REACTION OF 5-SUBSTITUTED 2-AMINO-2-OXAZOLINES WITH ETHOXYCARBONYL ISOThIOCYANATE

Christian Jarry, Isabelle Forfar, Jacqueline Thomas,
Jean Michel Leger, Michel Laguerre

1 Groupe de Recherche d'Hétérocycles à Potentialités Thérapeutiques
2 ER 61 CNRS, Université de Bordeaux II, 33076 Bordeaux cedex, France

Abstract - The reaction of 2-amino-2-oxazolines with ethoxycarbonyl isothiocyanate was found to give only 2,3,6,7-tetrahydro-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thiones, the structure of which was confirmed by X-ray crystallographic analysis. The direction of attack seems to be related to the more potent nucleophilic character of the endo nitrogen atom in 2-amino-2-oxazolines. In basic conditions the oxazoline ring can be easily hydrolyzed leading to 1-substituted 1,3,5-triazin-2,4-dione-6-thione.

INTRODUCTION

The discovery of in vivo active aldose reductase (AR) inhibitors has created the possibility of preventing, retarding, or reversing the complications of chronic diabetes. The various classes of compounds that have been investigated as aldose reductase inhibitors were recently reviewed.1 Because of the great variety of the AR inhibitors the structure-activity studies are fragmented, but they all insist about the necessity of weakly acidic compounds able to penetrate biological membranes.2 A recent report of our group described the pharmacological evaluation of some condensed heterocycles prepared from 2-amino-2-oxazolines by cycloaddition using the two nitrogen nucleophilic centers.3 With these compounds as a precedent we wanted to prepare bicyclic derivatives containing an acidic center for their evaluation as aldose reductase inhibitors.

This paper describes the synthesis of 2,3,6,7-tetrahydro-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thiones (3) obtained by cycloaddition from 2-amino-2-oxazolines (1) with ethoxycarbonyl isothiocyanate (ECIT) and preliminary investigations on their reactivity.

RESULTS AND DISCUSSION

ECIT reacts at ambient temperature with most nucleophilic compounds as the isothiocyanate group.5 The two nitrogen of 2-amino-2-oxazolines are potent nucleophilic centers and according to the direction of initial attack of ECIT, the cycloaddition reaction of ECIT with 2-amino-2-oxazolines (1) could lead to either or both two possible oxazolo[3,2-a]-1,3,5-triazines (2) and (3). The reaction involves a condensation of ECIT and subsequent cyclisation with loss of ethanol. In fact a single isomer is produced to which it was first assigned structure (2).7 Some of us have extensively studied the reactivity of the nitrogen nucleophilic centers in 5-substituted 2-amino-2-oxazolines (1). As we have noticed that the endo N-atom is more reactive than the exo one, thus at ambient temperature the nucleophilic substitution will preferably occur...
on the endo N-atom\(^9\) leading to 2,3,6,7-tetrahydro-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thiones (3) (Scheme 1). As it was not possible to obtain absolutely decisive structural informations from the \(^1\)H and \(^{13}\)C nmr spectra of synthesized compounds a crystal structure determination was undertaken for a representative oxazolo[3,2-a]-1,3,5-triazine (3b).

**Scheme 1**

![Scheme 1](image)

\[
\begin{array}{c}
\text{RCH}_2\text{O-C-NCS} \\
\text{OH} \\
\text{RCH}_2\text{O-C-NCS} \\
\end{array}
\]

**X-Ray Crystallographic Results**

The crystal data of 3b are given in Table 1. The molecule with atom numbering is presented in Figure 1. Bond lengths and angles are given in Table 2. Final positional and thermal parameters are reported in Table 3.

