NEW 1,3,5-HETEROCYCLOHEXANES: DIOXAZINES, OXADIAZINES, THIADIAZINES, OXATHIAZINES AND TRIAZINES AND THEIR AMINATION, TRANSAMINATION AND DISPROPORTIONATION REACTIONS

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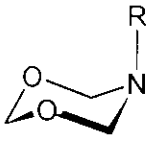
Abstract - New 1,3,5-heterocyclohexanes: 5-alkyl-1,3,5-dioxazines (R= *i*Pr, *t*Bu and *[R]*-α-methylbenzyl), 3,5-di(*[R]*-α-methylbenzyl)-1,3,5-oxadiazine, 3,5-di(*[R]*-α-methylbenzyl)-1,3,5-thiadiazine, 5-*iso*propyl-1,3,5-oxathiazine, 1-*iso*propyl-3,5-dimethyl-1,3,5-triazine, 1-*tert*-butyl-3,5-dimethyl-1,3,5-triazine are reported. Amination and transamination reactions of 1,3,5-heterocyclohexanes were investigated. Equilibria between different heterocycles were found. ^{13}C NMR studies allowed to observe new 1,3,5-heterocycles: 1,3,5-triazines bearing two different alkyl substituents, 3,5-di*tert*-butyl-1,3,5-thiadiazine, 3-*tert*-butyl-5-*iso*propyl-1,3,5-oxadiazine. 1,3,5-heterocyclohexanes present a ring fluxional behavior, the ring inversion energy was calculated for dioxazines, oxadiazine, thiadiazines and triazines

INTRODUCTION

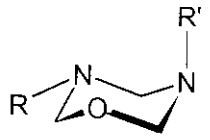
Ten classes of 1,3,5-heterocyclohexanes based on the different combinations of heteroatoms N, O or S are possible, but only few are known. The more common examples are dithiazines and triazines.[1] Some 3,5-dialkyl-1,3,5-thiadiazines (R= Me, Et, *i*Pr, C_6H_{11}, Bn and substituted Ph) have been reported.[2] In the family of 1,3,5-dioxazines and 1,3,5-oxadiazines only *N*-methyl derivatives have been reported as a mixture and characterized by ^{13}C NMR.[3] To our knowledge, there are no examples of 1,3,5-oxathiazines neither of non-symmetrically *N*-substituted 1,3,5-triazines.

The present research is connected with our interest in the syntheses, reactivity and coordinating properties of 1,3,5-heterocyclohexanes. Our findings related to stereochemistry and conformational behavior of 5-alkyl-1,3,5-dithiazines and 1,3,5-triazines have already been published.[1] Herein, we report the syntheses

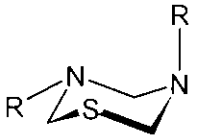
and structural characterization of 1,3,5-heterocyclohexanes: 5-alkyl-1,3,5-dioxazines (**1a-c**), 3,5-dialkyl-1,3,5-oxadiazines (**2b-c**), 3,5-dialkyl-1,3,5-thiadiazines (**3a,c-d**), 5-*iso*propyl-1,3,5-oxathiazine (**4**) and 1-*iso*propyl-3,5-dimethyl-1,3,5-triazine (**5a**) (Scheme 1).



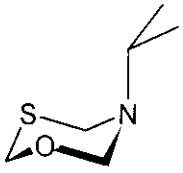
1a R= *i*Pr
1b R= *t*Bu
1c R= *[R]* CH(Me)Ph
1d R= Me



2a R= R'= *i*Pr
2b R= R'= *t*Bu
2c R=R'= *[R]* CH(Me)Ph
2d R= R'= Me
2e R= *i*Pr, R'= Me
2f R= *t*Bu, R'= Me
2g R= *[R]* CH(Me)Ph, R'= Me
2h R= *t*Bu, R'= *i*Pr



3a R= *i*Pr
3b R= *t*Bu
3c R= *[R]* CH(Me)Ph
3d R= Me



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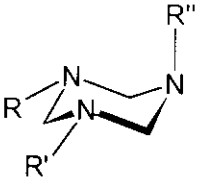
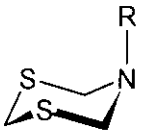


5a R= R"= Me, R'= *i*Pr
5b R= R"= Me, R'= *t*Bu
5c R= R"= Me, R'= *[R]* CH(Me)Ph
5d R= R'= *i*Pr, R"= Me
5e R= R'= *t*Bu, R"= Me
5f R= R'= *[R]* CH(Me)Ph, R"= Me
5g R= R'= *i*Pr, R"= *t*Bu
5h R= *i*Pr, R'=R"= *t*Bu
5i R= R'= R"= *i*Pr
5j R= R'= R"= *t*Bu
5k R= R'= R"= *[R]* CH(Me)Ph
5l R= R'= R"= Me



6a R= *i*Pr
6b R= *t*Bu
6d R= Me

Scheme I

1,3,5-Heterocyclohexanes bearing intracyclic nitrogen atoms appear at room temperature as fluxional species due to nitrogen and ring conformational equilibrium. The conformational behavior and the activation energy for ring inversion of **1a-c**, **2b**, **3a,c-d** and **4** have been calculated by variable temperature ^{1}H and ^{13}C NMR experiments.

During the NMR observation of the 1,3,5-heterocyclohexane compounds we discovered that they suffer amination and transamination reactions, as well as heteroatom exchange reactions when two different 1,3,5-heterocycles are mixed. Those reactions lead to the identification by ^{13}C NMR of fourteen new compounds. Their structures were assigned by analyses of several reaction products where compounds were in different ratios and by comparison with pure heterocycles (Schemes 2-5).

