2H, $JH_p$-$H_m$ = 7.3 Hz, $H_p$), 6.54 (d, 4H, $JH_o$-$H_m$ = 7.8 Hz, $H_o$), 4.17 (s, 4H, H2), 3.47 (s, 2H, H6), 3.42 (t, 4H, *J* = 6.6 Hz, H4), 3.13 (t, 4H, *J* = 6.6 Hz, H5). $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 146.7 ($C_i$), 129.4 ($C_m$), 116.5 ($C_p$), 111.8 ($C_o$), 74.5 (C6), 69.1 (C2), 51.0 (C5), 45.8 (C4). $^{15}$N NMR (41 MHz, $CDCl_3$) δ: −325.7 (N1), −309.4 (N3). LRMS (EI, 20 eV), *m*/*z* (%): 308 (1), 176 (1), 161 (100), 147 (47), 120 (5), 106 (48), 77 (6), 56 (20), 42 (5). EA calc. for $C_{19}H_{24}N_4$ 1/16$CH_2Cl_2$: C, 72.98; H, 7.75; N, 17.86. found: C, 72.77; H, 7.37; N, 17.51.

*2.4. Synthesis of 1,3,5-Tribenzyl-1,3,5-triazinane (**3**)*

Compound ***3*** is obtained from *N*-benzylamine (10 mL, 89.8 mmol) dissolved in distilled water (50 mL) and tetrahydrofuran (25 mL). The reaction mixture was placed in a water ice bath, and aqueous formaldehyde (7.4 mL, 98.8 mmol) was slowly added. The reaction was kept under stirring and after 24 h at room temperature the solvent was evaporated. Compound ***3*** was extracted with methylene chloride and dried with anhydrous sodium sulphate (10.5 g, 98%, Mp 50 °C). $^{1}$H NMR (400 Mhz, $CDCl_3$) δ: 7.45–7.25 (m, 15H, $H_{ar}$), 3.76 (s, 6H, H7), 3.52 (s br, 6H, H2, H4, H6). $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 138.7 ($C_i$), 129.1 ($C_o$), 128.4 ($_{Cm}$), 127.2 ($C_p$), 74.0 (C2, C4, C6), 57.2 (C7). $^{15}$N NMR (41 MHz, $CDCl_3$) δ: −329.7 (N1, N3, N5). LRMS (EI, 20 eV), *m*/*z* (%): 357 (10), 238 (14), 133 (19), 120 (72), 106 (12), 91 (100), 65 (6), 42 (9); HRMS (ESI+) *m*/*z* calc. for $(M + Na)^+$: 380.2103, found: 380.2097. EA calc. for $C_{24}H_{27}N_3$: C, 80.63; H, 7.61; N, 11.75. found: C, 80.28; H 7.42; N 11.45.

*2.5. Synthesis of 3,5-Dibenzyl-1,3,5-thiadiazinane (**4**)*

In a round-bottom flask provided with a magnetic stirrer, *N*-benzylamine (5 mL, 44.9 mmol) dissolved in distilled water (50 mL) was placed. The solution was cooled in an ice bath, and a cold solution (5 °C) of sodium hydrosulphide (7.6 g, 134.7 mmol) in aqueous formaldehyde (16.7 mL, 224.5 mmol) was slowly added. The reaction mixture

was stirred for 30 min at 5 °C and 24 h at room temperature. Compound ***4*** was extracted with methylene chloride and dried with anhydrous sodium sulphate. Compound ***4*** was obtained mixed with compound ***5***. However, the slow evaporation of methylene chloride allowed the obtaining of colourless crystals of compound ***4***, which were separated by filtration. (3.0 g, 47%, Mp 96 °C). $^{1}$H NMR (400 Mhz, $CDCl_3$) δ: 7.42–7.26 (m, 10H, $H_{ar}$), 4.26 (s br, 4H, H2, H6), 4.13 (s, 4H, H7), 4.08 (s br, 2H, H2). $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 138.7 ($C_i$), 128.9 ($C_o$), 128.6 ($C_m$), 127.4 ($C_p$), 73.8 (C4), 57.3 (C2, C6), 56.2 (C7). $^{15}$N NMR (41 MHz, $CDCl_3$) δ: −334.0 (N3, N5). MS (EI, 20 eV), *m*/*z* (%): 284 (2), 251 (6), 211 (1), 193 (2), 165 (28), 133 (31), 118 (38), 91 (100), 74 (2), 65 (13), 42 (17); HRMS (ESI+) *m*/*z* calc. for $(M + H)^+$: 285.1425, found: 285.1419. EA calc. for $C_{17}H_{20}N_2S$: C, 71.79; H, 7.09; N, 9.85. found: C, 71.84; H, 7.42; N, 9.73.

### *2.6. Synthesis of 5-Benzyl-1,3,5-dithiazinane (**5**)*

Compound ***5*** was obtained from *N*-benzylamine (5 mL, 44.9 mmol) dissolved in distilled water (50 mL). The solution was cooled in an ice bath, and a cold solution (5 °C) of 17.6 g of sodium hydrosulphide (314.3 mmol) in aqueous formaldehyde (73.6 mL, 987.8 mmol) was slowly added. The reaction mixture was stirred for 30 min at 5 °C and 24 h at room temperature. Compound ***5*** was extracted with methylene chloride and dried with anhydrous sodium sulphate (6.6 g, 70%). $^{1}$H NMR (400 Mhz, $CDCl_3$) δ: 7.42–7.22 (m, 5H, $H_{ar}$), 4.44 (s br, 4H, H4, H6), 4.24 (s, 2H, H7), 4.14 (s br, 2H, H2). $^{13}$C NMR (101 MHz, $CDCl_3$) δ: 137.4 ($C_i$), 129.4 ($C_o$), 128.7 ($C_m$), 127.6 ($C_p$), 58.0 (C4, C6), 53.4 (C7), 34.2 (C2). $^{15}$N NMR (41 MHz, $CDCl_3$) δ: −344.8 (N5). LRMS (EI, 20 eV), *m*/*z* (%): 211 (13), 165 (15), 133 (45), 120 (10), 118 (30), 91 (100), 65 (12), 42 (72); HRMS *m*/*z* calc. for $(M+H)^+$: 212.0568, found: 212.0562. EA calc. for $C_{10}H_{13}NS_2$: C, 56.83; H, 6.20; N, 6.63. found: C, 56.96; H 6.27; N 6.67.