The X-ray analysis of compound (3b) confirms the structure as an oxazolo [3,2-a]-1,3,5-triazin-2-one-4-thione with the sulfur atom on the C(4) atom. The oxazolo[3,2-a]-1,3,5-triazine ring is not planar with C(7) lying 0.272 Å from the plane N(1)-C(2)-N(3)-C(4)-N(5)-C(9) (0.016 Å in a corresponding thiazolo[3,2-a]-1,3,5-triazine).\(^{10}\) All the C-N bonds in the triazine ring are significantly shorter compared with the C(6)-N(5) distance. Compared with the C=S distance found in thiourea (1.76 Å),\(^{11}\) the C(4)-S(11) is shortened. So we can notice it may exist a delocalization of the double bond between atoms S(11), C(4) and N(3). The lateral chain is nearly perpendicular to the ring moiety (Figure 1). Intramolecular distances do not indicate interactions exceeding Van der Waals forces. An hydrogen bond is found between the O(10) and the N(3) atom. The O(10) (x,y,z)...N(3) (-x+2, -y, -z) distance is 2.833(4) Å and the O(10)...H(103)-N(3) angle 174°.\(^4\)
According to previously reported results, we observed, both by GC/MS and LC/MS, that analytical methylation of 2,3,6,7-tetrahydro-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thiones (3) by diazomethane led to a mixture of the two isomeric 2,3,6,7-tetrahydro-3-methyl-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thione (5) and 2,3,6,7-tetrahydro-4-methylthio-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one (6). The $^1$H nmr spectra of the crude mixture (dimethylsulfoxide $d_6$) indicated the presence of both NCH$_3$ (3.54 ppm) and SCH$_3$ (2.55 ppm) isomers (approximate ratio 3/1). $^{13}$C nmr spectra exhibited...
peaks at 34.65 (N-CH$_3$) and 12.84 ppm (S-CH$_3$). When the methylation was conducted with $N,N$-dimethylformamide dimethylacetal,$^{13}$ it led to the preponderate N-CH$_3$ isomer with traces of S-CH$_3$ isomer accompanied by a third thermolabile oxidized compound which could be formed by methoxy group exchange from $N,N$-dimethylformamide dimethylacetal.

Table 3: Fractional atomic coordinates and equivalent isotropic thermal parameters ($\text{Å}^2$)

<table>
<thead>
<tr>
<th>Atom</th>
<th>$x$</th>
<th>$y$</th>
<th>$z$</th>
<th>$B$ (Å$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (1)</td>
<td>1.4548 (6)</td>
<td>0.1495 (2)</td>
<td>0.0307 (3)</td>
<td>3.2 (1)</td>
</tr>
<tr>
<td>C (2)</td>
<td>1.2812 (7)</td>
<td>0.0878 (2)</td>
<td>0.0224 (3)</td>
<td>2.9 (1)</td>
</tr>
<tr>
<td>N (3)</td>
<td>1.1136 (6)</td>
<td>0.0739 (2)</td>
<td>0.1214 (3)</td>
<td>3.0 (1)</td>
</tr>
<tr>
<td>C (4)</td>
<td>1.1125 (7)</td>
<td>0.1154 (2)</td>
<td>0.2307 (3)</td>
<td>2.8 (1)</td>
</tr>
<tr>
<td>N (5)</td>
<td>1.2931 (6)</td>
<td>0.1750 (2)</td>
<td>0.2331 (3)</td>
<td>2.9 (1)</td>
</tr>
<tr>
<td>C (6)</td>
<td>1.3476 (8)</td>
<td>0.2302 (2)</td>
<td>0.3372 (4)</td>
<td>3.7 (2)</td>
</tr>
<tr>
<td>C (7)</td>
<td>1.5197 (8)</td>
<td>0.2911 (2)</td>
<td>0.2710 (4)</td>
<td>3.6 (2)</td>
</tr>
<tr>
<td>O (8)</td>
<td>1.6006 (5)</td>
<td>0.2510 (2)</td>
<td>0.1545 (2)</td>
<td>3.6 (1)</td>
</tr>
<tr>
<td>C (9)</td>
<td>1.4489 (7)</td>
<td>0.1806 (2)</td>
<td>0.1346 (3)</td>
<td>2.9 (1)</td>
</tr>
<tr>
<td>O (10)</td>
<td>1.2638 (6)</td>
<td>0.0454 (2)</td>
<td>-0.0712 (2)</td>
<td>3.7 (1)</td>
</tr>
<tr>
<td>S (11)</td>
<td>0.9201 (2)</td>
<td>0.0966 (1)</td>
<td>0.3485 (1)</td>
<td>3.9 (0)</td>
</tr>
<tr>
<td>C (12)</td>
<td>1.3800 (8)</td>
<td>0.3665 (2)</td>
<td>0.2379 (4)</td>
<td>4.1 (2)</td>
</tr>
<tr>
<td>O (13)</td>
<td>1.1556 (6)</td>
<td>0.3473 (2)</td>
<td>0.1642 (3)</td>
<td>4.0 (1)</td>
</tr>
<tr>
<td>C (14)</td>
<td>1.0268 (9)</td>
<td>0.4175 (3)</td>
<td>0.1238 (4)</td>
<td>4.5 (2)</td>
</tr>
</tbody>
</table>