RESULTS AND DISCUSSION

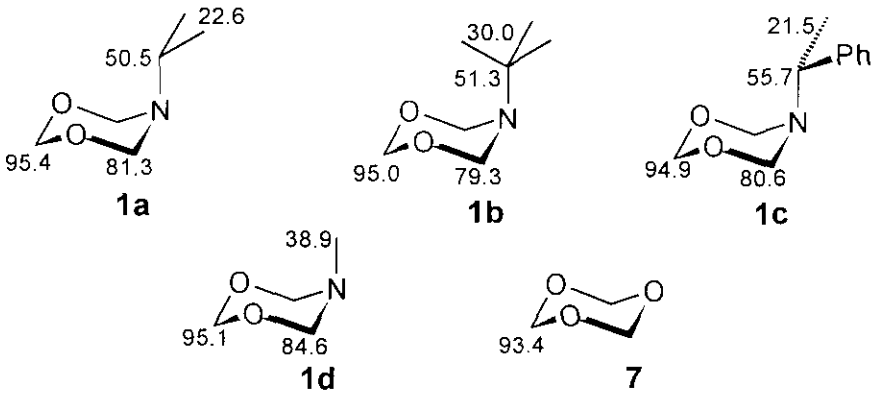
I Syntheses of 1,3,5-Heterocyclohexanes

a) *5-Alkyl-1,3,5-dioxazines (**1a-d**).*

A mixture of formaldehyde (37%) and a primary amine in a 6:1 ratio respectively affords mainly 5-alkyl-1,3,5-dioxazines (**1**). 5-Alkyl-1,3,5-dioxazines (**1a** R = *iso*propyl, **1b** R = *tert*-butyl, **1c** R = *[R]*-α-methylbenzyl) bearing *N*-bulky substituents are stable and could be isolated in good yields by distillation under vacuum, with exception of 5-methyl-1,3,5-dioxazine (**1d**) which could not be separated because it disproportionate to other 1,3,5-heterocycles, therefore **1d** was only characterized by ^{13}C NMR. Scheme 2 shows the ^{13}C NMR chemical shifts of 1,3,5-dioxazines (**1a-d**).

*b) 3,5-Dialkyl-1,3,5-oxadiazines (**2a-h**).*

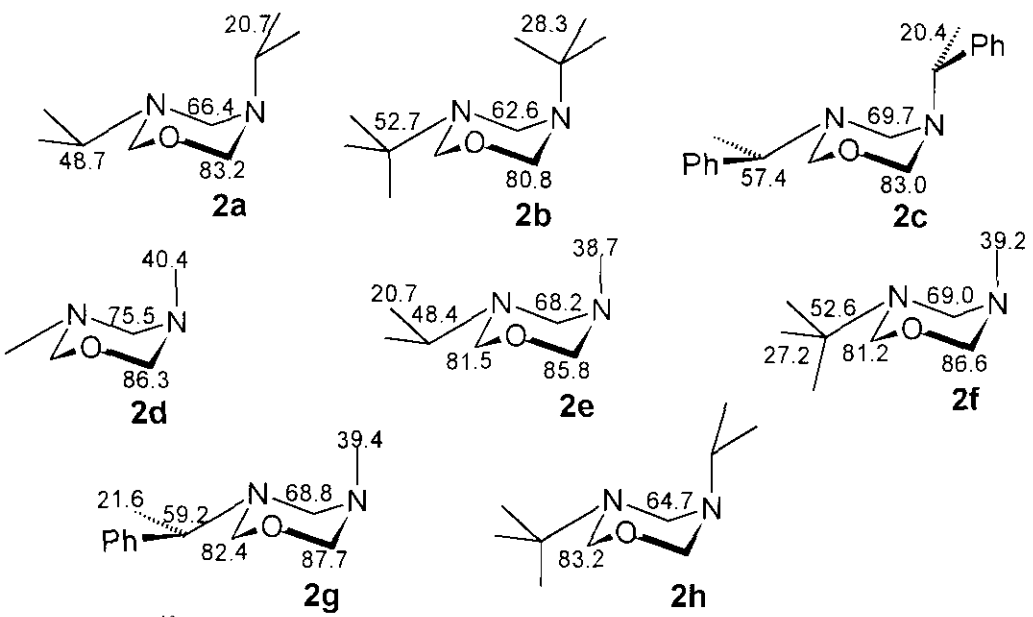
Symmetrically *N*-substituted 3,5-dialkyl-1,3,5-oxadiazines (**2a** R = *iso*propyl, **2b** R = *tert*-butyl, **2c** R = *[R]*-α-methylbenzyl, **2d** R = methyl) were obtained as secondary products in the synthesis of 1,3,5-dioxazines. We were unable to purify them because they disproportionate, however their ^{13}C NMR chemical shifts were directly obtained from the spectra of the reaction mixtures (Scheme 3). 1,3,5-Heterocycles (**2a-d**) are in conformational equilibrium and therefore the equatorial and axial groups are equivalent at room temperature. The non-symmetrically *N*-substituted compounds, 3,5-dialkyl-1,3,5-oxadiazines (**2e** R = *iso*propyl R'= methyl, **2f** R = *tert*-butyl R' = methyl, **2g** R = *[R]*-α-methylbenzyl, R' = methyl, **2h** R = *tert*-butyl R' = *iso*propyl) as well as **2a-d** have been observed as by-products in the amination reactions of 5-alkyl-1,3,5-dioxazines (*vide infra*).



