N-Halo Derivatives IV: Synthesis of Low Chlorine Potential Soft *N*-Chloramine Systems

JAMES J. KAMINSKI, NICOLAE BODOR ˣ, and TAKERU HIGUCHI

Abstract □ A number of low chlorine potential, soft *N*-chloramines containing nitrogen–chlorine bonds of different polarity were prepared. These novel *N*-chloramine systems were based on derivatization of 2-amino-2-methyl-1-propanol.

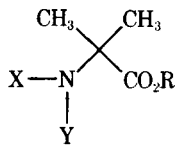
Keyphrases □ *N*-Halo derivatives—series of low chlorine potential, soft *N*-chloramines synthesized from 2-amino-2-methyl-1-propanol □ *N*-Chloramine systems, soft—series with low chlorine potential synthesized from 2-amino-2-methyl-1-propanol □ Antimicrobial agents, potential—*N*-chloramine series synthesized

Recently, the chlorination of α-amino acids and their related derivatives was examined (1) to investigate the relationship between the antimicrobial activity of the *N*-chloramine and the degree of polarization of the nitrogen–chlorine bond (2). As a result of the kinetic studies conducted on these *N*-chlorinated products, factors significantly influencing the stability and reactivity of the nitrogen–chlorine bond in these *N*-chloramines were elucidated.

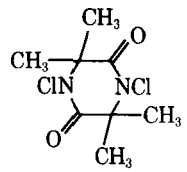
More importantly, these investigations led to the development of a class of stable, low-chlorine potential (3, 4), soft *N*-chloramines based on α-aminoisobutyric acid and related derivatives. The low chlorine potential of these *N*-chloramines was a result of the reduced polarity of the nitrogen–chlorine bond. By decreasing the polarity of the nitrogen–chlorine bond, the chemical reactivity of the *N*-chloramine was minimized. Therefore, these low chlorine potential *N*-chloramines were less readily deactivated by extraneous reaction with denaturing agents and exhibited a high degree of antimicrobial activity.

The soft nature of the *N*-chloramines rested primarily upon the mechanism of their antimicrobial action and upon the transient character of the *N*-chloramine precursor to generate nontoxic degradation products. It was hypothesized that the bactericidal action of *N*-chloramines was a manifestation of a chemical reaction involving the direct transfer of a positive chlorine from the *N*-chloramine to an appropriate receptor in the cell. This chemical reaction can effectively destroy or inhibit an enzymatic or metabolic cell process, resulting in the expiration of the organism. If it is assumed that the transfer of positive chlorine to an appropriate receptor in the cell is responsible for eliciting the antimicrobial effect of the *N*-chloramine, detoxification of the microorganism ultimately regenerates the parent molecule from which the *N*-chloramine is derived. By judiciously selecting the *N*-chloramine precursor from nontoxic entities and selectively incorporating into the molecular structure specific functional groups susceptible to hydrolysis, the inherent toxicity of the soft *N*-chloramine antimicrobial agents can be effectively controlled.

In continuing the investigation of the relationship between the antimicrobial activity of the *N*-chloramine and the degree of polarization of the nitrogen–chlorine bond, the present study describes the preparation of several novel classes of soft *N*-chloramines. Based on previous investigations (1) of the stability and reactivity of the nitrogen–chlorine bond in soft *N*-chloramines, derivatives of 2-amino-2-methyl-1-propanol were investigated as precursors to these soft *N*-chloramines.



Ia: X = Cl, Y = Cl, R = CH_3
Ib: X = H, Y = Cl, R = $(CH_2)_5CH_3$
Ic: X = H, Y = Cl, R = $(CH_2)_7CH_3$
Id: X = H, Y = Cl, R = $(CH_2)_{11}CH_3$
Ie: X = H, Y = Cl, R = $(CH_2)_{13}CH_3$
If: X = H, Y = Cl, R = $(CH_2)_{17}CH_3$
Ig: X = H, Y = Cl, R = $(CH_2)_2O(CH_2)_2O(CH_2)_3CH_3$
Ih: X = Cl, Y = Cl, R = $(CH_2)_5CH_3$
Ii: X = Cl, Y = Cl, R = $(CH_2)_7CH_3$
Ij: X = Cl, Y = Cl, R = $(CH_2)_{11}CH_3$
Ik: X = Cl, Y = Cl, R = $(CH_2)_{13}CH_3$
Il: X = Cl, Y = Cl, R = $(CH_2)_{17}CH_3$
Im: X = Cl, Y = Cl, R = $(CH_2)_2O(CH_2)_2O(CH_2)_3CH_3$



II

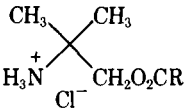
RESULTS AND DISCUSSION

Investigation of the chlorination of α-aminoisobutyrate esters and related derivatives led to the preparation of a number of low chlorine potential, soft *N*-chloramines, Ia–Im and II (1). To conduct a comprehensive and systematic investigation of the relationship between the antimicrobial activity of the *N*-chloramine and the degree of polarization of the nitrogen–chlorine bond, the preparation of additional low chlorine potential, soft *N*-chloramines containing nitrogen–chlorine bonds of different polarity was necessary.

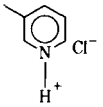
Based on the low polarity of the nitrogen–chlorine bond and the soft nature of the *N*-chloramines desired, derivatization of 2-amino-2-methyl-1-propanol was particularly attractive because of its inherent low toxicity (5). In addition, 2-amino-2-methyl-1-propanol contains the specific structural requirement essential for optimizing the stability and reactivity of the nitrogen–chlorine bond of the *N*-chloramine; that is, the *gem*-dimethyl substitution at the carbon atom adjacent to the nitrogen–chlorine bond in the *N*-chloramine (1). With these considerations in mind, 2-amino-2-methyl-1-propyl carboxylate hydrochlorides (IIIa–IIIf) were examined initially as precursors to an alternative class of low chlorine potential, soft *N*-chloramines.

