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## THE SYNTHESIS, STRUCTURE AND REACTIVITY OF 1-THIOXOTETRAHYDROPYRIDAZINO[1,2-*a*][1,2,4]TRIAZIN-4(1*H*)- ONE

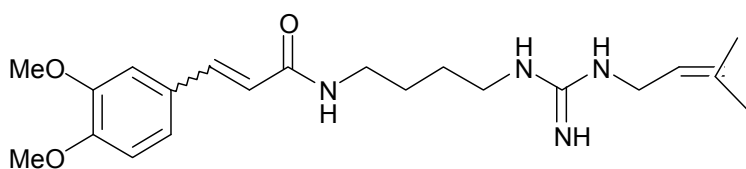
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 Jamaica

**Abstract** – The synthesis of 1-thioxotetrahydropyridazino[1,2-*a*][1,2,4]triazin-4-(1*H*)-one **3** in five steps from *tert*-butyl carbazate and its transformation into 3-benzylidene and 1-amino derivatives are described. Its crystal structure is presented showing it to be an axially chiral molecule that exists as a racemate in the solid state.

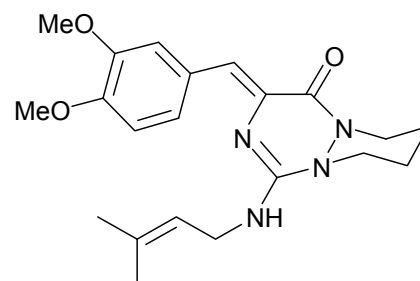
### INTRODUCTION

An interest in determining the bioactive conformation of the naturally occurring hypotensive guanidine, caracasamide **1**,<sup>1</sup> led us to design triazinone **2** as one of a number of conformationally restricted analogues.

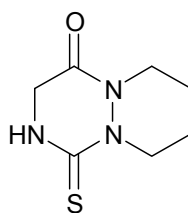


**1a** *E*-caracasamide

**1b** *Z*-caracasamide

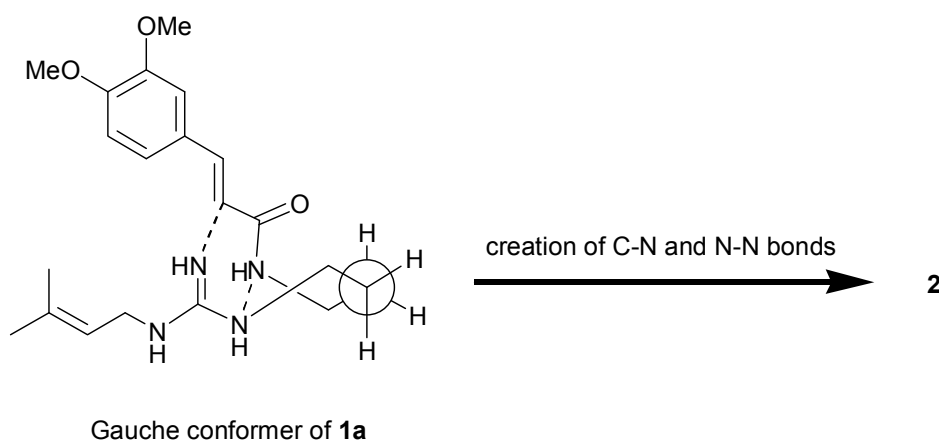


**2**



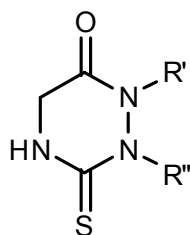
**3**

Compound **2** was based on a gauche conformation of **1a** attained by rotation about the C2-C3 bond of the flexible butyl chain that links the cinnamyl amide and prenyl guanidine moieties. By creating the C-N and N-N bonds as shown in Figure 1, we essentially locked the molecule into the novel 3-amino[1,2,4]triazinone structure **2**. If the gauche representation approximates the bioactive conformation of caracasamide **1**, then the rigidification achieved in **2** could result in an enhanced binding affinity and greater activity as there would now be less of the attendant loss of entropy<sup>2</sup> that occurs when a flexible molecule has to undergo conformational change in order to bind with its receptors.



**Figure 1.** Design of conformationally restricted analogue **2** based on a gauche conformer of **1a**

In our bid to synthesize **2**, the thioxotetrahydropyridazinotriazinone **3** emerged as a key intermediate. This molecule is interesting in its own right. It is a novel hexahydropyridazine derivative and the bicyclic counterpart of the 3-thioxo-1,2,4-triazin-6-ones **4a-c**. Prepared<sup>3</sup> by Böhme and Strahl *via* the isomerization and cyclization of thiocyanatoacetic hydrazides, **4a-c** are the only such thioxotriazinones to have hitherto been reported. By contrast, hexahydropyridazine derivatives have attracted a lot of attention.



