In view of the rather harsh reaction conditions used in the cycloaddition, the stereochemistry of the product was confirmed in a chemical fashion. Catalytic hydrogenation of **11** gave the dihydro compound **12**, mp 65–66°. The spectral properties and melting point of **12** were different from those of the authentic trans compound, **13**, mp 57.5–59°.[15,16] A positive comparison was made starting with the ketoacetate **14**.[16] Hydrolysis and Jones oxidation of **14** gave an authentic sample of **12**[17] undistinguishable with that prepared from the Diels–Alder route.

Studies of further applications of this active diene in Diels–Alder reactions as well as utilization of the octalones are in progress.

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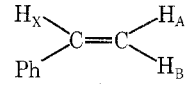
Hofmann Elimination with Diazomethane on Quaternary Curare Bases[1]

Summary: Treatment of (+)-tubocurarine, (+)-isotubocurarine, and (+)-chondocurarine at room temperature with an excess of diazomethane leads to Hofmann elimination type methine bases resulting from unique stereochemical pathways.

Sir: When O-methylating (+)-tubocurarine chloride (I) with excess diazomethane in the usual way to produce the O,O-dimethyl derivative, we observed that the crude reaction product, when examined by thin layer chromatography (tlc), showed anomalous spots which could logically be ascribed to unexpected tertiary bases on the basis of their R_f values. Additional experimentation indicated that the apparent intensities of the spots were enhanced with larger amounts of diazomethane. The same experiment repeated on (+)-isotubocurarine (II)[2] and chondocurarine chloride (III) reinforced the conclusion that a Hofmann elimination reaction had taken place to generate tertiary methine bases by the action of diazomethane on I, II, and III. This stimulated a more informative inquiry into the anomaly.[3]

The general aspects of the presently reported reaction were that the respective quaternary bases were treated in methanolic solution with a tenfold molar excess of ethereal diazomethane[4] added incrementally over a 24-hr period. The work-up of the products was essentially a separation on 1-mm precoated silica gel plates developed with a solvent system composed of 2.5% ammonia:ethyl acetate:2-propanol:methanol (0.7:3:3:4). The appropriate bands were removed and extracted with a suitable solvent mixture of methanol and ethyl acetate to yield the respective products.[5]

Examination of the nuclear magnetic resonance (nmr) spectra ($CDCl_3$, δ) of the methine bases obtained from I, II, and III provides an interesting comparison of steric factors directing the course of the Hofmann elimination (see Figure 1). The major elimination product of I isolated was the stilbene derivative (IV): 2.32 [s, 6, $N(CH_3)_2$], 2.46 (s, 3, NCH_3), 3.76 (d, 6, 2 OCH_3), 3.87 (d, 6, 2 OCH_3), 5.82–7.08 [m, 12, 10 aromatic and 2 vinyl (*i.e.,* stilbene)]. In the case of II, the methine base was exclusively a styrene derivative (V): 2.10 (s, 3, NCH_3), 2.25 [s, 6, $N(CH_3)_2$], 3.67 (d, 6, 2 OCH_3), 3.83 (d, 6, 2 OCH_3), 5.16–5.56 (4d, 2, the AB styrene protons in



J_{AX} = 9, J_{BX} = 17, J_{AB} = 1.5 Hz), 5.80–6.95 (m, 11, 10 aromatic and the X proton of the styrene product). III behaved in the expected manner to fom a monostilbene–monostyrene derivative (VI): 2.22 [s, 6, $N(CH_3)_2$], 2.34 [s, 6, $N(CH_3)_2$], 3.75 (d, 6, 2 OCH_3), 3.82 (d, 6, 2 OCH_3), 5.16–5.56 [4d, 2, the AB styrene protons (as in V)], 5.80–7.05 [m, 13, 10 aromatic, 3 vinyl (*i.e.,* 2 stilbene protons and the X proton of the styrene moiety)].

These unique stereochemical pathways become explicable by examining Dreiding models of the compounds. By orienting the molecules in their preferred conformations,[6,7] several observations account for the pathways that I, II, and III undergo in this Hofmann elimination reaction.

(1) Assuming that the eliminations proceed mostly by an E2 mechanism[8] wherein the groups must be anti-periplanar, it will be noticed that in the case of I the β hydrogens on C-4′ leading to a styrene product and those on C-a′ leading to a stilbene product can be oriented anti to the leaving quaternary group with equal ease. Thus, in I, since

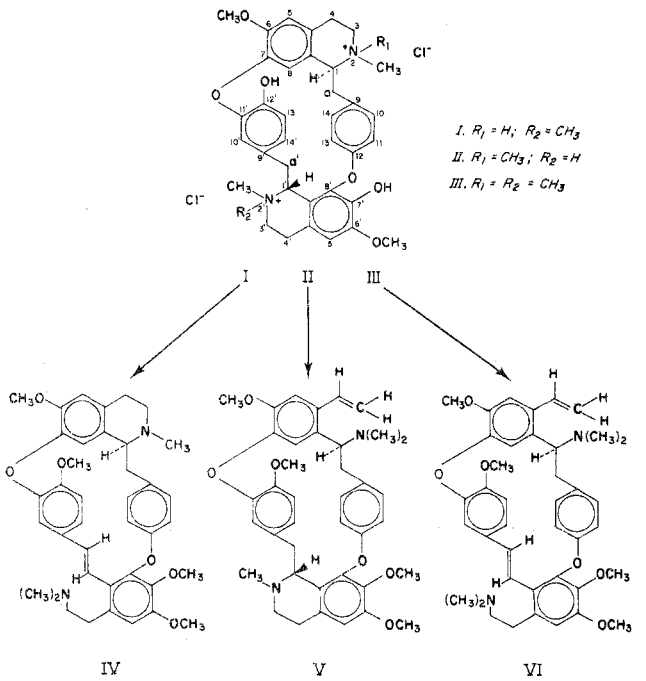


Figure 1. The generation of a stilbene derivative (IV) from (+)-tubocurarine (I), a styrene derivative (V) from (+)-isotubocurarine (II), and a stilbene-styrene derivative (VI) from (+)-chondocurarine (III) by the action of excess ethereal diazomethane on alcoholic solutions of the substrates.

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.

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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