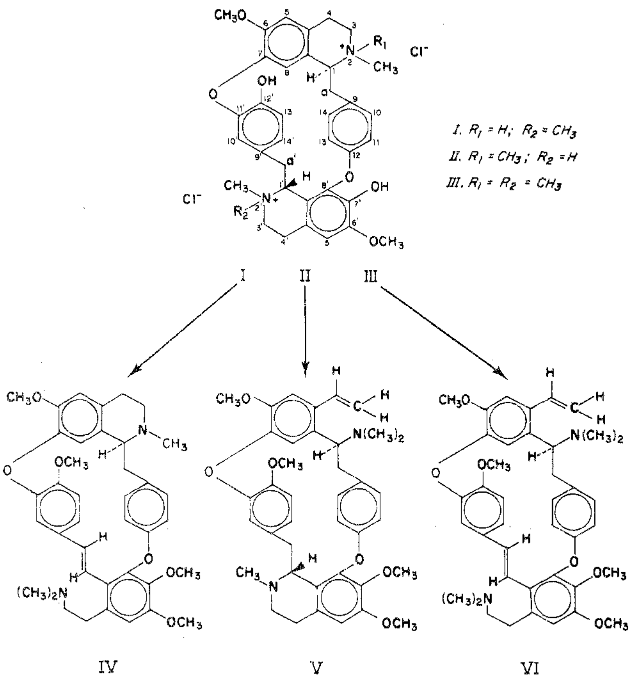

Figure 1. The generation of a stilbene derivative (IV) from (+)-tubocurarine (I), a styrene derivative (V) from (+)-isotubocurarine (II), and a stilbene-styrene derivative (VI) from (+)-chondocurarine (III) by the action of excess ethereal diazomethane on alcoholic solutions of the substrates.

the β hydrogens leading to both styrene and stilbene products are equally accessible, the driving force would be the greater stability derived from the extended conjugation when a stilbene rather than a styrene olefin is formed, and, therefore, the formation of IV is favored. In II, only the β hydrogens on C-4 leading to a styrene product can be oriented anti to the leaving group, and, thus, V is formed exclusively. It follows that VI (a stilbene on the lower portion and a styrene on the upper portion of the molecule) would be the product expected from the elimination reaction on III since no new conformational changes have been introduced.

(2) Other plausible explanations of this behavior rest on the natural structural restrictions placed on all compounds of the curine–chondocurine type.[9] This stems from the positions of the phenyl ether linkages present. In this subgroup of bisbenzyltetrahydroisoquinolines, the two phenolic junctions are not para–para (*i.e.*, symmetrical as in the isochondodendrine type) nor meta–meta (as in the hayatine type) but are, rather, meta–para. This structural feature is probably largely responsible for the unique course of reaction that I, II, and III undergo in the present Hofmann elimination. Specifically, two consequences of the restriction become evident.

(a) The conformation of the molecules is such that the phenolic ether oxygen between C-8′ and C-12 is less than 3 Å away from the β hydrogens at C-a′ (which lead to a stilbene product), whereas the other phenolic ether oxygen lying between C-7 and C-11′ is separated by more than 10 Å from the β-hydrogens at C-a. We feel that the proximity of this oxygen atom to the protons at C-a′ in I facilitates their removal and, consequently, contributes to the formation of the stilbene product (IV). This driving force is not operable to remove the protons at C-a in the case of II, hence the formation of the styrene product (V).

(b) In focusing attention on the possible olefinic products formed, the virtually exclusive formation of a stilbene product (IV) from I and a styrene product (V) from II would be expected because of the restrictions brought about by this type of phenyl ether linkage. A *trans*-stilbene[10] can only be accommodated in the lower portion of the molecule, *i.e.*, leading to IV, whereas in the upper portion only a *cis*-stilbene can be formed which would probably be unfavorable because of the resulting steric hindrance.

It may be noted that all of the above arguments rely on steric factors for their validity. We believe that electronic considerations play only a minor role, if any, in influencing the course of the Hofmann elimination in these compounds.