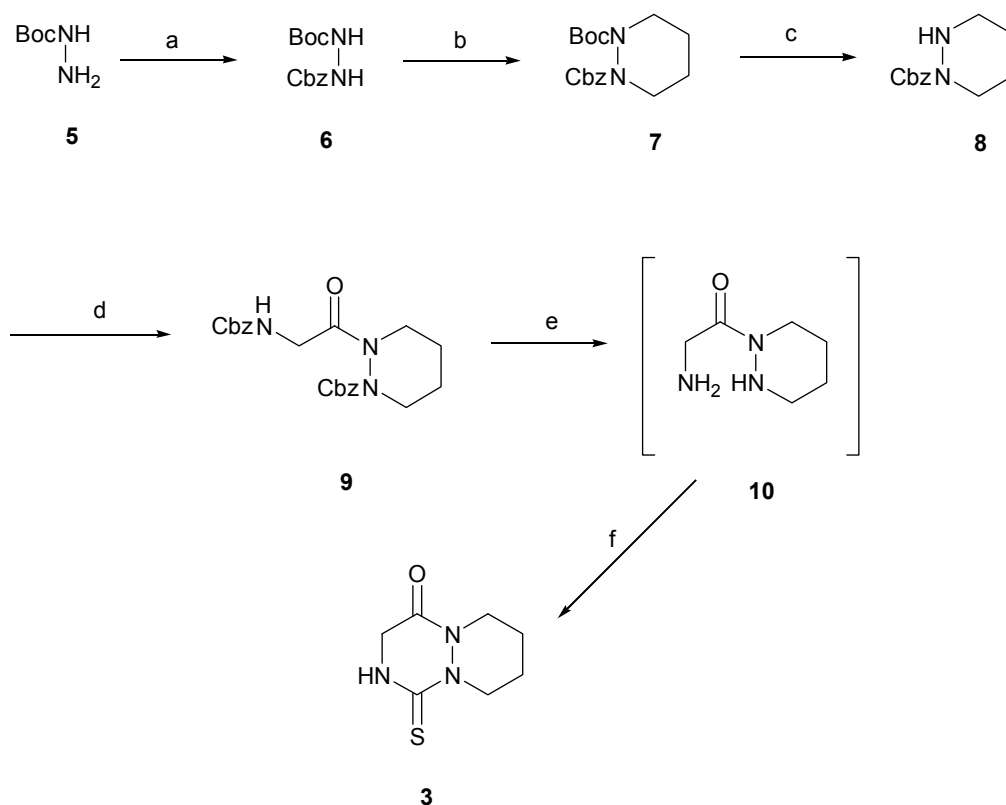
- 4a** R'=H, R''=H  
**4b** R'=Me, R''=H  
**4c** R'=Me, R''=Me

They have been shown to exhibit significant biological activity exemplified by the herbicidal 1,2,4-tetrahydro[1,2-*a*]triazolopyridazinedithiones,<sup>4</sup> the antiinflammatory 2-cyanotetrahydropyridazine-1-carboxylates<sup>5</sup> and the inducible nitric oxide synthase inhibiting hexahydropyridazine-1-carboximidamides, carbothioamides and carbothioimidic acid esters.<sup>6</sup> Moreover, *N,N'*-diacylhexahydropyridazines have featured in the field of peptidomimetics wherein they have been utilized in the synthesis of peptide sequences containing the unnatural azahomoproline residue.<sup>7,8</sup> Methods for the synthesis of hexahydropyridazines include the Diels Alder reaction<sup>9</sup> between 1,3-butadienes and azodicarboxylic acid esters, high pressure hydrogenation<sup>10</sup> of pyridazines and the reaction of 1,4-dihaloalkanes with hydrazine dicarboxylates.<sup>8,11</sup>

For compound **3** we chose the last of these approaches, with the expectation that sulfur could be introduced by way of a thiocarbonylation reaction. We now report the synthesis of 1-thioxotetrahydropyridazino[1,2,4]triazin-4(1*H*)-one (**3**), its crystal structure and reactivity.

## RESULTS AND DISCUSSION

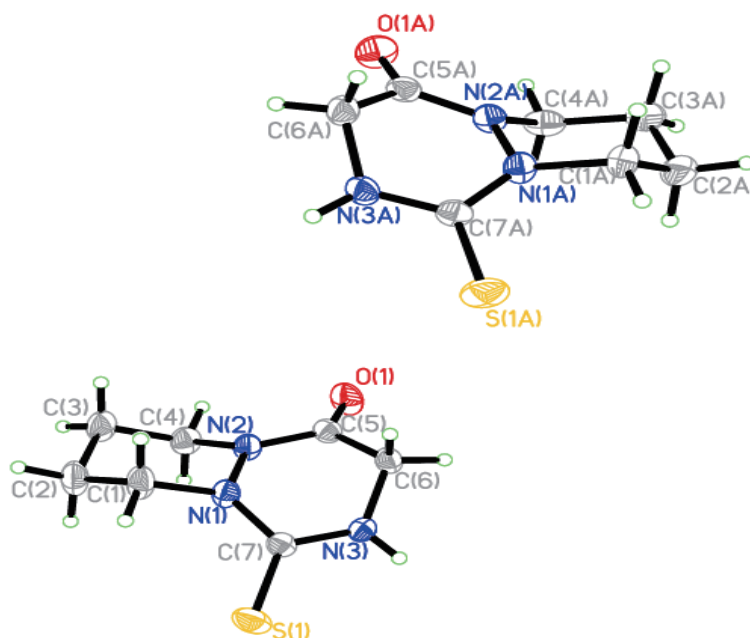
Our approach to **3** (Scheme 1) made use of the orthogonally protected hexahydropyridazine **7** which we synthesized using essentially the methodology described by Boussard and co-workers.<sup>7,8</sup> Treatment of commercially available *tert*-butylcarbazate (**5**) at 0 °C with benzyl chloroformate in the presence of triethylamine, gave the unsymmetrical hydrazine dicarboxylate **6** (83%). Deprotonation of **6** using NaH in DMF and annulation with 1,4-dibromobutane furnished **7** in 73% yield. Removal of the Boc group (82%) followed by acylation with *N*-Cbz-glycyl chloride (prepared from *N*-Cbz-glycine,<sup>12</sup> oxalyl chloride and DMF cat.) afforded the doubly Cbz-protected *N*-glycyl hexahydropyridazine **9** (62%). Catalytic hydrogenolysis of **9** carried out at atmospheric pressure removed both of the benzyloxycarbonyl (Cbz) groups. The resultant *N*-glycylhexahydropyridazine (**10**), a straw coloured oil, proved to be quite unstable and seemed to polymerize on standing at room temperature to give a highly insoluble solid. Consequently, **10** had to be used straight away in the next step – ring closing thiocarbonylation using thiocarbonyl diimidazole in MeCN. In this way, the thioxohexahydropyridazino-triazinone **3** was obtained (71% yield over two steps) as a cream solid. The structure of **3** was supported by the <sup>1</sup>H and <sup>13</sup>C NMR spectral data, notable features being the <sup>13</sup>C resonances at 162.5 and 178.9 ppm that distinguished the carbonyl and thiocarbonyl groups respectively.



