168.8 (C-1 and CONH), 200.4 (C-3); IR (film) 3400 (NH), 1750 (C=O), 1720 (C=O), 1650 cm^{-1} (C=O); mass spectrum, calcd for $C_{10}H_{11}O_3N$ 193.0739, found *m/e* 193.0737, *m/e* (relative intensity) 216 (1), 194 (7), 193 (43), 162 (2), 161 (16), 133 (4), 121 (7), 106 (9), 105 (100), 86 (4), 84 (4), 83 (11), 78 (2), 77 (48), 76 (2), 55 (41), 51 (18).

(B) Larger Scale. 4-Pentenoyl chloride (672 mg, 5.67 mmol) was added rapidly in one portion to 5.15 mmol of MHDA (prepared by using LHMDS) in 500 mL of THF at −78 °C. The reaction was quenched after 30 min. Isolation and column chromatography (silica gel, 20% hexane in ether) gave 0.863 g (61%) of pure **3d**.

Methyl 2-(Benzoylamido)-3-oxo-3-phenylpropionate (3e). Methyl hippurate (394 mg, 2 mmol) was converted to the dianion by the standard procedure using LHMDS but under high-dilution conditions (300 mL of THF). To the stirred homogeneous solution of MHDA at −78 °C was added neat benzoyl chloride (309 mg, 2.2 mmol) in one portion. The solution was quenched and worked up as in the general procedure after 1 h at −78 °C. The product **3e** was obtained in 45% yield by trituration with hexane from chloroform: ^1H NMR ($CDCl_3$, 200 MHz) δ 3.72 (s, 3 H, OCH_3), 6.43 (d, 1 H, J = 7.3 Hz, $OCCH(N)CO_2$), 7.25 (s, 1 H, NH), 7.44–7.65 (m, 6 H, aryl H's), 7.85–7.89 (m, 2 H, aryl H's), 8.15–8.20 (m, 2 H, aryl H's); ^{13}C NMR ($CDCl_3$) δ 53.2 (OCH_3), 58.3 (C-2), 127.4, 128.6, 128.8, 129.6, 132.0, 133.1, 134.1, 134.5, 166.8, 167.3 (C-1 and CONH), 191.5 (C-3); IR (KBr) 3300 (NH), 1760 (C=O), 1695 (C=O), 1645 cm^{-1} (C=O); mass spectrum, calcd for $C_{17}H_{15}NO_4$ 297.1001, found *m/e* 297.1014, *m/e* (relative intensity) 297 (1), 238 (1), 175 (2), 162 (1), 127 (1), 126 (6), 125 (100), 78 (3), 77 (27), 76 (1), 51 (6).

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Registry No. 1, 77320-35-5; **2a** (isomer 1), 77320-36-6; **2a** (isomer 2), 77320-37-7; **2b** (isomer 1), 19185-84-3; **2b** (isomer 2), 19185-85-4; **2c** (isomer 1), 77320-38-8; **2c** (isomer 2), 77320-39-9; **2d** (isomer 1), 77320-40-2; **3a**, 77320-41-3; **3b**, 77320-42-4; **3c**, 77320-43-5; **3d**, 77320-44-6; **3e**, 19185-45-6; propionaldehyde, 123-38-6; benzaldehyde, 100-52-7; crotonaldehyde, 123-73-9; cyclohexanone, 108-94-1; CH_3COCl, 75-36-5; CH_3CH_2COCl, 79-03-8; BuCOCl, 638-29-9; $CH_2{=}CH(CH_2)_2COCl$, 39716-58-0; PhCOCl, 98-88-4; methyl hippurate, 1205-08-9.

Transesterification in an *O*-[(Dialkylamino)alkyl]salicylate System

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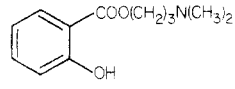
An abnormal reaction in an O-substituted salicylate system was observed in an attempt to carry out the transesterification of isopropyl *O*-[3-(dimethylamino)propyl]-salicylate in butanol under basic conditions. Neither the isopropyl group nor the butyl group signal was present in the NMR spectrum of this reaction product, which was proposed to be a sodium salt of 3-(dimethylamino)propyl salicylate (**1**) or *O*-[3-(dimethylamino)propyl]salicylic acid



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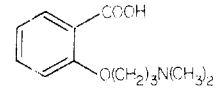

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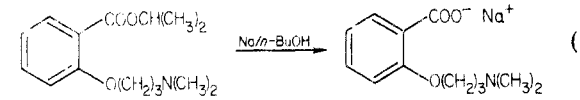
(**2**). The possibility of the product being the sodium salt of 3-(dimethylamino)propyl salicylate (**1**) was ruled out by an independent synthesis of it from salicylic acid and (dimethylamino)propyl chloride.[1] The sodium salt of *O*-[3-(dimethylamino)propyl]salicylic acid (**2**) could be obtained by the hydrolysis of *O*-[3-(dimethylamino)-propyl]salicylates in the presence of bases. The thus-obtained compound had the same R_f value and NMR and IR spectra as those of the previously mentioned transesterification product. Therefore, the reaction of isopropyl *O*-[3-(dimethylamino)propyl]salicylate in butanol in the presence of sodium butoxide was the sodium salt of *O*-[3-(dimethylamino)propyl]salicylic acid (**2**, eq 1).