Scheme 2. ^{13}C NMR chemical shifts of 1,3,5-dioxazines (**1a-d**) and tritiane (7)

c) 3,5-Dialkyl-1,3,5-thiodiazines (3a-d).

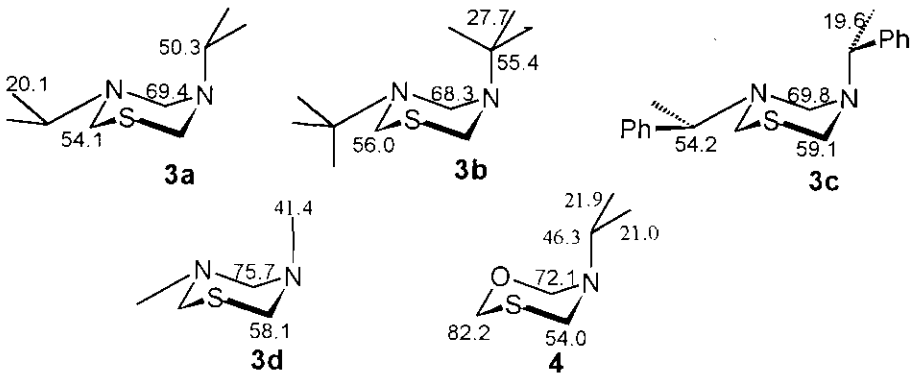
Reactions of formaldehyde, sodium hydrosulfide and primary amines produced the 3,5-dialkyl-1,3,5-thiodiazines (**3a** R = *iso*propyl, **3c** R = *[R]*-α-methylbenzyl, **3d**, R = methyl) in good yields, they were purified by distillation under vacuum.



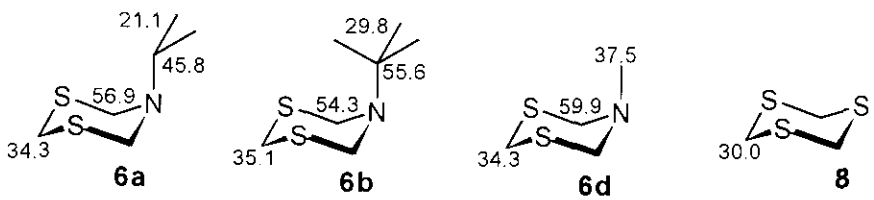
Scheme 3 ^{13}C NMR chemical shifts of 1,3,5-oxadiazinecyclohexanes (**2a-h**).

The reaction of *tert*-butylamine in the conditions depicted above gives as main product the 5-*tert*-butyl-1,3,5-dithiazine (**6b**, 80%) together with 3,5-di*tert*-butyl-1,3,5-thiadiazine (**3b**, 15%). Compound (**3b**) was

also obtained (40%) in the reaction of **6b** with *tert*-butylamine. Scheme 4 shows the ^{13}C NMR chemical shifts of 1,3,5-thiodiazines (**3a-d**) and Scheme 5 those of 1,3,5-dithiazines (**6a-b,d**) and 1,3,5-trithiane (**8**).



Scheme 4 ^{13}C NMR chemical shifts of thiadiazines (**3a-d**) and oxathiazine (**4**)



Scheme 5 ^{13}C NMR chemical shifts of dithiazines (**6a-b,d**) and trithiane (**8**)

*d) 5-Iso*propyl *-1,3,5-thioxazine (4)*

The reaction of *iso*propylamine with formaldehyde and sodium hydrosulfide produces 5-*iso*propyl-1,3,5-thiadiazine (**3a**, 80%) and 5-*iso*propyl-1,3,5-thioxazine (**4**, 20%), compounds were separated and purified by distillation under vacuum. NMR data of **4** is assigned in Scheme 4.

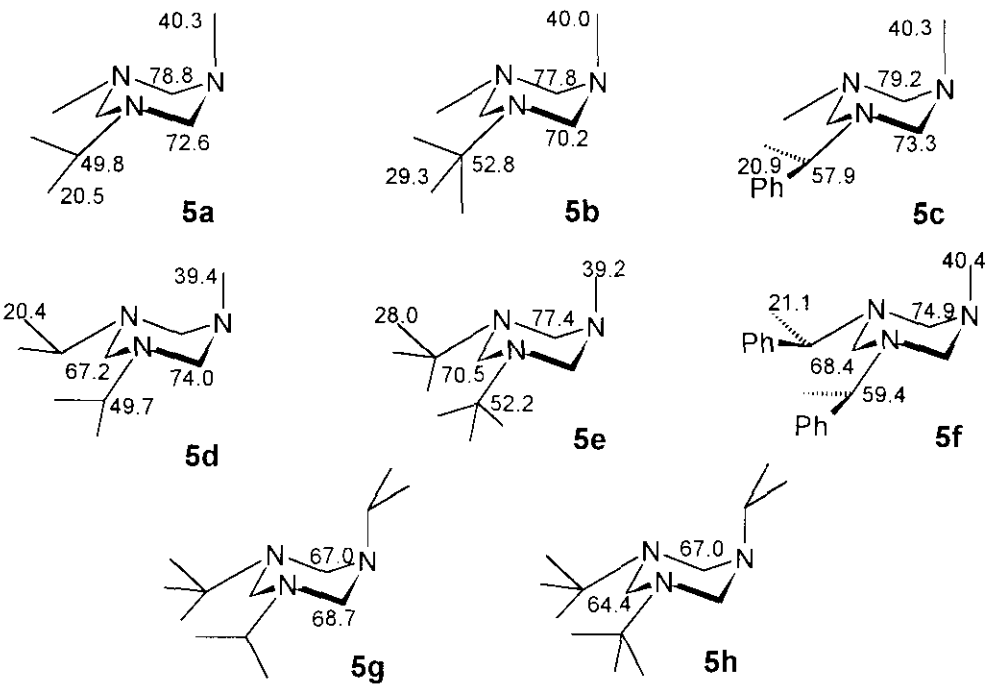
e) 1,3,5-Alkyl-1,3,5-triazines (5a-h).

