Registry No.—**1a**, 35611-54-2; **2**, 61177-89-7; **3**, 61177-90-0; **3** acetate, 61177-91-1; **4**, 1445-69-8; **5**, 61177-92-2; **6**, 61177-93-3; *N*-benzoyl-β-(4,5-dimethoxy-2-hydroxy)phenethylamine, 61177-94-4.

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Nitrogen-15 Nuclear Magnetic Resonance. Structure of Sulfaguanidine[1]

Glenn R. Sullivan and John D. Roberts*

Contribution No. 5155 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91125

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Sulfaguanidine (**1**)[2] is unusual compared to the many derivatives of sulfanilamide (4-aminobenzenesulfonamide) that contain the grouping $-SO_2HN-$ in being insoluble in aqueous alkali. Its 4-amino group is comparably basic to the other sulfanilamides (pK_B = 11.25) but its guanidino group is only very weakly basic (pK_B = 13.52).[3] The nonacidic character of the compound caused Schwenker[4] to investigate its infrared and ^1H NMR spectra and, by comparison of the infrared spectra in KBr pellets with those of several model compounds, it appeared that **1** had no infrared absorption which could be ascribed to the N–H bond of an $-SO_2NH-$ group. The ^1H NMR spectrum in dimethyl sulfoxide solution was less decisive because of serious overlap of the downfield N–H resonances with the resonances of the aromatic ring, but nonetheless, there appeared to be no evidence for the three different kinds of $-SO_2NHC(=NH)NH_2$ proton resonances predicted for the conventional guanidine structure. It was concluded therefore that the correct structure for sulfaguanidine is not **1a**, but instead the tautomer **1b**. Schwenker's work seems to have been largely, if not totally, ignored, and as recently as 1975, a ^{13}C investigation[5] formulates sulfaguanidine as **1a** in accord with the standard reference works.[6]

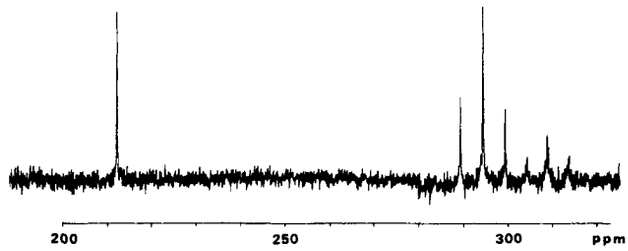
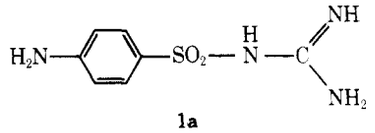
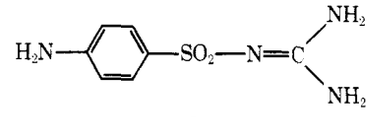


Figure 1. Natural-abundance ^{15}N NMR spectrum of sulfaguanidine in dimethyl sulfoxide with no proton decoupling. The chemical shifts are in parts per million upfield of $D^{15}NO_3/D_2O$.



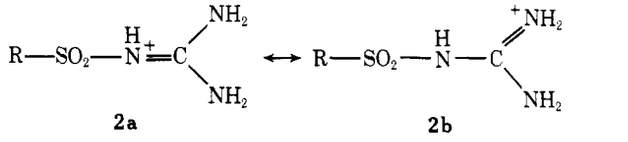
1a



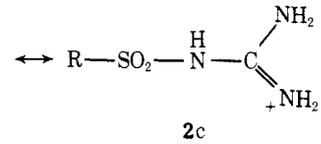
1b

Because the structure of **1** may not be the same in solution as it is in the solid, we have taken the natural-abundance ^{15}N spectrum with a Bruker WH-180 spectrometer at 18.23 MHz (8 g of **1** in 18 ml of dimethyl sulfoxide) *without* proton decoupling, using a 65° flip angle, a repetition rate of 20 s, and an accumulation time of 12 h. The upfield portion (Figure 1) of the resulting spectrum showed two triplet resonances, one over twice the intensity of the other, consistent with a structure having three $-NH_2$ groups. The lower intensity triplet (309.3 ppm upfield of $D^{15}NO_3$) arises from the 4-amino group and the larger intensity triplet (295.0 ppm) from the $=C(NH_2)_2$ amino groups of **1b**. The N–H coupling constants for the two triplets were 85 and 91 Hz, respectively. A downfield singlet resonance at 212.3 ppm upfield of $D^{15}NO_3$ corresponded to the $-SO_2N=C<$ nitrogen.