CHEMISTRY

Compounds IIIa–IIIf were prepared by: (a) *N*- to *O*-acyl transfer



IIIa: R = CH_3
IIIb: R = $(CH_2)_2CH_3$
IIIc: R = $C(CH_3)_3$
IIId: R = $(CH_2)_4CH_3$
IIIe: R = $(CH_2)_6CH_3$

IIIf: R = 

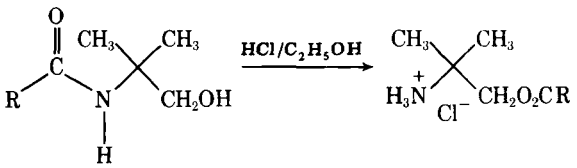
in the corresponding *N*-acylated amino alcohol *via* ethanolic hydrogen chloride (Scheme I) (6), (*b*) hydrolysis of the corresponding Δ^2-1,3-oxazoline (Scheme II), or (*c*) *O*-acylation of the *N*-protected amino alcohol with subsequent removal of the *N*-protective group (Scheme III).

The synthetic approaches utilized to obtain IIIa–IIIf merit discussion. Classically, several analogous derivatives have been prepared by *N*- to *O*-acyl transfer from the kinetically formed *N*-acylated amino alcohol by ethanolic hydrogen chloride (6). However, this method is ineffective for the preparation of *n*-aliphatic carboxylate derivatives of ethanolamines. More recently, Δ^2-1,3-oxazolines, based on 2-amino-2-methyl-1-propanol, received attention as a reversible protecting group for the carboxyl function in carboxylic acids (7). In certain instances, hydrolysis of the Δ^2-1,3-oxazoline afforded the 2-amino-2-methyl-1-propyl carboxylate hydrochloride as an intermediate in the regeneration of the initially protected carboxylic acid.

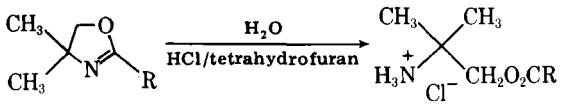
Utilization of either of these procedures to obtain the *N*-chloramine precursors IIIa–IIIe resulted in complete hydrolysis to the corresponding carboxylic acid and 2-amino-2-methyl-1-propanol. However, using a modification of the procedure described by Meyers and Temple (7), IIIb and IIIc could be conveniently obtained in satisfactory yields. Unfortunately, this approach was ineffective for the preparation of IIIa; IIIa was prepared by *O*-acetylation of the *N*-protected amino alcohol, with subsequent removal of the *N*-protective group by catalytic hydrogenation.

The *N*-chloramine precursors (IIIa–IIIf) were particularly interesting, since their *N*-chlorinated products (IVa–IVl) should contain a nitrogen–chlorine bond of lower polarity relative to the *N*-chloramines (Ia–Im and II). The lower polarity of the nitrogen–chlorine bond is a result of the decreased inductive effect of the carboxyl group on the nitrogen–chlorine bond in these *N*-chloramines. More importantly, IVd, IVh and IVe, IVi are isomeric with the *N*-chloramines Ib, Ih and Ic, Ii, respectively. The isomeric relationship between these *N*-chloramines provides an opportunity for comparing the antimicrobial activity of structurally related *N*-chloramines of different chlorine potentials.

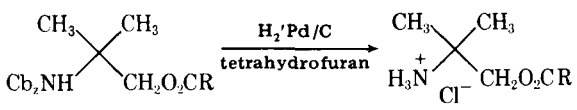
In addition, chlorination of the longer chain homologs (IIIb–IIIe) resulted in the preparation of both the *N*-chloroamino and *N,N*-dichloroamino derivatives. Therefore, the effect of the degree of chlorination of the nitrogen atom, as well as the effect of a branched



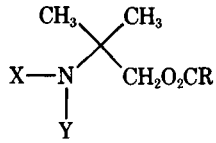
Scheme I



Scheme II

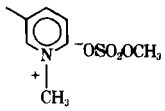


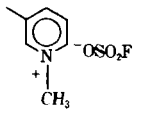
Scheme III



IVa: X = Cl, Y = Cl, R = CH_3
IVb: X = H, Y = Cl, R = $(CH_2)_2CH_3$
IVc: X = H, Y = Cl, R = $C(CH_3)_3$
IVd: X = H, Y = Cl, R = $(CH_2)_4CH_3$
IVe: X = H, Y = Cl, R = $(CH_2)_6CH_3$
IVf: X = Cl, Y = Cl, R = $(CH_2)_2CH_3$
IVg: X = Cl, Y = Cl, R = $C(CH_3)_3$
IVh: X = Cl, Y = Cl, R = $(CH_2)_4CH_3$
IVi: X = Cl, Y = Cl, R = $(CH_2)_6CH_3$

IVj: X = Cl, Y = Cl, R = 

IVk: X = Cl, Y = Cl, R = 

IVl: X = Cl, Y = Cl, R = 

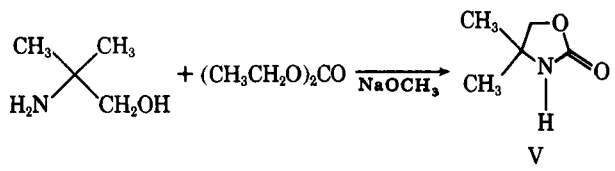
alkyl carboxyl chain on the antimicrobial activity of the *N*-chloramine, could be investigated. Furthermore, the effect of a delocalized positive charge in the *N*-chloramine and of different *gegen*-ions on the antimicrobial activity of the *N*-chloramine could be examined by comparison among IVj, IVk, and IVl. The identification of a number of low chlorine potential, soft *N*-chloramines based on the *N*-chlorinated products of 2-amino-2-methyl-1-propyl carboxylate hydrochlorides led to an investigation of alternative 2-amino-2-methyl-1-propanol derivatives as precursors to additional low chlorine potential, soft *N*-chloramine systems containing nitrogen–chlorine bonds of different polarity.