Syntheses and characterization of symmetrically substituted 1,3,5-triazines (**5i** R = R' = R'' = *iso*propyl, **5j**, R = R' = R'' = *tert*-butyl, **5k**, R = R' = R'' = *[R]*-α-methylbenzyl, **5l** R = R' = R'' = methyl) have been reported.[1b] Herein, we have investigated their transamination reactions that result in non-symmetrically *N*-substituted 1,3,5-triazines. The latter are also formed by amination of 1,3,5-dioxazines. 1,3,5-Triazines were isolated by distillation (**5a**, 70% and **5b**, 87%). Schemes 6 and 7 show the ^{13}C NMR chemical shifts of 1,3,5-triazines.

II. Amination Reactions of 1,3,5-Heterocycles

Amination reactions of 5-alkyl-1,3,5-dioxazines, 5-alkyl-1,3,5-dithiazines and 1,3,5-trialkyl-1,3,5-triazines with alkylamines or 1,3,5-trimethyl-1,3,5-triazine.

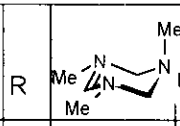
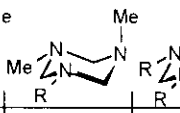
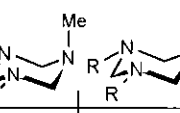
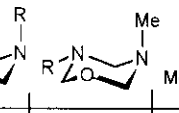
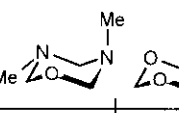
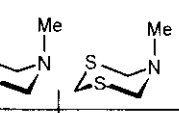
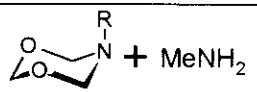
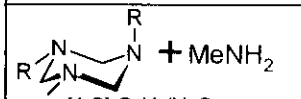
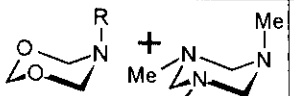
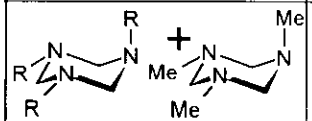
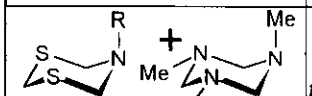
1,3,5-Dioxazines, 1,3,5-dithiazines and 1,3,5-triazines suffer amination reactions with methylamine (in aqueous solution 40%), *iso*propylamine or *[R]*-α-methylbenzylamine in benzene, acetonitrile or without solvent to give the substitution of one, two or three heteroatoms by the amine group. The ratio of the different products varies according to reaction conditions and reagents ratio, some results are shown in Table 1.



Scheme 6 ^{13}C NMR chemical shifts of non-symmetrically *N*-substituted triazines (**5a-h**)

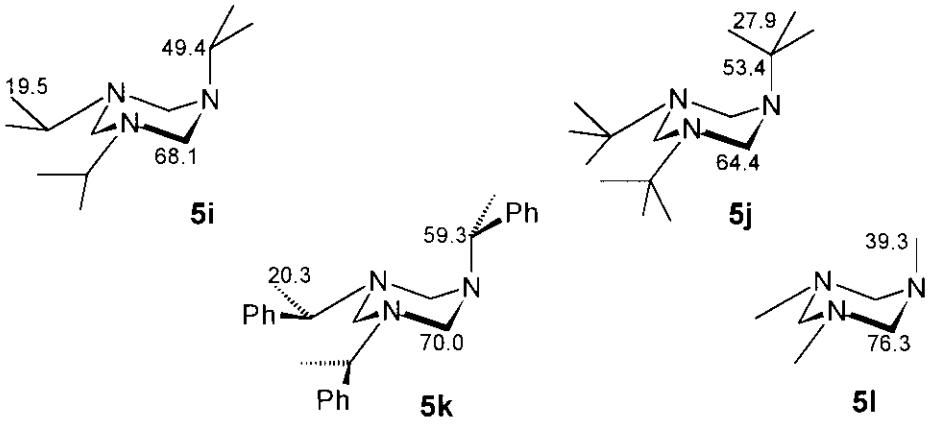
1,3,5-Trimethyl-1,3,5-triazine and 5-methyl-1,3,5-dithiazine do not give amination reactions with other primary amines, presumably due to their high thermodynamic stability. Amination or transamination reactions occur not only with free amines but also with 1,3,5-triazines as aminating source. We have

Table 1 Transamination reaction products of 1,3,5-heterocycles*

	R								
 [1:2] MeCN/H_2O	*t*-Bu	59%	A			A			
	i-Pr	A	52%	A	A				
[1:2] C_6H_6 /H_2O	*t*-Bu		87%	A		A			
	i-Pr	A	70%	A					
[1:1] C_6H_6/H_2O	*i*-Pr		44%	40%	A				
 R [1:2] C_6H_6/H_2O	*t*-Bu		40%	40%					
	i-Pr	A	5%	35%	60%				
 [1:2] without solvent	*t*-Bu		35%			A	A	A	
[2:1] without solvent	*t*-Bu			A		A	A	A	
 [1:1] without solvent	*i*-Pr		45%	A					
 [1:2] without solvent	*t*-Bu								90%

*) The products ratio were evaluated by ^{13}C NMR: (A) minor products (< 35%)