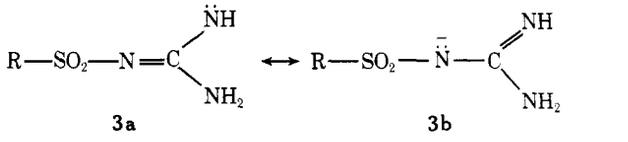
Why does structure **1b** correspond to a substance with a weakly basic and weakly acidic guanidine group? One can write the usual resonance forms for both the conjugate acid, **2**, and the conjugate base, **3**, of **1b**. To be sure, **2a** will be rendered less favorable by the close proximity of the RSO_2^- group to the positively charged nitrogen, but **2b** and **2c** should be



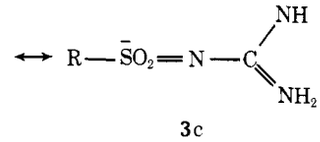
2a **2b**



2c



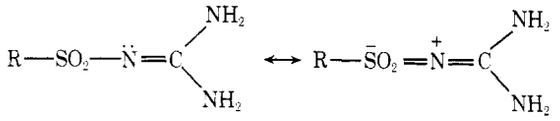
3a **3b**



3c

reasonably comparable to structures usually written for amidinium ions.[6] The resonance forms **3a–c** would appear, if anything, to enhance the acidity of **1b** by charge delocalization. However, there is a possibility that failure of **1** to dissolve in alkali, when other sulfa derivatives are soluble, could be ascribed to a very much lower water solubility of **1.** However, this cannot be the case, because, in fact, **1** is substantially more soluble in neutral water than the other sulfa derivatives.[2]

The only reasonable explanation for low basicity and acidity of **1b** vs. what might otherwise be expected seems to be through some special stabilizing characteristic of **1b** which is not shared to the same extent by **2** or **3** (or by the corresponding conjugate bases). One such possibility is delocalization of the lone pair on nitrogen to sulfur, as expressed by **4.** The fact that the two $-NH_2$ groups of the guanidine have



4

no appreciable chemical-shift difference is in accord with an important contribution of **4.**[8]

Registry No.—**1b**, 61116-95-8.

References and Notes

(1) Supported by the Public Health Service, Research Grant 11072 from the Division of General Medical Sciences, and by the National Science Foundation.
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"Abnormal" Displacement in the Reaction of 2-(*N*-Methylpyrrolyl)methyltrimethylammonium Salts with Sodium Cyanide

John R. Carson, John T. Hortenstine, Bruce E. Maryanoff,* and Albert J. Molinari

Chemical Research Department, McNeil Laboratories, Inc., Fort Washington, Pennsylvania 19034

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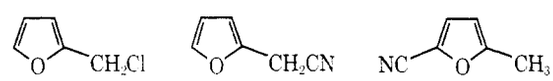
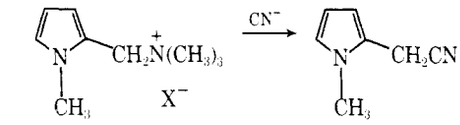
It has been known for some time that the reaction of 2-(chloromethyl)furan (**1**) with metal cyanides can proceed in two directions, "normal" displacement to afford **2,** as well as "abnormal" substitution to afford **3,**[1] whereas the reaction of