**Scheme 1.** Reagents and conditions: a) benzyl chloroformate, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C – rt, 83%. b) 1,4-dibromobutane, NaH, DMF, 0 °C – rt, 73%. c) 25% TFA:CH<sub>2</sub>Cl<sub>2</sub>, rt, 82%. d) *N*-Cbz-glycyl chloride, CH<sub>2</sub>Cl<sub>2</sub>, 62%. e) H<sub>2</sub>, 1 atm, 5 % Pd/C, MeOH, rt. f) thiocarbonyldiimidazole (TCDI), MeCN, rt-130 °C, sealed tube, 71% over 2 steps.

Single crystal X-ray diffraction studies<sup>13</sup> carried out at room temperature show that compound **3** crystallizes as a racemate in the monoclinic space group P2<sub>1</sub>/c. A view of the two independent molecules in the unit cell is given in Figure 2. The axial chirality that gives rise to this racemic compound can be considered to arise from a torsional barrier to rotation about the N-N bond caused by repulsion between the electron lone pairs of the nitrogen atoms. Thus inversion of the fused six membered rings is precluded resulting in the atropisomerism observed in Figure 2. The hexahydropyridazine ring in **3** adopts a *quasi* chair conformation in which both nitrogens are essentially planar. This is indicated by the average bond angle,  $\alpha_{av}$  around each nitrogen atom:  $\alpha_{av}(N1) = 120^\circ$ ,  $\alpha_{av}(N2) = 118.71^\circ$ ,  $\alpha_{av}(N1A) = 119.94^\circ$ ,  $\alpha_{av}(N2A) = 119.1^\circ$  (Table 2). The non-planar thioxotriazinone ring adopts a twist boat conformation with torsion angles C(1)-N(1)-N(2)-C(4) of  $-52.7^\circ$  and C(7)-N(1)-N(2)-C(5) of  $-30.8^\circ$  (C(1A)-N(1A)-N(2A)-C(4A) is  $+52.9^\circ$  and C(7A)-N(1A)-N(2A)-C(5A) is  $+30.0^\circ$ ). This is comparable to the corresponding torsion angles ( $55.9^\circ$  and  $27.7^\circ$  respectively) reported by Kaftory and co-workers<sup>14</sup> for the structurally related hexahydropyridazino[1,2-*a*]pyridazine-1,4-dione. Importantly, the twisted conformation of the thioxotriazinone ring in **3** allows the electron lone pairs of the N-N group to avoid co-planarity. The

N-CO, N-N and N-C bond lengths (Table 1) are all in the range seen for related compounds<sup>14</sup> with flat, non-coplanar hydrazine nitrogens. Crystal packing diagrams of **3** show two non-interacting, infinite one dimensional chains that have an inversion relationship and feature alternating atropisomers linked *via* intermolecular N-H $\cdots$ O=C hydrogen bonds in a sinusoidal pattern (Figures 3 and 4).