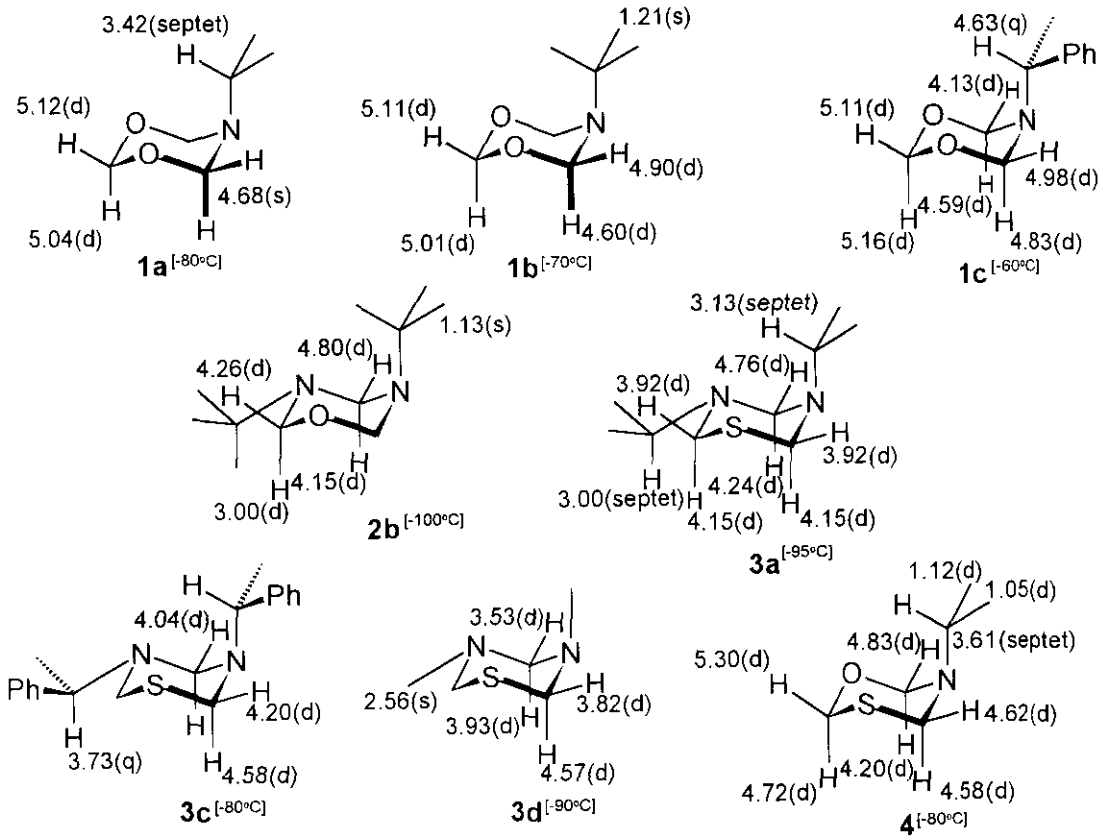
detected that the studied heterocycles are in equilibrium with imines which can be trapped with strong Lewis acids.[4] These imines could be intermediates in amination or transaminations reactions.



Scheme 7 ^{13}C NMR chemical shifts of symmetrically *N*-substituted triazines (**5i-l**)

III. *Conformational Study of Alkyl-1,3,5-heterocycles*

Nitrogenated six-membered heterocycles present a ring conformational equilibrium along with fast nitrogen inversion. In the preferred chair conformation 1,3,5-heterocyclohexanes bearing nitrogen atoms have one *N*-substituent in axial position, which normally is the smallest group.[1] The nitrogen atom inversion process demands less energy (≈15 KJ/mol)[5a] that the ring inversion (45.1 KJ/mol).[5b-c] We were interested in to know how the nature of heteroatoms or *N*-substituents influences the energy barrier for the ring inversion. Therefore, we have calculated by ^1H variable temperature experiments[6] the ring inversion energy for several new 1,3,5-heterocycles. At room temperature, the ^1H NMR spectra of 1,3,5-heterocycles show a simple signal for the methylene protons, which can be explained in terms of a rapid exchange between axial and equatorial hydrogen atoms. On lowering the temperature the methylene ^1H resonances broaden, coalesce and then appear as separated multiplets for axial and equatorial hydrogen atoms. The chemical shifts of compounds (**1a-c**, **2b** and **3a**,**c**,**d**) obtained at low temperature are shown in Scheme 8. Assuming that the peak separation $\Delta\nu$ and the ring inversion rate constant k are larger than the band width in the absence of exchange, the free energy of the activated complex ΔG^* at coalescence can be calculated[6] and the energy barrier values for ring inversion are in Table 2.



Scheme 8 ^{1}H NMR chemical shifts (ppm) of the preferred conformers of compounds (**1a-c**, **2b**, **3a**,**c-d** and **4**) obtained at low temperature in C_4D_8O.

Table 2 Energy barrier values for ring inversion (KJ/mole) of 1,3,5-heterocycles.

