

Abstract

New topical antimicrobial compounds comprised of *N,N*-dichloro- β,β -disubstituted taurines (**1a-k**) have been examined for structure-stability relationships (SSR) based upon various alkyl, heteroalkyl and cycloalkyl β -substitutions. These substitutions affect order-of-magnitude changes in the aqueous stability of these *N,N*-dichloroamines which can undergo Stieglitz rearrangement of alkyl groups under extremely mild conditions (H₂O, pH 4-7, 0-20 mM acetate or phosphate buffer, 20-40 °C). This process produces β -ketosulfonic acids which function as substrates for chlorination by the *N*-chlorotaurines which leads to their further degradation.

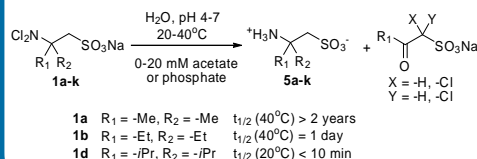


Figure 1: Stieglitz rearrangement of *N,N*-dichlorotaurine derivatives

Syntheses of β,β -Disubstituted Taurines

The synthesis of β,β -disubstituted taurines (**5**) was accomplished by one of two general synthetic schemes, and the routes chosen based upon the commercial availability of the required starting materials.

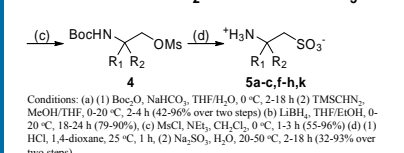


Figure 2: Synthesis via Amino Acid Route.

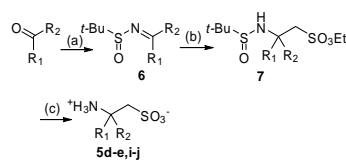
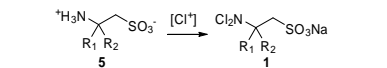


Figure 3: Synthesis via Sulfinimine Route⁴.

Chlorination and Stability



series	R ₁ , R ₂	Method ^a	1 (%)	Temp.	t _{1/2} (pH 4)	t _{1/2} (pH 7)
a	-Me, -Me	A	28	40 °C	>2 y	>2 y
b	-Et, -Et	C	76	40 °C	1 d	0.5 d
c	-iPr, -iPr	B	60	40 °C	0.5 d	2 d
d	-i-Pr, -i-Pr	B	NA ^b	25 °C	<10 min	NA
e	-(CH ₂) ₃	B	NA ^b	25 °C	6 h	NA
f	-(CH ₂) ₄	B	34	40 °C	5 d	1 d
g	-(CH ₂) ₅	A	24	40 °C	7 d	NA
h	-(CH ₂) ₆	C	43	40 °C	2 d	NA
i	-(CH ₂ Me) ₂ (CH ₃)	C	51	40 °C	1 d	NA
j	-Me, -CH ₂ OMe	B	61	25 °C	1.5 d	NA
k	-(CH ₂) ₂ O(CH ₂)	B	NA ^b	25 °C	<1 d	NA

^a A (trichloroisocyanuric acid (TCl) in water), B (HOCl, prepared *in situ* at pH 4-5), or C (t-BuOCl in methanol). ^b Unstable compound, not isolated in pure form.

Solution stabilities of 1-4 mM compounds **1a-k** were evaluated at a variety of pH values (4-7) and buffer concentrations (4-20 mM). The samples were incubated at 25 °C or 40 °C and quantified either by the UV signature of the dichloroamine chromophore (A₂₈₀₋₃₁₀) or by HPLC.

Surprisingly, the stabilities of **1** varied by several orders of magnitude for the examples studied. Thus, some decomposed at room temperature in minutes, while others were stable for years at elevated temperatures.

Identification of Decomposition Products

Parent Compound	1b R ₁ = R ₂ = -Et	1c R ₁ = R ₂ = -iPr	1f R ₁ , R ₂ = -(CH ₂) ₄	1g R ₁ , R ₂ = -(CH ₂) ₅	1h R ₁ , R ₂ = -(CH ₂) ₆
Degradants	8b 1.0 (151) 5b 1.4 (180) 9b 1.5 (185*) 10b 2.5 (219**) 11b 3.3 (253***)	8c 1.4 (165) 9c 2.3 (199*) 5c 2.7 (208) 10c 3.2 (233**) 11c 3.7 (267***)	5f 1.2 (178) 13f 1.6 (224*) 14f 2.2 (258**) 15f 2.7 (292***)	12g 1.4 (204) 5g 1.6 (192) 13g 1.9 (238*) 14g 2.6 (272**)	12h 1.9 (218) 5h 2.1 (206) 13h 2.5 (252*) 14h 3.1 (286**) 15h 3.8 (320***)

Figure 4: Degradants, with their ELSD retention times in minutes and mass-to-charge ratios in parentheses. Asterisks (*) indicate the presence of chlorine(s) as evidenced by the isotopic ratio in the mass spectrum (e.g. 200* indicates a 3:1 ratio of m/z 200 to m/z 202, while 286** indicates a 9:6:1 ratio of m/z 286 to m/z 288 to m/z 290).