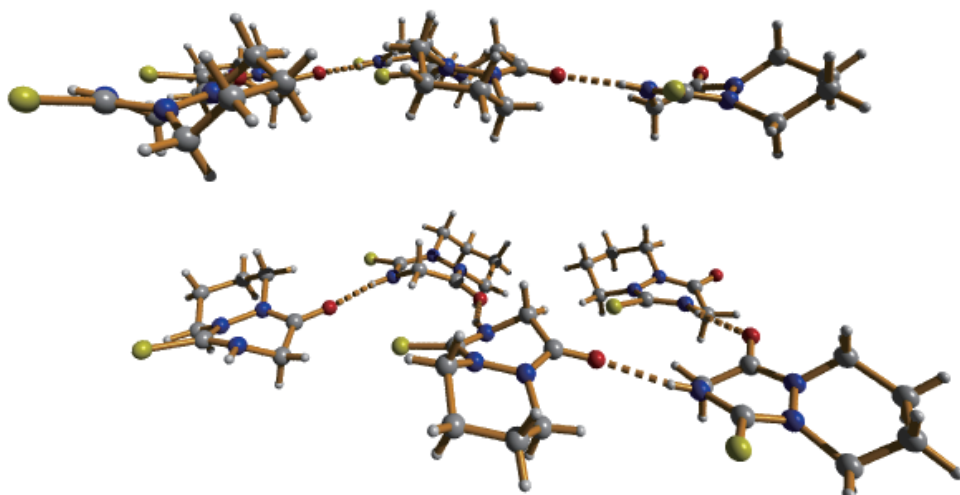


**Figure 2.** The asymmetric unit of compound **3**. The ellipsoids are drawn to 30% probability.

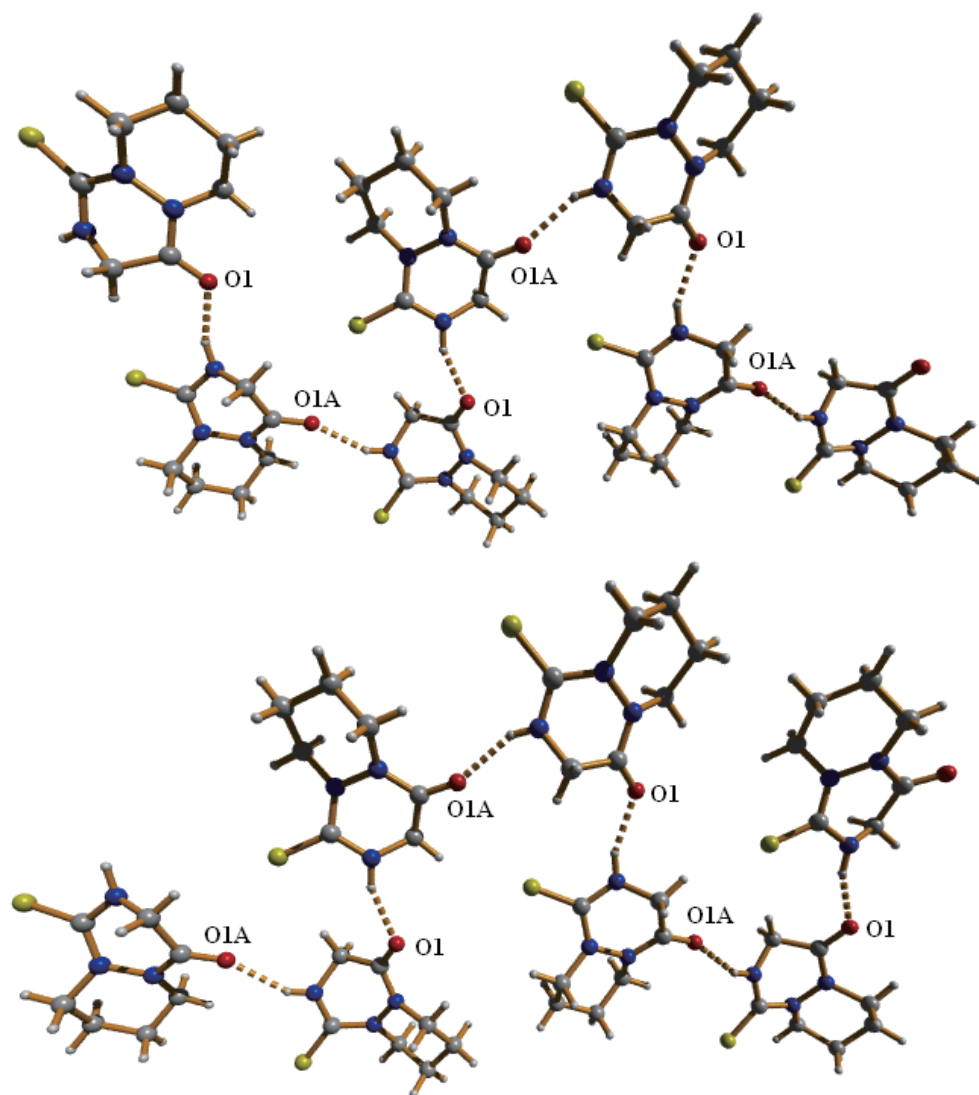
**Table 1.** Selected structural and geometric features of **3**.

Bond lengths (Å)	N(1)-N(2)	1.413(2)	N(1A)-N(2A)	1.416(2)
	C(7)-S(1)	1.6734(19)	C(7A)-S(1A)	1.6743(19)
	C(5)-O(1)	1.218(2)	C(5A)-O(1A)	1.229(2)
	N(2)-C(5)	1.350(2)	N(2A)-C(5A)	1.341(3)
	N(1)-C(7)	1.360(2)	N(1A)-C(7A)	1.355(3)
Bond angles (°)	C(4)-N(2)-C(5)	121.92(16)	C(4A)-N(2A)-C(5A)	122.67(16)
	C(4)-N(2)-N(1)	114.49(15)	C(4A)-N(2A)-N(1A)	114.62(16)
	N(1)-N(2)-C(5)	119.71(15)	N(1A)-N(2A)-C(5A)	120.00(15)
	$\alpha_{av}$ (N2) <sup>a</sup>	118.71(15)	$\alpha_{av}$ (N2A) <sup>a</sup>	119.10(16)
	C(1)-N(1)-N(2)	114.15(15)	C(1A)-N(1A)-N(2A)	114.03(15)
	N(2)-N(1)-C(7)	120.39(15)	N(2A)-N(1A)-C(7A)	120.24(16)
	C(1)-N(1)-C(7)	125.46(16)	C(1A)-N(1A)-C(7A)	125.54(16)
	$\alpha_{av}$ (N1) <sup>a</sup>	120.00(15)	$\alpha_{av}$ (N1A) <sup>a</sup>	119.94(16)
Torsion angles (°)	C(1)-N(1)-N(2)-C(4)	-52.7(2)	C(1A)-N(1A)-N(2A)-C(4A)	+52.9(2)
	C(7)-N(1)-N(2)-C(5)	-30.8(3)	C(7A)-N(1A)-N(2A)-C(5A)	+30.0(3)

<sup>a</sup> Average of the bond angles around the nitrogen atom.

