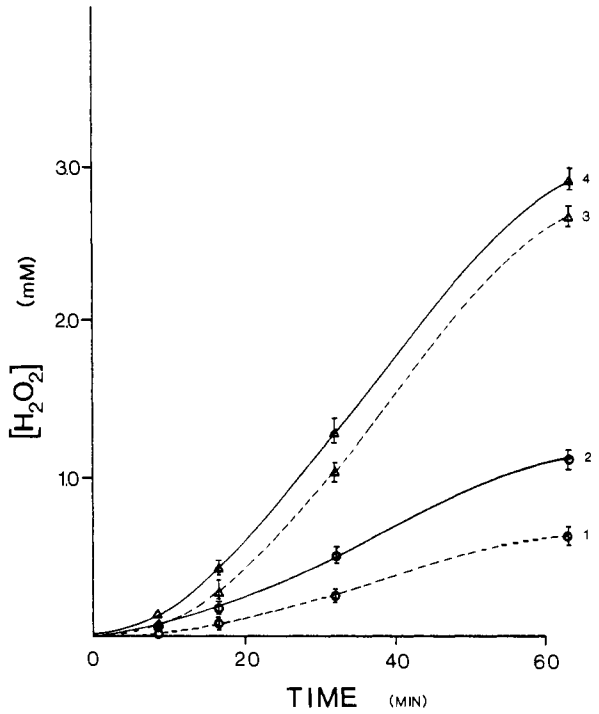

Figure 1. Formation of H_2O_2 during tryptophan (**1**) photooxidation in the presence and absence of SOD (0.04 mg/mL): curve 1, **1** alone, pH 6.0; curve 2, **1** alone, pH 8.5; curve 3, **1** + SOD, pH 6.0; curve 4, **1** + SOD, pH 8.5.

$HO_2\cdot$), but also indicates that only a portion of this species is transformed into H_2O_2 in the absence of SOD. These observations are consistent with the fates of $O_2^-\cdot$ shown, where $k_s + k_{dis}$ account for at most 30% and 40% of $O_2^-\cdot$ reaction at pH values of 6.0 and 8.5, respectively.[17,18]

$$H_2O_2 \underset{k_s}{\overset{\text{substrate, } H^+}{\longleftarrow}} O_2^-\cdot \underset{k_{SOD}\ (2\times10^9\ M^{-1}\ s^{-1})}{\overset{k_{dis}\ (<10^2\ M^{-1}\ s^{-1})}{\longrightarrow}} H_2O_2 + O_2$$

The formation of $O_2^-\cdot$ (or $HO_2\cdot$) presumably is mediated by **2**,[7,19] a conclusion which is supported by the acceleration of the rate of H_2O_2 production in the early stages of the photolysis, followed by a decline in that rate as the reaction exhausts **1**.[20] The extent of $^1O_2$ involvement in H_2O_2 formation can be estimated by the results of photolyses carried out in the presence of 0.05 M N_3^-,[21] which reduced the rate of H_2O_2 generation ~25 and 35% at pH values of 6.0 and 8.5, respectively, compared with the values obtained for **1** alone. Added N_3^- in photolysis mixtures containing SOD did not affect the amount of H_2O_2 produced.

The demonstration that $O_2^-\cdot$ is indeed formed upon near-UV photooxidation of **1** provides a basis for the synthesis of results acquired from experiments conducted separately concerning the chemical effects of $O_2^-\cdot$ and of near-UV on biological systems. Furthermore, the formation of $O_2^-\cdot$ and H_2O_2 together raises the possibility that this process can lead to the generation of the strongly oxidizing hydroxy radical.[2,22] These possibilities underscore the importance of further chemical and photochemical experiments to uncover the extent to which these results are applicable to in vivo processes stimulated by near-UV radiation, including the intriguing synergistic toxicity of near-UV and H_2O_2 to bacteria and bacteriophage.[23]

Acknowledgments. We thank Professor R. Kuntz for stimulating discussions and the Public Health Service for financial support (PHS Grant No. 5 R01 FD00674).

