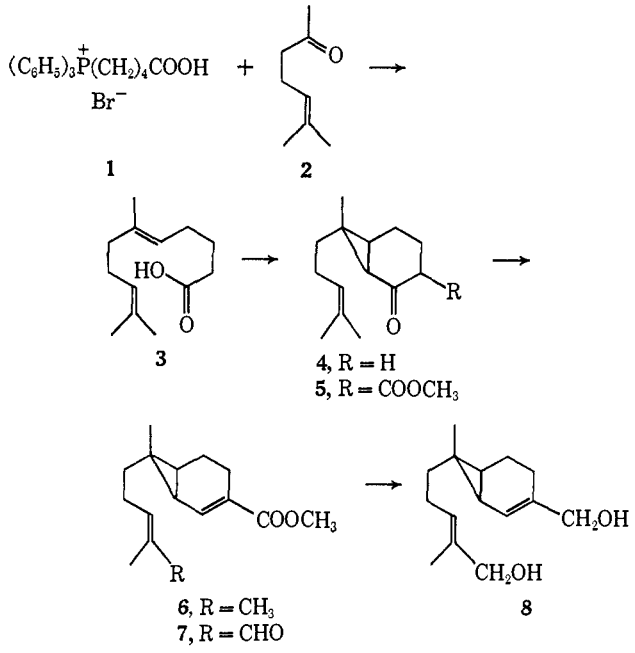


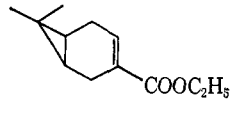
afforded the bicyclic ketone **4** [40% yield from diene acid **3**; bp 95–100° (0.3 mm); ir: 1680 cm^{-1}] as a mixture of isomers. This mixture was easily separated by preparative glpc on 30% QF-1 at 180° into equal amounts of the *exo*-methyl isomer (retention time 27 min 45 sec; nmr: δ 1.13, cyclopropyl CH_3) and the *endo*-methyl isomer (retention time 32 min 8 sec; nmr: δ 1.11, cyclopropyl CH_3), the latter corresponding to the stereochemistry as shown for **4**.

Condensation of bicyclic ketone **4** with dimethyl carbonate (sodium hydride, 90°, 1 hr) gave a quantitative yield of β-keto ester **5** [bp 115–120° (0.2 mm); ir: 1610, 1645 cm^{-1}; nmr: δ 1.03, cyclopropyl CH_3].

Reduction of β-keto ester **5** to an isomeric mixture of β-hydroxy esters was effected by sodium borohydride (2-propanol, 0°, 70% yield), and this mixture (ir: 3500, 1735 cm^{-1}) was dehydrated *via* the xanthate procedure (potassium in xylene followed by carbon disulfide and methyl iodide, then distillation) to the α,β-unsaturated bicyclo[4.1.0] ester **6** [bp 98–108° (0.2 mm); ir: 1695, 1635 cm^{-1}; nmr: δ 0.88, cyclopropyl CH_3; 7.12, cyclic vinyl H; uv: $\lambda_{max}^{C_2H_5OH}$ 252 nm[7]].

Oxidation of unsaturated ester **6** with selenium dioxide in ethanol[8] was highly selective and gave a 55% yield of aldehyde **7** (nmr: δ 0.89, cyclopropyl CH_3; 6.47, acyclic vinyl H; 7.12, cyclic vinyl H; 9.37, CHO). The chemical shift of the aldehyde proton clearly establishes **7** as exclusively the *trans* isomer.[9]

(7) This ultraviolet absorption is identical with what we find for a corresponding α,β-unsaturated ester conjugate with a cyclopropyl group (unpublished work, C. Tang).



(8) V. M. Sathe, K. K. Chakravarti, M. V. Kadival, and S. C. Bhattacharyya, *Indian J. Chem.*, 4, 393 (1966).

(9) K. C. Chan, R. A. Jewell, W. H. Nutting, and H. Rapoport, *J. Org. Chem.*, 33, 3382 (1968). Simpler model compounds have similarly given exclusively *trans* aldehydes. In the case of aldehyde **7**, the crude aldehyde was isolated by filtration, evaporation of the filtrate, solution of the residue in ether, washing with bicarbonate, and evaporation of the ether. It was all-*trans* at this point; thus if any *cis* isomer was formed during the oxidation, it was isomerized.