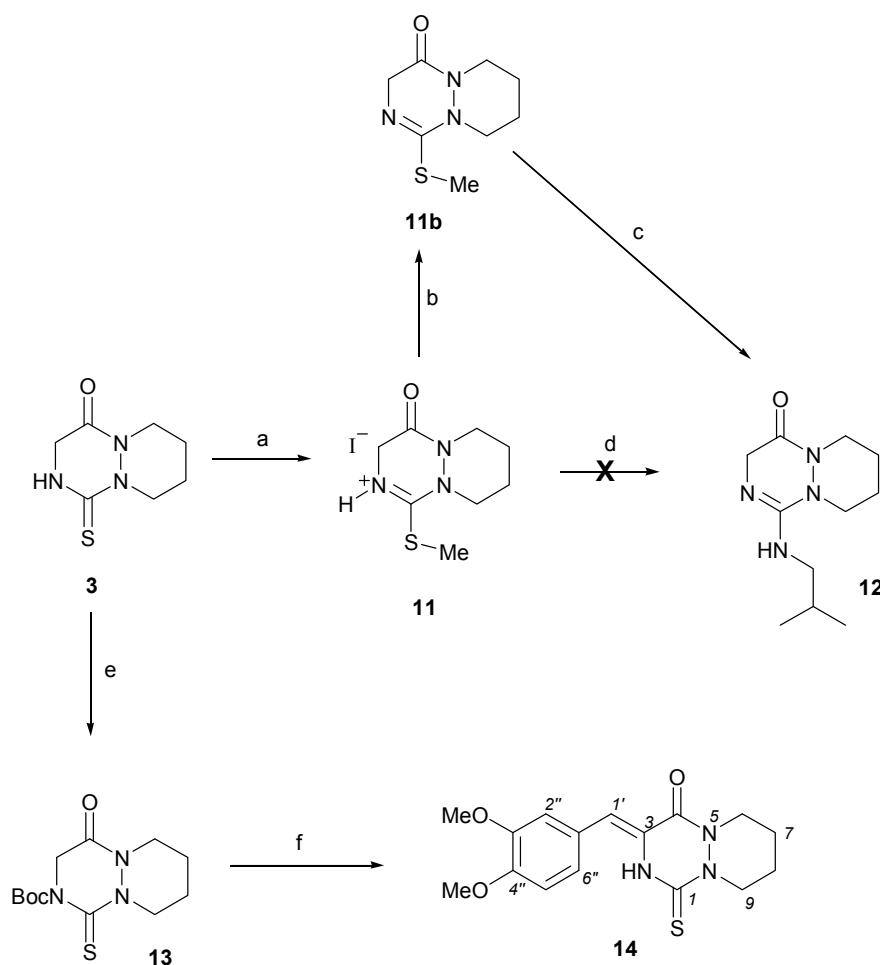


**Figure 3.** The two infinite one dimensional chains of **3**. Intermolecular H-bonds between atropisomeric pairs within each chain are shown *via* dashed bonds.



**Figure 4.** View of each of the two one-dimensional chains showing the H-bonding interactions between different atropisomers, the sinusoidal motif that results and the inversion relationship between the two chains.

Our synthetic strategy for triazinone **2** was contingent on compound **3** being able to react in two ways. The cyclic thiourea moiety must undergo guanylation and this was considered achievable *via* the *S*-methyl isothioureia.<sup>15,16</sup> Furthermore, a Knoevenagel reaction between Boc-protected **3** and an aryl aldehyde should establish a benzylidene moiety such as that found in **2**. To test our ideas, we set out to prepare the isobutylaminotriazinone **12** and the benzylidene **14** (Scheme 2). The *S*-methyl isothiuronium iodide **11** derived from **3** by its treatment with methyl iodide was subjected to reaction with isobutylamine in acetonitrile in a sealed tube. The reaction did not yield **12** but instead, **11** underwent demethylation of the type observed by Sandin *et al.*<sup>16</sup> and reverted to **3**. This is likely to have occurred by nucleophilic attack on the methyl group by the iodide ion with displacement of thiourea. Use of an isothiuronium salt having the less nucleophilic trifluoroacetate counterion proved useful as triazinone **12** was obtained in 40% yield by heating a mixture of the cyclic isothioureia **11b** (obtained by treatment of **11** with saturated aqueous NaHCO<sub>3</sub>), one equivalent of trifluoroacetic acid and an excess of isobutylamine in a sealed tube at 165 °C. It was anticipated that the electron withdrawing Boc group in **13** would engender enolate formation and indeed this occurred as the Knoevenagel reaction between **13** and veratraldehyde took place in the presence of sodium hydride in tetrahydrofuran.



**Scheme 2.** Reagents and conditions: a) MeI, MeCN, 60 °C, 90%. b) saturated aq. NaHCO<sub>3</sub>, 78%. c) TFA, isobutylamine, MeCN, 165 °C, sealed tube, 40%. d) isobutylamine, MeCN, reflux. e) Boc<sub>2</sub>O, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, reflux, 74%. f) veratraldehyde, NaH, THF, 0 °C – rt, 43%.

Interestingly it was the deprotected product **14** that was obtained in 43% yield. The concomitant loss of the Boc group during the condensation mirrored the observations of Gallina<sup>16</sup> and Bergman<sup>17</sup> who reported the loss of an *N*-acetyl group *via* intramolecular acyl transfer in similar condensation reactions between aldehydes and diketopiperazines. The *Z*- geometry of the product **14** was confirmed by its NOESY spectrum which displayed cross-peaks between NH and the aromatic protons, 5''-H and 6''-H. That **14** was isolated in the *Z*- configuration might reflect a greater thermodynamic stability of the *Z*- over the *E*- form and this would match the assertions made by Gallina,<sup>17</sup> Bergman<sup>18</sup> and Sammes<sup>19</sup> about 3-ylidenepiperazine-2,5-diones. Attempts at guanylation of **14** have not yet furnished our synthetic target **2** as treatment of the *S*-methyl derivative of **14** with prenylamine and also with the more nucleophilic isobutylamine in the presence of TFA has been unsuccessful. Use of copper (I) halides<sup>20</sup> as well as nickel (0)<sup>21</sup> species in this effort might be useful and will be explored.