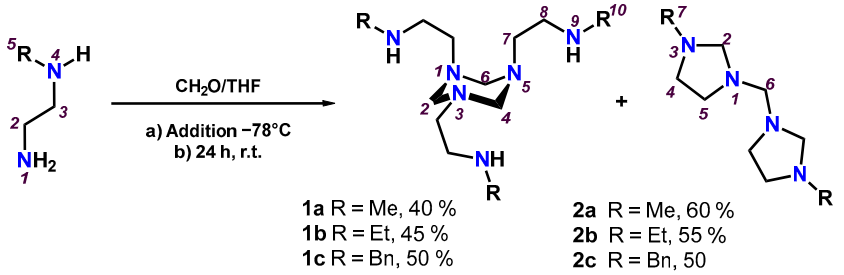
## 3. Results and Discussion

Condensation reactions between *N*-alkylethylenediamines, formaldehyde and sodium hydrosulphide in a stoichiometric ratio [1:5:3] led to the formation of *N*-alkyl-ethylene-dithiazinanes, which were previously reported by our research group [24]. However, by varying stoichiometry, by-products were obtained, such as *N*-alkylethylenethiadiazinanes, or *N*-alkylethylenetriazinanes, which made it difficult to isolate pure compounds. Therefore, we decided to explore the condensation reactions between *N*-alkylethylenediamines and formaldehyde in the absence of sodium hydrosulphide, favouring the formation of sulphur-free heterocycles, such as 1,3,5-triazinanes (***1a***-***1d***) and bis(imidazolidinyl)methanes (***2a***-***2d***).

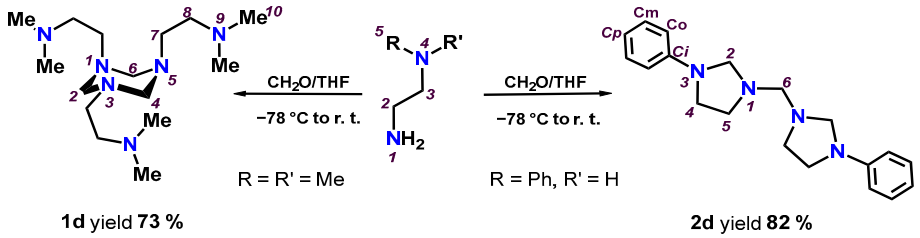
### *3.1. Preparation of 1,3,5-Triazinanes (**1a**-**1d**)*

To a solution of the *N*-alkylethylenediamines (R = Me, Et or Bn) in tetrahydrofuran at –78 °C was added dropwise an equivalent of formaldehyde, previously cooled. After twenty-four hours of stirring at room temperature, a mixture of 1,3,5-triazinanes (***1a***-***1c***) and bis(imidazolidinyl)methanes (***2a***-***2c***) was obtained in proportions of: ***1a***/***2a*** 40:60, ***1b***/***2b*** 45:55, and ***1c***/***2c*** 50:50; see Scheme 1. The 1,3,5-triazinanes (***1a***-***1c***) could not be isolated pure by any of the known separation techniques, so they were only identified by NMR. However, reactions to tetrahydrofuran reflux for six hours and subsequent distillation led exclusively to the formation of bis(imidazolidinyl)methanes (***2a***-***2c***); see Section 3.2.

Under the same reaction conditions, the *N*,*N*-dimethylethylenediamine produced exclusively the 1,3,5-triazinane (***1d***), while *N*-phenylethylenediamine gave the bis(imidazolid inyl)methane (***2d***); see Scheme 2. The 1,3,5-triazinanes (***1a***-***1c***) discussed in this section had not previously been reported in the literature, except compound ***1d***, which had already been described under different reaction conditions [25].



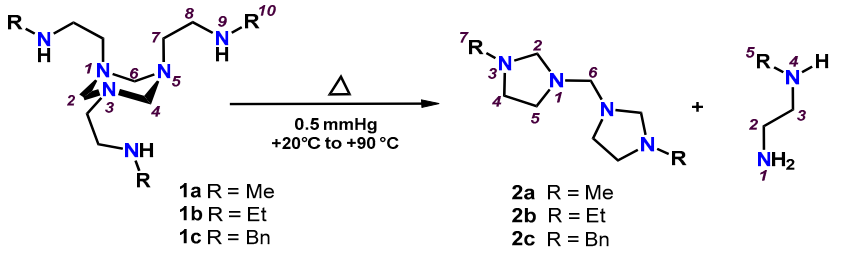

**Scheme 1.** Preparation of 1,3,5-triazinanes (***1a-1c***) and bis(imidazolidinyl)methanes (***2a-2c***).




**Scheme 2.** Preparation of ***1d*** and ***2d***.

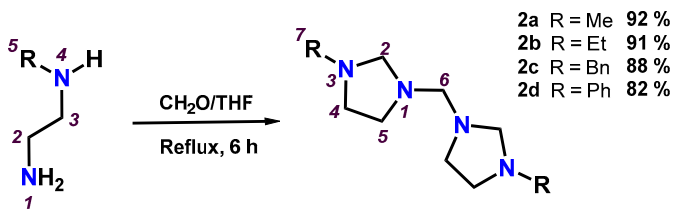
*3.2. Preparation of Bis(imidazolidinyl)methanes (**2a-2d**)*

Attempts to purify 1,3,5-triazinanes (***1a-1c***) by vacuum distillation (0.5 mmHg, +20 °C to +90 °C) showed that heating the reaction mixture transforms them into bis(imidazolidinyl)m ethanes (***2a-2c***); see Scheme 3.




**Scheme 3.** Preparation of the bis(imidazolidinyl)methanes (***2a-2c***) by heating the 1,3,5-triazinanes (***1a-1c***).