Finally, reduction of aldehyde **7** ($LiAlH_4$–$AlCl_3$, 0°, 1 hr) followed by chromatography on alumina (activity 2.5, elution with benzene–chloroform) resulted in an 86% yield of *dl*-sirenin (**8**), identical spectrally (ir, nmr, mass spectra), chromatographically (tlc on SiO_2), and biologically[10] with natural *l*-sirenin. This synthesis also provides a facile approach to various analogs[11] of sirenin which are being prepared for biological evaluation.

(10) The *dl* material is indistinguishable from natural *l*-sirenin by bioassay. Since the assay is not sensitive to a factor of two, these results leave unanswered the question of the biological activity of the *d* isomer; however, they do indicate that the *d* isomer is not inhibitory (personal communication from L. Machlis).

(11) For example, details of the isomeric series in which the cyclopropyl methyl is *exo* will be presented in our full paper.

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The Lactone Bond in Thiostrepton. Thiostreptonic Acid, a Degradation Product of the Antibiotic

Sir:

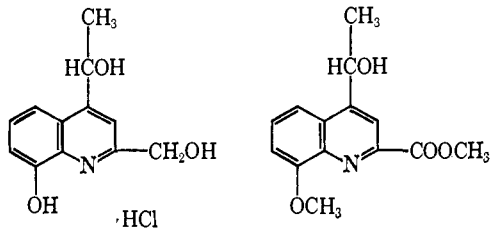
In the ir spectrum of the antibiotic thiostrepton,[1] a sharp carbonyl band of moderate intensity appears at 1750 cm^{-1}. The band is absent in the product obtained on treatment of the antibiotic with dilute sodium hydroxide. Since during this hydrolysis no cleavage of the molecule into two or more parts could be observed, saponification of a lactone bond was suspected. Evidence for this lactone bond was found when a solution of thiostrepton (5 g) was reduced in tetrahydrofuran (200 ml) and methanol (30 ml) with sodium borohydride (2.5 g) at room temperature. After acidification with hydrochloric acid and removal of the solvents, the residue was hydrolyzed with constant boiling hydrochloric acid (250 ml) under reflux in an atmosphere of nitrogen for 22 hr. The solution was evaporated to dryness, the residue was dissolved in water (130 ml), and the filtered solution was extracted with ether and ethyl acetate. The aqueous layer was neutralized and extracted with ether, and the extract was converted to the hydrochloride. Addition of acetone to an ethanolic solution of this salt yielded crystals (390 mg) of compound I; mp 188–190°, $[\alpha]^{24}D$ −95° (*c* 1.2, ethanol); $\lambda_{max}^{H_2O}$ 243 mμ (ϵ 37,000). *Anal.* Calcd for $C_{12}H_{13}NO_3 \cdot HCl$: C, 56.37; H, 5.52; N, 5.48; Cl, 13.9. Found: C, 56.34; H, 5.78, N, 5.62; Cl, 14.7. The uv absorption of the hydrolysate reveals that 1 mole of I was liberated from 1 mole of the antibiotic.

The absorption maximum of I is shifted to 256 mμ in acidic and 258 mμ in alkaline media. Oxidation of I with nitric acid followed by sublimation yielded a mixture of cinchomeronic acid, nicotinic acid, and isonicotinic acid, suggesting that I is related to the quinaldic acids obtained from thiostrepton.[2] The close sim-

(1) J. F. Pagano, M. J. Weinstein, H. A. Stout, and R. Donovick, *Antibiot. Ann.*, 1955–1956, 554 (1956); J. Vandeputte and J. D. Dutcher, *ibid.*, 1955–1956, 560 (1956); B. A. Steinberg, W. P. Jambor, and L. O. Suydam, *ibid.*, 1955–1956, 562 (1956); M. Bodanszky, J. D. Dutcher, and N. J. Williams, *J. Antibiot.* 16, 76 (1963).