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(17) These values will be lower if SOD does not react quantitatively with $O_2^-\cdot$. They also will be lower, to as low as 0.5 of those given, to the extent that k_s accounts for formation of H_2O_2. A steady increase in the rate of H_2O_2 production as the pH rises from 3 to 9, as determined in related experiments, suggests that k_{dis} is small relative to k_s, since at pH values of 6 or greater k_{dis} is much smaller than at lower pH.[18]
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(20) After 60 min, UV determination after separation on G-10 Sephadex indicated 13 and 23% destruction of **1** at pH 6.0 and 8.4, respectively, and at these pH values 7 and 13 mol % formation of **2** (based on destroyed **1**).
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Total Synthesis of (±)-Thienamycin

Sir:

Thienamycin (**1**, R = R′ = R″ = H)[1] is a novel β-lactam antibiotic isolated from *Streptomyces cattleya*. Its unusually high potency against both gram-positive and gram-negative bacteria is quite surprising since the single 6-substituent is not only α but also lacks the traditional amide functionality. Of particular interest is its activity against *Pseudomonas* spp. and its resistance to bacterial β-lactamase.[2] Possibly the hydroxyl group can bind the same site normally bound by the 6β-amido group of the traditional β-lactam antibiotics when complexing with the bacterial cell wall enzymes, while the backbone of the 6α-substituent may mimic the 6α-methoxy group of the cephamycins to provide lactamase resistance. This unique and highly reactive compound offers a challenging synthetic problem, particularly the construction of the unusual ring

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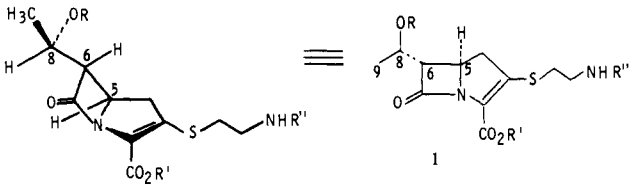
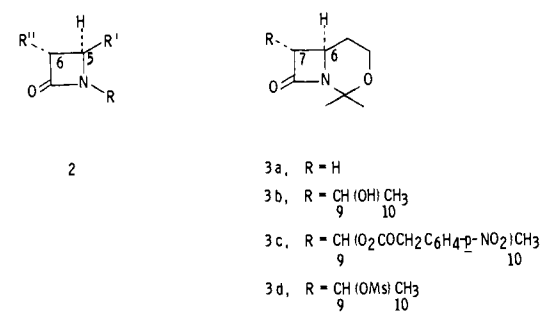
system, and we wish to report the first total synthesis of (±)-thienamycin.



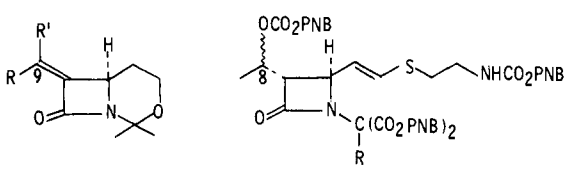
1

The formation of azetidinones by $_2\pi_s + _2\pi_a$ cycloaddition of chlorosulfonyl isocyanate and olefins, including conjugated dienes, is known.[3] We have found that 1-acetoxybutadiene reacts with chlorosulfonyl isocyanate (ether, −20 °C) to give azetidinone **2** (R = SO_2Cl; R′ = CH=CHOAc; R″ = H). Reductive hydrolysis[4] (H_2O, K_2HPO_4, Na_2SO_3, 0 °C) of the chlorosulfonyl group yielded the crystalline acetoxyvinylazetidinone **2** (R = R″ = H; R′ = CH=CHOAc) in 42% overall yield based on isocyanate. Hydrogenation (10% Pd/C, EtOAc, 40 psi, 100%), followed by deacetylation (MeOH, NaOMe, 0–25 °C, 95%) afforded **2** (R = R″ = H; R′ = CH_2CH_2OH). Conversion (2,2-dimethoxypropane, BF_3·Et_2O, CH_2Cl_2, 77%) to acetonide **3a,** followed by treatment with LDA at −78 °C in THF,[5] and addition of acetaldehyde gave, after chromatography (benzene–ethyl acetate, silica gel), the *trans*-hydroxyethyl derivative **3b** in 89% yield as a 2:3 mixture of epimers at the hydroxyl bearing carbon based on the ^1H NMR.[6] Evidence for the assignment of stereochemistry at C_9 was obtained via the two-step conversion of alcohol mixture **3b** to ene-lactams **4a** and **4b.** Mesylation (mesyl chloride, triethylamine, CH_2Cl_2, 0 °C, 75%) gave two separable (1:9 acetone–hexane, silica gel) mesylates (**3d**)[7] in a ratio reflecting that of the starting mixture **3b.** Each mesylate underwent elimination ($NaHCO_3$, MeOH, reflux, 42–50%)[1c] exclusively to a different ene-lactam, that from the major mesylate being assigned structure **4b** and that from the minor mesylate being assigned structure **4a,** based on the ^1H NMR.[8,9] If a transcoplanar configuration for the mesyloxy group and H_7 is presumed necessary for the elimination, the major component of **3d** may be assigned the 9*S** [10] configuration. Since the major isomers of **3b** and **3d** both have δ_{H_7} at lower field, as well as smaller $J_{7,9}$ than the corresponding minor isomers, we felt it reasonable to assume that the major component of **3b** also had the 9*S** configuration.