References and Notes

(1) This research was supported by the National Institutes of Health through Grant No. NS 08427.
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(3) A more broadly based investigation concerning the action of diazomethane on quaternary ammonium salts is currently under way in order to obtain a better understanding of this unique reaction.
(4) All precautions (*e.g.*, drying, distillation, etc.) were taken to prevent the possibility of carryover alkalinity from the generation of diazomethane from *N*-nitroso-*N*-methylurea with strong base. No alkalinity was detected.
(5) Compounds IV, V, and VI have been characterized by analytical (C, H, N) and spectral (uv, ir, nmr) data.
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(7) R. Egan, R. Stanaszek and D. Williamson, *J. Chem. Soc., Perkin Trans. 2*, 716 (1973).
(8) We are aware that in the Hofmann elimination reaction other mechanistic pathways may be operative. Nevertheless, although one cannot be completely sure of an E2 elimination, the circumstances and product pathways seem to agree with this assumption.
(9) M. Shamma, "The Isoquinoline Alkaloids, Chemistry and Pharmacology," Academic Press, New York, N.Y., 1972, p 117.
(10) In general, for steric reasons, a *trans*-stilbene is more stable and is usually favored in formation over a *cis*-stilbene.

Department of Medicinal Chemistry
College of Pharmacy
University of Minnesota
Minneapolis, Minnesota 55455

Janette Naghaway
Nadim A. Shaath
Taito O. Soine*

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The Nature of the λ 263 Chromophore in the Palytoxins[1]

Summary: Palytoxins, the toxic constituents of zoanthids of the genus *Palythoa*, are substituted *N*-(3-hydroxypropyl)-*trans*-3-amidoacrylamides.

Sir: Except for certain polypeptides and proteins from bacteria (botulinus, tetanus, and diphtheria toxins) and plants (ricin), the palytoxins are the most poisonous substances known to date. We first isolated a palytoxin from a marine coelenterate known to the Hawaiians as *limu-make-o-Hana* (the deadly seaweed of Hana)[2] and now designated *Palythoa toxica* Walsh and Bowers.[3] Since then, seemingly identical toxins have been isolated from several other species of zoanthids of the genus *Palythoa*.[4–6] The palytoxins from *P. toxica*, *P. mammilosa* Ellis and Solander from Jamaica, and a new species of *Palythoa* from Tahiti possess identical lethal and anticancer properties[5] and exhibit the same uv spectra (λ_{max} 233, 263 nm). Subtle differences, however, can be seen in the pmr and cmr spectra of the three toxins (Figure 1) despite their large molecular weights and absence of repetitive amino acid or sugar units.[7] We now wish to report identification of a moiety that contains two of the four nitrogens in palytoxin and exhibits the 263-nm chromophore of the toxin.

The cmr spectra of the palytoxins show signals at 169.2 and 175.6 ppm[8] which are assigned to two amide[9] carbons. The 300-MHz pmr spectra of the palytoxins in 100% DMSO-d_6[10] display two amide NH absorptions. One is a

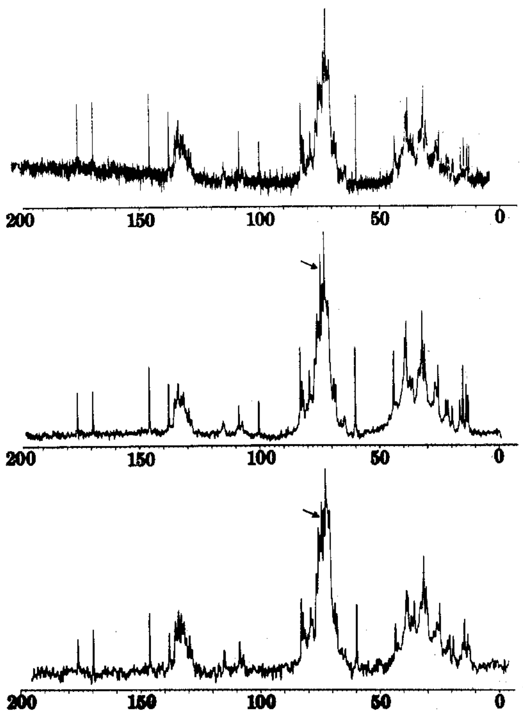
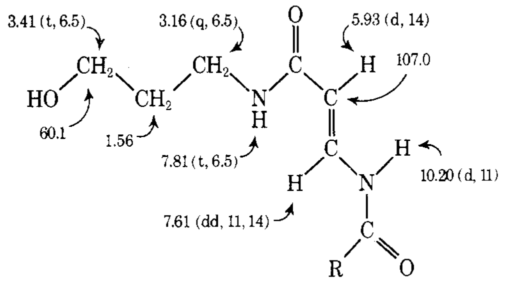