## CONCLUSION

We have presented thioxotriazinone **3**, its aminotriazinone and 5-benzylidene derivatives **12** and **14** respectively, as new hexahydropyridazine derivatives synthesized *en route* to a conformationally restricted analogue of the antihypertensive agent caracasamide **1**. They are also perhydro derivatives of the pharmacologically important class of [1,2,4]triazin-6-ones, members of which have exhibited antihypertensive as well as antibacterial, antifungal, antiasthmatic and bronchodilatory properties.<sup>22</sup> Pharmacological evaluation of compounds **3**, **12** and **14** will therefore be undertaken and the results reported at a later date.

## EXPERIMENTAL

NMR spectra were obtained on a Bruker Vector 2000-200 spectrometer using tetramethylsilane (TMS) as internal standard. IR spectra were run on a Bruker Vector 22 FTIR spectrometer. Melting points are uncorrected and were determined on a Reichert melting point apparatus. Analytical thin layer chromatography (TLC) was performed using 250  $\mu\text{m}$  silica and visualization was achieved with UV light as well as  $\text{KMnO}_4$  and vanillin spray reagents. Flash chromatographic separation was carried out on 230-400 mesh silica. THF (from Na/benzophenone),  $\text{CH}_2\text{Cl}_2$  (from  $\text{P}_2\text{O}_5$ ) and MeCN (from  $\text{K}_2\text{CO}_3$ ) were distilled immediately prior to use. DMF was dried over 4Å sieves. Unless otherwise stated, reactions were carried out under nitrogen utilizing oven-dried glassware. Elemental analyses and high resolution mass spectrometry were carried out by MEDAC Ltd., Egham, Surrey, U.K.

### 1-Benzyl tetrahydropyridazine-(2*H*)-carboxylate (**8**)

1-Benzyl-2-*tert*-butyl tetrahydropyridazine dicarboxylate (**7**)<sup>7</sup> (5.67 g, 18 mmol) was added in portions to



a 25% TFA:CH<sub>2</sub>Cl<sub>2</sub> solution (100 mL) whilst cooling in an ice salt bath. The resulting solution was then gradually brought to room temperature and stirred overnight (18 h). The solvent was removed *in vacuo* and the residue carefully treated with saturated NaHCO<sub>3</sub>(aq) to effect neutralization. This was followed by extraction with CH<sub>2</sub>Cl<sub>2</sub>. The organic phase was washed with H<sub>2</sub>O (2 x 20 mL), dried over anh. Na<sub>2</sub>SO<sub>4</sub> and concentrated to give compound **8** as a tan oil (3.45 g, 88%). IR (neat)  $\nu_{\max}$  3032, 2941, 1700, 1624 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  1.63 (4H, br s, -(CH<sub>2</sub>)<sub>2</sub>-), 2.92 (2H, t, -CH<sub>2</sub>-N), 3.58 (2H, t, -CH<sub>2</sub>-N), 5.14 (2H, s, -CH<sub>2</sub>-O), 7.31(5H, s, ArH); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  23.3, 24.3, 41.7, 45.7, 67.3, 127.9, 128.4, 136.3, 155.4.

### 1-Benzyl-2-[(benzyloxycarbonyl)amino]acetyl tetrahydropyridazine carboxylate (**9**)

Oxalyl chloride (0.8 mL, 1.16 g, 9.2 mmol) was added dropwise to a suspension of *N*-carbobenzyloxyglycine<sup>12</sup> (1.49 g, 8.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> in the presence of DMF (0.1 mL) whilst cooling in an ice-salt bath. When effervescence ceased the resulting solution was stirred for 1 h then brought to room temperature. The solvent was removed and the residual acid chloride re-dissolved in CH<sub>2</sub>Cl<sub>2</sub> (7 mL). This solution was then added to 1-benzyl tetrahydropyridazine-(2*H*)-carboxylate (**8**) (1.89 g, 8.6 mmol) and Et<sub>3</sub>N (1.3 mL, 943 mg, 9.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) with cooling. The reaction was then allowed to stir at room temperature for 5 h. Removal of the solvent and chromatography using EtOAc-hexane (1:1) as eluent furnished the title compound as a viscous tan oil (2.37 g, 65%). [HRMS (FAB) calcd for C<sub>22</sub>H<sub>25</sub>N<sub>3</sub>O<sub>5</sub> (MH<sup>+</sup>) 412.18724, found 412.188306]; IR (neat)  $\nu_{\max}$  3351, 1730, 1685, 1257 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  1.65 (4H, br s, -CH<sub>2</sub>CH<sub>2</sub>-), 2.73 (1H, br m, CHH<sub>a</sub>N1), 2.99 (1H, br m, CHH<sub>a</sub>N2), 3.81 (1H, dd, *J* = 3.8, 17.9 Hz, CH<sub>b</sub>HN1), 4.17 (2H, m, HNCH<sub>2</sub>C=O), 4.46 (1H, d, *J* = 11.9 Hz, CH<sub>b</sub>HN2), 5.09 (2H, s, -CH<sub>2</sub>O-), 5.24 (2H, s, -CH<sub>2</sub>O-), 5.62 (1H, br s, NH), 7.31 (10H, br s Ar-H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  23.2, 23.3, 42.2, 47.6, 66.8, 68.7, 128.0, 128.1, 128.5, 128.6, 128.7, 135.4, 136.4, 155.9, 156.2, 169.2.