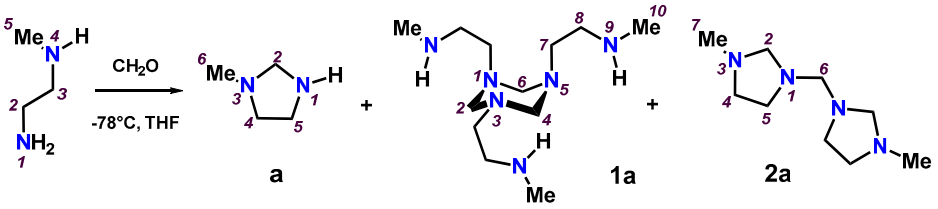
Bis(imidazolidinyl)methanes (***2a-2d***) are very stable compounds and were synthesized directly with good yields, from the equimolar reaction between formaldehyde and the corresponding *N*-alkylethylenediamine. The addition was made at room temperature, and the reaction mixture was subsequently maintained at reflux in tetrahydrofuran for six hours; see Scheme 4. The bis(imidazolidinyl)methanes (***2a-2d***) were obtained in good yields and are colourless liquids, soluble in polar organic solvents, such as tetrahydrofuran, dimethyl sulfoxide, chloroform, methylene chloride, methanol, ethanol, etc. The bis(imidazolidinyl)methanes ***2a*** [5,8,9], ***2c*** [5] and ***2d*** [2–6] discussed in this section had previously been reported in the literature under different reaction conditions, except compound ***2b***, which had never been synthesized and characterized.




**Scheme 4.** Preparation of bis(imidazolidinyl)methanes (***2a-2d***) by refluxing in tetrahydrofuran.

### *3.3. NMR Reaction Evaluation*

The results in Section 3.1 showed that the reaction products depend on the amine structure, the reaction conditions and the stoichiometry. Therefore, to have more information about the evolution of different reactions, the equimolar reaction between *N*-methylethylenediamine and formaldehyde was monitored by $^{13}C$ and $^{1}H$ NMR in tubes at different acquisition temperatures; see Scheme 5. The experimental strategy was to evaluate the reaction in 1:1 stoichiometry using two solvents with a wide range between their boiling (Bp) and melting points (Mp). Tetrahydrofuran-$d_8$ allowed the temperature to be lowered to −78 °C and dimethylsulfoxide-$d_6$ allowed the temperature to be raised to 120 °C. Therefore, the experiments were carried out at −78, 25, 65 °C (for tetrahydrofuran-$d_8$) and 5, 25, 120 °C (for dimethylsulfoxide-$d_6$). The reaction times used were 0.1, 1, 6 and 24 h. In addition, the stoichiometric ratios 1:2 and 2:1 were analysed in order to verify their influence on the reaction. The intensity and integration of the signals assigned by NMR to the [N-$CH_2$-N] fragment and to the N-$CH_3$ group were used in the quantification of the ratio of compounds ***a***, ***1a*** and ***2a***. In an NMR tube at −78 °C, the spectra acquired immediately after mixing the reagents in tetrahydrofuran-$d_8$ showed three compounds: imidazolidine (***a***, 42%), 1,3,5-triazinane (***1a***, 21%) and bis(imidazolidinyl)methane (***2a***, 37%). The spectra recorded after six hours of reaction at room temperature showed an increase in 1,3,5-triazinane (***1a***, 43%) and a decrease in imidazolidine (***a***, 21%) and bis(imidazolidinyl)methane (***2a***, 36%). When the reaction was monitored in dimethylsulfoxide-$d_6$, initially at 5 °C and later at room temperature, results similar to those found with tetrahydrofuran-$d_8$ were observed. Additionally, with this solvent the NMR tube was heated for one hour at 120 °C, changing the ratio between the products 1,3,5-triazinane (***1a***, 26%) and bis(imidazolidinyl)methane (***2a***, 74%); see Table 1.




**Scheme 5.** Condensation products of *N*-methyl-ethylenediamine and formaldehyde.

When the reaction was carried out in dimethylsulfoxide-$d_6$ in a 2:1 ratio between *N*-methylethylenediamine and formaldehyde, the spectra acquired a few minutes after mixing the reagents showed: imidazolidine (71%), 1,3,5-triazinane (***1a***, 17%) and bis(imidazolidinyl)methane (***2a***, 12%). The spectra of the solution after heating for three hours at 120 °C have a mixture of 1,3,5-triazinane (***1a***) and the free diamine. The spectra of the reaction carried out in dimethylsulfoxide-$d_6$ in a 1:2 stoichiometric ratios between *N*-methylethylenediamine and formaldehyde showed the signals corresponding to bis(imidazolidinyl)methane (***2a***) as a majority product. The 1,3,5-triazinane (***1a***) and imidazolidine were observed in small amounts, even when the reaction was heated at 120 °C for two hours; see Table 1. From the results obtained, we can determine that in excess of formaldehyde, the main product is bis(imidazolidinyl)methane (***2a***), while in excess of *N*-methylethylenediamine, 1,3,5-triazinane (***1a***) is the predominant compound. It is interesting to note that imidazolidine is precursor to 1,3,5-triazinane (***1a***).

The previous results allow us to discuss the preliminary thermodynamic and kinetic stability of the products obtained from the equimolar reaction between *N*-methylethylenedia mine and formaldehyde. The kinetically controlled product is 1,3,5-triazinane (***1a***), since it is the least stable product and is obtained by lowering the temperature in short reaction times. Additionally, the thermodynamically controlled product is bis(imidazolidinyl)methane (***2a***), since it is the most stable product and is obtained by increasing the temperature in long reaction times. That is, 1,3,5-triazinane (***1a***) is formed faster than bis(imidazolidinyl)methane (***2a***) because the activation energy for bis(imidazolidinyl)methane (***2a***) is lower than for

bis(imidazolidinyl)methane (***2a***), even though bis(imidazolidinyl)methane (***2a***) is more stable. However, to confirm these assertions, a deeper study is necessary, gradually modifying the reaction conditions for a better comparison.

