TRIAZINOBENZOTHIAZINE - A NEW HETEROCYCLIC SYSTEM VIA A NOVEL CYCLIZATION REACTION

John H. Musser*, Susan C. Lewis, and Reinhold H.W. Bender

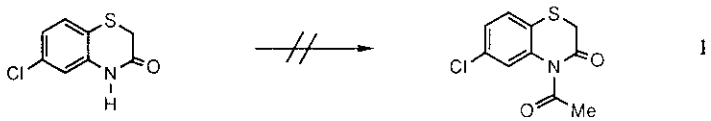
Wyeth-Ayerst Research, Princeton, N. J. 08543-8000, U. S. A.

Abstract - The synthesis and X-ray structure of 9-chloro-2,4-dimethyl[1,3,5]triazino[2,1-c]-1,4-benzothiazine-1,3(2H,4H)-dione (2) are reported. A mechanism is proposed for the formation of this novel heterocyclic system.

In the course of our search for pharmacologically active compounds, we discovered a novel heterocyclization. We wish to report details of the reaction and suggest a reaction mechanism.

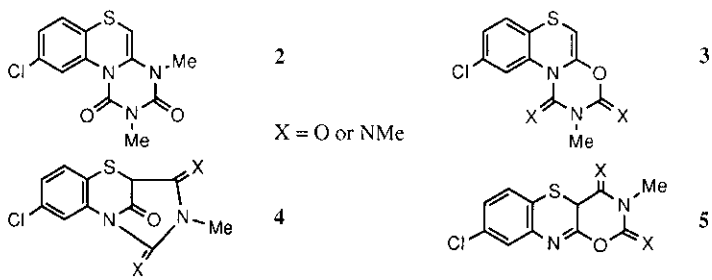
When 6-chloro-3,4-dihydro-2H-1,4-benzothiazinone was reacted with a 2- to 4-fold excess of methyl isocyanate and triethylamine neat or in DMSO the only isolable product containing the original heterocycle was a 1:2 adduct (48 to 65 % yield) and not the expected 1:1 adduct **1** (Scheme 1). A 1:2 addition could result in a product having one of several structures including **2** through **5** (Figure 1).

Scheme 1



1

Figure 1



2 X = O or NMe **3**

4 **5**

Since the structures in Figure 1 could not be easily differentiated by ir and nmr spectroscopy,[1] an X-ray diffraction was carried out on the isolated product (Figure 2); it confirmed the structure as 9-chloro-2,4-dimethyl[1,3,5]triazino[2,1-c]-1,4-benzothiazine-1,3(2H,4H)-dione **2**.[2]

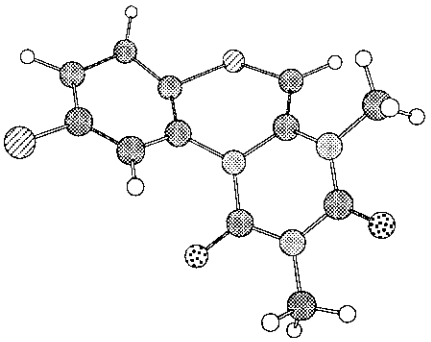
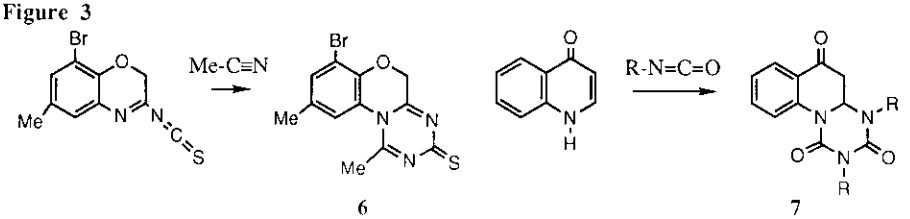


Figure 2 An X-ray crystal structure determination confirmed that the isolated material has structure **2.**

A literature search for substituted [1,3,5]triazino[2,1-c]-1,4-benzothiazines did not identify any compounds containing this system, however, two closely related examples, 1,4-benzoxazine **6**[3] and 4-quinolone **7**[4] were found (Figure 3). Compound **6** is formed by 1,4-cycloaddition with acetonitrile, whereas, compound **7** is formed as a 1:2 adduct of 4-quinolone and isocyanate by a stepwise addition. In this case ring closure is the result of an intramolecular Michael addition.

Figure 3

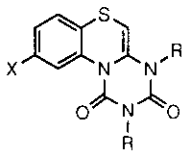


6 7

Mechanistically, neither example in Figure 3 constitutes an exact precedent for the formation of product **2** although the stepwise addition of two isocyanate residues which occurs in the formation of **7**[4] probably also occurs in the formation of **2**. At this point the scope of the reaction was examined by employing various isocyanates. The results are summarized in Table 1.