### 1-Thioxotetrahydropyridazino[1,2-*a*][1,2,4]triazin-4(3*H*)-one (**3**)

A solution of 1-benzyl-2-[(benzyloxycarbonyl)amino]acetyltetrahydropyridazine carboxylate (**9**) (1.79 g, 4.4 mmol) in MeOH (35 mL) was hydrogenated (1 atm) in the presence of 5% palladium on carbon (99.4 mg). After 2.5 h the catalyst was removed by filtration and the mixture concentrated at room temperature under reduced pressure. The crude de-protected material was then immediately dissolved in MeCN (45 mL) and thiocarbonyldiimidazole (1.11 g, 6.3 mmol) introduced. The resulting bright orange solution was stirred at room temperature for 21 h followed by heating in a sealed tube for 3 h at 130 °C. Concentration *in vacuo* and subsequent purification by chromatography eluting with EtOAc-hexane (7:3) gave the thioxotriazinone **3** as a cream-coloured solid (581 mg, 71%); mp 163-165 °C (CHCl<sub>3</sub>). (Anal.

Calcd for C<sub>7</sub>H<sub>11</sub>N<sub>3</sub>OS: C, 45.39; H, 5.99; N, 22.67; S, 17.31. Found: C, 45.48; H, 6.08; N, 22.31; S, 16.83; IR (solid film)  $\nu_{\max}$  3317, 1682, 2947, 1682, 1511, 1320 cm<sup>-1</sup>, <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  1.83 (4H, br m, -CH<sub>2</sub>CH<sub>2</sub>-), 3.76 (2H, m, C(O)NCH<sub>2</sub>), 3.83 (2H, d, *J* = 2.3 Hz, HN-CH<sub>2</sub>C=O), 4.24 (2H, m, C(S)NHCH<sub>2</sub>), 7.08 (1H, br s, NH); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  22.5, 23.3, 44.1, 45.2, 49.7, 162.4, 178.9.

### 2-*tert*-Butyloxycarbonyl-1-thioxotetrahydropyridazino[1,2-*a*][1,2,4]triazin-4(3*H*)-one (13)

Di-*tert*-butyldicarbonate (0.2 mL, 190 mg, 0.87 mmol) was added to a solution of thioxotriazinone **3** (0.128 mg, 0.69 mmol) and Et<sub>3</sub>N (72.6 mg, 0.1 mL, 0.72 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). The resulting solution was heated at reflux until starting material was consumed. Removal of the solvent and flash chromatography using EtOAc-hexane (1:1) as eluent yielded the Boc-protected thioxotriazinone as a cream solid (145 mg, 74%); mp 143-145 °C (CHCl<sub>3</sub>). IR (solid film)  $\nu_{\max}$  2978, 1715, 1695, 1365, 1213 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  1.58 (9H, s, (CH<sub>3</sub>)<sub>3</sub>C), 1.75 (2H, m, CH<sub>2</sub>CH<sub>2</sub>), 1.95 (2H, m, CH<sub>2</sub>CH<sub>2</sub>), 3.86 (2H, m, CH<sub>2</sub>NC=O), 4.17 (2H, m, NCH<sub>2</sub>C(O)N), 4.25 (2H, m, CH<sub>2</sub>NC=S); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  22.7, 23.3, 27.9, 43.4, 47.2, 50.0, 84.7, 151.5, 164.2, 177.4.

### 3-*Z*-(3,4-Dimethoxybenzylidene)-1-thioxohexahydropyridazino[1,2-*a*][1,2,4]triazin-4-one (14)

Sodium hydride (292 mg, 0.73 mmol) was added to a solution of 3,4-dimethoxybenzaldehyde (veratraldehyde) (35.2 mg, 0.21 mmol) and the *N*-Boc- thioxotriazinone **13** (60.8 mg, 0.21 mmol) in THF (5 mL) whilst cooling at 0 °C. After 10 min the solution was gradually brought to room temperature and stirred for 41 h whereupon the reaction was quenched by the dropwise addition of cold, saturated NH<sub>4</sub>Cl (aq). The mixture was taken up in EtOAc, dried, concentrated *in vacuo* then chromatographed using EtOAc- hexane (1:1) as eluent. The benzylidene **14** was obtained as a yellow solid (29.6 mg, 42%); mp 187-190 °C (CHCl<sub>3</sub>-CH<sub>2</sub>Cl<sub>2</sub>). [HRMS (FAB) calcd for C<sub>16</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>S (MH<sup>+</sup>) 334.1225, found 334.1229]; IR (solid film)  $\nu_{\max}$  3533, 2957, 1600, 1517, 1336 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  1.88 (4H, br s, -CH<sub>2</sub>CH<sub>2</sub>), 3.91 (6H, s, OCH<sub>3</sub>), 3.92 (2H, m, CH<sub>2</sub>NC=S), 4.32 (2H, m, -CH<sub>2</sub>NC=O), 6.67 (1H, s, CH=C), 6.92 (1H, d, 5''-H, *J* = 8.3 Hz), 6.95 (1H, s, 2''-H), 7.02 (1H, dd, 6''-H, *J* = 1.8, 8.3 Hz), 8.38 (1H, br s, NH); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  22.4, 23.0, 44.4, 52.0, 55.9, 111.2, 111.9, 112.8, 121.0, 122.5, 125.5, 134.5, 149.6, 157.9, 171.8.