**Table 1.** Proportion of the products obtained from the reaction between *N*-methylethylenediamine and formaldehyde by NMR.

| Reagents (Eq.) | | | Reaction Conditions | | Products (%) | | |
|---|---|---|---|---|---|---|---|
| **A** | **B** | **Solvent** | **Temperature** | **Time** | **C** | **D** | **E** |
| 1 | 1 | THF-$d_8$ | −78 °C | 6 min (0.1 h) | 42 | 21 | 37 |
| 1 | 1 | THF-$d_8$ | 25 °C | 360 min (6 h) | 21 | 43 | 36 |
| 1 | 1 | THF-$d_8$ | 25 °C | 1440 min (24 h) | 0 | 40 | 60 |
| 1 | 1 | THF-$d_8$ | 65 °C | 360 min (6 h) | 0 | 0 | 100 |
| 1 | 1 | DMSO-$d_6$ | 5 °C | 6 min (0.1 h) | 25 | 39 | 36 |
| 1 | 1 | DMSO-$d_6$ | 25 °C | 6 min (0.1 h) | 21 | 43 | 36 |
| 1 | 1 | DMSO-$d_6$ | 120 °C | 60 min (1 h) | 0 | 26 | 74 |
| 2 | 1 | DMSO-$d_6$ | 5 °C | 6 min (0.1 h) | 71 | 17 | 12 |
| 2 | 1 | DMSO-$d_6$ | 120 °C | 150 min (2.5 h) | 0 | 50 * | 0 |
| 1 | 2 | DMSO-$d_6$ | 5 °C | 6 min (0.1 h) | 1 | 1 | 98 |
| 1 | 2 | DMSO-$d_6$ | 120 °C | 90 min (1.5 h) | 0.5 | 0.5 | 99 |

* Excess diamine, A = *N*-methylethylenediamine, B = formaldehyde, C = imidazolidine, D = 1,3,5-triazinane E = bis(imidazolidinyl)methane, DMSO-$d_6$: Mp 18.5 °C, bp 189 °C, THF-$d_8$: Mp −108.5 °C, bp 66 °C.

### *3.4. Spectroscopic Characterization of 1,3,5-Triazinanes (**1a-1d**)*

The $^{13}$C NMR spectra confirmed the formation of 1,3,5-triazinanes, since the signal corresponding to the equivalent carbons (C2, C4 and C6) showed a characteristic displacement for this type of derivative at approximately 70 ppm. The C8 of compound ***1d*** showed a different shift from that of 1,3,5-triazinanes (***1a-1c***), since it has a tertiary amine attached in that position. Table 2 summarizes the chemical shifts of $^{1}$H and $^{13}$C NMR ($CDCl_3$, 25 °C) of 1,3,5-triazinanes (***1a-1d***); the protons of the heterocycle are characterized by a broad signal for equivalent hydrogens (H2, H4 and H6) that integrate for six protons. The unequivocal assignment of H7 and H8, as well as its correlation with $^{13}$C, was completed by experiments in two dimensions: COSY, NOESY and HETCOR.

**Table 2.** NMR data of $^{13}$C and $^{1}$H (δ, *J*, $CDCl_3$, 25 °C) for 1,3,5-triazinanes (***1a-1d***).

| Prod. | C2, C4, C6 | C7 | C8 | R Group | H2, H4, H6 | H7 | H8 | R Group |
|---|---|---|---|---|---|---|---|---|
| ***1a*** | 72.3 | 54.2 | 45.7 | 39.5, (Me) | 3.29 (s) | 2.50 (t) *J* 7.0 | 2.96 (t) *J* 7.0 | 2.25 (s), (Me) |
| ***1b*** | 70.3 | 51.9 | 45.2 | 47.5, 14.1, (Et) | 3.24 (s) | 2.42 (t) *J* 7.0 | 2.86 (t) *J* 7.0 | 2.31 (c), 0.92 (t), (Et) |
| ***1c*** | 70.7 | 52.3 | 45.4 | 58.0, 139.0, 128.7, 128.5, 127.2, ($CH_2$Ph) | 3.42 (s) | 2.62 (t) *J* 7.1 | 3.02 (t) *J* 7.1 | 3.59 (s), 7.4–7.2 (m), ($CH_2$Ph) |
| ***1d*** | 74.7 | 50.4 | 57.5 | 45.6 (Me) | 3.12 (s) | 2.29 (t) *J* 6.8 | 2.12 (t) *J* 6.8 | 1.96 (s), (Me) |

The $^{15}$N NMR spectroscopic data ($CDCl_3$, 25 °C) showed the signal corresponding to the equivalent nitrogen atoms (N1, N3 and N5) at approximately −340 ppm. This displacement is characteristic for heterocyclic nitrogen at 1,3,5-triazinanes, as reported in the literature for similar compounds [26–28]. Table 3 compares the $^{15}$N NMR chemical shifts of 1,3,5-triazinanes (***1a-1d***) and the *N*-alkylethylenediamines (***a-d***) from which they come and shows that the primary amine (N1) in the *N*-alkylethylenediamine about 22 ppm was deprotected by forming the heterocycle and becoming a tertiary amine (N1, N3 and N5) in the new 1,3,5-triazinanes (***1a-1d***). The change in the nitrogen displacement of the

secondary amine of the *N*-alkylethylenediamines (N4), by forming 1,3,5-triazinanes (N9), could be explained by the intramolecular hydrogen bridge N●●●H-N that forms exocyclic N-H with endocyclic nitrogen in these compounds (***1a-1c***). This hydrogen bond cannot be formed in derivative ***1d***, so the shift does not change significantly with respect to that of the initial amine.