			R	
Heterocycles:	*Iso*propyl	*tert*-butyl	methyl	*[R]*-α-methylbenzyl
Dioxazines (**1**)	45.0	46.0	----	49.0
Oxadiazines (**2**)	----	43.0	----	----
Thiadiazines (**3**)	43.0	----	47.5	47.0
Thioxazine (**4**)	45.0	----	----	----
Triazines (**5**)	47.7[7]	42.7[7]	53.6[7]	51.6[1b]
Dithiazines (**6**)	43.1[1c]	39.7[1f]	47.3[1f]	48.2[1c]

Data show that 1,3,5-triazines have the highest energy barriers, an explanation for this behavior could be that 1,3,5-triazines have two *N*-alkyl groups in equatorial position that stabilize the ring conformation giving a high energy barrier, while 1,3,5-dioxazines, 1,3,5-thiadiazines, 1,3,5-thioxazine, and 1,3,5-thiadiazines have similar values indicating that the nature of the heteroatom is not relevant for the inversion mechanism. The exception are *tert*-butyl 1,3,5-heterocycles which have the lowest values,

presumably due to the strong steric effect of the *tert*-butyl group that diminishes the energy difference between the two chair conformers and the transition state.

CONCLUSIONS

Several 1,3,5-heterocycles (**1a-d**, **2a-h**, **3a-d**, **4** and **5a-h**) were prepared pure and analyzed by NMR spectral techniques. Amination reactions showed equilibria between 1,3,5-heterocycles and CH_2=X species that allow the formation of compounds bearing nitrogen atoms with different substituents. Variable temperature NMR analyses indicate that 1,3,5-heterocycles were in conformational equilibria and the ring inversion energies were determined.

EXPERIMENTAL

General procedures. All solvents were freshly distilled. Melting points were measured on a Gallenkamp apparatus and are uncorrected. The ^{1}H, ^{13}C and ^{15}N NMR spectra were recorded with a JEOL GXS-270 (^{1}H 270 MHz) or a JEOL Eclipse (^{1}H 400 MHz). Chemical shifts are given on the δ scale (ppm) ^{1}H and ^{13}C data with tetramethylsilane as internal reference. The ^{15}N spectra were obtained at 27.25 MHz (JEOL GXS-270) by the refocused INEPT pulse sequence with $^2J(^{15}N\text{-}^1H)$ = 2 Hz, with nitromethane as reference. Variable temperature experiments were performed with a temperature controller to keep the temperature constant within 0.3°C. Samples were dissolved in THF-d_8. Elemental analyses were performed by Oneida Research Services, Whitesboro, New York. The MS spectra were obtained to 20 eV in a HP 5989 spectrometer.

Preparation of 5-alkyl-1,3,5-dioxazine (1a-c) and 3,5-dialkyl-1,3,5-oxadiazines (2a-c). General Procedure. The corresponding amine (0.42 mol) at 0°C was mixed with an aqueous solution of formaldehyde (37%, 187.0 mL, 2.5 mol) previously cooled at 0°C and the reaction mixture was stirred 12 h. The reaction products were extracted with ether and dried with Na_2SO_4. The solvent was removed to give a liquid, which was distilled, under vacuum.

5-*Iso*propyl-1,3,5-dioxazine (1a). Colorless liquid (90%). bp 20°C (0.7 mmHg). *m/z* (%): 40 (60), 56 (75), 59 (33), 72 (30), 86 (100), 116 (72), 131 (M^+, 46). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ (ppm) 5.07 (s, 2H, 2H-2), 4.66 (s, 4H, 2H-4 and 2H-6), 3.41 (septet, J = 6.6 Hz, 1H, H-7), 1.15 (d, J = 6.6 Hz, 6H,

2[CH_3]). ^{1}H NMR (400 MHz, THF-d_8, -80°C): δ (ppm) 4.68 (s, 2H, 2H-2), 5.04 (d, J = 5.9 Hz, 2H, Heq-4 and Heq-6), 3.42 (septet, J = 6.6 Hz, 1H, H-7), 1.13 (d, J = 6.6 Hz, 6H, 2[CH_3]). ^{13}C NMR (67.9 MHz, $CDCl_3$, 25°C): δ (ppm) 95.4 (C-2), 81.3 (C-4 and C-6), 49.4 (C-7), 22.4 (C-8 and C-9). ^{15}N NMR (27.25 MHz, $CDCl_3$): δ (ppm) –306.6. *Anal.* Calcd for $C_6H_{13}NO_2$: C, 54.92; H, 9.99; N, 10.68. Found: C, 54.32; H, 9.79; N, 10.90.

5-*Tert*-butyl-1,3,5-dioxazine (1b). Colorless liquid (85%). b.p. 22°C (0.5 mmHg). *m/z* (%): 45 (100), 75 (62), 100 (25), 130 (30), 145 (M^+, 10). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ (ppm) 5.17 (s, 2H, 2H-2), 4.83 (s, 4H, 2H-4 and 2H-6), 1.28 (s, 9H, 3[CH_3]). ^{1}H NMR (400 MHz, THF-d_8, -70°C): δ (ppm) 5.11 (d, J = 5.0 Hz, 1H, Heq-2), 5.01 (d, J = 5.0 Hz, 1H, Hax-2), 4.90 (d, J = 11.0 Hz, 2H, Heq-4 and Heq-6), 4.60 (d, J = 11.0 Hz, 2H, Hax-4 and Hax-6), 1.21 (s, 9H, 3[CH_3]). ^{13}C NMR (67.9 MHz, $CDCl_3$, 25°C): δ (ppm) 95.0 (C-2), 79.3 (C-4 and C-6), 51.3 (C-7), 30.0 (C-8, C-9 and C-10). *Anal.* Calcd for $C_7H_{15}NO_2 \cdot (H_2O)_{1/2}$: C, 55.22; H, 9.29; N, 9.21. Found: C, 55.43; H, 9.20; N, 9.54.