The ideal proximity between the amino and hydroxyl groups in 2-amino-2-methyl-1-propanol suggested investigation of the 2-oxazolidinone and the 1,3-oxazolidine systems as precursors to low chlorine potential, soft *N*-chloramines. 4,4-Dimethyl-2-oxazolidinone (V) was prepared by the reaction between 2-amino-2-methyl-1-propanol and diethyl carbonate in the presence of a catalytic amount of sodium methoxide (Scheme IV) (8). On the other hand, azeotropic removal of water from benzene or toluene solutions containing 2-amino-2-methyl-1-propanol and acetone, cyclohexanone, or 1-methyl-4-piperidone gave the corresponding *N*-chloramine precursors, VIa, VIb, and VIc, respectively (Scheme V) (9).

Chlorination of V gave 3-chloro-4,4-dimethyl-2-oxazolidinone (VII) (10). Relative to 1,4-dichloro-2,2,5,5-tetramethyl-3,6-piperazinedione (II), the degree of polarization of the nitrogen–chlorine bond in VII should be decreased as a result of the inductive and resonance effects of the oxygen atom adjacent to the carbonyl group in the 2-oxazolidinone structure. Compounds VIa–VIc are particularly interesting, since their *N*-chlorinated products (VIIIa–VIIIf) should contain the least polar nitrogen–chlorine bond of all the low chlorine potential, soft *N*-chloramine systems examined. The low polarity of the nitrogen–chlorine bond in these systems is a result of the electron-donating inductive effect of the tetraalkyl substitution adjacent to the nitrogen–chlorine bond. More importantly, VIIIc–VIIIf provide an opportunity for comparing the effect of a localized positive charge in the *N*-chloramine on its antimicrobial activity. With the preparation of a number of low chlorine potential, soft *N*-chloramine systems containing nitrogen–chlorine bonds of different polarity accomplished, comparative antimicrobial activity studies for these systems were initiated (11).

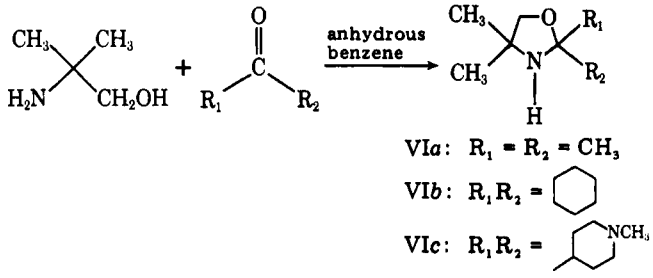
EXPERIMENTAL

2-Amino-2-methyl-1-propyl Acetate Hydrochloride (IIIa) —To a dichloromethane solution containing 17.1 g (0.1 mole) of carbobenzoxy chloride at 0° was added dropwise, with stirring, 18.4 g (0.2 mole) of 2-amino-2-methyl-1-propanol. The reaction mixture was stirred at room temperature overnight, and the 2-amino-2-methyl-



V

Scheme IV



VI*a*: $R_1 = R_2 = CH_3$

VI*b*: R_1R_2 =

VI*c*: R_1R_2 =

Scheme V

1-propanol hydrochloride which formed was removed by filtration. Removal of the dichloromethane under reduced pressure afforded a colorless, viscous liquid. Distillation gave 14.9 g (0.07 mole), 70%, of 2-carbobenzoxyamino-2-methyl-1-propanol, bp 144–148°/0.3 mm; IR (neat): 3400, 3020, 2980, 1710, 1510, 1455, 1270, 1070, 730, and 680 cm^{-1}; PMR ($CDCl_3$): δ 7.2 (s, 5H), 5.4 (broad s, 1H), 4.9 (s, 2H), 4.2 (broad s, 1H), 3.4 (s, 2H), and 1.2 (s, 6H) ppm.

To a dichloromethane solution containing 2.52 g (0.011 mole) of 2-carbobenzoxyamino-2-methyl-1-propanol and 1.17 g (0.015 mole) of acetyl chloride was added dropwise, with stirring, 1.11 g (0.011 mole) of triethylamine. The reaction was stirred at ambient temperature overnight, and the dichloromethane was removed under reduced pressure. The triethylamine hydrochloride residue was triturated in anhydrous ether. Following filtration, the ether was removed under reduced pressure to afford 2.38 g (0.009 mole), 82%, of crude 2-carbobenzoxyamino-2-methyl-1-propyl acetate as a pale-yellow liquid; PMR ($CDCl_3$): δ 7.2 (s, 5H), 5.4 (broad s, 1H), 5.0 (s, 2H), 4.2 (s, 2H), 2.0 (s, 3H), and 1.2 (s, 6H) ppm.