2

3a, R = H
3b, R = CH(OH)CH$_3$ (9, 10)
3c, R = CH(O$_2$COCH$_2$C$_6$H$_4$-*p*-NO$_2$)CH$_3$ (9, 10)
3d, R = CH(OMs)CH$_3$ (9, 10)

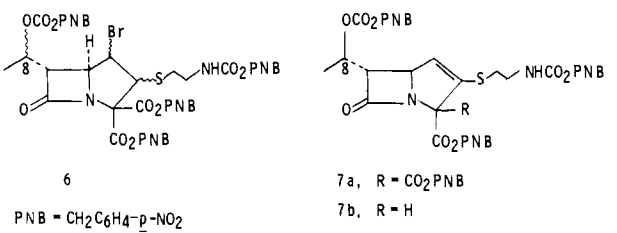


4a, R = H; R′ = CH$_3$ (10)
4b, R = CH$_3$ (10); R′ = H

5a, R = OH
5b, R = Cl
5c, R = H

PNB = $CH_2C_6H_4$-*p*-NO_2

The mixture of **3b** epimers was converted (*n*-BuLi, THF, − 78 °C; *p*-$NO_2C_6H_4CH_2O_2CCl$, 85%) to **3c,** and the acetonide was then removed (1:4 H_2O·HOAc, 65 °C, 1.25 h, 82%) giving **2** (R = H; R′ = CH_2CH_2OH; R″ = CH(O-$CO_2CH_2C_6H_4$-*p*-NO_2)CH_3)[11] from which two-thirds of the pure major isomer could be isolated by direct crystallization. The ^1H NMR of this isomer had (acetone-d_6) $J_{6,8}$ = 4.5 Hz, with δ_{H_6} falling in the downfield region of the H_6 band present in the ^1H NMR of the mother liquor mixture. Hence, by the same arguments offered above, it was assigned the 8*S** configuration. Since thienamycin possesses the 8*R* configuration, the mother liquor mixture, consisting of ca. equal parts of the 8*R** and 8*S** isomers, was carried on. Oxidation (CrO_3, pyridine, CH_3CN, Celite)[12] gave the aldehyde which was immediately converted (*p*-$NO_2C_6H_4CH_2O_2CNHCH_2CH_2SH$,[13] CH_3CN, BF_3·Et_2O, 0 °C, 46%) to thioacetal **2** (R = H; R′ = $CH_2CH(SCH_2CH_2NHCO_2CH_2C_6H_4$-*p*-$NO_2)_2$; R″ = $CH(OCO_2CH_2C_6H_4$-*p*-$NO_2)CH_3$).[11] This was transformed (Br_2, Et_2O–THF, 0 °C; cyclohexene, 0 °C; triethylamine, DMF, 87%) to a mixture of thioenol ethers which, after chromatography (0–3% methanol–$CHCl_3$, silica gel), afforded mainly the *E* isomer. Condensation[14] with bis(*p*-nitrobenzyl) ketomalonate[15] (toluene, reflux, 44%) gave, after chromatography (0.5–1% MeOH–$CHCl_3$, silica gel), the hydroxymalonate **5a.** Replacement of OH with Cl ($SOCl_2$, pyridine, THF, −20–20 °C)[14] yielded crude **5b** which was immediately reduced (P(*n*-Bu)$_3$, 9:1 DMF·H_2O; K_2HPO_4, 60%)[16] to **5c.** Cyclization to **6** (58%) was achieved by successive treatment with Br_2/ether/THF/0 °C, followed by triethylamine/DMF.