5-(*[R]*-α-Methylbenzyl)-1,3,5-dioxazine (1c). Colorless liquid (75%). bp 28°C (0.25 mmHg). $[\alpha]_D^{25}$= +55.3°(c= 0.1, THF). *m/z* (%): 29 (64), 77 (83), 91 (88), 105 (100), 118 (93), 178 (92), 193 (M^+, 27). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ (ppm) 5.14 (s, 2H, 2H-2), 4.51 (d, J = 11.0 Hz, 2H, Hax-4 and Hax-6), 4.74 (d, J = 11.0 Hz, 2H, Heq-4 and Heq-6), 4.64 (q, J = 6.7 Hz, 1H, H-7), 1.41 (d, J = 6.7 Hz, 3H, [CH_3-8]), 7.0-7.2 (m, 5H). ^{1}H NMR (400 MHz, THF-d_8, -80°C): δ (ppm) 5.11 (d, J = 5.9 Hz, 1H, Heq-2), 5.16 (d, J = 5.9 Hz, 1H, Hax-2), 4.63 (q, J = 6.2 Hz, 1H, H-7), 4.98 (d, J = 11.4 Hz, 1H, Heq-6), 4.83(d, J = 11.4 Hz, 1H, Hax-6), 4.59 (d, J = 10.6 Hz, 1H, H-6), 4.13 (d, J = 10.6 Hz, 1H, Heq-4), 1.35 (q, J = 6.2 Hz, 3H, [CH_3]). ^{13}C NMR (67.9 MHz, $CDCl_3$, 25°C): δ (ppm) 94.9 (C-2), 80.6 (C-4 and C-6), 55.7 (C-7), 21.5 (C-8), 144.4 (Ci), 127 (2Co, 128 (2Cm), 126.9(Cp). ^{15}N NMR (27.25 MHz, $CDCl_3$): δ (ppm) –304.3. *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.68; H, 7.65; N, 7.29.

3,5-Di*iso*propyl-1,3,5-oxadiazine (2a) (10%) was identified in presence of **1a**. ^{13}C NMR (67.9 MHz, $CDCl_3$, 25°C): δ (ppm) 83.2 (C-2 and C-6), 66.4 (C-4), 48.7 (C-7), 20.7 (C-8).

3,5-Di*tert*-butyl-1,3,5-oxadiazine (2b) (8%) was identified in presence of **1b**. ^{13}C NMR (67.9 MHz, $CDCl_3$, 25°C): δ (ppm) 80.8 (C-2 and C-6), 62.0 (C-4), 53.3 (C-7), 28.3 (C-8).

3,5-Bis(*[R]*-α-methylbenzyl)-1,3,5-oxadiazine (2c). Compound (**2c**) (40%) was identified in presence of **1c** (50%). ^{13}C NMR (67.9 MHz, $CDCl_3$, 25°C): δ (ppm) 83.0 (C-2 and C-6), 69.7 (C-4), 57.4 (C-7), 20.4 (C-8), 144.1 (Ci). ^{15}N NMR (27.25 MHz, $CDCl_3$): δ (ppm) –318.3.

Preparation of 3,5-dialkyl-1,3,5-thiadiazines (3a-d) and 5-*iso*propyl-1,3,5-oxathiazine (4). General Procedure. The corresponding amine (0.83 mol) was cooled at 0°C, aqueous formaldehyde (37%, 187.0 mL, 2.5 mol) previously cooled at 0°C and an aqueous solution of NaSH-xH_2O (56 g, 1 mmol) were

added and the reaction mixture was stirred 12 h. The product was extracted with ether and dried with Na_2SO_4. The solvent was removed and a yellow liquid was obtained and distilled under vacuum.

3,5-Di*iso*propyl-1,3,5-thiadiazine (3a). Yellow liquid (90%). bp 70°C (0.5 mmHg). *m/z* (%): 42 (25), 45 (100), 58 (21), 70 (28), 72 (100), 75 (52), 85 (84), 105 (36). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ (ppm) 4.07(s, 4H, 2H-2 and 2H-6), 3.76 (s, 2H, 2H-4), 3.16 (septet, *J* = 6.6 Hz, 2H, H-7 and H-8), 1.02 (d, *J* = 6.6 Hz, 12H, 4[CH_3]). ^{13}C NMR (67.9 MHz, $CDCl_3$, 25°C): δ (ppm) 54.1 (C-2 and C-6), 69.4 (C-4), 50.3 (C-7 and C-8), 20.1 (4[CH_3]). ^{15}N NMR (27.25 MHz, $CDCl_3$) δ (ppm) –329.7. *Anal.* Calcd for $C_9H_{20}N_2S\cdot(H_2O)_{1/3}$: C, 55.62; H, 10.72; N, 14.41. Found: C, 55.13; H, 10.63; N, 14.30.

3,5-Di(*/R/*-α-methylbenzyl)-1,3,5-thiadiazine (3c).Yellow liquid (70%). bp 80°C (0.25 mmHg). $[\alpha]_D^{25}$=+70.5° (c= 0.1, THF). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ (ppm) 4.22 (s, 4H, 2H-2 and 2H-6), 3.81 (s, 2H, 2H-4), 3.75 (septet, *J* = 7.0 Hz, 2H, H-7 and H-8), 1.31 (d, *J* = 7.0 Hz, 6H, 2 [CH_3]). ^{13}C NMR (67.9 MHz, $CDCl_3$, 25°C): δ (ppm) 59.1 (C-2 and C-6), 69.8(C-4), 54.2 (C-7 and C-8), 19.6 (2 [CH_3]). ^{15}N NMR (27.25 MHz, $CDCl_3$) δ (ppm) –329.7. *Anal.* Calcd for $C_6H_{13}NO_2$: C, 73.04; H, 7.75; N, 8.97. Found: C, 73.61; H, 8.10; N, 8.47.