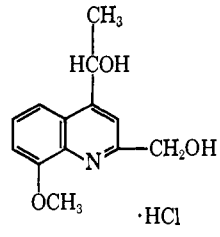
(2) M. Bodanszky, J. Fried, J. T. Sheehan, N. J. Williams, J. Alicino, A. I. Cohen, B. T. Keeler, and C. A. Birkhimer, *J. Am. Chem. Soc.*, 86, 2478 (1964); *cf.* also C. N. C. Drey, G. W. Kenner, H. D. Law, R. C. Sheppard, M. Bodanszky, J. Fried, and N. J. Williams, *ibid.*, 83, 3906 (1961).

ilarity of the nmr spectrum of I with the spectrum of compound II[2] and the presence of a two-proton singlet at 5.6 ppm suggest that compound I is 2-hydroxymethyl-4-(1′-hydroxyethyl)-8-hydroxyquinoline hydrochloride.



I

II

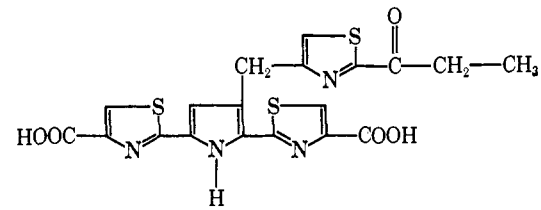


III

This structural assignment was confirmed by the reduction of II with sodium borohydride under conditions similar to those used for thiostrepton. The reaction was complete within a few minutes and the product was isolated as the crystalline hydrochloride (mp 178–179°, compound III). It shows the same two-proton singlet at 5.67 ppm as compound I. The ready reduction with borohydride indicates a reactive ester and the low wavelength of the carbonyl band in the ir spectrum points in the same direction. The amide[3] of 4-(1′-hydroxyethyl)-8-methoxyquinaldic acid was recovered unchanged after attempted reduction under the above-described conditions. The isolation of compound I proves that the carboxyl of the quinaldic acid precursor in thiostrepton is linked through an ester bond to the rest of the molecule.

The formation of a water-insoluble material during acid hydrolysis of thiostrepton[1] was observed earlier.[2] Because of its characteristic uv absorption the substance was provisionally designated as the "362 fragment." Recently, new attempts were made for its purification. Countercurrent distribution[4] in the solvent system chloroform–toluene–methanol–water (6:4:7:3) through 492 transfers led to the isolation of a yellow compound with a K value of 0.53. Homogeneity was indicated by the excellent agreement between calculated and experimental distribution curves. *Anal.* Calcd for $C_{19}H_{14}N_4O_5S_3$: C,48.2; H, 3.0; N, 11.8; S, 20.2. Found: C, 48.0; H, 3.1; N, 11.8; S, 19.6. Titration with base gave a neutralization equivalent of 257, pointing to a dicarboxylic acid (237). We propose the name "thiostreptonic acid" and formula IV for this degradation product.

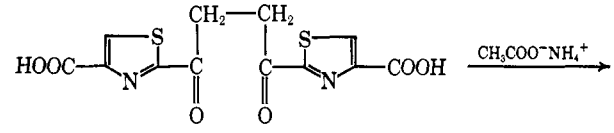
On slow evaporation of its solutions in ethanol or in methanol compound IV separated in the form of square platelets, while needles of a monoacetate monohydrate were obtained on cooling solutions if IV in warm acetic acid. *Anal.* Calcd for $C_{19}H_{14}N_4O_5S_3 \cdot C_2H_4O_2 \cdot H_2O$:



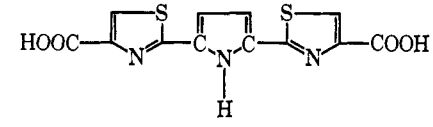
IV, thiostreptonic acid

C, 45.6; H, 3.6; N, 10.0; S, 17.3. Found: C, 45.5; H, 3.5; N, 9.7; S, 17.3.

The chromophore (λ_{max}^{alc} 362 mμ) generated in the reaction of the diketo acid V[2,5] with ammonium acetate and presumably having structure VI gave an important clue to the structure of compound IV.



V



VI

Reaction of V with benzylamine resulted in a similar but not identical chromophore (λ_{max} 340 mμ). The furan derivative, obtained by heating V with sulfuric acid, has its maximum at 355 mμ. A major difference between the uv spectra of IV and of VI is the presence of a band at about 300 mμ in the former. This band could be attributed to the carbonyl function in a 2-acylthiazole.[6] In the ir spectrum a carbonyl band at 1670 cm^{-1} could be correlated with a ketone group.[7] On reduction of IV with sodium borohydride this band disappeared, with the concomitant disappearance of the above-mentioned absorption at 300 mμ.

