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*

D. Howard Miles* and Shirley Randle

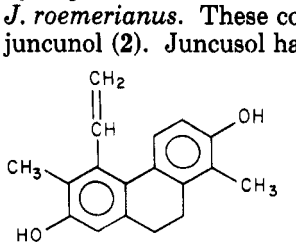
Department of Chemistry, Mississippi State University, Mississippi State, Mississippi 39762

Riz Shakir and Jerry L. Atwood

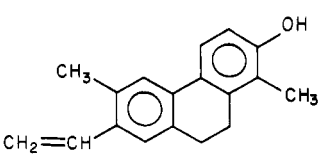
Department of Chemistry, The University of Alabama, University, Alabama 35486

Received December 15, 1980

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-



1

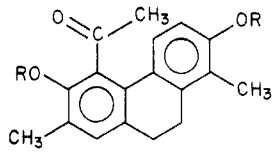


2

(1) D. H. Miles, J. Bhattacharyya, N. V. Mody, J. L. Atwood, S. Black, and P. A. Hedin, *J. Am. Chem. Soc.*, **99**, 618 (1977).
(2) J. Bhattacharyya and D. H. Miles, *Tetrahedron Lett.*, 2749 (1977).

0022-3263/81/1946-2813$01.25/0

totoxic activity (ED_{50} 0.3 μg/mL) against the NCI 9 KB (human epidermoid carcinoma of the nasopharynx) test system. The unique arrangement of carbon atoms in the 9,10-dihydrophenanthrene derivatives has provided a target for biogenetic speculation and synthesis.[3,4] We now report the isolation from *J. roemerianus* of another novel 9,10-dihydrophenanthrene, juncunone (**3**).

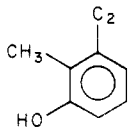


3, R = H

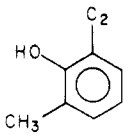
4, R = Ac = $\overset{O}{\overset{\|}{C}}CH_3$

The dry, ground tops (above ground) of *J. roemerianus* were extracted with chloroform. Chromatography of the concentrated chloroform extract on silica gel followed by preparative thin-layer chromatography on silica gel and crystallization from benzene yielded the yellow compound juncunone (**3**): $C_{18}H_{18}O_3$; mass spectrum, *m/e* 282 (M^+); mp 196–197 °C. The IR spectrum of juncunone showed bands at 3330 (OH), 1615 (carbonyl), and 1360 cm^{-1} (methyl attached to a carbonyl). The UV spectrum gave a λ_{max} of 250 nm (ε 7931) (acetyl group attached to an aromatic ring). The ^1H NMR spectrum showed singlets at δ 2.05 (3 H), 2.26 (3 H), and 2.28 (3 H) for the three methyl groups, a doublet at δ 6.60 (1 H) and 6.80 (1 H) and a singlet at 7.10 (1 H) for the three aromatic protons, a multiplet at δ 2.70 (4 H) for the four protons on ring B, and singlets at δ 5.85 (1 H) and 10.24 (1 H) for the two hydroxyl groups. Structure **3** was confirmed by a single-crystal X-ray diffraction experiment on juncunone diacetate (**4**). Figure 1 shows the molecular structure and the atom numbering scheme for juncunone diacetate.

Although approximately 20 of the relatively rare 9,10-dihydrophenanthrene derivatives are known from nature, juncunone is unique in the arrangement of its carbon skeleton and in the presence of an acetyl group. Juncunone also provides a further target for biogenetic speculation. McDonald and Martin[4] have speculated that the related phenol, juncusol, could have its origin from precursor **5** via electrophilic aromatic substitution and oxi-



5



6

dative phenolic coupling. Similarly, juncunone could have its biogenetic origin via unsymmetrical coupling of precursors **5** and **6**. One can also speculate concerning other possible precursors, such as a dialkylpyrene system, for both juncunone and juncusol.