We already noticed the possibility to open the oxazine ring in basic conditions leading to compounds with an interesting propane-2-ol moiety.$^{14}$ In order to study the behaviour of the oxazolo[3,2-a]-1,3,5-triazines towards hydrolysis, 3c was treated with 0.1N sodium hydroxide at room temperature. 1-[3-(1-Phenoxypropan-2-ol)]-1,3,5-triazin-2,4-dione-6-thione (4c) was isolated in a good yield. The hydrolytic cleavage occurred on the oxazine ring but left the thiocarbonyl group intact unlike previously published results.$^{15}$ A charge calculation was performed on the heterobicyclic oxazolo[3,2-a]-1,3,5-triazine moiety as the involved mechanism suggested a nucleophilic attack by hydroxide on the C(9) atom. Using classical methods (CNDO/2, MOPAC/MNDO, AMPAC/AM1) the atomic charge on C-9 atom was always found to be 50 to 70% higher than C-4 one, thus accounting for the observed reactivity.

A similar behaviour of the oxazine ring towards hydrolysis led to use oxazolopyrimidines as synthons for nucleoside analogues.$^{16,17}$

An analytical study was performed using 3c, 3l, 3j, 4c as representative compounds. The partition coefficients between octanol and water (log $P_{\text{O/W}}$) and the dissociation constants ($pK_a$) were determined by a spectrophotometric method.$^{18}$ 2,3,6,7-Tetrahydro-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thiones behaved like amphiphilic weak acids compared to barbituric acids. The measured values indicated only a slight influence of the nature of the lateral chain on C-7 atom. Compounds (3b) and (3c) were tested in vitro for their ability to inhibit aldose reductase.$^{19}$ No significant activity was noticed.

The reaction of 2-amino-2-oxazolines (1) with ethoxycarbonylisothiocyanate which probably proceeds by a two-step dielectrophilic addition mechanism led to 2,3,6,7-tetrahydro-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thiones (3). The direction of attack seems to be related to the more potent nucleophilic character of the endo nitrogen atom in 2-amino-2-
oxazolines (1). In basic conditions the oxazoline ring in 3c can be easily hydrolyzed leading to 1-substituted 1,3,5-triazin-2,4-dione-6-thione (4c) suggesting a nucleophilic attack by hydroxide on the C(9) atom.

**EXPERIMENTAL**

**Crystal structure determination**

1548 Reflection intensities were collected from a crystal of dimensions 0.1 x 0.2 x 0.4 mm$^3$ on an Enraf-Nonius CAD-4 diffractometer with CuKα radiation (λ = 1.5418 Å). Only 1233 reflections having $I > 3o(I)$ were used in the refinement. The structure was solved by direct methods: MULTAN.$^{20}$ The 200 normalized structure factors with $|F| > 1.50$ were included in the phase determination. The set of phases with the highest combined figure of merit gave a reasonable structure with all the non-hydrogen atoms. Hydrogen atoms were located by a Fourier map. The parameters were refined by block diagonal least-squares to a R value of 0.052 using observed reflections. List of structure factors, anisotropic thermal parameters and H-atom coordinates is available as supplementary material.

**Charge calculation**

Calculations were performed on a local network consisting of a 3100-20 and 3100-80 MicroVax station computers. We started from the 2,3,6,7-tetrahydro-4H-oxazolo[3.2-a]-1,3,5-triazin-2-one-4-thione moiety found in the X-ray structure of compound 3b which was fully minimized using MacroModel program$^{21}$ (version 3.0) and the MM2 force field as implemented (1987 parameters).$^{22}$ The crude structure was first minimized to a final RMS gradient ≤ 0.1 kJ/Å via the block diagonal Newton-Raphson method (BDNR) with terminal atom movement enabled (TAMov on) and then fully minimized to a final RMS gradient ≤ 0.005 kJ/Å using the full-matrix Newton-Raphson method (FMNR). The obtained file was converted into a CSSR format and exported towards CHEMX software$^{23}$ where atomic charge calculations were performed using the facilities implemented in this program. The following methods have been used successively:

- CNDO/2 with QCPE program no 274$^{24}$ - MOPAC (version 6.0) and MNDO Hamiltonian with QCPE program no 455$^{25}$ - AMPAC (version 2.1) and AM1 Hamiltonian with QCPE program no 506.$^{26}$

The charge obtained on C(9) and C(4) atoms are resumed in the following table.