2-Carbobenzoxyamino-2-methyl-1-propyl acetate, 2.38 g (0.009 mole), was dissolved in 100 ml of anhydrous hydrogen chloride in tetrahydrofuran (2 *M*). Then 1.0 g of 10% palladium on carbon was added to the solution, and the resulting mixture was hydrogenated at 50 psi for 2 hr. The catalyst was removed by filtration and thoroughly washed with tetrahydrofuran. Removal of the tetrahydrofuran under reduced pressure gave an off-white solid. Recrystallization from acetone–hexane afforded 1.0 g (0.006 mole) of III*a* as a hygroscopic white solid, mp 146–149°; PMR (D_2O): δ 4.0 (s, 2H), 2.0 (s, 3H), and 1.2 (s, 6H) ppm.

Anal.—Calc. for $C_6H_{14}ClNO_2 \cdot \frac{1}{2}H_2O$: C, 40.79; H, 8.56; N, 7.93. Found: C, 40.31; H, 8.36; N, 8.28.

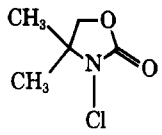
2-Amino-2-methyl-1-propyl Butanoate Hydrochloride (III*b*)—To 65 ml of a solution of anhydrous hydrogen chloride in tetrahydrofuran (1 *M*) containing 1 ml of water was added 7.3 g (0.052 mole) of 2-*n*-propyl-4,4-dimethyl-Δ^2-1,3-oxazoline, which was prepared using the method of Allen and Ginos (12). The solution was heated under reflux with stirring for 1 hr. The tetrahydrofuran was removed under reduced pressure to afford a semisolid residue, which crystallized at 0° upon the addition of anhydrous ether. The solid was triturated in anhydrous ether overnight and isolated by filtration under a nitrogen atmosphere. After drying *in vacuo* over calcium sulfate, 7.0 g (0.036 mole), 70%, of III*b*, was obtained, mp 104–107°; IR (KBr): 2900, 1740, and 1160 cm^{-1}; PMR [$(CD_3)_2CO$–D_2O]: δ 4.2 (s, 2H), 3.8 (broad s, 3H), 2.5 (t, 2H), 1.6 (m, 2H), 1.5 (s, 6H), and 1.0 (t, 3H) ppm.

Anal.—Calc. for $C_8H_{18}ClNO_2$: C, 49.10; H, 9.27; N, 7.16. Found: C, 50.01; H, 9.62; N, 7.54.

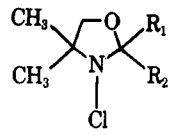
By using the procedure described for the preparation of III*b*, the following 2-amino-2-methyl-1-propyl carboxylate hydrochlorides were prepared:

2-Amino-2-methyl-1-propyl 2,2-Dimethylpropanoate Hydrochloride (III*c*)—mp 113–118°; IR (KBr): 3430, 2980, 1735, 1520, 1470, 1270, and 1150 cm^{-1}; PMR (D_2O): δ 4.10 (s, 2H), 1.40 (s, 6H), and 1.23 (s, 9H) ppm.

Anal.—Calc. for $C_9H_{20}ClNO_2 \cdot H_2O$: C, 47.46; H, 9.74; N, 6.15. Found: C, 47.86; H, 9.34; N, 6.06.



VII



VIII*a*: $R_1 = R_2 = CH_3$

VIII*b*: R_1R_2 =

VIII*c*: R_1R_2 =

VIII*d*: R_1R_2 =

VIII*e*: R_1R_2 =

VIII*f*: R_1R_2 =

2-Amino-2-methyl-1-propyl Hexanoate Hydrochloride (III*d*)—mp 100–101°; IR (KBr): 2900, 1745, and 1165 cm^{-1}; PMR [$(CD_3)_2CO$–D_2O]: δ 4.3 (s, 2H), 3.7 (broad s, 3H), 2.5 (t, 2H), 1.2–1.8 (m, 6H), 1.5 (s, 6H), and 0.9 (t, 3H) ppm.

Anal.—Calc. for $C_{10}H_{22}ClNO_2$: C, 53.68; H, 9.91; N, 6.26. Found: C, 53.02; H, 10.21; N, 6.71.

2-Amino-2-methyl-1-propyl Octanoate Hydrochloride (III*e*)—mp 106–108°; IR (KBr): 2900, 1750, and 1175 cm^{-1}; PMR (D_2O): δ 4.2 (s, 2H), 2.5 (t, 2H), 1.5 (s, 6H), 1.2–1.8 (m, 10H), and 0.9 (t, 3H) ppm.

Anal.—Calc. for $C_{12}H_{26}ClNO_2$: C, 57.24; H, 10.41; N, 5.56. Found: C, 57.29; H, 10.52; N, 5.28.

2-Amino-2-methyl-1-propyl Nicotinate Dihydrochloride (III*f*)—Ethyl nicotinate, 100 g (0.66 mole), and 88 g (0.99 mole) of 2-amino-2-methyl-1-propanol were mixed and heated together under reflux for 2 hr. The excess amino alcohol was removed by distillation, bp 50–60°/1 mm. The yellow residue was recrystallized from ether–acetone to give 87.3 g (0.45 mole), 68%, of *N*-(1-hydroxy-2-methyl-2-propyl)nicotinamide, mp 91–93°; IR (KBr): 3385, 3200, 1665, and 1590 cm^{-1}; PMR ($CDCl_3$): δ 7.3–8.8 (m, 4H), 6.7 (broad s, 1H), 5.0 (s, 1H), 3.7 (s, 2H), and 1.4 (s, 6H) ppm.

Anal.—Calc. for $C_{10}H_{14}N_2O_4$: C, 61.90; H, 7.23; N, 14.50. Found: C, 61.87; H, 7.26; N, 14.55.