Figure 1. Comparison of the 25.2-MHz cmr spectra of palytoxins from Hawaiian *Palythoa toxica* (bottom), Jamaican *P. mammilosa* (middle), and an unknown Tahitian *P. ssp.* (top): 0.2, 0.5, and 0.4 g/2.5 ml of D_2O, respectively. Arrows point out a line at 73.5 ppm in the spectral traces of the Hawaiian and Jamaican toxins that is missing in the spectrum of the Tahitian sample. Note also that the line at 100.2 ppm in the upper and center traces is absent in the lower spectrum.

triplet (J = 6.5 Hz) at δ 7.81, which was subsequently assigned to a 3-amidopropanol residue and corroborated by nmdr and deuterium exchange experiments. The other NH signal is a doublet (J = 11 Hz) at δ 10.20 ascribed to an amido group attached to the β position of a trans disubstituted α,β-unsaturated carbonyl system. The α and β protons appear as a doublet and a doublet of doublets at δ 5.93 (J = 14 Hz) and 7.61 (J = 11 and 14 Hz). Irradiation of the NH at δ 10.20 or addition of D_2O reduces the signal for the β proton to a doublet. The doublet resonance experiment also causes an appreciable sharpening of the NH triplet at δ 7.81, showing long range coupling between the two NH protons.

These data suggested to us two partial structures **1** and **2** for palytoxin. After studying model compounds such as **3** [mp 88–89°; λ_{max} 264 nm (ϵ 22,000)], **4**,[11] **5** (mp 77.5–78.5°), and **6** it was clear that the β-amidoacrylamide (**1**) provides a better fit. In disubstituted ureas (**6**) no W coupling is observed between the two NH protons. Furthermore the chemical shifts of the NH protons and the carbonyl carbon of disubstituted ureas are observed at higher field than those for palytoxin.[12] Confirmation was achieved by acid hydrolysis and hydrogenation of palytoxin.



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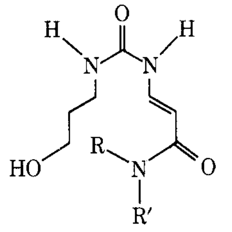

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When a palytoxin is hydrolyzed in refluxing 2 N HCl for 4 hr the 263-nm uv band disappears as does toxicity. After ultrafiltration of the hydrolysate through a Diaflo UM-2 membrane,[13] only 3-aminopropanol is identified in the diffusate (pmr). The other products are either volatile and are lost during work-up or have molecular weights greater than 1000 and would be found in the retentate. When the palytoxin is catalytically hydrogenated (Pt/aqueous EtOH) prior to acid hydrolysis, equivalent amounts of β-alanine and 3-aminopropanol are obtained in the diffusate after ultrafiltration. These data suggest **7** and **8** as possible partial structures for hydrogenated palytoxin. Of these only **7** should yield on brief acid hydrolysis, in addition to β-alanine and 3-aminopropanol, a third ninhydrin-active product of low molecular weight, N-(3-hydroxypropyl)-3-aminopropionamide (**9**). In fact, synthetic N-(3-hydroxypropyl)-3-acetamidopropionamide [**10**, from β-alanine: (1) Ac_2O; (2) $ClCO_2Et$, Et_3N, 0°; (3) 3-aminopropanol], mp 102–103°, produces a maximum amount of **9** after a 0.5-hr reflux in 1 N HCl. In a parallel experiment, hydrolysis of hydrogenated palytoxin also gave **9** which was isolated by ultrafiltration (Diaflo UM-2 membrane) and chromatogra-