Experimental Section

The nuclear magnetic resonance spectrum was obtained by using a 60-MHz Varian spectrometer. Tetramethylsilane was used as the internal standard and chloroform-*d* (99.8%, $CDCl_3$) as solvent. The high-resolution mass spectrum was obtained from the National Institutes of Health mass spectrometry facility at the Massachusetts Institute of Technology (Dr. Catherine E. Costello, Director). The infrared spectrum was determined on a Nicolet 7199 Fourier transform infrared interferrometer by using a cast film of the compound. The ultraviolet spectrum was obtained in methanol with a Beckman DK-2A spectrometer. The X-ray structure was determined on a Enraf Nonius CAD-4 diffractometer. The melting point was determined on a Mel-Temp apparatus and is uncorrected. Column chromatography was performed with silica gel (70–230-mesh silica, Woelm Pharma) as the solid support. Thin-layer chromatography (TLC) was performed by using 20 × 20 cm glass plates coated with silica gel 7G (J. T. Baker Co.) mixed with a fluorescent indicator from the J. T. Baker Co. Plates with a thickness of 0.25-mm were used for analytical TLC, and plates of 1.0-mm thickness were used for preparative TLC. The 0.25- and 1.0-mm plates were activated at 110 °C for 2 and 4 h, respectively. Ultraviolet light was used as the TLC detecting agent.

Isolation of Juncunone (3). The dry, ground tops of *Juncus roemerianus* (1900 g) were extracted for 16 h in Soxhlet extractors with chloroform (18 L). The solvent was evaporated in vacuo to yield 46.0 g of crude extract (fraction A). Fraction A, dissolved in a minimum of benzene–hexane (1:1), was placed on a chromatography column [4.5-cm diameter, 500 g of silica gel, wet packing in benzene–hexane (1:1)] and eluted in 500-mL fractions with benzene–hexane (1:1), benzene–hexane (3:1), benzene, chloroform–benzene (1:3), and chloroform–benzene (1:1), respectively. The separation was monitored by TLC using chloroform–acetone–diethylamine (5:4:1) as the developing solvent. The fractions eluted with benzene–hexane (3:1) and benzene were combined to give fraction B (8.3 g). The concentrated fraction was dissolved in a minimum amount of benzene, and juncusol (**1**, 0.3 g) was crystallized out after 48 h at room temperature. Fraction B minus juncusol was then chromatographed on a column (3.5-cm diameter, 200 g of silica gel, wet packing in benzene) and eluted in 500-mL fractions with benzene, chloroform, chloroform–ethanol (9:1), and chloroform–ethanol (1:1), respectively. Using the same TLC monitoring system as above, the last 56 fractions eluted with benzene were combined to give fraction C (3.3 g). This fraction, dissolved in benzene, was rechromatographed on a column (2.5-cm diameter, 100 g of silica gel, wet packing in benzene) and eluted in 250-mL fractions with the same solvent sequence as for the chromatography of fraction B. Fractions 15–18 eluted with benzene were combined after a TLC check to give fraction D (2.5 g). Fraction D was further separated by using preparative TLC in the solvent system chloroform–acetone–diethylamine (5:4:1). The yellow band (R_f 0.5) was removed from the plates and extracted from the support with hot chloroform to give fraction E (1.5 g). This fraction was separated again by using the same procedure to give fraction F (R_f 0.5). Fraction F (0.09 g) was further resolved by preparative TLC in the solvent system chloroform–methanol (9.5:0.5). The dominant yellow band (R_f 0.54) was taken and chromatographed once more under the same conditions as for fraction F. This final separation yielded pure juncunone (**3**, 40 mg) which crystallized from benzene as yellow crystals with a melting point of 196–197 °C. The spectral properties of juncunone are as follows: UV (CH_3OH) λ_{max} 250 nm (ε 7931); IR λ_{max} 3330, 1615, 1360 cm^{-1}; 60-MHz ^1H NMR ($CDCl_3$) δ 2.05 (3 H, s), 2.26 (3 H, s), 2.28 (3 H, s), 2.70 (4 H, m), 5.85 (1 H, s), 6.60 (1 H, d), 6.80 (1 H, d), 7.10 (1 H, s), 10.24 (1 H, s); high-resolution mass spectrum for $C_{18}H_{18}O_3$, *m/e* 282 (M^+).

Preparation of the Diacetate 4. Juncunone (**3**, 5 mg) was dissolved in 0.5 mL of acetic anhydride and 1 mL of dry pyridine. After being stirred overnight at room temperature, the solution was freed of excess pyridine in vacuo and then was poured over cold water (20 mL). The water was extracted with chloroform, and the chloroform was successively washed with 5% HCl, H_2O, 10% Na_2CO_3, and H_2O. The chloroform was dried over anhydrous $MgSO_4$ and then evaporated in vacuo to yield 5 mg of juncunone diacetate (**4**), mp 182–184 °C.