**Table 3.** NMR data of $^{15}N$ (δ, $CDCl_3$, 25 °C) for 1,3,5-triazinanes (***1a-1d***) and their *N*-alkylethylenediamines (***a-d***).

| *N*-Alkyl-Ethylenediamine | N1 | N4 | 1,3,5-Triazinane | N1, N3, N5 | N9 |
|---|---|---|---|---|---|
| ***a*** | −363.5 | −360.8 | ***1a*** | −340.0 | −327.1 |
| ***b*** | −362.9 | −341.2 | ***1b*** | −341.2 | −326.1 |
| ***c*** | −362.0 | −343.3 | ***1c*** | −340.9 | −318.8 |
| ***d*** | −363.5 | −360.3 | ***1d*** | −334.1 | −355.6 |

### *3.5. Spectroscopic Characterization of Bis(imidazolidinyl)methanes (**2a-2d**)*

The $^{13}C$ NMR spectra showed the characteristic signals around 70 ppm for C2 and C6. The C2 integrates for two carbons and the C6 for one. Table 4 summarizes the chemical shifts of $^{13}C$ and $^{1}H$ ($CDCl_3$, 25 °C) of bis(imidazolidinyl)methanes (***2a-2d***); protons H2 and H6 are characterized by being simple signals that integrate for four and two protons, respectively. The unambiguous allocation of H4 and H5, as well as the correlation between carbon and hydrogen, was completed by experiments in two dimensions: COSY, NOESY, HETCOR and COLOC. The coupling constants ($^3J_{H4\text{-}H5}$) and dihedral angles from the Karplus curve of compounds (***2a-2d***) confirm that the nitrogen is in the *syn* position: ***2a*** ($^3J_{H4\text{-}H5}$ = 6.7) 34° and 137°, ***2b*** ($^3J_{H4\text{-}H5}$ = 6.6) 34° and 136°, ***2c*** ($^3J_{H4\text{-}H5}$ = 7.2) 30° and 140°, and ***2d*** ($^3J_{H4\text{-}H5}$ = 6.6 Hz) 34° and 136°; see Figure 1.

**Table 4.** NMR data of $^{13}C$ and $^{1}H$ (δ, *J*, $CDCl_3$, 25 °C) for bis(imidizalodinyl)methanes (***2a-2d***).

| Prod. | C2 | C6 | C4 | C5 | R Group | H2 | H6 | H4 | H5 | R Group |
|---|---|---|---|---|---|---|---|---|---|---|
| ***2a*** | 76.6 | 77.0 | 54.1 | 51.0 | 40.6, (Me) | 3.26 (s) | 3.23 (s) | 2.55 (t) *J* 6.7 | 2.75 (t) *J* 6.7 | 2.19 (s), (Me) |
| ***2b*** | 74.6 | 76.4 | 51.7 | 50.3 | 48.5, 13.7, (Et) | 3.09 (s) | 3.01 (s) | 2.36 (t) *J* 6.6 | 2.53 (t) *J* 6.6 | 2.14 (c), 0.73 (t), (Et) |
| ***2c*** | 75.2 | 76.7 | 52.3 | 50.7 | 59.1, 139.1, 128.7, 128.4, 127.1, ($CH_2$Ph) | 3.42 (s) | 3.33 (s) | 2.70 (t) *J* 7.2 | 2.86 (t) *J* 7.2 | 3.60 (s), 7.4–7.2 (m), ($CH_2$Ph) |
| ***2d*** | 69.1 | 74.5 | 45.8 | 51.0 | 146.7, 129.4, 116.5, 111.8, (Ph) | 4.17 (s) | 3.47 (s) | 3.42 (t) *J* 6.6 | 3.13 (t) *J* 6.6 | 7.3–6.5 (m), (Ph) |

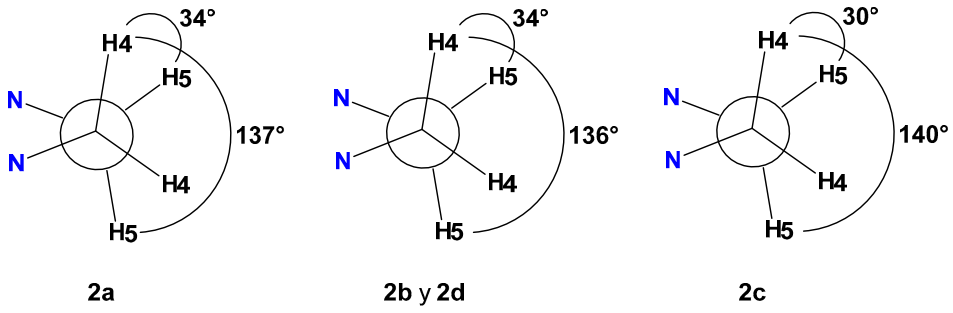



**Figure 1.** Newman projections for compounds (***2a-2d***) showing dihedral angles according to coupling constants $J_{H\text{-}H}$.

The $^{15}N$ NMR spectroscopic data ($CDCl_3$, 25 °C) showed a signal around −326 ppm, which corresponds to the bridging carbon between the two five-membered heterocycles, and their value is characteristic for nitrogen atoms in similar compounds reported in the literature [26–28]. Table 5 compares the $^{15}N$ NMR chemical shifts of bis(imidazolidinyl)methanes (***2a-2d***) and the *N*-alkylethylenediamines (***a-d***) from which they come. It is observed that in the *N*-alkylethylenediamines, the nitrogen of the N1 and N4 positions was depro-

tected around 35 and 20 ppm, respectively, when forming the N1 and N3 positions of the bis(imidazolidinyl)methanes, both becoming tertiary amines.

**Table 5.** NMR data of $^{15}N$ (δ, $CDCl_3$, 25 °C) for bis(imidizalodinyl)methanes (***2a-2d***) and their *N*-alkylethylenediamines (***a-d***).

| *N*-Alkyl-Ethylenediamine | N1 | N4 | Bis(imidizalodinyl) Methanes | N1 | N3 |
|---|---|---|---|---|---|
| ***a*** | −363.5 | −360.8 | ***2a*** | −326.9 | −340.7 |
| ***b*** | −362.9 | −341.2 | ***2b*** | −327.2 | −328.8 |
| ***c*** | −362.0 | −343.3 | ***2c*** | −327.6 | −327.9 |
| ***d*** | −361.8 | −316.7 | ***2d*** | −325.7 | −309.4 |

### *3.6. Spectrometric Characterization of Bis(imidazolidinyl)methanes (**2a-2d**)*

These derivatives were studied by electronic impact mass spectrometry at 20 eV. This technique allowed us to observe odd molecular ions in molecules with an even number of nitrogen, *m*/*z*(%): 183(2) (***2a***), 191(4) (***2b***), 335(4) (***2c***) and 307(1) (***2d***). The four compounds have several possibilities of rupture. The bis(imidazolidyl)methanes (***2a-2d***) had the same fragmentation pattern, so that the compound ***2a*** is analysed by way of example. The molecular weight of the compound is 184 g/mol, but it has an even number of nitrogen, so the molecular ion found is 183 and is observed with a 2% abundance; the base peak 44(100) corresponds to the fragment $[(Me)_2N]^+$; see Figure 2.

