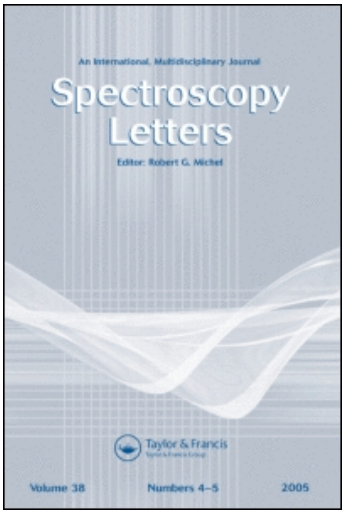

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Structural Elucidation of the Hitherto 2,3-Dihydro-1,2,3,5-Benzothiatriazepine-1,1-Dioxide Ring System[1,2]

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STRUCTURAL ELUCIDATION OF THE HITHERTO 2,3-DIHYDRO-1,2,3,5-BENZOTHIATRIAZEPINE-1,1-DIOXIDE RING SYSTEM[1,2]

Key Words: 8-Chloro-4-phenyl-7-methyl-2,3-dihydro-1,2,3,5-benzothiatriazine-1,1-dioxide, Mass Spectrometry, ^{1}H-NMR, ^{13}C-NMR

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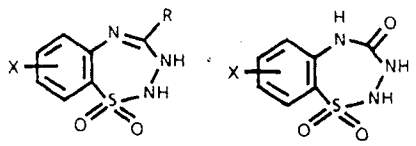
ABSTRACT

The structure of the product from the successive reaction of pyridinium 2-benzamido-5-chloro-4-methylbenzenesulfonate with PCl_5 and excess anhydrous hydrazine has been established as 8-chloro-4-phenyl-7-methyl-2,3-dihydro-1,2,3,5-benzothiatriazine-1,1-dioxide, 1. MS, IR, ^{1}H and ^{13}C NMR have provided definite proof of 1.



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INTRODUCTION

4-Substituted-2,3-dihydro-1,2,3,5-benzothiatriazepine-1,1-dioxide, 1, and the related 2,3-dihydro-1,2,3,5-benzo-thiatriazepine-4-one-1, 1-dioxide, 2, are unknown compounds. No references to the 1,2,3,5-benzothiatriazepine-1,1-dioxide ring system could be found. This is surprising in view of these ring systems' structural simplicity and given the intense activity in diazepine and triazepine chemistry over the last 30 years.[3-7] The interest in benzotriazepines has been based on the well known therapeutic value of the benzodiazepines.[5,8]

Is ring system 1 unstable or is there another reason why it has not been made? Is the 2,3-dihydro tautomer stable or will it convert to the 3,5-dihydro form?

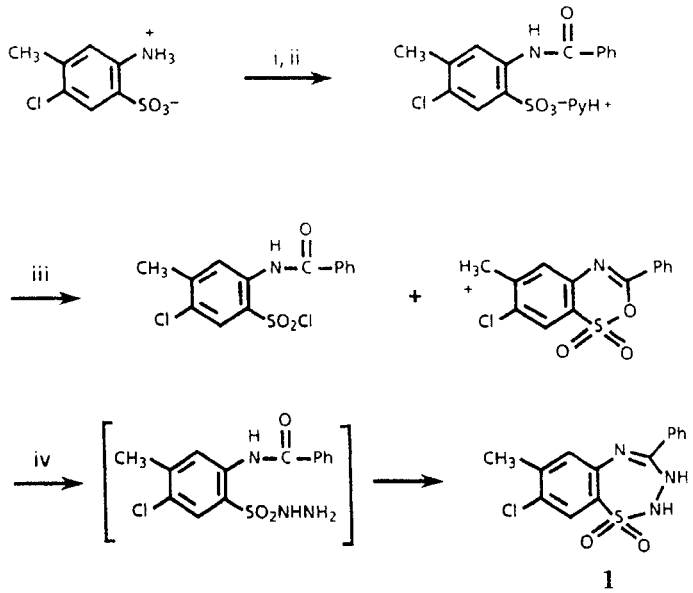
EXPERIMENTAL

The title compound studied was synthesized in analytical purity by using the scheme below.[2,9,10]

1-D ^{1}H and ^{13}C and 2-D NMR spectra were obtained on a General Electric QE 300 NMR spectrometer. Infrared spectra were obtained on a Perkin-Elmer model 283B grating instrument. Mass spectra were recorded at 70 eV with a Finnigan 4500 GC-MS. Microanalyses were performed at Galbraith Laboratories, Inc., Knoxville, Tennessee.

RESULTS AND DISCUSSION

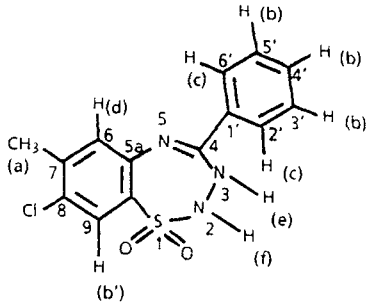
To confirm the structure of 1 both the tautomeric structure 3 and the six-membered ring isomeric 2-amino-1,2,4-benzothiadiazine-1,1-dioxide, 4 had to be



Scheme. Reagents and conditions: i, pyridine, PhCOCl; ii, ether wash; iii, PCl_5, $CHCl_3$, 60°C; iv, excess NH_2NH_2, $CHCl_3$, 0°C.

eliminated as possibilities of the above reactions outcome product. It gave a molecular ion, M^+, at 321 m/z (50%) and $M^+ + 1$ and $M^+ + 2$ peaks were 20% and 38% as intense as the 321 m/z M^+ peak versus theoretical values of 18% and 38% based on isotope ratios.