6

7a, R = CO_2PNB
7b, R = H

PNB = $CH_2C_6H_4$-*p*-NO_2

Upon dehydrobromination (AgF, pyridine, 68%) to **7a,** the 8*R** and 8*S** epimers (ca. equal parts) became separable by chromatography (1:1 ethyl acetate–$CHCl_3$, silica gel). The desired 8*R** epimer[17] was decarbalkoxylated (collidine, LiI, 120 °C, 30 min, 47%) to give **7b.** Isomerization with diisopropylamine in Me_2SO for a few hours gave a 4:1 mixture, separable chromatographically (1:1 ethyl acetate–$CHCl_3$, silica gel) into **7b** and **1** (R = R″ = CO_2R'; R′ = $CH_2C_6H_4$-*p*-NO_2), respectively.[18] The latter, upon hydrogenolysis with 10% Pd/C in a water–dioxane–ethanol–K_2HPO_4 mixture, followed by purification on an XAD-2 column, eluting with deionized water, afforded (±)-thienamycin in 23% yield, which exhibited an antibacterial potency ca. half that of thienamycin against a variety of microorganisms. The UV and ^1H NMR spectra of the synthetic and natural thienamycin were identical.

The use of this synthesis for the preparation of other isomers and analogues will be the subject of future communications.

Acknowledgments. We thank Dr. Byron H. Arison and Mr. Herman Flynn for the ^1H NMR spectra, Ms. Jean S. Kahan for the antibacterial assays, and Dr. C. H. Shunk for help in the preparation of intermediates.

References and Notes

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R. E. Rhodes, and J. L. Smith. (b) G. Albers-Schönberg, B. H. Arison, E. A. Kaczka, F. M. Kahan, J. S. Kahan, and R. E. Rhodes, submitted for publication. (c) R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, and B. G. Christensen, submitted for publication. (d) K. Hoogsteen, J. M. Hirshfield, O. D. Hensens, and G. Albers-Schönberg, submitted for publication.
(2) Papers presented at the Sixteenth Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Ill., Oct 1976: (a) "Thienamycin, A New β-Lactam Antibiotic. I. Discovery and Isolation" by J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, and H. B. Woodruff; (b) "Thienamycin, A New β-Lactam Antibiotic. II. *In Vitro* and *In Vivo* Evaluation" by H. Kropp, J. S. Kahan, F. M. Kahan, J. Sundelof, G. Darland, and J. Birnbaum.
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(7) Major mesylate: ^{1}H NMR (C_6D_6) δ 1.34 (d, 3 H, $J_{9,10}$ = 6.5 Hz, H_{10}), 2.67 (dd, 1 H, $J_{6,7}$ = 1.8 Hz, $J_{7,9}$ = 4.5 Hz, H_7), 4.80 (dq, 1 H, $J_{9,10}$ = 6.5 Hz, $J_{7,9}$ = 4.5 Hz, H_9). Minor mesylate: ^{1}H NMR δ 1.30 (d, 3 H, $J_{9,10}$ = 6.5 Hz, H_{10}), 2.61 (dd, 1 H, $J_{6,7}$ = 1.8 Hz, $J_{7,9}$ = 8.0 Hz, H_7), 4.82 (dq, 1 H, $J_{9,10}$ = 6.5 Hz, $J_{7,9}$ = 8.0 Hz, H_9).
(8) Ene–lactam from major mesylate: ^{1}H NMR ($CDCl_3$) δ 2.00 (d, 3 H, J = 7.5 Hz, H_{10}), 5.70 (q, 1 H, J = 7.5 Hz, H_9). Ene–lactam from minor mesylate: ^{1}H NMR δ 1.73 (d, 3 H, J = 7 Hz, H_{10}), 6.10 (q, 1 H, J = 7 Hz, H_9).
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(12) Procedure developed by Dr. J. Fahey.
(13) Kindly supplied by Dr. David G. Melillo of Developmental Research.
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(15) Prepared by SeO_2 oxidation of bis(4-nitrobenzyl) malonate.
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(17) Identification was made by carrying the pure crystalline 8*S** epimer of **2** (R = H; R′ = CH_2CH_2OH; R″ = $CH(OCO_2CH_2C_6H_4$-*p*-$NO_2)CH_3$), through the same sequence of reactions.
(18) Recovered **7b** was recycled several times to improve the overall conversion, the final yield being 47% based on recovered **7b**.