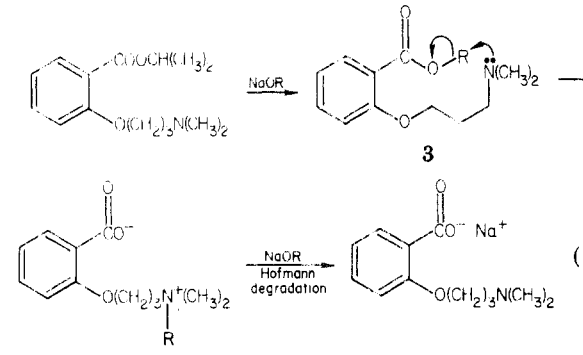
(1)

In order to check whether this unexpected product came from the hydrolysis of the salicylate, i.e., whether it was possible that the moisture in the solvent hydrolyzed the salicylate, all the solvent used was purified by dehydration of the alcohol with sodium followed by distillation. When the anhydrous solvent was used, the previously mentioned reaction had the same result as before. This indicated that the formation of *O*-[3-(dimethylamino)propyl]salicylic acid did not result from the hydrolysis of the salicylate.

It is proposed that the phenomenon observed in this work proceeds through a neighboring-group mechanism. Carboxylic esters are known to react with tertiary amine to yield quaternary ammonium salt[2] (eq 2). In our case,

$$RCOOMe + N(CH_3)_2(C_{12}H_{25}) \rightarrow RCOO^- {}^+N(CH_3)_3(C_{12}H_{25}) \rightarrow RCOOC_{12}H_{25} + N(CH_3)_3 \quad (2)$$

a carboxylic ester and tertiary amine are not only in the same molecule but also in a good relative position, which will allow the tertiary amino group to react easily with the carboxylic ester group as shown in structure **3** (eq 3).



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(3)

4

The first step in this reaction is the desired transesterification. This is supported by the facts that isopropyl alcohol is detected in the distillate of the reaction mixture by GC/MS (see supplementary material) and that the transesterification product (**3**) is isolated under milder reaction conditions (e.g., room temperature reaction). In the presence of a base, as soon as the transesterification product is transformed into a quaternary salt intermediate (**4**),[2] Hofmann degradation predominates the reaction

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course to form the sodium salt of O-[3-(dimethylamino)-propyl]salicylic acid.

If this is the mechanism, with sodium methoxide/methanol as the base/solvent system, trimethylamine should be able to be detected in the distillate. This was indeed observed (see supplementary material), and the proposed compound (4, R = CH_3) was proved to be an intermediate. This type of reaction should not occur under acidic conditions, because under these conditions the tertiary amine will transform into a quaternary ammonium salt and will no longer possess the ability to interact with the alkyl ester. Under neutral conditions, transesterification and Hofmann degradation do not take place readily, and this reaction will not occur either. These things were indeed observed. Isopropyl O-[3-(dimethylamino)propyl]salicyclate was refluxed in n-butyl alcohol with or without a small amount of sulfuric acid. After suitable treatment all the starting material was recovered.

The desired transesterification product, n-butyl O-[3-(dimethylamino)propyl]salicylate, can be obtained in high yield by refluxing isopropyl O-[3-(dimethylamino)-propyl]salicylate in butyl alcohol in the presence of 6-7 equiv of sulfuric acid.

Experimental Section

General Methods. The NMR data were obtained with a Varian A-60 spectrometer with Me_4Si as an internal standard. GC/MS data were obtained with a Finnigan 4021 GC/MS (manifold temperature 83 °C, electron energy 70 eV, emmission current 0.32 A, ion source temperature 250 °C, vacuum 2.1×10^{-7} torr). 3-(Dimethylamino)propyl salicylate (1) was synthesized from salicylic acid and (dimethylamino)propyl chloride by Horenstein and Pählicke's method.[1]

O-[3-(Dimethylamino)propyl]salicylic Acid (2). Method A. A mixture of alkyl O-[3-(dimethylamino)propyl]salicylate in an aqueous NaOH (or sulfuric acid) solution was heated at reflux for 2-3 h. The resulting mixture (after basification, if necessary) was extracted with ether. The separated aqueous layer was neutralized with aqueous 20% HCl solution and then evaporated under reduced pressure. The white residue obtained was extracted with ethanol. The ethanol solution was then evaporated at vacuo to yield O-[3-(dimethylamino)propyl]salicylic acid: 80-100%; NMR (D_2O) 2.15 (m, 2 H), 2.88 (s, 6 H), 3.31 (t, 2 H), 4.13 (t, 2 H), 6.88-7.73 ppm (m, 4 H); mass spectrum, m/e (relative intensity) 223 (P^+, 5), 58 (100). For detailed information see the supplementary material.