A suspension of 73.3 g (0.38 mole) of *N*-(1-hydroxy-2-methyl-2-propyl)nicotinamide in 300 ml of anhydrous hydrogen chloride in absolute ethanol (4 *M*) was heated under reflux for 2 hr. The ethanol was removed under reduced pressure to afford a semisolid residue, which crystallized from acetone on standing. The solid was isolated by filtration under a nitrogen atmosphere and was thoroughly washed with acetone. After drying *in vacuo* over calcium sulfate, 74 g (0.28 mole), 74%, of III*f* was obtained, mp 215–216° dec.; IR (KBr): 3200–2500, 1735, 1630, and 1600 cm^{-1}; PMR (D_2O): δ 9.5 (broad s, 1H), 9.1–9.4 (m, 2H), 8.3 (q, 1H), 4.6 (s, 2H), and 1.6 (s, 6H) ppm.

Anal.—Calc. for $C_{10}H_{16}Cl_2N_2O_2$: C, 44.98; H, 5.99; N, 10.49. Found: C, 45.29; H, 6.15; N, 10.06.

2-*N,N*-Dichloroamino-2-methyl-1-propyl Acetate (IV*a*)—To 50 ml of 0.75 *M* sodium hypochlorite at 0° was added, in portions over 5 min, 3.19 g (0.019 mole) of III*a*. The reaction mixture was adjusted to pH 4–6 by the addition of 1 *M* HCl, and the suspension was vigorously stirred at 0° for 1 hr. The *N*-chloramine was extracted into dichloromethane, and the extracts were combined and dried over anhydrous sodium sulfate. Following filtration, the dichloromethane was removed under reduced pressure to afford a dark-yellow liquid. Distillation gave 2.0 g (0.010 mole), 55%, of IV*a*, bp 55–60°/0.4 mm; IR (neat): 1750, 1230, and 1040 cm^{-1}; PMR ($CDCl_3$): δ 4.2 (s, 2H), 2.1 (s, 3H), and 1.4 (s, 6H) ppm.

Anal.—Calc. for $C_6H_{11}Cl_2NO_2$: C, 36.02; H, 5.54; N, 7.00. Found: C, 36.40; H, 5.63; N, 6.90.

By using the procedure described for the preparation of IV*a*, the following 2-*N,N*-dichloroamino-2-methyl-1-propyl carboxylates were prepared:

2-N,N-*Dichloroamino-2-methyl-1-propyl Butanoate* (IV*f*)—bp 70–75°/0.4 mm; IR (neat): 2940, 1740, and 1160 cm^{-1}; PMR ($CDCl_3$): δ 4.3 (s, 2H), 2.4 (t, 2H), 1.7 (m, 2H), 1.4 (s, 6H), and 1.0 (t, 3H) ppm.

Anal.—Calc. for $C_8H_{15}Cl_2NO_2$: C, 42.14; H, 6.63; N, 6.14. Found: C, 42.30; H, 6.60; N, 6.04.

2-N,N-*Dichloroamino-2-methyl-1-propyl 2,2-Dimethylpropanoate* (*IV*g)—bp 67.5–68.5°/0.45 mm; IR (neat): 2990, 1740, 1475, 1360, 1270, and 1140 cm^{-1}; PMR ($CDCl_3$): δ 4.3 (s, 2H), 1.4 (s, 6H), and 1.2 (s, 9H) ppm.

Anal.—Calc. for $C_9H_{17}Cl_2NO_2$: C, 44.64; H, 7.08; N, 5.70. Found: C, 44.51; H, 7.11; N, 5.58.

2-N,N-*Dichloroamino-2-methyl-1-propyl Hexanoate* (*IV*h)—IR (neat): 2930, 2910, 2840, 1745, and 1155 cm^{-1}; PMR ($CDCl_3$): δ 4.2 (s, 2H), 2.3 (t, 2H), 1.2–1.8 (m, 6H), 1.4 (s, 6H), and 0.9 (t, 3H) ppm.

Anal.—Calc. for $C_{10}H_{19}Cl_2NO_2$: C, 46.88, H, 7.48; N, 5.47. Found: C, 46.90; H, 7.49; N, 5.22.

2-N,N-*Dichloroamino-2-methyl-1-propyl Octanoate* (*IV*i)—IR (neat): 2940, 2860, 1750, and 1150 cm^{-1}; PMR ($CDCl_3$): δ 4.2 (s, 2H), 2.3 (t, 2H), 1.1–2.0 (m, 8H), 1.4 (s, 6H), and 0.9 (t, 3H) ppm.

Anal.—Calc. for $C_{12}H_{23}Cl_2NO_2$: C, 50.71; H, 8.16; N, 4.93. Found: C, 50.38; H, 8.00; N, 4.70.

2-*N*-Chloroamino-2-methyl-1-propyl Butanoate (IV*b*)—To 50 ml of 0.75 *M* sodium hypochlorite at 0° was added, in portions over 5 min, 7.41 g (0.038 mole) of III*b*. The suspension was vigorously stirred at 0° for 1 hr. The *N*-chloramine was extracted into dichloromethane, and the extracts were combined and dried over anhydrous sodium sulfate. Following filtration, the dichloromethane was removed under reduced pressure to afford a pale-yellow liquid. Distillation gave 5.2 g (0.027 mole) of IV*b*, bp 60–65°/0.4 mm; IR (neat): 3230, 2930, 1740, and 1160 cm^{-1}; PMR ($CDCl_3$): δ 4.2 (s, 2H), 2.4 (t, 2H), 1.7 (m, 2H), 1.4 (s, 6H), and 1.0 (t, 3H) ppm.

Anal.—Calc. for $C_8H_{16}ClNO_2$: C, 49.61; H, 8.33; N, 7.23. Found: C, 49.00; H, 8.47; N, 6.94.