X-ray Structure Determination of 4. Juncunone diacetate (**4**) was crystallized from chloroform as colorless polyhedra which belong to the monoclinic crystal system. Single crystals of the substance were sealed in thin-walled capillaries prior to X-ray examination. The unit cell parameters are *a* = 11.681 (7) Å, *b* = 17.053 (9) Å, *c* = 9.460 (6) Å, β = 93.83 (4)°, and ρ_c = 1.27 g cm^{-3} for four molecules in the unit cell. The diffracted intensities were collected by the ω–2θ scan technique in the usual manner.[5]

(3) A. S. Kende and D. P. Curran, *Tetrahedron Lett.*, 3003 (1978).
(4) E. McDonald and R. T. Martin, *Tetrahedron Lett.*, 4723 (1978).

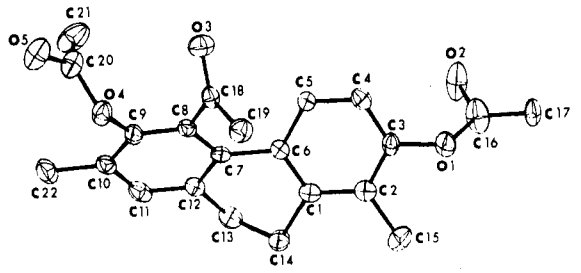


Figure 1. Molecular structure of juncunone diacetate with atoms displayed as 30% probability ellipsoids for thermal motion. Hydrogen atoms are not shown.

As a check on the stability of the instrument and the crystal, two reflections were measured after every 50 reflections; the standards fluctuated within a range of ±2%.

One independent quadrant of data was measured out to $2\theta = 50°$; a slow scan was performed on a total of 1808 reflections. Since these data were scanned at a speed which would yield a net count of 4000, the calculated standard deviations were all very nearly equal. No reflection was subjected to a slow scan unless a net count of 20 was obtained in the prescan. On the basis of these considerations, the data set of 1808 reflections (used in the subsequent structure determination and refinement) was considered observed and consisted mainly of those for which $I > 3\sigma(I)$. The intensities were corrected for Lorentz and polarization effects but not for absorption ($\mu = 0.93$ cm^{-1}).

The structure was solved by direct methods using the program MULTAN[6] and refined by full-matrix least-squares techniques[7] to give discrepancy indexes of $R = 0.088$ and $R_w = 0.096$ which are calculated as in eq 1 and 2. Carbon and oxygen atoms were

$$R = \sum||F_o| - |F_c||/\sum|F_o| \quad (1)$$

$$R_w = [\sum w(|F_o| - |F_c|)^2/\sum w(F_o)^2]^{1/2} \quad (2)$$

refined with anisotropic thermal parameters. All hydrogen atoms were located on a difference Fourier map. Those of the methyl substituents were refined as rigid groups. One of the acetate groups was disordered about the C–O bond; the occupancy factors converged at 0.60 and 0.40. The bond lengths and angles agree well (esd's of 0.008 Å and 0.6°, respectively) with generally accepted values.[8]

Acknowledgment. This work was supported by a grant from the National Cancer Institute (2-ROI-CA13268), National Institutes of Health, Bethesda, MD. We thank Dr. Sidney McDaniel for collection of plant material.

Registry No. 1, 62023-90-9; 3, 77305-81-8; 4, 77305-82-9.

Supplementary Material Available: The fractional coordinates (Table I), important bond distances and angles (Table II), and a complete listing of structure factor amplitudes (13 pages). Ordering information is given on any current masthead page.