<table>
<thead>
<tr>
<th>Atoms</th>
<th>CNDO/2</th>
<th>MOPAC/MNDO</th>
<th>AMPAC/AM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(4)</td>
<td>0.270</td>
<td>0.232</td>
<td>0.172</td>
</tr>
<tr>
<td>C(9)</td>
<td>0.437</td>
<td>0.386</td>
<td>0.295</td>
</tr>
</tbody>
</table>

Microanalyses were carried out at the Service central d'analyse CNRS, Vernaison, France. Melting points were determined with a Kofler hot-stage apparatus and were uncorrected. The ir spectra were obtained with a Beckman Acculab spectrophotometer. Nmr spectra were recorded with a Bruker WH-90 or a Bruker AC-200 spectrometer. All signals were expressed in ppm with respect to TMS. Silica gel (SDS, 70-230 mesh, 60Å) suitable for chromatographic use was employed for column chromatography. Mass spectra were recorded using a Fisons-Instruments Autospec-EQ equipped with a Hewlett-Packard HP 5890 gas chromatograph and with a Waters 600 MS liquid chromatograph.

**General procedure for the preparation of 2,3,6,7-tetrahydro-4H-oxazolo[3.2-a]-1,3,5-triazin-2-one-4-thiones (3)**

Under vigorous stirring ethoxycarbonyl isothiocyanate (0.02 mol) was added at room temperature to a solution of the required 2-amino-2-oxazoline (0.02 mol) in chloroform (20 ml). The mixture was stirred three hours at room temperature.
The precipitated white solid was collected, washed with chloroform and recrystallized.

2.3.6.7-Tetrahydro-7-chloromethyl-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thione (3a) : mp > 250°C (MeOH); yield : 83%; ir (KBr) cm⁻¹ : 3420 (NH); 1680 (C=O); 1630 (C=N); 1H nmr (dimethylsulfoxide d₆), δ ppm : 12.8 (s, 1H, NH), 5.4 (m, 1H, 7-H), 4.3 and 3.9 (2m, 1H each, 6-H), 4.05 (m, 2H, CH₂Cl); 13C nmr, δ ppm : 174.6 (C-4), 161.5 (C-2), 153.7 (C-9), 78.2 (C-7), 48.4 (C-6), 45.1 (CH₂Cl).

Anal. Calcd for C₉H₆N₃O₂ClS : C, 32.80; H, 2.73; N, 19.13; S, 14.58. Found : C, 32.74; H, 2.85; N, 18.88; S, 14.47.

2.3.6.7-Tetrahydro-7-methoxymethyl-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thione (3b) : mp 200°C (MeOH); yield : 74%; ir (KBr) cm⁻¹ : 3400 (NH); 1710 (C=O); 1650 (C=N); 1H nmr (dimethylsulfoxide d₆), δ ppm : 12.7 (s, 1H, NH), 5.25 (m, 1H, 7-H), 4.6 and 4.0 (2m, 1H each, 6-H), 3.85 (m, 2H, OCH₂), 3.5 (s, 3H, OCH₃); 13C nmr, δ ppm : 173.6 (C-4), 161.7 (C-2), 157.8 (C-9), 77.7 (C-7), 71.5 (OCH₂), 58.7 (OCH₃), 47.4 (C-6).


2.3.6.7-Tetrahydro-7-phenoxyethyl-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thione (3c) : mp 212°C (MeOH); yield : 81%; log Pₐ/w : 1.44, pKₐ : 7.04; ir (KBr) cm⁻¹ : 3420 (NH); 1700 (C=O); 1690 (C=N); 1H nmr (dimethylsulfoxide d₆), δ ppm : 12.8 (s, 1H, NH), 7.3 (m, 2H, Ar-H), 6.9 (m, 3H, Ar-H), 5.4 (m, 1H, 7-H), 4.3 (m, 3H, 6-H₈ and OCH₂), 4.05 (m, 1H, 6-H₈); 13C nmr, δ ppm : 174.7 (C-4), 161.7 (C-2), 157.8 (C-9), 153.8, 129.8, 121.3, 114.6 (CA₉), 77.7 (C-7), 67.6 (OCH₂), 47.3 (C-6).