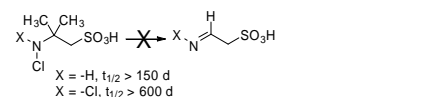
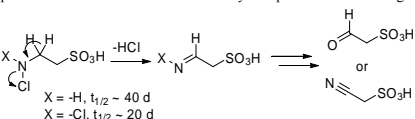


Figure 2: Dehydrohalogenation of *N,N*-dichlorotaurine and β,β -dimethyl substitution (**1a**). Stability studies conducted at 20 °C, 150 mM NaCl, pH 3.5.

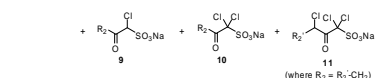


Figure 5: Decomposition of acyclic derivatives **1b-d**. The location of the chlorines in **9**, **10**, and **11** was confirmed by observation of desymmetrization and resymmetrization of R₂ protons by ¹H NMR.

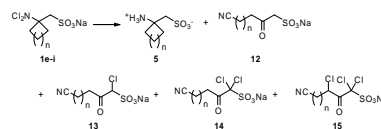


Figure 6: Decomposition of cyclic derivatives **1e-i**. The location of chlorines in **13**, **14**, and **15** were confirmed by ¹H NMR as in Figure 5.

Stieglitz Rearrangement of *N,N*-Dichloro- β,β -Disubstituted Taurines

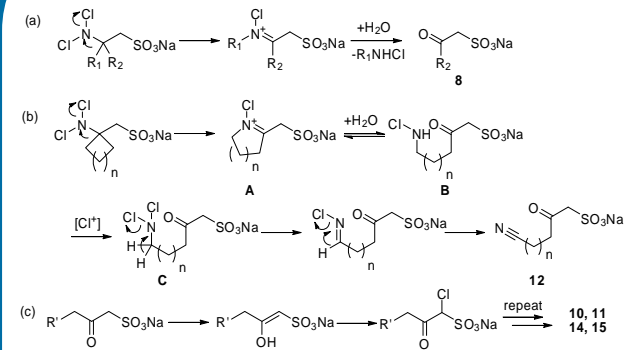


Figure 7: Decomposition of (a) acyclic and (b) cyclic *N,N*-dichloro- β,β -disubstituted taurines, followed by (c) chlorination of the resulting β -ketosulfonic acids.

Our proposed mechanism involves an initial Stieglitz rearrangement⁵ of the alkyl and cycloalkyl derivatives to generate an intermediate *N*-chloroiminium species, which is readily hydrolyzed to the ketone and the *N*-chloroalkylamine. Acyclic derivatives produce **8** (Figure 7a). However, the formation of the nitrile moiety in **12f-h** from the cyclic derivatives **1f-h** suggests that the corresponding hydrolysis of **A** giving **B** may be preferred, stabilizing **B** until it is further chlorinated to **C** through transchlorination (Figure 7b). The double dehydrochlorination of **C** could then provide the observed nitrile **12**. Chlorination of the enolic forms of the β -ketosulfonates leads to the observed mono- (**9b-c**, **13f-h**), di- (**10b-c**, **14f-h**) and trichloro- (**11b-c**, **15f-h**) derivatives (Figure 7c).

Conclusions

Primary Substituents	Secondary Substituents
1a : t _{1/2} > 2 yr @ 40 °C	1d : t _{1/2} < 10 min @ 25 °C
1b : t _{1/2} = 1 d @ 40 °C	1e : t _{1/2} = 6 h @ 25 °C
1c : t _{1/2} = 0.5 d @ 40 °C	1f : t _{1/2} = 5 d @ 40 °C
1g : t _{1/2} = 7 d @ 40 °C	1h : t _{1/2} = 2 d @ 40 °C
1i : t _{1/2} = 2 d @ 40 °C	1j : t _{1/2} = 1.5 d @ 25 °C
1k : t _{1/2} = 1 d @ 40 °C	1l : t _{1/2} < 1 d @ 25 °C

>> increasing decomposition rate

Figure 8: Half-lives of selected derivatives

Stieglitz rearrangements of *N,N*-dichloro- β,β -disubstituted taurines have been observed in aqueous buffers at 20 °C to 40 °C. The decomposed products are β -ketosulfonic acids and ω -cyano- β -ketosulfonic acids which chlorinate through an enol-mediated chlorination pathway.

References

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