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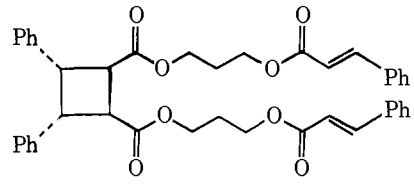
Internal Photocycloaddition between Chromophores Separated by 17 Bonds

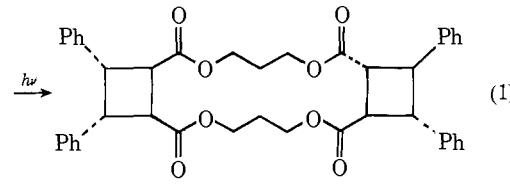
Sir:

Intramolecular photochemical interaction between two chromophoric units bridged by more than four bonds has been studied by a few groups[1-3] with a view to determine the formation of exciplexes and/or products. Internal formation of exciplexes and emission from such transients has been observed in molecules with separations between the chromophores which extend up to 23 bonds.[2] Compound formation between internal chromophores which may be subject to more restrictive conditions (and certainly is less easy to detect) has been successfully studied by De Schryver and his coworkers in the cases of 7,7′-polymethylenedioxycoumarins with separations up to 14 bonds,[1] polymethylenedicarboxylic acid (7-coumarino) diesters (s = 12),[1] as well as polymethylene bis-2-anthroates (s = 14).[1b]

We wish to report the internal photochemical [2 + 2] addition reaction in the α,ω-dicinnamate **1** which leads to the tricyclic molecule **2** (eq 1), a reaction which represents photochemical addition between chromophores separated by 17 bonds. Internal photocycloaddition in α,ω-dicinnamates has been studied by Rennert et al.[4-6] in **3** and **4** and Rennert[5] has mentioned that similar [2 + 2] photocycloaddition between internal chromophores has been observed in dicinnamates with longer methylene chains separating the ester groups but no details were given. The photodimerization of cinnamic acid and its derivatives in the solid state which has been extensively studied[7] has also been used to construct macrocyclic rings.[8]



1



(1)

2

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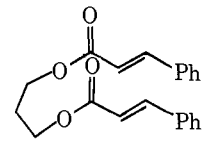

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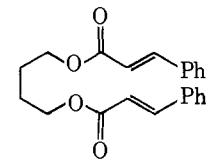

4

1 was synthesized from β-truxinic acid[9] by esterifying first with an excess of propylene glycol in the presence of toluenesulfonic acid followed by cinnamoylation of the dihydric diester alcohol with cinnamoyl chloride. A sample of **1**, which had been purified by chromatography, in its NMR spectrum[10] showed 20 aromatic protons in two well-separated groups of 10 H each (δ 7.18 and 6.92, complex), two pairs of olefinic protons centered at δ 7.85 and 6.50 (J = 16 Hz), protons belonging to the central methylene chain at δ 1.9 (4 H, quintet) and 4.28 (8 H, triplet, J = 6 Hz), and cyclobutane protons in two groups at δ 4.5–4.7 and 3.7–3.9. The protons thus were distributed into three distinct entities of relative areas 24 (downfield), 12 (midfield), and 4 (upfield). On irradiation in ether at 300 nm (direct irradiation) with cuprous chloride as catalyst, the NMR spectrum first showed a rapid change corresponding to the trans → cis isomerization of the olefinic bonds. On prolonged irradiation, a white crystalline solid **2** slowly separated from solution (mp 159–161 °C, 32% isolated yield, mol wt 672[11]). Its NMR spectrum showed a distribution of 10, 16, and 4 protons in the down-, mid-, and upfield regions. Since this compound was isomeric with **1**, the chemical reaction corresponded to the disappearance of the 4 olefinic protons in **1** and their replacement by new absorptions at δ 4.18 and 3.30 attributable to cyclobutane protons. The spectral evidence is therefore consistent with **2** being the internal [2 + 2] photoadduct of **1**. The stereochemistry at the point of closure was readily seen by a comparison of the chemical shifts and coupling of the newly formed cyclobutane protons to those of authentic samples of α-truxillic, β-truxinic, and δ-truxinic acids and their esters.[12]

It may be noted that, in the solid state,[7] photodimerization of cinnamic acid and its derivatives leads to α-truxillic or β-truxinic acid derivatives only.[7] In solution, **3** was found to give[4,5] a mixture of the internal diester of β-truxinic acid (90%) and δ-truxinic acid (10%), while **4** gave the diester of the δ acid exclusively. The stereochemistry of the closure in the present instance is therefore consistent with these observations in solution phase. Quantum yields for the closure reaction as well as the trans ⇄ cis isomerization of **1** were measured under a variety of conditions. These are listed in Table I relative to the photoisomerization of *trans,trans*-1,3-propanediol dicinnamate to the cis,trans diester which was measured by Rennert et al.[6] The absolute value of this quantum yield was reported by them to be 0.473. The analogue of **1** derived from α-truxillic acid

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