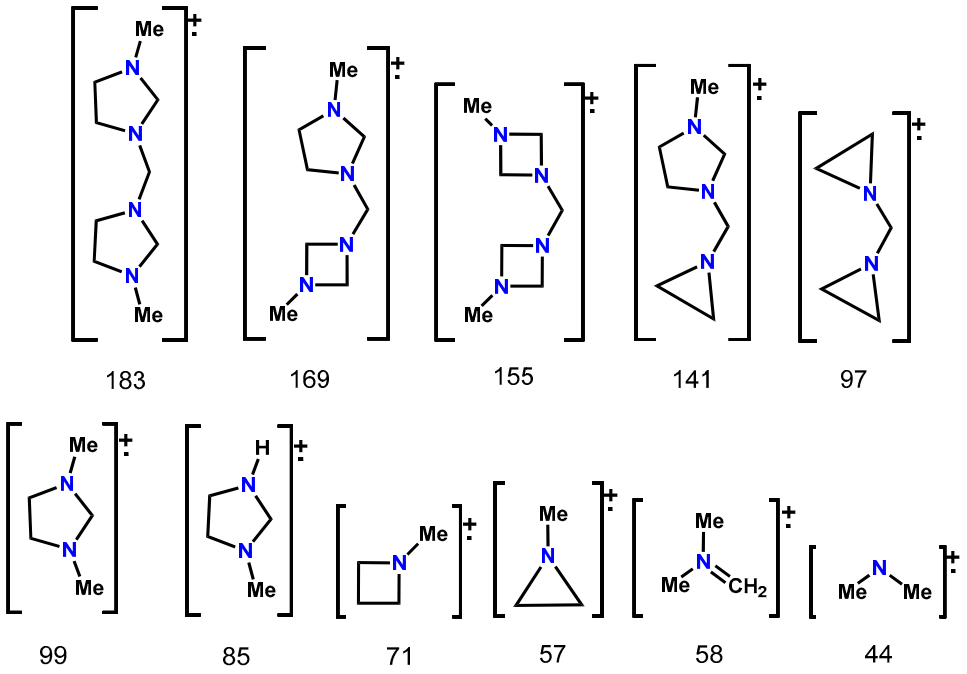



**Figure 2.** Fragments observed in the ionization process of compound ***2a*** by electronic impact mass spectrometry.

These derivatives were also studied by high-resolution mass spectrometry (MS-TOF), using electrospray ionization (ESI). Although this technique did not allow us to observe the characteristic molecular ions $(M + H)^+$, despite the mild ionization and high sensitivity, this offered us valuable information about the stability of the methylene bridge in C6, which fragments easily during ionization. Fracture of the C-N bond in C6 produces characteristic fragments in bis(imidazolidyl)methanes (***2a-2d***). Compounds ***2a*** and ***2b***, after breaking the bond, react with the methanol in the medium and form fragments at 131.1197 and 145.1382, respectively; see Figure 3.

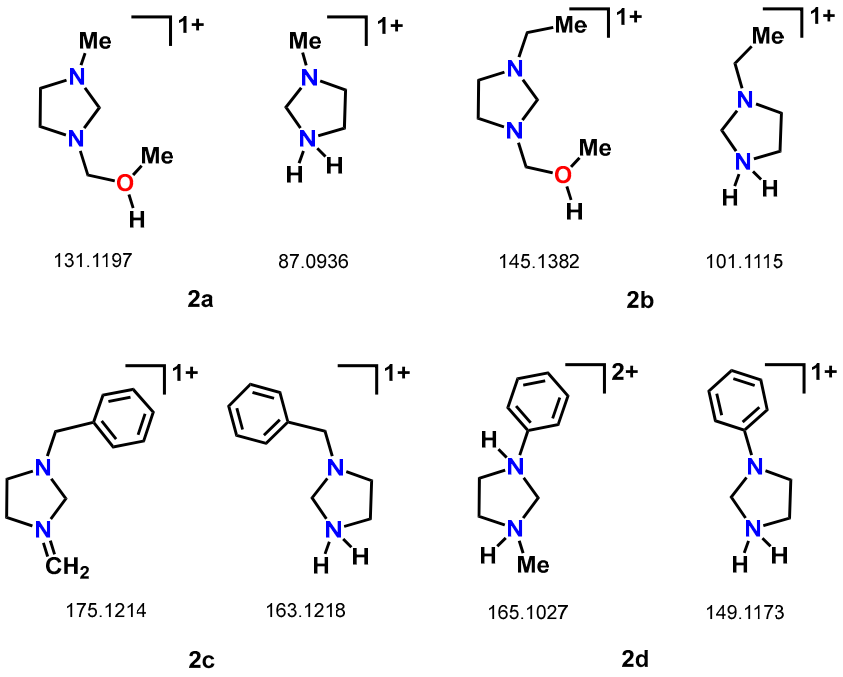
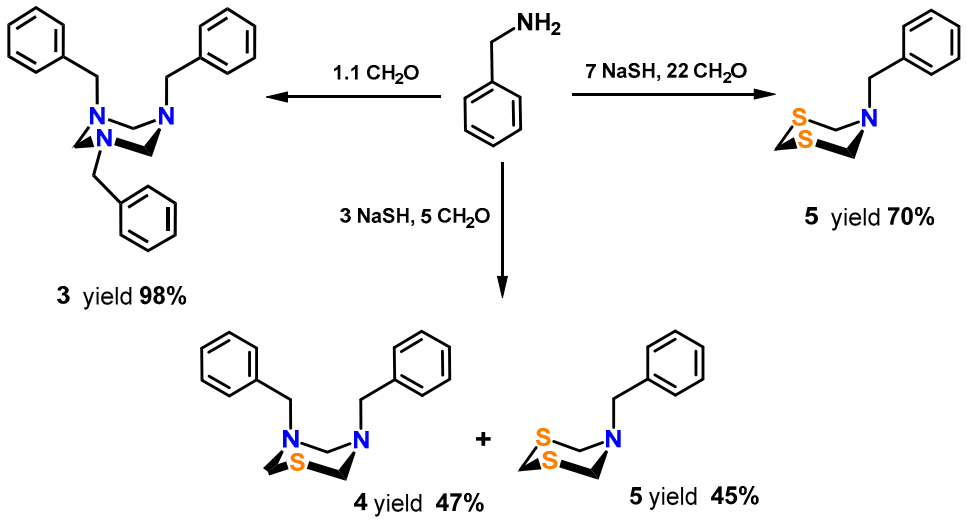