By using the procedure described for the preparation of IV*b*, the following *N*-chloroamino-2-methyl-1-propyl carboxylates were prepared:

2-N-*Chloroamino - 2-methyl - 1-propyl 2,2-Dimethylpropanoate* (*IV*c)—bp 61.5–63°/0.45 mm; IR (neat): 3280, 2990, 1730, 1475, 1275, and 1140 cm^{-1}; PMR ($CDCl_3$): δ 4.6 (broad s, 1H), 4.0 (s, 2H), 1.3 (s, 9H), and 1.2 (s, 6H) ppm.

Anal.—Calc. for $C_9H_{18}ClNO_2$: C, 52.04; H, 8.73; N, 6.75. Found: C, 52.04; H, 8.70; N, 6.37.

2-N-*Chloroamino-2-methyl-1-propyl Hexanoate* (*IV*d)—IR (neat): 3240, 1745, and 1160 cm^{-1}; PMR ($CDCl_3$): δ 4.5 (broad s, 1H), 4.1 (s, 2H), 2.2 (t, 2H), 1.1–2.0 (m, 6H), 1.3 (s, 6H), and 1.0 (t, 3H) ppm.

Anal.—Calc. for $C_{10}H_{20}ClNO_2$: C, 54.16; H, 9.09; N, 6.32. Found: C, 55.04; H, 9.82; N, 6.70.

2-N-*Chloroamino-2-methyl-1-propyl Octanoate* (*IV*e)—IR (neat): 3260, 2920, 1740, and 1150 cm^{-1}; PMR ($CDCl_3$): δ 4.5 (broad s, 1H), 4.1 (s, 2H), 2.4 (t, 2H), 1.1–2.0 (m, 8H), 1.3 (s, 6H), and 0.9 (t, 3H) ppm.

Anal.—Calc. for $C_{12}H_{24}ClNO_2$: C, 57.70; H, 9.68; N, 5.61. Found: C, 57.14; H, 9.72; N, 5.39.

2-*N,N*-Dichloroamino-2-methyl-1-propyl Nicotinate (IV*j*)—To 58 ml of 0.7 *M* sodium hypochlorite at 0° was added, in portions over 10 min, 5.32 g (0.02 mole) of III*f*. After 0.5 hr at 0°, the pale-yellow solid was isolated by filtration and thoroughly washed with cold water. The solid was dried *in vacuo* over calcium sulfate to give 3.7 g (0.014 mole), 70%, of IV*j*, mp 53–55° with sublimation at 50°/0.25 mm; IR (KBr): 3020, 3000, 1720, 1580, 1280, 1110, 720, and 670 cm^{-1}; PMR ($CDCl_3$): δ 9.3 (s, 1H), 8.9 (d, 1H), 7.6–8.2 (m, 2H), 4.6 (s, 2H), and 1.5 (s, 6H) ppm.

Anal.—Calc. for $C_{10}H_{12}Cl_2N_2O_2$: C, 45.64; H, 4.60; N, 10.65. Found: C, 45.69; H, 4.71; N, 10.46.

2-*N,N*-Dichloroamino-2-methyl-1-propyl *N*-Methylnicotinate Methylsulfate (IV*k*)—To 1.3 g (0.005 mole) of IV*j* was added 0.63 g (0.005 mole) of dimethyl sulfate. The mixture was heated at 60° under a nitrogen atmosphere for 2.5 hr and the solid mass was triturated with anhydrous ether. The solid was isolated by filtration under a nitrogen atmosphere and thoroughly washed with anhydrous ether. After drying *in vacuo* over calcium sulfate, 1.87 g (0.0048 mole), 93%, of IV*k* was obtained, mp 95–100° dec.; IR (KBr): 3020, 2980, 1730, 1240, 1200, 1000, and 730 cm^{-1}; PMR (D_2O): δ 9.5 (s, 1H), 9.2 (d, 2H), 8.3 (t, 1H), 4.6 (s, 2H), 3.8 (s, 3H), and 1.6 (s, 6H) ppm; UV (H_2O): λ_{max} 303 nm ($\epsilon = 263\ M^{-1}\ cm^{-1}$).

Anal.—Calc. for $C_{12}H_{18}Cl_2N_2O_6S$: C, 37.02; H, 4.66; N, 7.20. Found: C, 36.84; H, 4.75; N, 6.92.

2-*N,N*-Dichloroamino-2-methyl-1-propyl *N*-Methylnicotinate Fluorosulfonate (IV*l*)—To an ethereal solution containing 1.3 g (0.005 mole) of IV*j* at 0° was added dropwise, with stirring, 0.57 g (0.005 mole) of methyl fluorosulfonate in 25 ml of anhydrous ether. After stirring at room temperature for 4 days, the yellow gummy mass was crystallized by repeated scratching at ambient temperature to a white solid. The solid was triturated with anhydrous ether and isolated by filtration under a nitrogen atmosphere. Then 1.32 g (0.0035 mole), 70%, of IV*l* was obtained as an extremely hygroscopic white solid, mp (sealed) 112–118° dec.; PMR (D_2O): δ 9.4 (s, 1H), 9.0 (d, 2H), 8.2 (t, 1H), 4.6 (s, 2H), 4.5 (s, 3H), and 1.6 (s, 6H) ppm.

Anal.—Calc. for $C_{11}H_{15}Cl_2FN_2O_5S{\cdot}H_2O$: C, 33.42; H, 4.34; N, 7.09. Found: C, 33.37; H, 4.42; N, 6.58.