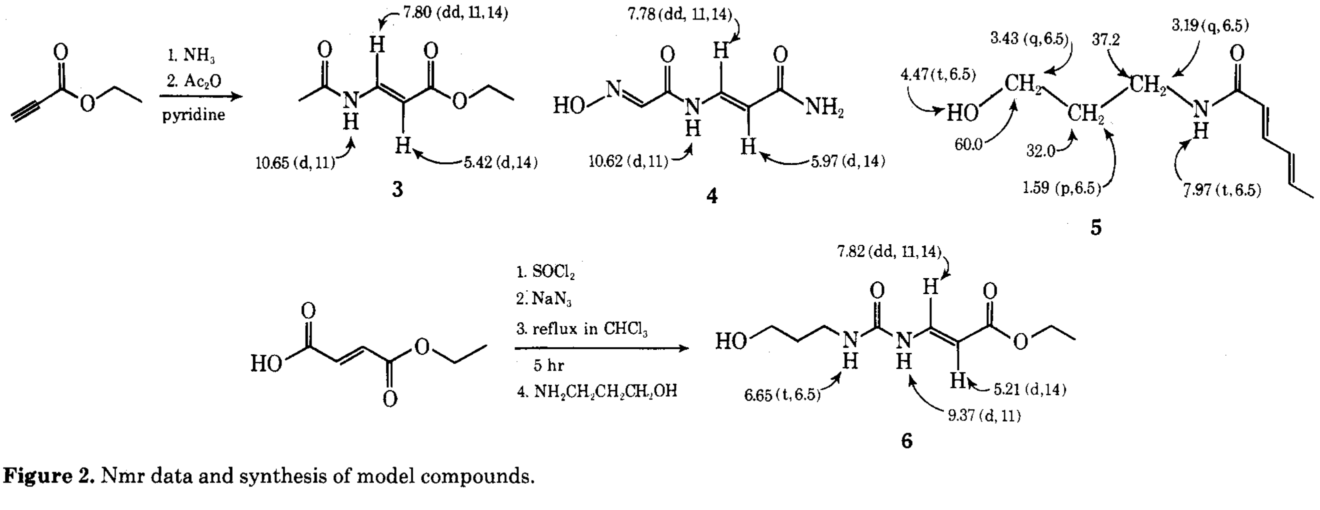
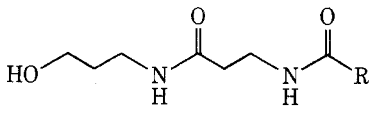


Figure 2. Nmr data and synthesis of model compounds.



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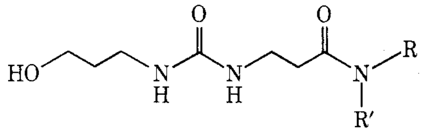

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phy of the diffusate on silica gel with a 7:2:1 mixture of 2-propanol–water–concentrated ammonia. Compound **9** was eluted between 3-aminopropanol and β-alanine and proved to be identical in all respects with synthetic **9** obtained by hydrolysis of **10** or by treatment of *N*-(3-hydroxypropyl)-β-phthalimidopropionamide [**11**, from β-alanine: (1) phthalic anhydride; (2) $ClCO_2Et$, Et_3N, 0°; (3) 3-aminopropanol], mp 166–167°, with hydrazine hydrate in EtOH (reflux) for 1 hr.[14]

The palytoxins are therefore substituted *N*-(3-hydroxypropyl)-*trans*-3-amidoacrylamides (**1**).

Acknowledgments. This work was supported by the U.S. Public Health Service. We are grateful to Lewis Cary and William Jankowski, Varian Associates, for determining the pmr and cmr spectra of Jamaican palytoxin.

Supplementary Material Available. The 300-MHz pmr spectrum of palytoxin from *Palythoa mammilosa* in 100% DMSO-d_6 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-540.

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(6) The palytoxin of *Palythoa tuberculosa* Esper appears to be associated with the eggs of the female polyps [S. Kimura, Y. Hashimoto, and K. Yamazato, *Toxicon*, **10**, 611 (1972)].
(7) The molecular weight of palytoxin from *P. toxica* was estimated to be 3300 and its molecular formula $C_{145}H_{264}N_4O_{78}$ from combustion and spectral (pmr and uv) data.[1]
(8) Carbon chemical shifts are reported in δ units (parts per million) relative to *p*-dioxane (δ 67.4 relative to Me_4Si) as an internal standard in D_2O.
(9) Only amide carbonyl absorption is observed in the infrared spectrum of palytoxin (see ref 1).
(10) Proton chemical shifts are reported in δ units (2 parts per million) relative to Me_4Si (δ 0) and the residual DMSO-d_5 peak (δ 2.52) as internal standards.
(11) P. F. Wiley, R. R. Herr, F. A. MacKellar, and A. D. Argoudelis, *J. Org. Chem.*, **30**, 2330 (1965).
(12) The urea carbonyl carbon-13 signals for 1-(3-hydroxypropyl)-3-phenylurea (in DMSO-d_6), 1-(3-hydroxypropyl)-3-*n*-propylurea (in $CDCl_3$), and 4,8,14,18-tetraoxo-7,9,15-triaza-3,13,19-trioxa-*trans,trans*-heneicosa-5,16-diene (in $CDCl_3$) are found at 155.3, 160.1, and 153.4 ppm from Me_4Si. The NH protons resonate at 6.15 and 8.45, 5.75 and 5.81, and 9.39 and 6.75 ppm, respectively, in DMSO-d_6.
(13) Obtained from the Amicon Corp.
(14) All new compounds gave satisfactory elemental analyses.