**Figure 3.** Fragments observed in the ionization process of compounds (**2*a*-2*d***) by electrospray (ESI).

### *3.7. Versatility of Formaldehyde in the Synthesis of Six-Member Heterocycles*

In order to explore the versatility of formaldehyde in the synthesis of other six-membered heterocycles, the reactions of *N*-benzyl-amine in the presence of formaldehyde and sodium hydrosulphide in different proportions were explored. The equimolar reaction between *N*-benzylamine and formaldehyde led exclusively to the formation of *N*-benzyl-triazinane (***3***, 98% yield), which has already been previously reported by other research groups under different reaction conditions [29–44]. The reaction of one equivalent of *N*-benzylamine with five of formaldehyde and three of sodium hydrosulphide was explored, obtaining a mixture of products in 50:50 ratios: *N*-benzyl-thiadiazinane (***4***) and *N*-benzyl-dithiazinane (***5***). Compound ***4*** is a colourless crystalline solid while compound ***5*** is a yellow liquid, so they were easily separated by filtration. The *N*-benzyl-dithiazinane was also obtained pure (***5***, 70% yield) of the condensation of one equivalent of *N*-benzylamine with twenty-two of formaldehyde and seven of sodium hydrosulphide; this compound had already been reported by other authors [45–47]; see Scheme 6.




**Scheme 6.** Preparation of triazinane, thiadiazinane and dithiazinane by condensation.

### *3.8. Crystallographic Characterization of N-Benzyl-triazinane (3) and N-Benzyl-thiadiazinane (**4**)*

The *N*-benzyl-triazinane ***3*** is a crystalline solid that was obtained by slow evaporation of the solution obtained from the equimolar reaction between formaldehyde and *N*-benzylamine. The crystals were studied by DRX (monoclinic *P* $2_1/n$). Crystallographic data and structure refinement are summarized in Table S1. The lengths and angles of the bonds are presented in Table S2. In compound ***3***, the heterocycle has a chair conformation; in addition, according to the NMR data obtained in solution [$^{13}$C 57.2 ppm (C7), $^{1}$H 3.76 (s) (H7), benzyl carbon], the three substituents would be expected to be in equilibrium between the axial and equatorial positions. However, in the solid state it is observed that the first substituent is placed in an equatorial position, the second in an axial position, and the third is in equilibrium between both positions. For this reason, the disorder of the third benzyl substituent was modelled; see Figure 4. The nitrogen atoms N1 and N5 have a trigonal pyramidal geometry: C2-N1-C7 115.1(4)°, C2-N1-C6 102.9(5)°, C6-N1-C7 110.7(4)° [$\Sigma_{angles}$ for N1(equatorial) = 328.7°, 100% $sp^3$ character], C4-N5-C6 110.9(4)°, C6-N5-C21 115.0(5)°, C4-N5-C21 116.3(4)° [$\Sigma_{angles}$ for N5(axial) = 342.2°, 49.7% $sp^3$ character]. The percentage $sp^3$ hybridization of N3 atoms was not determined due to the disorder of the benzyl group at that position. The conformational behaviour in the solid state and in solution of some other triazinanes analogous to compound ***3*** has been widely discussed by our working group [48–51].

