Synthesis of Aromatic Amino Acids for Antibacterial Surfactants

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Five new antibacterial agents of the N-(2-hydroxy substituted phenoxy propyl)glycine type have been synthesized. Results of bacteriostatic tests to *Staphylococcus aureus* (G^+) and *Escherichia coli* (G^-) showed that ammonium cations were strongest and compounds with a *p*-methylphenyl were more active than those with a *o*-methylphenyl.

KEY WORDS: Antibacterial surfactants, bacteriostatic activity, epichlorohydrin, ethylglycinate, glycine, phenol, synthesis, tetrabutylammonium bromide.

Some amino acid derivatives are good amphoteric surface-active germicides. Their antibacterial activity is not influenced by pH and albumin. In 1984, Osanai *et al.* (1) prepared $ROCH_2CH(OH)CH_2NHR'$ (**1**), where $R = C_{10}H_{21}$, $C_{12}H_{25}$ or $C_{14}H_{29}$, and $R' = C_2H_4CO_2H$, $CHMeCO_2H$, $CHMECH_2CO_2H$ or $CHEtCO_2H$, and studied their antibacterial activity. The chiral hydroxy propylene raised bacteriostatic activity, and β-type amino propanoic acid derivatives were more active than α-type. In 1986, Osanai *et al.* (2) reported the bacteriostatic activity of the aryl compounds of $p\text{-}HOC_6H_4CO_2CH_2CH(OH)CH_2O(CH_2)_{11}CH_3$ (**II**). The aryl and alkyl moieties in the molecule all have the function to increase antibacterial activity.

For this paper, glycine derivatives with aryl and hydroxy propylene groups were prepared [$X\text{-}C_6H_4\text{-}OCH_2CH(OH)CH_2NHCH_2CO_2H$ (X = H, CH_3, Cl)], and their bacteriostatic activities against *Staphylococcus aureus* (G^+) and *Escherichia coli* (G^-) were studied.

EXPERIMENTAL PROCEDURES

Preparation of 1-(2,3-epoxypropoxy)substituted benzene (3).

$$X\text{-}C_6H_4\text{-}OH + Cl\text{-}CH_2\text{-}\underline{CH(O)CH_2} \rightarrow X\text{-}C_6H_4\text{-}OCH_2\text{-}\underline{CH(O)CH_2}$$

[Compounds 1-5]

(**1**, X = H; **2**, X = *o*-CH_3; **3**, X = *p*-CH_3; **4**, X = *o*-Cl; and **5**, X = *p*-Cl). A mixture of 0.1 mol of phenol, 28 g (0.2 mol) of K_2CO_3, 30 mL (0.4 mol) of epichlorohydrin in 250 mL acetone and 1.6 g of tetrabutylammonium bromide was heated to reflux for 12 h. After the reaction products were separated and column chromatography was carried out (3), pure compounds **1-5** were obtained. Yields were: **1**, 84.5%; **2**, 72.6%; **3**, 75.8%; **4**, 88.1%; **5**, 89.3%.

Ethyl glycinate hydrochloride (4).

$$H_2NCH_2CO_2H + C_2H_5OH \rightarrow HCl + NH_2CH_2CO_2Et$$ [Compound 6]

While stirring, 280 g (2.35 mol) of thionyl chloride was added dropwise to a mixture of 150 g (2 mol) of glycine in 1500 mL of anhydrous ethanol. After the mixture was stirred for 48 h at room temperature, it was filtered and washed with anhydrous ethanol, then dried to give 303 g of product **6**, a white solid (96.6%), m.p. = 143–147°C.

Ethyl N-(2-hydroxy-3-substituted phenoxy propyl)glycinate.

$$1\text{-}5 + 6 \rightarrow X\text{-}C_6H_4\text{-}OCH_2CH(OH)CH_2NHCH_2CO_2Et$$

[Compounds 7-11]

(**7**, X = H; **8**, X = *o*-CH_3; **9**, X = *p*-CH_3; **10**, X = *o*-Cl; and **11**, X = *p*-Cl). An aqueous solution of 20 g (0.14 mol) of ethyl glycinate hydrochloride and 40 g K_2CO_3 in 100 mL of water was stirred at room temperature. The mixture was extracted with ether. The ether phase was dried with Na_2SO_4 and evaporated under reduced pressure at a temperature not exceeding 40°C, to provide 10.5 g (71%) of yellowish-green ethyl glycinate free amine. The free amine (10.3 g) was used immediately by reacting it with 0.03 mol of **1-5** in refluxing ethanol (50 mL). After 4 h, the reaction medium was evaporated under reduced pressure, and after the separating treatment (3), the products were crystallized from ethyl acetate. Melting points and yields of pure compounds **7-11** are listed in Table 1.