Unbranched alkyl (R = ethyl, n-butyl) and phenyl isocyanates produce the corresponding substituted [1,3,5]triazino[2,1-c]-1,4-benzothiazines. Although when R = n-butyl a low yield of product is isolated from a mixture composed mainly of N,N'-di(n-butyl)urea. This indicates that the reaction is sluggish and n-butylamine is formed which subsequently reacts with the excess isocyanate. The introduction of further bulk (eg isoproyl or n-octyl) to the reagent isocyanate under our standard conditions results in no reaction. However, with carboethoxymethyl isocyanate an additional product is isolated and its structure was assigned by ms, ir, nmr, and microanalysis as **8** (Figure 4).[5]

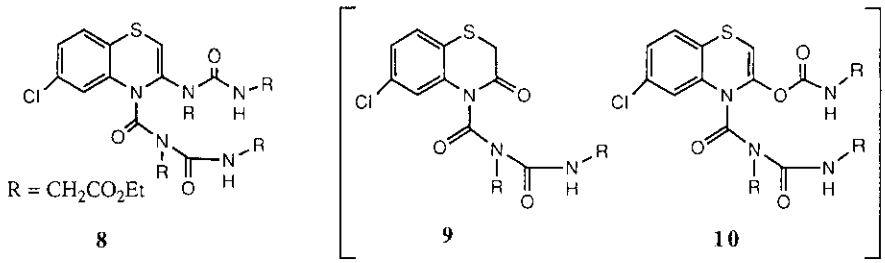
Table 1 Substituted [1,3,5]triazino[2,1-c]-1,4-benzothiazines.[a]



R	X	mp (°C)	% yield[b]
Me	Cl	248-250	65
Et	Cl	162-165	61
Ph	Cl	248-249	62
n-Bu	Cl	oil	24
CH_2CO_2Et	Cl	116-119	68
Me	H	238-240	90
CH_2CO_2Et	H	158-161	72

[a] Elemental analyses were within 0.4% of theoretical value. [b] 6-Chloro-3,4-dihydro-2H-1,4-benzothiazinone and 3,4-dihydro-2H-1,4-benzothiazinone were reacted with a 4-fold excess of both isocyanate and triethylamine in DMSO.

Figure 4



The above results suggest the following mechanism. First, intermediate **9** (Figure 4) is formed by a stepwise addition of 2 isocyanates to benzothiazinone.[4] Next the enol of **9**[6] reacts with an additional isocyanate to give the intermediate 1:3 adduct **10** which is supported by the isolation of **8**. [It would appear that when R = CH_2CO_2Et steric hindrance and electronic factors combine to force reaction but to hinder ring closure; therefore, **10** reacts with traces of NH_2R initially present to liberate carbon dioxide and more amine (RNH_2). The resulting intermediate then reacts with a fourth isocyanate to form **8**.] Finally, ring closure of **10** with the liberation of carbon dioxide and amine (RNH_2) wound give **2.**

In summary, the new [1,3,5]triazino[2,1-c]-1,4-benzothiazine system **2** was synthesized by a novel heterocyclization. Whether intermediates **9** and **10** , or other intermediates are involved in the formation of **2** remains to be determined.

NOTES AND REFERENCES

1. From elemental analysis and mass spectrum the product (mp 248-250 °C) was assigned molecular formula $C_{12}H_{10}N_3O_2ClS$. The mass spectrum displayed an ion [M^+ 295] corresponding to parent. Ir indicated C=O and C=N stretchings at 1745, 1690 and 1610 cm^{-1}. The nmr (100 MHz, $CDCl_3$) showed (δ ppm): two methyl singlets, 3.24, 3.31; a methine singlet 5.15; an aromatic ABX with a multiplet centered at 7.16 and a doublet at 7.52.

2. Suitable crystals formed from ethyl acetate with space group symmetry of Pna2 and cell constants of a = 15.493 (2), b = 7.786 (2), c = 20.537 (3) Å, V =2477 (1) $Å^3$, calculated density =1.59 g/cc. A total of 2251 reflections were measured, 1801 observed (I ranged from 0.964 to 1.032) on an Enraf-Nonius CAD4 computer controlled kappa axis diffractometer equipped with Mo radiation. The structure was solved by direct methods approach and difference Fourier analysis and refined by full-matrix least-squares techniques. The function $R^1 = \Sigma||Fo| - |Fc|| / \Sigma|Fo|$ was minimized to give an unweighted agreement factor of 0.085.

3. M. B. Hogale, N. P. Dhore, and B. R. Khot, *J. Indian Chem. Soc.*, 1986, *63*, 412.

4. M. Sawada, M. Ichihara, Y. Furukawa, Y. Takai, T. Ando, and T. Hanafusa, *Tetrahedron Lett.*, 1982, *23*, 3181.

5. From elemental analysis and mass spectrum the product (mp 110-111 °C) was assigned molecular formula $C_{27}H_{34}N_5O_{11}ClS$. The mass spectrum (FAB) displayed an ion [M^+H 672] corresponding to parent. Ir indicated C=O stretchings at 1775, 1745, 1725, 1690 and 1655 cm^{-1}. The nmr (100 MHz, $CDCl_3$) showed (δ ppm): four methyl triplets centered at 1.22,; four methylene quadruplets centered at 4.14; four methylene singlets centered at 3.78, 3.82, 4.51 and 4.57; a methine singlet at 5.90; an aromatic multiplet centered at 7.41.

6. The enolization of substituted benzothiazinones under basic conditions has precedent. For examples see, a) R. N. Prasad, *J. Med. Chem.*, 1969, *12*, 290. b) F. Eiden and F. Meinel, *Arch. Pharm.*, 1979, *312*, 302.

Received, 23rd October, 1990