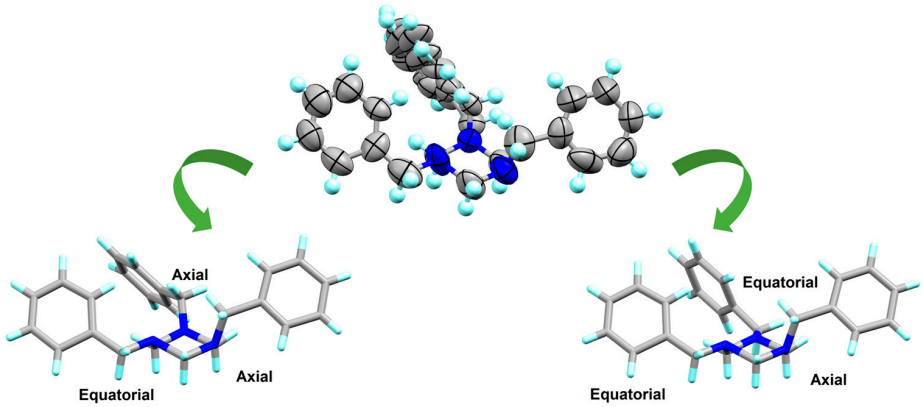



**Figure 4.** ORTEP representation of compound ***3*** showing the location of the three benzyl substituents.

In the same way, the *N*-benzyl-thiadiazinane ***4*** is a crystalline solid that was obtained by slow evaporation of the solution containing it, mixed with compound ***5***. The crystals were studied by single-crystal X-ray diffraction (orthorhombic *P* $2_12_12_1$). Crystallographic data and structure refinement are summarized in Table S3. The lengths and angles of the bonds are presented in Table S4. Compound ***4*** is in a chair conformation; it would be expected that, according to the data obtained from NMR in solution [$^{13}$C 56.2 ppm (C7), $^{1}$H 4.13 (s) (H7), benzyl carbon], one substituent will be placed in axial position and the other in the equatorial position. However, in the solid state, the two substituents were placed in axial position; see Figure 5. The nitrogen atoms N3 and N5 have a trigonal pyramidal geometry: C4-N3-C8 115.4(4)°, C2-N3-C8 113.4(3)°, C2-N3-C4 111.3(4)° [$\Sigma_{angles}$ for N3 = 340.1°, 49.5% $sp^3$ character], C4-N5-C6 112.0(4)°, C4-N5-C7 116.9(4)°, C6-N5-C7 113.5(3)° [$\Sigma_{angles}$ for N5 = 342.4°, 49.7% $sp^3$ character]. The bond angles around sulphur are C2-S1-C6 93.3(3)°, which indicates only 86.3% $sp^2$ hybridization, leaving the free electron pairs in one $sp^2$ and other *p* pure orbitals. Two hydrogen atoms in the benzyl groups have a shorter distance than the sum of the van der Waals radii ($\Sigma r_{vdW}$ [H•••H] = 2.40 Å). The above indicates that the steric interaction in axial is of lower energy than the electronic repulsion between the free electron pairs of the nitrogen and sulphur atoms when the substituents are equatorial. This behaviour is similar to that found for other thiadiazinanes reported by our work group [48–51]. Additionally, a polymorphic structure of compound ***4*** is reported, which was obtained by

slow evaporation of the crude reaction. The structure crystallized in a monoclinic space group, $P\ 2_1$. Crystallographic data and structure refinement are summarized in Table S5. The bond lengths and angles are presented in Table S6. Both polymorphs showed intra- and intermolecular S●●●H interactions smaller than the sum of van der Waals radii ($\Sigma r_{vdW}$ [S●●●H] = 3.00 Å).

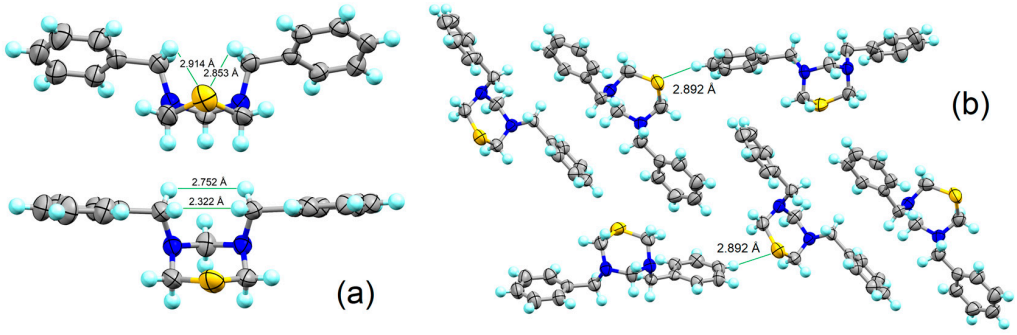



**Figure 5.** (**a**) ORTEP representation and intramolecular interactions (H●●●H and S●●●H) of compound ***4*** (orthorhombic $P\ 2_12_12_1$). (**b**) Intermolecular interactions (S●●●H) of compound ***4*** (monoclinic $P\ 2_1$).

## 4. Conclusions

Formaldehyde, a basic but highly reactive compound, is widely used in the chemical industry due to its versatility, low cost, and easy production. This compound is also known as methanal and is mainly used in the production of phenolic and amino resins, acetal resins, polyhydric alcohols, fertilizers, and paraformaldehyde. Furthermore, this compound reacts with various organic derivatives including amines, forming heterocycles with one or more C-N bonds. Therefore, in this work, the reactivity of formaldehyde against *N*-alkylethylenediamines was explored using different reaction conditions, such as variations in reaction time and temperature, and modifications in the stoichiometric ratio, among others. Under mild conditions (addition at −78 °C and stirring for 24 h), mixtures were obtained between the products bis(imidazolidinyl)methanes (***2a-2c***) and 1,3,5-triazinanes (***1a-1c***), when the alkyl substituents were methyl, ethyl or benzyl. However, when the substituent was phenyl, the reaction led exclusively to bis(imidazolidinyl)methane ***2d***. When more severe conditions were used (addition at room temperature and reflux for 6 h) it exclusively led to the formation in good yields of the bis(imidazolidinyl)methanes (***2a-2d***). In the case of *N*,*N*-dimethylethylenediamine, when it reacts with formaldehyde it exclusively leads to the formation of 1,3,5-triazinane ***1d*** under both mild and severe reaction conditions. To confirm the versatility of formaldehyde, its reaction with *N*-benzylamine was explored in the absence and presence of sodium hydrosulphide in different stoichiometric ratios. The manipulation of these three reagents led to the obtaining of three 1,3,5-heterocyclohexanes (triazinane, thiadiazinane and dithiazinane) with an interesting conformational behaviour.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/org4020024/s1, Table S1: Crystallographic data for compound ***3***; Table S2: Selected bond distances (Å) and bond angles (°) for the compound ***3***; Table S3: Crystallographic data for compound ***4*** (orthorhombic polymorph); Table S4: Selected bond distances (Å) and bond angles (°) for the compound ***4*** (orthorhombic polymorph); Table S5: Crystallographic data for compound ***4*** (monoclinic polymorph); Table S6: Selected bond distances (Å) and bond angles (°) for the compound ***3*** (monoclinic polymorph). Crystallographic data have been deposited at the Cambridge Crystallographic Data Center as numbers (CCDC): 2251551–2251553 for compound ***3*** and ***4***. Copies can be obtained, free of charge, on applications to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or https://www.ccdc.cam.ac.uk/structures/ (accessed on 24 March 2023).

**Author Contributions:** R.C.-P. investigation and writing the paper; S.A.S.-R. performed the experiments; A.F.-P. conceptualization, formal analysis, supervision, writing and editing review. All authors have read and agreed to the published version of the manuscript.

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