Department of Chemistry
University of Hawaii
Honolulu, Hawaii 96822

Richard E. Moore*
Robert F. Dietrich
(in part) Billie Hatton
Tatsuo Higa
Paul J. Scheuer*

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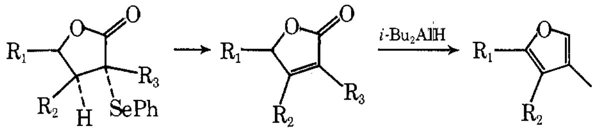
Organoselenium Chemistry. A General Furan Synthesis

Summary: An efficient four-step synthesis of 2,4- and 2,3,4-substituted furans from γ-lactones *via* their corresponding butenolides is described.

Sir: The facile elimination of selenoxides derived from α-phenylselenenyl-γ-lactones with almost complete formation of endocyclic α,β-unsaturated butenolides suggested a general route to furans (eq 1).[1,2] We wish to report a general method for the conversion of substituted γ-lactones into 2,4- and 2,3,4-substituted furans[3] *via* their corresponding butenolides (see Table I). The α-selenenylated γ-lactones of type I can be efficiently prepared by selenenylation of the corresponding α-substituted γ-lactones which are prepared by direct alkylation of lactone enolates[2,4] or by conjugate-addition of an organocopper reagent to an α-methylene-γ-lactone (eq 2).[5] The reaction sequence constitutes a widely applicable method. As indicated in Table I, yields are generally high.



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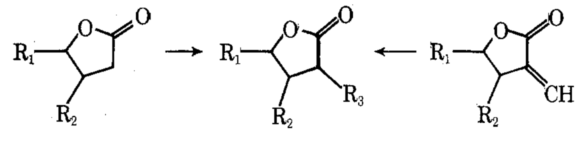

(2)

The method outlined above, however, is critically dependent upon only one of the two possible syn[6] modes of elimination predominating. α-Phenylselenenylated lactones have previously[2] been employed in the construction of fused α-methylene lactones with complete exclusion of the endocyclic double bond isomers.[7] We have observed, however, that selenoxides derived from I (R_3 = alkyl), in which there exists the possibility for two syn modes of elimination, result in >95% yield of the endocyclic olefin despite the statistical preference for exocyclic olefin formation. The high propensity for endocyclic olefin formation thus provides a useful $\Delta^{\alpha,\beta}$-butenolide synthesis as well as providing direct access to furans *via* reduction with diisobutylaluminum hydride[8] (see Table I).

A typical furan synthesis is illustrated below for the conversion of γ-decalactone[9] to 2-butyl-4-benzylfuran. The lithium enolate of γ-decalactone was prepared at −78° by slow addition (1 mmol/hr) of a solution of γ-decalactone (1 equiv, 1 *M* in THF) to a solution of lithium diisopropylamide (LDA) (1.05 equiv, 0.3 *M* in THF). After the mixture was stirred for 20 min, a solution of benzyl bromide (1.05 equiv, 1 *M* in THF) containing hexamethylphosphoramide (HMPA) (1.05 equiv) was added. The temperature was raised to *ca.* −40° and was maintained at that temperature for 3 hr. The reaction was quenched by the addition of 10% HCl and after usual work-up and chromatography on silica gel (hexanes/ether, 3:1) afforded α-benzyl-γ-decalactone (88%) [ir (film) 5.66 and 6.25 μ; nmr (CCl_4) δ 7.15 (s, 5 H), 4.18 (m, 1 H), 2.6–3.2 (m, 3 H)].

Selenenylation of α-benzyl-γ-decalactone was carried out by slowly adding (1 mmol/hr) a solution of the lactone (1.0 equiv, 1 *M* in THF) to a solution of LDA (1.1 equiv, 0.3 *M* in THF) cooled to −78°. After 20 min, the reaction mixture was treated with a solution of phenylselenenyl chlo-