### 1-(Methylsulfonyl)-6,7,8,9 tetrahydropyridazino[1,2-*a*][1,2,4]triazin-4(3*H*)-one (11b)

Methyl iodide (912 mg, 0.4 mL, 6.4 mmol) was added to a solution of thioxotriazinone **3** (56.1 mg, 0.3 mmol) in MeCN (2 mL) and the mixture heated at 60 °C for 3 h resulting in the precipitation of the

isothiuronium salt **11** as a white solid. After removal of the solvent *in vacuo* the residue was taken up in saturated NaHCO<sub>3</sub> (aq) then the aqueous solution was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic extract was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Flash chromatography eluting with EtOAc-hexane (7:3) yielded the *S*-methyl compound **11b** as a yellow semi-solid (46.4 mg, 78%). IR (solid film)  $\nu_{\max}$  2927, 1670 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  1.70 (2H, m, CH<sub>2</sub>CH<sub>2</sub>), 1.73 (2H, m, CH<sub>2</sub>CH<sub>2</sub>), 2.30 (3H, s, SCH<sub>3</sub>), 3.51 (2H, m, CH<sub>2</sub>NC=O), 3.65 (2H, m, CH<sub>2</sub>NCS), 4.02 (2H, s, NCH<sub>2</sub>C=O); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  13.4, 23.2, 23.4, 41.1, 49.8, 50.7, 157.7, 162.6.

### 1-(Isobutylamino)-6,7,8,9 tetrahydropyridazino[1,2-*a*][1,2,4]triazin-4(3*H*)-one (**12**)

A solution of isobutylamine (32.5 mg, 0.4 mmol) in MeCN (0.3 mL) was added to a solution of methylsulfanyltriazinone **11b** (46.4 mg, 0.24 mmol) and TFA (37.4 mg, 0.3 mmol) in MeCN (1.7 mL). The mixture was then heated in a sealed tube at 165 °C for 5 h. Concentration *in vacuo* and chromatography of the crude residue eluting with CH<sub>2</sub>Cl<sub>2</sub> – MeOH (9:1) yielded the isobutylaminotriazinone **12** as a yellow oil (0.0210 g, 40%). [HRMS (FAB) calcd for C<sub>11</sub>H<sub>20</sub>N<sub>4</sub>O (MH<sup>+</sup>) 225.17204, found 225.17204]; IR (solid film)  $\nu_{\max}$  2963, 1668, 1201 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  0.96 (6H, d, *J* = 6.7 Hz, (CH<sub>3</sub>)<sub>2</sub>CH), 1.75 (2H, m, CH<sub>2</sub>-), 1.92 (3H, m, CH<sub>2</sub>-, (CH<sub>3</sub>)<sub>2</sub>CH), 3.02 (2H, d, *J* = 7.0 Hz, CH<sub>2</sub>NH), 3.49 (2H, br m, CH<sub>2</sub>NC=N), 3.75 (2H, br s, CH<sub>2</sub>NC=O), 3.94 (2H, s, NCH<sub>2</sub>C(O)N); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  19.9, 22.9, 23.4, 28.7, 42.4, 43.4, 51.7, 52.4, 156.9, 163.3.

### X-Ray Crystallography

Colourless prisms of 1-thioxotetrahydropyridazino[1,2-*a*][1,2,4]triazin-4-(1*H*)-one (**3**) were harvested from a chloroform-dichloromethane mixture after slow evaporation at room temperature. A single crystal was mounted on a thin glass fiber using Super Glue<sup>®</sup>. Data were collected at room temperature on a Bruker AXS P4 Diffractometer using Mo-K $\alpha$  radiation and a graphite monochromator. XSCANS software package was used to refine cell parameters and to collect and reduce data. The structure was solved and refined using the SHELXTL software package version 6.1.<sup>23</sup> A partial structure was obtained by direct methods, and the remaining non-hydrogen atoms in the structure were located using difference Fourier techniques. H atoms on all carbons were placed at calculated positions and refined using a riding model but those on nitrogens were found from the difference map. All non-hydrogen atoms were refined with anisotropic parameters. Thermal ellipsoid plots were generated with XP in SHELXTL while H-bonding and packing plots were generated using Diamond version 3 with Pov-Ray interface for graphics. Additional crystallographic information including cell parameters and details concerning data collection and refinement are given in Table 2.

**Table 2.** Crystal data and structure refinement for **3**

Empirical formula	C <sub>7</sub> H <sub>11</sub> N <sub>3</sub> OS
Formula weight	185.25
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic P2 <sub>1</sub> /c
Unit cell dimensions	a = 8.6194(8) Å    α = 90° b = 14.824(2) Å    β = 93.483(12)° c = 13.788(2) Å    γ = 90°
Volume	1758.5(4) Å <sup>3</sup>
Z, Calculated density	8, 1.399 Mg m <sup>-3</sup>
Absorption coefficient	0.323 mm <sup>-1</sup>
F(000)	784
Crystal size	0.52 x 0.48 x 32 mm
Limiting indices	-10 ≤ h ≤ 1, -1 ≤ k ≤ 17, -16 ≤ l ≤ 16
Reflections collected/unique	3873/3059 [R(int) = 0.0332]
Completeness to theta = 25.00	98.7%
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data/restraints/parameters	3059/0/226
Goodness-of-fit on F <sup>2</sup>	1.040
Final R indices [I > 2σ(I)]	R1 = 0.0384, wR2 = 0.0975
R indices (all data)	R1 = 0.0446, wR2 = 0.1028
Extinction coefficient	0.0235(15)
Largest diff. peak and hole	0.289 and -0.276 eÅ <sup>-3</sup>

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