2,2,4,4-Tetramethyl-1,3-oxazolidine (VI*a*)—To 237 g (3.0 moles) of 2-amino-2-methyl-1-propanol was added 750 ml of anhydrous benzene containing 174 g (3.0 moles) of acetone. A few crystals of *p*-toluenesulfonic acid were added to the reaction mixture, and the solution was heated at reflux temperature. When the theoretical amount of water was collected, the reaction mixture was distilled. Compound VI*a* was collected, 220 g (1.7 mole), 57%, as a clear, colorless liquid, bp 128–130°; IR (neat): 3300, 2950, 1450, 1380, 1230, 1050, and 790 cm^{-1}; PMR ($CDCl_3$): δ 3.6 (s, 2H), 1.85 (broad s, 1H), 1.4 (s, 6H), and 1.3 (s, 6H) ppm.

Anal.—Calc. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.34; H, 11.80; N, 11.00.

By using the procedure described for the preparation of VI*a*, the following 1,3-oxazolidine derivatives were prepared:

3,3-Dimethyl-1-oxa-4-azaspiro[4,5]decane (*VI*b) (*13*)—bp 99–103°/21 mm; IR (neat): 3300, 2910, 1440, 1350, 1110, 1040, 910, and 780 cm^{-1}; PMR ($CDCl_3$): δ 3.4 (s, 2H), 1.8 (broad s, 11H), and 1.2 (s, 6H) ppm.

Anal.—Calc. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 71.03; H, 11.60; N, 8.08.

3,3,8-Trimethyl-1-oxa-4,8-diazaspiro[4,5]decane (*VI*c)—bp 63–65°/1.2 mm; IR (neat): 3300, 2920, 1460, 1350, 1260, 1100, 1040, 890, and 800 cm^{-1}; PMR ($CDCl_3$): δ 3.5 (s, 2H), 2.4 (t, 4H), 2.2 (s, 3H), 1.7 (t, 4H), and 1.2 (s, 6H) ppm.

Anal.—Calc. for $C_{10}H_{20}N_2O$: C, 65.17; H, 10.94; N, 15.21. Found: C, 64.88; H, 11.19; N, 15.33.

3-Chloro-2,2,4,4-tetramethyl-1,3-oxazolidine (VIII*a*)—To 175 ml of 0.65 *M* sodium hypochlorite at 0° was added dropwise, with vigorous stirring, 14.2 g (0.11 mole) of VI*a*. The reaction mixture was adjusted to pH 4–6 by the addition of 1 *M* HCl. After 0.5 hr at 0°, the reaction mixture was extracted with dichloromethane. The extracts were combined and dried over anhydrous sodium sulfate. Following filtration, the dichloromethane was removed under reduced pressure to afford a pale-yellow liquid. Distillation gave 9.78 g (0.06 mole), 56%, of VIII*a*, bp 51–53°/12 mm; IR (neat): 2990, 1460, 1370, 1230, 1140, 1040, 900, 820, and 790 cm^{-1}; PMR ($CDCl_3$): δ 3.6 (s, 2H), 1.3 (s, 6H), and 1.2 (s, 6H) ppm; UV (H_2O): λ_{max} 265 nm ($\epsilon = 228\ M^{-1}\ cm^{-1}$).

Anal.—Calc. for $C_7H_{14}ClNO$: C, 51.37; H, 8.62; N, 8.56. Found: C, 51.36; H, 8.77; N, 8.77.

By using the procedure described for the preparation of VIII*a*, the following *N*-chloro-1,3-oxazolidine derivatives were prepared:

3,3-Dimethyl-4-chloro-1-oxa-4-azaspiro[4,5]decane (*VIII*b)—bp 45–47°/0.3 mm; IR (neat): 2920, 1440, 1360, 1090, 1050, 900, 830, and 780 cm^{-1}; PMR ($CDCl_3$): δ 3.8 (s, 2H), 1.7 (broad s, 10H), and 1.2 (s, 6H) ppm; UV (H_2O): λ_{max} 265 nm ($\epsilon = 160\ M^{-1}\ cm^{-1}$).

Anal.—Calc. for $C_{10}H_{18}ClNO$: C, 58.96; H, 8.90; N, 6.88. Found: C, 58.84; H, 8.76; N, 6.28.

3,3,8 - Trimethyl - 4-chloro - 1-oxa-4,8 - diazaspiro[4,5]decane (*VIII*c)—mp 46–48° with sublimation at 35°/0.5 mm; IR (neat/melt): 2930, 1460, 1300, 1090, 840, and 790 cm^{-1}; PMR ($CDCl_3$): δ 3.8 (s, 2H), 1.4–3.0 (m, 8H), 2.4 (s, 3H), and 1.4 (s, 6H) ppm; UV (H_2O): λ_{max} 265 nm ($\epsilon = 270\ M^{-1}\ cm^{-1}$).

Anal.—Calc. for $C_{10}H_{19}ClN_2O$: C, 54.91; H, 8.76; N, 12.81. Found: C, 54.77; H, 8.90; N, 12.85.

3,3,8,8-Tetramethyl-4-chloro-1-oxa-4,8-diazaspiro[4,5]decane Fluorosulfonate (*VIII*d)—mp 123–125°; PMR (D_2O): δ 3.8 (s, 2H), 3.4 (m, 4H), 3.1 (s, 6H), 1.5–3.0 (m, 4H), and 1.2 (s, 6H) ppm; UV (H_2O): λ_{max} 265 nm ($\epsilon = 261\ M^{-1}\ cm^{-1}$).

Anal.—Calc. for $C_{11}H_{22}ClFNO_4S$: C, 39.68; H, 6.66; N, 8.42. Found: C, 39.07; H, 6.67; N, 7.91.