Method B. A mixture of isopropyl O-[3-(dimethylamino)-propyl]salicylate (1.20 g, 5 mmol) and 0.14 g (5 mmol) of sodium in 5 mL of anhydrous n-butyl alcohol was heated at reflux for 3 h. The resulting brown mixture was distilled. The distillate was analyzed by GC/MS to show the presence of isopropyl alcohol (see supplementary material). The residue was neutralized with aqueous 20% HCl solution and then treated as in the above-mentioned procedure to give the title compound 2 in 90% yield.

Method C. If the preceeding reaction (method B) was run at room temperature, 60% of O-[3-(dimethylamino)propyl]salicylic acid (2) and 37% of n-butyl O-[3-(dimethylamino)salicylate (3, R = n-Bu) can be isolated.

Attempted Transesterification Using the NaOMe/MeOH System. A mixture of isopropyl O-[3-(dimethylamino)propyl]-salicylate (1.33 g, 5 mmol) and 0.11 g (5 mmol) of sodium in 2 mL of dried methanol was heated at reflux for 6 h. The resulting mixture was distilled. The distillate, which had an strong amine odor, was analyzed by GC/MS which showed the presence of trimethylamine (see supplementary material). No desired transesterification product was isolated.

Attempted Transesterification under Neutral Conditions. Isopropyl O-[3-(dimethylamino)propyl]salicylate (0.5 g, 9 mmol) in 2 mL of butyl alcohol was gently refluxed for 3.5 h. The resulting mixture was evaporated in vacuo, and the residue thus obtained was partitioned between ether and water. The separated ether layer was washed with water and saturated NaCl solution. After the mixture was dried over anhydrous $MgSO_4$, the ether was removed in vacuo to the starting material in quantitative yield.

Attempted Transesterification under Acidic Conditions. n-Butyl O-[3-(Dimethylamino)propyl]salicylate. Method A. A mixture of isopropyl O-[3-(dimethylamino)propyl]salicylate (0.23 g) and 2 drops of sulfuric acid in 2 mL of n-butyl alcohol was heated at reflux for 6 h. The resulting mixture was basified with 20% NaOH solution and then treated by the previously mentioned procedure to yield the starting material (0.2 g).

Method B. A mixture of isopropyl O-[3-(dimethylamino)-propyl]salicylate (0.36 g) and 0.5 mL of sulfuric acid in 2 mL of n-butyl alcohol was heated at reflux for 6 h. The resulting mixture was treated as in procedure A to yield 0.3 g of n-butyl O-[3-(dimethylamino)propyl]salicylate: NMR ($CDCl_3$) 0.75-2.71 (m, 17 H), 4.11 (t, 2 H), 4.45 (t, 2 H), 6.75-7.20 (m, 2 H), 7.32-7.70 (m, 1 H), 7.77-8.05 ppm (m, 1 H); mass spectrum, m/e (relative intensity) 279 (P^+, 0.5), 58 (100). For detailed information see the supplementary material. Anal. Calcd for $C_{16}H_{25}NO_3$: N, 5.02. Found: N, 5.14.

Acknowledgment. We acknowledge support of this work from Union Industrial Research Laboratories, Industrial Technology Research Institute.

Registry No. 2, 77305-78-3; **2** isopropyl ester, 77305-79-4; **3** (R = n-Bu), 77305-80-7; butyl alcohol, 71-36-3; isopropy alcohol, 67-63-0; trimethylamine, 75-50-3.

Supplementary Material Available: GC-mass spectra of the distillate from the reaction of isopropyl O-[3-(dimethylamino)propyl]salicylate with Na/n-BuOH or with Na/MeOH and the mass spectra of O-[3-(dimethylamino)propyl]salicylic acid (2) and n-butyl O-[3-(dimethylamino)propyl]salicylate (6 pages). Ordering information is given on any current masthead page.

Structure of Juncunone: A Biogenetically Intriguing Molecule from the Marsh Plant *Juncus roemerianus*

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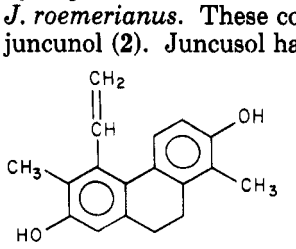
Juncus roemerianus (NO Juncaceae) is the most dominant plant of a group commonly referred to as "marsh grass", which grows on the coast of the southeastern United States. The 95% ethanolic extract of the aerial part of *J. roemerianus* has shown confirmed activity against the National Cancer Institute's Murine P388 lymphocytic leukemia (PS system). We have previously reported[1,2] the isolation and structure elucidation of two novel 9,10-dihydrophenanthrene derivatives from the $CHCl_3$ extract of *J. roemerianus*. These compounds are juncusol (1) and juncunol (2). Juncusol has demonstrated confirmed cy-



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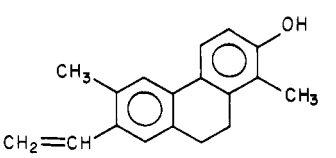

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