3,5-Dimethyl-1,3,5-thiadiazine (3d). Yellow liquid (70%). bp 45°C (0.25 mmHg). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ (ppm) 4.05 (s, 4H, 2H-2 and 2H-6), 3.62 (s, 2H, 2H-4), 2.49 (s, 6H, H-7 and H-8). ^{13}C NMR (67.9 MHz, $CDCl_3$, 25°C): δ (ppm) 58.1 (C-2 and C-6), 75.7 (C-4), 41.4 (C-7 and C-8). *Anal.* Calcd for $C_5H_{12}N_2S\cdot H_2O$: C, 39.97; H, 9.39; N, 18.65. Found: C, 39.95; H, 9.35; N, 18.55.

5-*Iso*propyl-1,3,5-thioxazine (4). Yellow liquid (20%). bp 40°C (1 mmHg). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ (ppm) 5.05 (s, 2H, 2H-2), 4.65 (s, 2H, 2H-4), 4.46 (s, 2H, 2H-6), 3.29 (septet, *J* = 6.2 Hz, 1H, H-7), 1.10 (d, *J* = 6.2 Hz, 6H, 2 [CH_3]). ^{13}C NMR (67.9 MHz, $CDCl_3$, 25°C): δ (ppm) 82.2 (C-2), 54.0 (C-4), 72.1 (C-6), 46.3 (C-7), 21.0 and 21.9 (C-8 and C-9). *Anal.* Calcd for $C_6H_{13}NOS$: C, 48.94; H, 8.90; N, 9.51. Found: C, 48.95; H, 8.55; N, 9.45.

Amination reaction of 5-*tert*-butyl-1,3,5-dioxazine (1b). General procedure for amination reactions. Pure 1,3,5-dioxazine (**1b**) (1.0 mL, 6.88 mmol) was dissolved in benzene (100 mL) and an aqueous solution of methylamine (40%, 1.11 mL, 13.76 mmol) was added and the mixture was refluxed for 5 h. The volatiles were evaporated under vacuum. The mixture (1.17 g) was analyzed by NMR, compound (**5b**) was the main product (87%).

5-Dimethyl-1-*iso*propyl-1,3,5-triazine (5a). Compound (**5a**) (70%). *m/z* (%) 157 (M^+, 4), 114 (20), 72 (30), 56 (45), 44 (100), 30 (18). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ (ppm) 3.10-2.72 (br s, 6H, 2 [H-2, H-4 and H-6]), 2.63 (septet, *J* = 6.4 Hz 1H, H-7), 1.93 and 1.87 (2s, 6H, 2 [$NC\underline{H}_3$]), 0.71 (d, *J* = 6.4 Hz, 6H, 2 [$CC\underline{H}_3$]). ^{13}C NMR (67.9 MHz, $CDCl_3$, 25°C): δ (ppm) 78.8 (C-4), 72.6 (C-2 and C-6), 49.8 (C-7),

40.3 (2 [N$\underline{C}H_3$]), 20.5 (2 [C$\underline{C}H_3$]). *Anal.* Calcd for $C_8H_{19}N_3$: C, 61.04; H, 12.18; N, 26.73. Found: C, 61.57; H, 12.01; N, 26.2.

3,5-Dimethyl-1-*tert*-butyl-1,3,5-triazine (5b). *m/z* (%) 171 (M^+, 1), 128 (12), 70 (46), 57 (56), 44 (100), 42 (36), 30 (26). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ (ppm) 3.30-3.46 (br s, 6H, 2 [H-2, H-4 and H-6]), 2.21 and 2.24 (2s, 6H, 2 [NC$\underline{H}_3$]), 1.00 (s, 9H, 3 [CC$\underline{H}_3$]). ^{13}C NMR (67.9 MHz, $CDCl_3$, 25°C): δ (ppm) 77.8 (C-3), 70.2 (C-2 and C-6) 52.8 (C-7), 40.0 (2 [N$\underline{C}H_3$]), 29.3 (3 [C$\underline{C}H_3$]. *Anal.* Calcd for $C_9H_{21}N_3$: C, 63.09; H, 12.36; N, 24.54. Found: C, 63.45; H, 12.66; N, 24.10.

Transamination reaction of 1,3,5-tri*iso*propyl-1,3,5-triazine (5i). General procedure for transamination reactions. Pure 1,3,5-triazine (**5i**) (10 mL, 46.83 mmol) was dissolved in benzene (300 mL), and two equivalent of an aqueous solution of methylamine (40%, 7.56 mL, 93.66 mmol) was added. The volatiles were evaporated under vacuum. A colorless liquid was obtained (9.4 g) that was analyzed by ^{13}C NMR. Three compounds were observed in the reaction mixture: 1,3,5-tri*iso*propyl-1,3,5-triazine (**5i**, 60%), 1,3-di*iso*propyl-5-methyl-1,3,5-triazine (**5d**, 5%) and 3,5-dimethyl-1-*iso*propyl-1,3,5-triazine (**5a**, 35%).

Amination reaction of 5-*tert*-butyl-1,3,5-dioxazine (1b) and 5-*tert*-butyl-1,3,5-dithiazine (6b). General procedure for amination with reactions triazines. Pure 1,3,5-dithiazine (**6b**) (0.56 mmol, 0.1 g), was mixture with two equivalents of trimethyl-1,3,5-triazine (**5l**) (1.25 mmol, 0.17 mL) and heated at 68°C for 3 h. The volatiles were evaporated under vacuum. A colorless solid was obtained (90%, 0.09 g) identified as compound (**6d**), by NMR.

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