3,3,8,8-Tetramethyl-4-chloro-1-oxa-4,8-diazaspiro[4,5]decane Methylsulfate (*VIII*e)—mp 131–133°; PMR (D_2O): δ 3.8 (s, 2H), 3.6 (s, 3H), 3.4 (m, 4H), 3.1 (s, 6H), 1.5–3.0 (m, 4H), and 1.2 (s, 6H) ppm; UV (H_2O): λ_{max} 268 nm ($\epsilon = 263\ M^{-1}\ cm^{-1}$).

Anal.—Calc. for $C_{12}H_{25}ClN_2O_5S$: C, 41.79; H, 7.31; N, 8.12. Found: C, 41.71; H, 7.29; N, 7.84.

3,3,8,8-Tetramethyl-4-chloro-1-oxa-4,8-diazaspiro[4,5]decane p-Toluenesulfonate (*VIII*f)—mp 94–97°; PMR (D_2O): δ 7.8–7.0 (s,

4H), 3.8 (s, 2H), 3.2–3.7 (m, 4H), 3.0 (s, 6H), 1.4–2.9 (m, 4H), 2.3 (s, 3H), and 1.2 (s, 6H) ppm.

Anal.—Calc. for $C_{18}H_{29}ClN_2O_4S \cdot H_2O$: C, 51.11; H, 7.39; N, 6.62. Found: C, 50.70; H, 7.37; N, 6.59.

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N-Halo Derivatives V: Comparative Antimicrobial Activity of Soft *N*-Chloramine Systems

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Abstract □ Comparative antimicrobial activity studies for certain new classes of soft *N*-chloramines derived from α-aminoisobutyric acid and 2-amino-2-methyl-1-propanol were examined using the minimum inhibitory concentration (MIC) and/or the contact germicidal efficiency (CGE) procedures. Several factors significantly influence the antimicrobial activity of the soft *N*-chloramines: (*a*) the aliphatic chain length in a homologous series, (*b*) the degree of chlorination of the nitrogen atom, (*c*) the solution pH, (*d*) the presence of a denaturant, and (*e*) the nature of a positive charge.

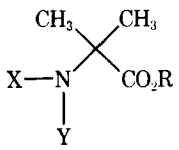
Keyphrases □ *N*-Halo derivatives—low chlorine potential, soft *N*-chloramines, antimicrobial activity evaluated and compared □ *N*-Chloramines, soft—series with low chlorine potential, antimicrobial activity evaluated and compared □ Antimicrobial activity—*N*-chloramine derivatives of α-aminoisobutyric acid and 2-amino-2-methyl-1-propanol evaluated □ Structure–activity relationships—*N*-chloramine derivatives of α-aminoisobutyric acid and 2-amino-2-methyl-1-propanol evaluated for antimicrobial activity

Recently, the *N*-chlorinated derivatives of α-amino acids and their related derivatives were synthesized and their various reactions were studied (1). Based on the stability and reactivity of the nitrogen–chlorine bond in these *N*-chloramines, new types of soft *N*-chloramines were developed which are derivatives of 2-amino-2-methyl-1-propanol (2).

RESULTS AND DISCUSSION

A comprehensive and systematic investigation of the relationship between the antimicrobial activity of the *N*-chloramines and the various factors influencing the polarity, reactivity, and stability of the nitrogen–chlorine bond was examined using the following compounds. Class I represents the esters of the monochloro and dichloro derivatives of α-aminoisobutyric acid; Class II represents the corresponding diketopiperazines. Compounds in Class III have an even lower chlorine potential than those in Class I, while a number of the compounds are structural isomers, such as the III*h*–I*e*, III*i*–I*d*, III*k*–I*f*, and III*l*–I*g* isomeric pairs, which permit a direct comparison of the structure–activity relationship. Compound IV is a stable derivative of 2-amino-2-methyl-1-propanol, representing a whole series of *N*-chloro-2-oxazolidinones. Class V represents the corresponding 1,3-oxazolidine derivatives characterized by a lower chlorine potential and an enhanced soft character.

Minimum Inhibitory Concentration (MIC)—The antimicrobial activity of the various soft *N*-chloramine systems was examined first



I*a*: X = Cl, Y = Cl, R = CH_3
I*b*: X = H, Y = H, R = $C_6H_{13} \cdot HCl$
I*c*: X = H, Y = Cl, R = C_6H_{13}
I*d*: X = Cl, Y = Cl, R = C_6H_{13}
I*e*: X = H, Y = H, R = $C_8H_{17} \cdot HCl$
I*f*: X = H, Y = Cl, R = C_8H_{17}
I*g*: X = Cl, Y = Cl, R = C_8H_{17}
I*h*: X = H, Y = H, R = $C_{12}H_{25} \cdot HCl$
I*i*: X = H, Y = Cl, R = $C_{12}H_{25}$
I*j*: X = Cl, Y = Cl, R = $C_{12}H_{25}$
I*k*: X = H, Y = H, R = $C_{14}H_{29} \cdot HCl$
I*l*: X = H, Y = Cl, R = $C_{14}H_{29}$
I*m*: X = Cl, Y = Cl, R = $C_{14}H_{29}$
I*n*: X = H, Y = H, R = $C_{18}H_{37} \cdot HCl$
I*o*: X = H, Y = Cl, R = $C_{18}H_{37}$
I*p*: X = Cl, Y = Cl, R = $C_{18}H_{37}$
I*q*: X = H, Y = H, R = $(CH_2)_2O(CH_2)_2O(CH_2)_3CH_3 \cdot HCl$
I*r*: X = H, Y = Cl, R = $(CH_2)_2O(CH_2)_2O(CH_2)_3CH_3$
I*s*: X = Cl, Y = Cl, R = $(CH_2)_2O(CH_2)_2O(CH_2)_3CH_3$