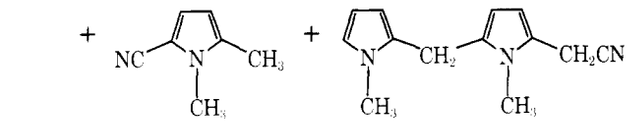
1 **2** **3**

benzyl halides with cyanide occurs with direct substitution. Although much attention has been focused on this process in the chemistry of furans,[2] no intensive studies have been performed on cyanide displacement with corresponding pyrrole derivatives. We wish to report on the reaction of 2-pyrrolylmethylammonium salts (**4**) with sodium cyanide. Under a variety of conditions, this operation produces not only *N*-methylpyrrole-2-acetonitrile (**5**), as reported earlier by others,[3]



4a, X = I
b, X = OSO_2OCH_3
c, X = OSO_2-4-$CH_3C_6H_4$
d, X = Cl
e, X = OSO_2CF_3

5



6 **7**

but also significant amounts of heretofore unrecognized, "abnormal" nitrile (**6**). Furthermore, thorough analysis of the reaction mixtures revealed minor dipyrrolylmethane byproducts, **7** and **8,** signaling the participation of an ion-pair process in the cyanolysis.

When quaternary ammonium salts[4] **4** were heated in solution with sodium (or potassium) cyanide, trimethylamine was evolved. Temperatures of 80–95 °C afforded a reasonable reaction rate, with total reaction times of 1.5–3 h. GLC analysis of a crude organic product from the reaction of **4d** (xylene/water) revealed that three volatile substances were generated. Distillation of the product mixture provided in 78% yield a fraction composed of isomeric (mol wt 120) nitriles (GLC/MS, IR) in a ratio of ca. 9:1, assigned structures **5** and **6,** respectively (vide infra). Kugelrohr distillation of the residue furnished a yellow solid (mol wt 213) nitrile (MS, IR) in 8% yield, leaving behind some dark tar.

A mixture of the isomeric nitriles was resolved by fractional distillation to provide a sample of pure **5** (mp 28–29 °C) and a fraction highly enriched in **6;** recrystallization (CH_3OH) supplied a sample of pure **6** (mp 53–55 °C). The higher boiling nitrile was recrystallized (Et_2O) to give a pure sample of **7** (mp 88–89 °C). Full spectral data, which support these structural assignments, are provided in the Experimental Section.

Five salts differing in their counterion were investigated under various circumstances. In every case, a mixture of isomeric products **5** and **6** was formed. Compound **7** was generally a minor product (1–8%), although slightly higher yields of **7** (10–15%) were obtained when the reaction was conducted in aqueous solution under comparatively dilute conditions. Results of some representative experiments are presented in Table I. The data indicate that the amount of "abnormal" substitution, ranging from 10 to 40%, is greatly dependent on the reaction medium (cf., e.g., entries 2, 7, 11, 12, 15, and 16; 4, 9, 13, and 14) and, to a lesser extent, on the counterion of substrate **4** (cf. entries 1–5; 6–10). No conditions have yet been discovered where the "abnormal" reaction mode is absent, or for that matter, reduced below a minimum level of 8–10%.[5] In contrast to the solvent dependence observed here, 2-(chloromethyl)furan (**1**) yields predominantly "abnormal" product **3** in polar, protic media and "normal" product **2** in dipolar, aprotic media.[2b]

Salt **4b** decomposed in water in less than 3 h at 90 °C (but decomposed slowly at 50 °C). Subsequent addition of sodium cyanide to the decomposed material (in situ) did not generate any **5** or **6.** Of eight volatile substances detected (GLC) in the tarry product derived from the thermal degradation experiment, the three major ones were identified (MS) as **8a–c.** This suggests the possible existence of an electrophilic intermediate such as **9,** which combines in situ with *N*-methylpyrrole originating from **4,** presumably via a demethylation/retro-Mannich reaction sequence.[6] Similarly, the source of dipyrrolylmethane **7** may be explained in terms of the interception