Anal. Calcd for C₁₂H₁₁N₃O₃S : C, 51.98; H, 3.97; N, 15.16; S, 11.55. Found : C, 52.02; H, 3.85; N, 15.04; S, 11.33.

2.3.6.7-Tetrahydro-7-diethylaminomethyl-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thione (3d) : mp 209°C (CCl₄); yield : 73%; ir (KBr) cm⁻¹ : 3420 (NH); 1700 (C=O); 1690 (C=N); 1H nmr (chloroform-d₆), δ ppm : 8.1 (s, 1H, NH), 4.4-3.8 (m, 3H, 7-H and 6-H), 2.8-2.6 (m, 6H, NCH₂), 1.05 (t, 6H, 2CH₃); 13C nmr, δ ppm : 173.9 (C-4), 154.5 (C-2), 147.3 (C-9), 78.1 (C-7), 54.6, 52.1 (NCH₂), 49.2 (C-6), 11.8 (CH₃).


2.3.6.7-Tetrahydro-5-[(1-phenyl-piperazinyl)methyl]-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thione (3e) : mp > 250°C (MeOH); yield : 82%; ir (KBr) cm⁻¹ : 3420 (NH); 1700 (C=O); 1630 (C=N); 1H nmr (dimethylsulfoxide d₆), δ ppm : 12.7 (s, 1H, NH), 7.2 (m, 2H, Ar-H), 6.9 (m, 2H, Ar-H), 6.8 (m, 1H, Ar-H), 5.2 (m, 1H, 7-H), 4.3 and 3.9 (2m, 1H each, 6-H), 3.3 (m, 2H, NCH₂-C-7), 3.1 and 2.6 (2m, 4H each, NCH₂); 13C nmr, δ ppm : 174.8 (C-4), 161.6 (C-2), 153.9 (C-9), 150.9, 128.9, 118.8, 115.4 (CA₉), 78.1 (C-7), 59.2, 53.2, 48.2 (NCH₂), 48.9 (C-6).

Anal. Calcd. for C₁₁H₁₄N₅O₃S : C, 55.65; H, 5.50; N, 20.29; S, 9.27. Found : C, 55.44; H, 5.48; N, 20.05; S, 9.07.

2.3.6.7-Tetrahydro-5-[(1-piperidinyl)methyl]-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thione (3f) : mp 220°C (MeOH); yield : 84%; ir (KBr) cm⁻¹ : 3420 (NH); 1700 (C=O); 1630 (C=N); 1H nmr (dimethylsulfoxide d₆), δ ppm : 12.5 (s, 1H, NH), 5.15 (m, 1H, 7-H), 4.25 and 4.0 (2m, 1H each, 6-H), 2.8-2.4 (m, 6H, NCH₂), 1.5 (m, 6H, CH₂-piperidine); 13C nmr, δ ppm : 173.9 (C-4), 154.7 (C-2), 148.2 (C-9), 78.2 (C-7), 54.1 and 50.1 (NCH₂), 48.9 (C-6), 25.7 and 23.9 (CH₂-piperidine).

Anal. Calcd. for C₁₁H₁₆N₄O₂S : C, 49.25; H, 5.97; N, 20.89; S, 11.94. Found : C, 49.4; H, 6.05; N, 20.72; S, 12.05.
2.3.6.7-Tetrahydro-5-[4-(4-morpholino)methyl]-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thione (3g): mp 234°C (CCl₄); yield: 73%; ir (KBr) cm⁻¹: 3420 (NH), 1700 (C=O), 1630 (C=N); ¹H nmr (dimethylsulfoxide d₆), δ ppm: 12.5 (s, 1H, NH), 5.15 (m, 1H, 7-H), 4.3 and 3.9 (2m, 1H each, 6-H), 3.5 (m, 4H, OCH₂), 2.6-2.2 (m, 6H, NCH₂); ¹³C nmr, δ ppm: 174.9 (C-4), 161.6 (C-2), 153.3 (C-9), 77.8 (C-7), 66.3 (OCH₂), 58.7 (NCH₂), 53.8 (NCH₂-C-7), 48.9 (C-6).


