Ring Closure of Thiosemicarbazides With Sulfuric Acid. A Structure Correction

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The dehydration of **2a** with sulfuric acid at ambient temperature produces the sulfonated product **3a**.

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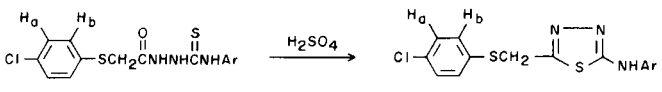
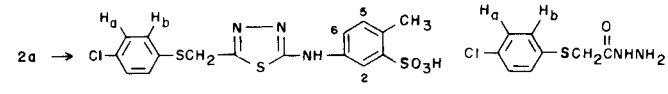
As part of our program to prepare potential chemotherapeutic agents [1], we needed to repeat the synthesis of the reported virucidal thiadiazole **1a**. In 1982 Bahadur, *et al.*, [2] claimed that thiosemicarbazides **2a-d** in sulfuric acid cyclized to compounds **1a-d**.



2 **1**

Ar = a, 4-$CH_3C_6H_4$ c, 2-$(OC_2H_5)C_6H_4$
b, C_6H_5 d, 4-ClC_6H_4

We have carried out the procedure for the preparation of **1a** as described [2], and have found that a ring sulfonated product, **3a**, is formed instead.



3a **4**

All spectral and analytical data for **3a** are fully consistent with the assigned structure (see Experimental section).

A marked discrepancy between the reported [2] mp (240-241°) and that which we obtained is evident. The melting behavior reflects a suspected desulfonation. Thus, when heated slowly to above 200°, **3a** melts erratically between 230° and 250°, depending on the rate of heating, while if the hot stage is preheated to 200°, the melting point is 212-215°.

This desulfonation also presumably occurs in the mass spectrometer, giving first the M^+-SO_3 peak at m/e 347, followed by scission of the S-CH_2 bond, resulting in the base peak at m/e 204; no parent ion at m/e 427 is seen.

Assignment of the sulfonic acid group to the toluidine ring was aided by the examination of the ^{1}H nmr data for **4** and **2a**. In **4**, a singlet is seen at δ 7.37 in dimethylsulfoxide-d_6 (accidental equivalence of H_a and H_b). In **2a**, therefore, the singlet at δ 7.48 is due to H_a and H_b, while the doublets centered at δ 7.20 and 7.45 are from the protons of the toluidine ring. Thus, the singlet at δ 7.37 in **3a** must also be assigned to H_a and H_b, while the remaining three observed aromatic protons at δ 7.77, 7.47 and 7.13 are clearly part of a 1,2,4-trisubstituted benzene system.

Placement of the sulfonic acid substituent ortho to the methyl group was aided by a comparison of the ^{1}H-nmr spectral data for **3a** in dimethylsulfoxide-d_6 alone and with trifluoroacetic acid added. The multiplets centered at δ 7.13 and 7.47 move downfield upon addition of trifluoroacetic acid, while the peak centered at 7.77 moves upfield [5].

The evidence put forward by the authors in support of the structural assignments of **1a-d** consists only of nitrogen elemental analysis [2]. However, a re-examination of these analytical data show them to be in error. We suggest that ring sulfonated products may also have been formed from **2b-d**, since activated aromatic rings are known to sulfonate readily under mild conditions [6].

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary or Fisher-Johns melting apparatus and are uncorrected. The nmr spectra were recorded on a Varian T-60 spectrometer. Spectra are expressed in parts per million from TMS as internal standard. Infrared spectra were obtained on a Perkin-Elmer 700 spectrometer. Microanalyses were performed by Atlantic Microlab, Inc.

N-1-(4'-Chlorophenylthioacetyl)-*N*-4-(4-methylphenyl)thiosemicarbazide (**2a**).

This compound was prepared according to the literature procedure [2] from *p*-tolylisothiocyanate and *p*-chlorophenylthioacetic acid hydrazide (**4**) [3], mp 185-187° (lit [2] 181°); ^{1}H-nmr (dimethylsulfoxide-d_6): δ 9.4-10.4 (m, 3H, exchanges with deuterium oxide, N*H*) , 7.48 (s, 4H, H_a and H_b), 7.45 (d, 2H, J = 8 Hz, C_3-*H*), 7.20 (d, 2H, J = 8 Hz, C_2-*H*), 3.93 (s, 2H, S-CH_2), 2.47 (s, 3H, CH_3).

2-(4'-Methyl-3'-sulfophenyl)amino-5-(4''-chlorophenylthiomethyl)-1,3,4-thiadiazole (**3a**).

A solution of **2a** (3.0 g, 8.2 mmoles) in 80 ml of concentrated sulfuric acid was stirred at 25° for 22 hours. Thin layer chromatography (elution with 20% chloroform-methanol) then showed complete conversion to a single more polar (R_f = 0.25) product. The reaction mixture was poured into ice water and the precipitated solid was washed with water. In contrast to the treatment described in the published procedure [2], this material could not be washed with ammonium hydroxide, as it dissolved readily. Drying over phosphorus pentoxide gave 1.9 g (54%) of **3a** as an off-white solid which was recrystallized from methanol, mp (stage preheated to 200°) 212-215° (lit [2] 240-241°); ir (potassium bromide): 3040, 1610, 1480, 1300, 1180, 1080, 1010 cm^{-1}; ^{1}H-nmr (dimethylsulfoxide-d_6): δ 7.77 (d, 1H, J = 7 Hz, C_5-*H*), 7.47 (d, 1H, J = 2 Hz, C_2-*H*), 7.37 (s, 4H, H_a and H_b), 7.13 (dd, 1H, J = 2, 8 Hz, C_6-*H*), 4.55 (s, 2H, SCH_2), 3.9-4.3

(m, 2H, exchanges with deuterium oxide, N*H* and O*H*), 2.30 (s, 3H, CH_3); m/e (relative intensity) 347 (M^+-SO_3, 9), 204 (M^+-SO_3-SC_6H_4Cl, 100).

Anal. Calcd. for $C_{16}H_{14}ClN_3O_3S_3 \cdot H_2O$: C, 43.09; H, 3.62; N, 9.42; S, 21.57. Found: C, 42.80; H, 3.61; N, 9.36; S, 21.43.

Acknowledgements.

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REFERENCES AND NOTES

[1] Carried out under Master Contract N01-CM-37637 awarded by the National Cancer Institute.

[2] S. Bahadur, S. P. Singh and M. K. Shukla, *Arch. Pharm.*, **315**, 312 (1982).

[3] Prepared from ethyl (4-chlorophenylthio)acetate (which was in turn synthesized from ethyl bromoacetate and 4-chlorothiophenol) using standard methods, mp 99-101° (lit [4] mp 99-101°).

[4] F. L. Rose and B. R. Wilson, British Patent 782,420; *Chem. Abstr.*, **52**, 2907 (1958).

[5] Authentic samples of 4-aminotoluene-2-sulfonic acid and 4-aminotoluene-3-sulfonic acid were considered as model compounds for **3a**, however, an examination of their ^{1}H-nmr spectral characteristics did not prove helpful in assigning the sulfonic acid group in **3a**.

[6] *Org. Synth.*, **2**, 42.