(5) J. Holton, M. F. Lappert, D. G. H. Ballard, R. Pearce, J. L. Atwood, and W. E. Hunter, *J. Chem. Soc., Dalton Trans.*, 45 (1979).
(6) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(7) The following crystallographic programs were used: D. J. Hodgson's version of Dellaca and Robinson's Fourier program as locally implemented for the UNIVAC 1110, University of Alabama; W. R. Busing, K. O. Martin, and H. A. Levy, "A Fortran Crystallographic Least-Squares Program", Report ORNL-TM 305, Oak Ridge National Laboratory, Oak Ridge, TN, 1965; C. Johnson, "ORTEP, A Fortran Thermal-Ellipsoid Plot Program", Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, TN, 1965; W. R. Busing, K. O. Martin, and H. A. Levy, "ORFFE, A Fortran Crystallographic Function and Error Program", Report ORNL-TM 306, Oak Ridge National Laboratory, Oak Ridge, TN, 1964.
(8) O. Kennard, D. G. Watson, F. H. Allen, N. W. Issacs, W. D. S. Motherwell, R. C. Pettersen, and W. G. Town, Eds., "Molecular Structures and Dimensions", Vol. A1, N. V. A. Oosthoek, Utrecht, The Netherlands, 1972.

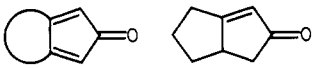
Synthesis of Bicyclo[3.3.0]oct-1(2)-en-3-one

Dennis K. Klipa and Harold Hart*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

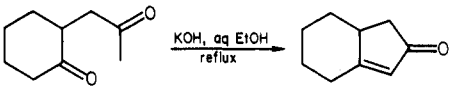
Received March 4, 1981

In connection with a project on the synthesis of cyclopentadienones containing a ring fused to the C3–C4 bond, as in **1**, we required the title compound **2**. Surprisingly this relatively simple enone, which is of current interest because the ring system is present in many biologically active natural products, has eluded synthesis.



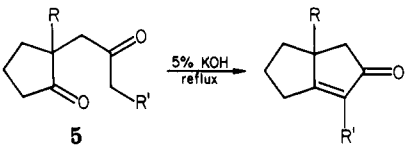
1 **2**

A variety of condensations which might reasonably be expected to give **2** have failed. For example, although base-catalyzed intramolecular aldol condensation of **3**[1]



3 **4** (83%)

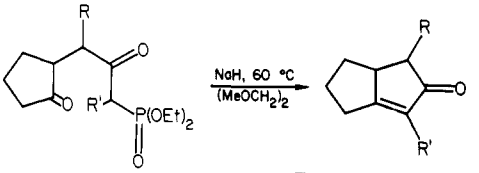
gives a good yield of the next higher homologue **4** and similar conditions give simple methyl derivatives of **2** (i.e., **6**–**8**), these methods failed to give **2** from **5** (R = R′ = H). Only complex intractable mixtures were obtained.[2]



5

6,[1] R = CH_3; R′ = H (79%)
7,[2] R = H; R′ = CH_3 (83%)
8,[1] R = R′ = CH_3 (88%)

In a very recent paper[3] the Wadsworth–Emmons modification of the Wittig reaction also failed when applied to **2**. Thus whereas **7** and **10** could be obtained in good yield, only a "tarry mass" was obtained when the same procedure was applied to **9** (R = R′ = H).[4]



9

7, R = H; R′ = CH_3 (80%)
10, R = CH_3; R′ = H (70%)

We have been able to prepare the long-sought **2** in 38% overall yield from the known precursors **11**[5] and **12**.[6] Carefully controlled conditions are required for the hydrolysis and decarboxylation of **12**. An improved procedure for the synthesis of **11** is given in the Experimental Section. By Becker's procedure,[6] cyclization of **11** with

(1) Miyashita, M.; Yanami, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1976**, *98*, 4679 and earlier references cited therein.
(2) Paul, H.; Wendel, I. *Chem. Ber.* **1957**, *90*, 1342.
(3) Bailey, M. J.; Cooper, K.; Pattenden, G. *Tetrahedron Lett.* **1981**, 257. Since it may lead to some confusion, we call attention to the fact that the title and text of this paper give an incorrect (indeed, impossible) name to these compounds.
(4) At 25 °C with 2 equiv of NaH the authors isolated a novel dimer of **2** and "in only one experiment" were they able to isolate a "small amount" of **2**.
(5) Herz, W. *J. Am. Chem. Soc.* **1956**, *78*, 1485.
(6) Becker, D.; Brodsky, N. C.; Kalo, J. *J. Org. Chem.* **1978**, *43*, 2557.

0022-3263/81/1946-2815$01.25/0