TABLE 1

Melting points and Yields of Intermediates 7-11 and the Characterization of End Products 12-16

Compound	m.p. (°C)	Yield (%)	Formula	Calcd. (found) C	H	N	Cl
7	44-45	27.8					
8	30-32.5	67.3					
9	83-85	68.7					
10	42-44	35					
11	72-74	34.4					
12	186-188	78.7	$C_{11}H_{15}NO_4$	58.65 (58.37)	6.71 (6.31)	6.22 (608)	
13	183-184	65.4	$C_{12}H_{17}NO_4$	60.23 (59.97)	7.16 (7.29)	5.86 (5.66)	
14	201-202	68.8	$C_{12}H_{17}NO_4$	60.23 (60.08)	7.16 (6.94)	5.86 (5.85)	
15	197-199	52.9	$C_{11}H_{14}ClNO_4$	50.87 (50.55)	5.43 (5.40)	5.40 (5.14)	13.65 (13.36)
16	188-190	54.3	$C_{11}H_{14}ClNO_4$	50.87 (50.46)	5.43 (5.32)	5.40 (5.37)	13.65 (13.30)

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TABLE 2

Bacteriostatic Activity of the Sample for *Escherichia coli* and *Staphylococcus aureus*

	Escherichia coli [conc. (mM)]			*Staphylococcus aureus* [conc. (mM)]			
Sample	5	0.5	0.05	5	0.5	0.05	0.005
Ammonium cations							
12	−[a]	+[a]	+	−	−	+	+
13	−	+	+	−	−	+	+
14	−	−	+	−	−	−	+
15	−	+	+	−	−	+	+
16	−	+	+	−	−	+	+
Sodium salts							
12	+	+	+	−	+	+	+
13	+	+	+	−	+	+	+
14	+	+	+	−	+	+	+
15	+	+	+	−	+	+	+
16	+	+	+	−	+	+	+

[a]−, Inhibition of growth; +, growth.

N-(2-hydroxy-3-substituted phenoxy propyl) glycine.

$$\textbf{7-11} + H_2O \rightarrow X\text{-}C_6H_4\text{-}OCH_2CH(OH)CH_2NHCH_2CO_2H$$

[Compounds **12-16**]

(**12**, X = H; **13**, X = *o*-CH_3; **14**, X = *p*-CH_3; **15**, X = *o*-Cl; and **16**, X = *p*-Cl). To the mixture of 1 g of **12–16** and 0.3 g of sodium hydroxide was added 10 mL of water. The mixture was heated to gentle boiling for 4 h. After cooling, the pH was adjusted to 5–6 (isoelectric point). The N-substituted glycine precipitated out. Characterization of end products **12–16** are listed in Table 1.

To examine the bacteriostatic activity of the synthetic products for *E. coli* and *S. aureus,* products **12–16** were converted to ammonium cations with hydrochloric acid and to sodium salts with sodium hydroxide. Bacteriostatic activities were measured at the Shangdong Academy of Medical Sciences, Jinan, China.

RESULTS AND DISCUSSION

The ammonium cations and sodium salts of products **12–16** demonstrated bacteriostatic activities against *S. aureus* (Table 2). However, with *E. coli,* the ammonium cations had activity but the sodium salts did not. The bacteriostatic activity of the ammonium cations against *E. coli* was tenfold greater than that with *S. aureus.*

The bacteriostatic active center on the aryl hydroxy propylene glycine derivatives is probably due to the nitrogen positive ion in the molecule, and the activities are dependent on the position of the substituents in the aromatic ring. The ammonium cation and sodium salt of compound **14** (substituent on the benzene ring is *p*-methyl) were more bacteriostatically active than the corresponding compounds **13** (substituent is *o*-methyl) and **16** (substituent is *p*-Cl).

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