The infrared spectrum exhibited an NH stretch at 3320 cm^{-1}, a C=N stretch at 1640 cm^{-1} and SO_2 asymmetric and symmetric stretches at 1320 and 1120 cm^{-1}, respectively. The ^1H NMR 300 MHz spectrum (DMSO-d_6) exhibited peaks at δ in PPM of 2.37 (s, 3H, $\underline{CH_3}$), 7.52-7.68 (m, 4 aryl hydrogens (b) and (b')), 7.93-7.97 (m, 2, aryl hydrogens (c)), 8.53 (s, 1, aryl hydrogen (d)), 11.29 (s, NH (e)) and 14.12 (s, SO_2NH (f)). The NH proton at 11.29 ppm is very sharp (without quadrupolar broadening) as is expected for either 1 or tautomer 3 in analogy with secondary amide protons. Structure 4 would have exhibited a single NH peak with an area for two protons. Also, structure 4 is not consistent with the FT-IR spectrum (KBr) which



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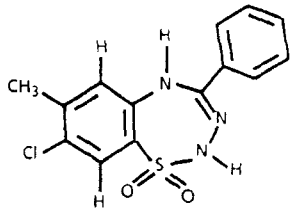

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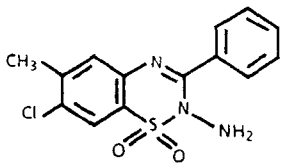

4

gave a single sharp NH stretch at 3320 cm^{-1} whereas the amino group in 4 should give both asymmetric and symmetric NH stretching modes.

The compound was unreactive with *p*-nitrobenzaldehyde over a 12 h period in both methylene chloride and warm chloroform. No Schiffs base was obtained and both reactants were recovered unchanged. Structure 4 would have been expected to react with aldehyde. Tautomers 1 and 3 both have acidic NH protons adjacent to the sulfone function and would be expected to dissolve in cold aqueous base, whereas, 4, without an acidic hydrogen, would not. The compound dissolved readily in 5% aqueous NaOH to give a clear yellow solution from which it could be reisolated upon rapid acidification. Thus, structure 4 is ruled out. The aqueous base solutions produced a gel-like appearance on standing which proved to correspond to some hydrolysis to 2-amino-5-chloro-4-methylbenzenesulfonic acid.

Further NMR studies confirmed 1, not its tautomer, 3, was the correct structure. The assignment of the 8.53 ppm peak to H(d) was confirmed by observing an NOE enhancement upon irradiation of the methyl protons at 2.37 ppm.

Table. ^{13}C NMR Assignments for 8-c oro-4-phenyl-7-methyl-2,3-dihydro-1,2,3,5-benzothiatriazine-1,1-dioxide.

Carbon Atom	δ ppm	Carbon Atom	δ ppm
C(1'')	20.26	C(5a)	134.72
C(3',5')	122.51	C(9a)	135.34
C(9)	126.00	C(8,1')	137.34
C(6,4')	127.00	C(4)	164.42

The spectrum was obtained in DMSO-d_6 and the chemical shift values (δ) are given in ppm relative to Me_4Si. The spectra was obtained at 75.2MHz.

Irradiation of the proton at 11.29 did not give an NOE for H(d) at 8.53 ppm. An NOE at the 8.53 ppm peak would be expected upon irradiation of the 11.29 proton if tautomer 3 was the correct structure. It is not expected for 1 therefore favoring the assignment of 1 as the correct structure. The peak for H(f) at 14.12 ppm occurred with a nonintegral area (1.2 to 1.3) in the DMSO-d_6 first used and peak was significantly broadened. This suggested rapid exchange with small amounts of water in the DMSO-d_6. When the solvent was predried with activated alumina this peak moved to 7.67 ppm with an area of approximately 1.0 while the rest of the spectrum was unchanged. The chemical shifts of exchanging proton H(f) is expected to be sensitive to changes in pH.

Other NOE experiments confirmed structure 1 to be correct. Irradiation of H(e), at 11.29 ppm, should produce an NOE enhancement in the ortho phenyl protons, H(c), which appear at 7.93-7.97 ppm if structure 1 is correct. Indeed, a 13% enhancement was observed. A similar NOE enhancement is predicted for 3. However, if 3 were the correct structure, then irradiation of the N-H at 11.29 ppm should have given an NOE enhancement of the adjacent aromatic proton H(d) at 8.53 ppm. The latter enhancement did not occur. This ruled against tautomer 3.

One might at first glance expect that irradiation of H(e) would give an NOE enhancement at H(f) in structure 1, but no such enhancement was observed. However, if the proton exchange rate between $SO_2N\underline{H}$ and $DMSO/H_2O$ is faster than the dipole-dipole relaxation between these two protons then the NOE enhancement would not be observed. In structure 1 one might expect H(b') to occur at lower field than H(d) sinceH(b') is flanked by ortho chlorine and ortho sulfonamide electron withdrawing functions. However, the diamagnetic anisotropy of the N=C, held coplanar with the aromatic ring, helps explain the downfield shift of H(d).

The ^{13}C NMR assignments are given in the table using the numbering system shown in structure 1. Since the chemical shifts of C-6, 4' and 9 were very close these assignments were proved by heteronuclear correlation (HETCOR) experiments.

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