In the nmr spectrum of IV in CD_3COOD, a three-proton triplet at 1.2 ppm and a two-proton quartet at 3.16 ppm correspond to a propionyl group. The complete agreement of these chemical shifts with those of the ethyl group in the spectrum of 2-propionylthiazole-4-carboxylic acid[8] was quite suggestive. The four low-field, one-proton singlets at 6.84, 7.56, 8.32, and 8.36 ppm could be interpreted as corresponding to a H-4 pyrrole and three H-5-thiazole protons. The nonequivalence of the two lowest field signals points to 3 substitution on the pyrrole ring, since N substitution would result in a symmetrical molecule in which the two H-5 thiazole protons of the conjugated system derived from thiostreptoic acid[5] would be identical and should appear as a two-proton singlet. The uv spectrum of a N-substituted derivative from diketo acid V and benzylamine also serves as an argument for an unsubstituted nitrogen of the pyrrole. Positions 2 and 5 of this ring cannot carry

(3) This compound (mp 193–195°) was prepared by ammonolysis of compound II in methanol.

(4) L. C. Craig and T. P. King, *Federation Proc.*, 17, 1126 (1958).

(5) M. Bodanszky, J. T. Sheehan, J. Fried, N. J. Williams, and C. A. Birkhimer, *J. Am. Chem. Soc.*, 82, 4747 (1960).

(6) P. Brookes, A. J. Fuller, and J. Walker, *J. Chem. Soc.*, 689 (1957). Thiostreptonic acid shows considerable similarity with micrococcinic acid (*cf.* M. N. G. James and J. K. Watson, *ibid.*, 1361 (1966); G. E. Hall, N. Sheppard, and J. Walker, *ibid.*, 1371 (1966)).

(7) N. P. V. Mijovic and J. Walker, *ibid.*, 3381 (1961).

(8) This acid occurs in small amounts among the products of acid hydrolysis of thiostrepton[2] and is also a constituent of micrococcin P.[6]

substituents other than the thiazole nuclei without disruption of the chromophore system. This leaves C-3 of pyrrole as the point of attachment between the chromophoric system corresponding to compound VI and the rest of the thiostreptonic acid molecule. The methylene group which appears at 4.42 ppm as a two-proton singlet connects the C-3 of pyrrole with the 2-propionylthiazole; its chemical shift is one expected for CH_2 protons between two aromatic nuclei.

Supporting evidence for the above assignments was found in the nmr spectrum of IV taken in D_2SO_4.[9] A one-proton singlet at 6.84 ppm disappears when the solution is heated. Exchange with deuterium identifies it as the H-4 of pyrrole and allows the assignment of the one-proton singlet at 7.56 ppm as corresponding to the C-5 hydrogen of the 2-propionylthiazole portion.

In the nmr spectrum of IV the H-5 thiazole protons appear as singlets at 7.56, 8.32, and 8.36 ppm. The spectrum of thiostrepton itself exhibits peaks in corresponding positions, suggesting that these three thiazole nuclei are present as such in the parent molecule.

Acknowledgment. This work was supported by Public Health Service Grant No. NIH AI 07515. The authors express their gratitude to Dr. John T. Sheehan of The Squibb Institute for Medical Research, New Brunswick, N. J., for a synthetic sample of the diketo acid II.

(9) M. H. Palmer, "The Structure and Reactions of Heterocyclic Compounds," St. Martin's Press, New York, N. Y., 1967, p 276.
(10) National Institutes of Health Predoctoral Fellow, 1967–1969.