General procedure for the preparation of 2,3,6,7-tetrahydro-3-methyl-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thione (5) A solution of compound (3) (0.01 mol) in toluene (50 ml) and N,N-dimethylformamide dimethylether (0.04 mol) was refluxed under protection from moisture. After 6 h the solvent and the excess of reagent were distilled under reduced pressure leading to a mixture of methylated products, total yield: 72% (3b): 75% (3c). The mixture was chromatographed over silica gel and the column eluted with chloroform-methanol (9:1) as the eluent to provide (5). The S-CH₃ isomer (6) was not isolated as a pure product and was identified by high resolution LC/MS.²⁷

2.3.6.7-Tetrahydro-5-[4-(4-methoxyphenyl)-4-piperazinylmethyl]-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thione (3i): mp >300°C (MeOH); yield: 53%; log P₂o/w =1.30, pKₐ = 7.10; ir (KBr) cm⁻¹: 3420 (NH), 1700 (C=O), 1630 (C=N); ¹H nmr (dimethylsulfoxide d₆), δ ppm: 12.5 (s, 1H, NH), 6.8 (m, 4H, Ar-H), 5.8 (m, 1H, 7-H), 4.3 and 3.9 (2m, 1H each, 6-H), 4.25 (m, 2H, OCH₂), 3.6 (s, 3H, OCH₃); ¹³C nmr, δ ppm: 174.7 (C-4), 161.7 (C-2), 153.9, 151.8, 117.5, 114.7 (CAr), 7.77 (C-7), 68.3 (OCH₃), 55.4 (OCH₃), 47.3 (C-6).

2.3.6.7-Tetrahydro-3-methyl-7-phenoxymethyl-4H-oxazolo[3,2-a]-1,3,5-triazin-2-one-4-thione (5c) isolated yield: 41%; mp: 198°C (MeOH); logP Ow = 1.90; pK a = 8.3; δ (KBr) cm⁻¹: 1710 (C=O), 1670 (C=N); 1H nmr (dimethylsulfoxide d6), δ ppm: 7.4 (m, 2H, Ar-H), 6.8 (m, 3H, Ar-H), 5.4 (m, 1H, 7-H), 4.5-4.0 (2dd, 2H, 6-H), 4.4-4.3 (d, 2H, CH₂O), 3.5 (s, 3H, NCH₃); 13C nmr, δ ppm: 175.0 (C-4), 160.1 (C-2), 157.7 (C-9), 153.3, 129.6, 121.3, 114.6 (CAr), 77.8 (C-7), 67.5 (CH₂O), 49.0 (C-6), 34.6 (NCH₃). MS m/z (%): 291 (100) M⁺, 218 (40) M⁺CH₃NCS, 94 (32) C₆H₅O.

**Anal.** Calcd. for C₁₃H₁₃N₃O₃S: C, 53.61; H, 4.47; N, 14.43; S, 11.00. Found: C, 53.55; H, 4.61; N, 14.00; S, 11.40.

1-[3-(1-Phenoxypropan-2-yl)-1,3,5-triazin-2,4-dione-6-thione (4c)]

To a stirred solution of compound (3c) (1.5 g, 5.4 mmol) in 20ml of ethanol were added 15 ml of 0.1N sodium hydroxide. The clear solution was stirred for 12 h at room temperature then the solvents were removed under reduced pressure. The residue was dissolved in water (20 ml) and acidified to pH = 4.5 with 0.01N hydrochloric acid. The precipitate was collected by filtration, washed with water, dried and recrystallized from methanol to provide analytically (4c) (1.3 g, 83%) mp 140°C (EtOH); δ (KBr) cm⁻¹: 3300 (NH) and (OH), 1730, 1700 (C=O); 1H nmr (dimethylsulfoxide d6), δ ppm: 12.6 (s, 1H NH), 11.8 (s, 1H NH), 7.4-6.7 (m, 5H, phenyl), 5.3 (d, 1H, OH), 4.3-4.1 (m, 3H, OCH₂ and CH), 3.9-3.8 (m, 2H, CH₂N) 13C nmr, δ ppm: 179 (C-6), 158.4 and 148.6 (C-2, C-4), 146.5, 129.4, 120.5, 114.3 (CAr), 70.4 (CH), 65.3 (CH₂O), 48.6 (CH₂N).

**Anal.** Calcd. for C₁₂H₁₃N₃O₄S: C, 48.81; H, 4.41; N, 14.24, S, 10.85. Found: C, 48.62; H, 4.61; N, 14.12; S, 10.81.

**REFERENCES**


23. CHEM X developed and distributed by Chemical Design Ltd, Oxford, UK.


Received, 17th February, 1993