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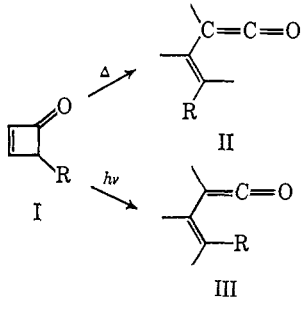
Electronic Control of the Stereospecific Thermal Opening of Cyclobutenones[1]

Sir:

Baldwin and McDaniel[2] have pointed out the difficulty of rationalizing the stereospecific opening of substituted cyclobutenones (I) to α-unsaturated ketenes (II, III) by the Woodward–Hoffmann generalizations.[3]



Nevertheless, since different products are uniquely associated with the ground and excited states of the cyclobutenones, the reactions would seem to be electronically controlled. Because of the lack of helpful symmetry in this problem, it is tedious to construct the correlation diagrams necessary to a full Woodward–Hoffmann analysis; MO calculations at many points along several reaction coordinates would be required. Here we describe an application to the thermal opening of cyclobutenones of a numerical means of by-passing the construction of correlation diagrams, while still reaching a decision whether a certain product can be obtained from a molecule in a given electronic state.

The basis of the Woodward–Hoffmann analyses is that the (adiabatic) perturbation arising from nuclear motion will leave the nodal structure of individual orbitals unchanged, while altering their amplitude from point to point in the molecule. In other words, there exists a topological mapping R which transforms the orbitals associated with geometry A into the orbitals of geometry B. The electronic state B_k of B can be obtained from state A_i of A if the orbitals ϕ_i^A occupied in state A_i are mapped by R into the orbitals ϕ_k^B occupied in the state B_k. For thermal processes, A_i and B_k are the ground states of A and B. The overlap between the wave function for the desired product and the wave function obtained by the application of the mapping to the wave function for the reactant, $S = \langle A\Pi_i R\phi_i^A | A\Pi_k \phi_k^B \rangle$, is a convenient expression of whether the process is allowed. If $S = 1$, the mapping of the orbitals occupied in A produces precisely the orbitals occupied in B. If, however, the mapping of orbitals occupied in A produces one or more orbitals vacant in B, $S = 0$, indicating that the process is forbidden.

To evaluate S, we must form the mapping operator R. According to simple topological notions,[4] a mapping may twist, stretch, bend, or otherwise distort the surface associated with an orbital, but may not cut or puncture the surface if topological invariance is desired. That is, R cannot add or remove nodes in the orbital which it acts upon. The twisting and bending operations are the most important aspects of most concerted reactions, and are relatively simple to describe mathematically. The conrotatory opening of cyclobutenes, for example, consists in large part of twists of the σ-bonded methylenes, with slight bends at the π-bonded carbons. The effect of twists may be simply considered as rotation of the atomic p orbitals, while the effect of bending is simply a rehybridization of the atomic basis. Therefore, the bends and twists can be represented by a series of 4×4 unitary transformations mixing the four valence atomic orbitals on each first-row atom.

The determination of the elements of the 4×4 transforms can be described only briefly. We are interested in the overlap between wave functions $\det(R\phi_1^A R\phi_2^A \ldots) = \det(\phi_1^{B'} \ldots \phi_N^{B'})$ and $\det(\phi_1^B \ldots \phi_N^B)$ where "det" indicates that we form the antisymmetrized product of the orbitals. The overlap is conveniently evaluated by the method of equivalent orbitals,[5] in which the matrix $D_{im} = \langle R\phi_i^A | \phi_m^B \rangle$ is formed. In terms of the mapping transform and the basis functions $D_{im} = \Sigma_{ab} c_{ia}^A R_{ab} c_{mb}^B \langle b|b \rangle$. Here the c_{ta}^A and the c_{mb}^B are the expansion coefficients in the LCAO expression for the orbitals. Assuming that the basis set is orthonormal $D_{im} = \Sigma_{ab} c_{ia}^A R_{ab} c_{mb}^B$. The overlap

(1) Based on work performed under the auspices of the U. S. Atomic Energy Commission.
(2) J. E. Baldwin and M. C. McDaniel, *J. Am. Chem. Soc.*, **90**, 6118 (1968).
(3) (a) R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 395, 3511 (1965); (b) R. Hoffmann and R. B. Woodward, *ibid.*, **87**, 2046, 4389 (1965).
(4) W. J. Thorn, "Topological Structures," Holt, Rinehart and Winston, New York, N. Y., 1966.
(5) H. F. King, R. E. Stanton, H. Kim, R. E. Wyatt, and R. G. Parr, *J. Chem. Phys.*, **47**, 1936 (1967).