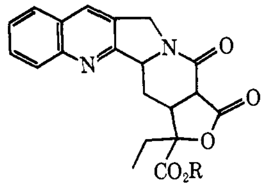
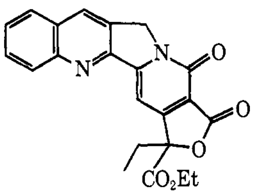
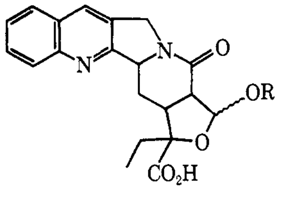


12, R = Et
14, R = H

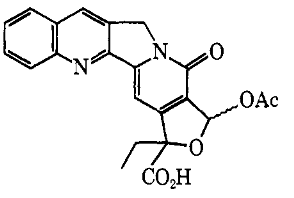


13

Hydrolysis of the ethyl ester function in **12** was accomplished in high yield by refluxing $\sim$2 hr with concentrated hydrochloric acid. The carboxylic acid **14**, isolated as the crude amine hydrochloride, was treated with excess sodium borohydride in ethanol at room temperature (20 hr), to form the hemiacetal **15**. Reaction of **15** with excess acetic anhydride in pyridine resulted in the formation of acetylated hemiacetal **16**, ir 3.0–4.0, 5.75, and 6.05 μ. Dehydrogenation of **16** with 2 equiv of DDQ in refluxing *p*-dioxane (4 hr) gave the pyridone **17**, which was converted to *dl*-camptothecin (**1**) by successive treatment with (1) 0.1 *M* aqueous sodium hydroxide (0.5 hr, room temperature), followed by (2) addition of excess sodium borohydride (room temperature, 6 hr), and finally (3) acidification with dilute hydrochloric acid, followed by chromatography (silica gel–chloroform) and crystallization from acetonitrile–methanol. The tlc properties, low-resolution mass spectra, and 300-MHz spectra (in CF_3CO_2H) of synthetic ($\pm$)-camptothecin, mp 287–288° dec, *m/e* 348.1098, were identical with those of the natural material.[7,8] The attempted resolution of *dl*-camptothecin is currently in progress.



15, R = H
16, R = Ac



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Acknowledgment. We wish to thank the National Science Foundation and the National Institutes of Health for their support of this work.

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[7] We wish to thank Mr. L. Cary of Varian Associates, Palo Alto, Calif., for taking the 300-MHz nmr spectra. The high-resolution mass spectra were obtained through the courtesy of Hoffmann La Roche, Inc., Nutley, N. J.

[8] A sample of authentic natural camptothecin was kindly supplied by Dr. Robert B. Ing of the Cancer Chemotherapy National Service Center, National Cancer Institute.

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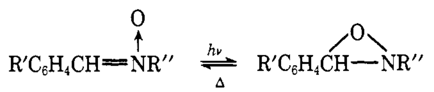
Orbital Symmetry Control in the Nitrone–Oxaziridine System. Nitrone Photostationary States

Sir:

Recently the orbital symmetry rules[1] have been shown to apply to heteroatom systems such as nitrone thermal cycloaddition reactions[2] and the thermal and photochemical aziridine ring cleavage at the C–C bond.[3] The concerted photocyclization is disrotatory and the reverse thermal cleavage is conrotatory in these molecules with four π electrons.[1]

In contrast to the azomethine ylide–aziridine system, the stereochemistry of the nitrone photocyclization to oxaziridine can only be observed on carbon and nitrogen atoms because the oxygen atom has lone-pair electrons instead of substituents. For the reverse thermal ring opening of oxaziridine to the nitrone, the two possible conrotatory motions of C–O bond cleavage should result in a mixture of the cis and trans isomers of the nitrone,[4] in contrast to the photoclosure which should be stereospecific.

Boyd, *et al.*,[5] recently reported the formation of mixtures of *cis-* and *trans*-oxaziridines from the irradiation of *trans*-nitrones. However, there has been some evidence for the stereospecific formation of oxaziridine from nitrones.[6] We wish to report our results obtained from the photolysis of several nitrones at −60°,[7] including IIIa and IVa which were studied by Boyd, *et al.*,[5] at room temperature, and the thermolysis of Ib at −8°. Under these conditions thermal isomerization of the oxaziridine and nitrone isomers was suppressed.



$$\underset{a}{R'C_6H_4CH{=}\overset{\overset{O}{\uparrow}}{N}R''} \underset{\Delta}{\overset{h\nu}{\rightleftharpoons}} \underset{b}{R'C_6H_4\overset{O}{CH{-}N}R''}$$

I, R′ = $(CH_3)_2N$; R″ = CH_3
II, R′ = H; R″ = CH_3
III, R′ = NO_2; R″ = CH_3
IV, R′ = NO_2; R″ = CH_2CH_3

The nmr spectra of these nitrones at −60° indicated the presence of only one nitrone isomer, the trans configuration as discussed by Koyano and Suzuki.[8] Irradiation of *trans*-Ia and -IIa at −60° in CD_3OD and $CDCl_3$ yielded exclusively *trans*-oxaziridines,[9] as observed by nmr at −60°. However, under the same conditions in CD_3OD, *trans*-IIIa and -IVa yielded a mixture of 69% *cis*–31% *trans*-oxaziridines, which was in contrast to the predominantly *trans*-oxaziridines found by Boyd, *et al.*[5] With successive partial irradiations of *trans*-IVa at −60°, the presence of *cis*-IVa was demonstrated by nmr,[10] and a photostationary state of 37% *cis*–63% *trans*-IVa was reached at approximately 15% conversion to oxaziridines. The *cis*-IVa rapidly

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[1] R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1969.

[2] R. Huisgen, H. Seidl, and I. Brüning, *Chem. Ber.*, **102**, 1102 (1969).

[3] R. Huisgen, W. Scheer, and H. Huber, *J. Amer. Chem. Soc.*, **89**, 1753 (1967).

[4] J. S. Splitter and M. Calvin, *J. Org. Chem.*, **30**, 3427 (1965). An oxaziridine was found to cleave at least partially to a *cis*-nitrone.

[5] D. R. Boyd, W. Jennings, and R. Spratt, *Chem. Commun.*, 745 (1970). Photochemical or thermal equilibration of *cis-* and *trans*-IIIb and -IVb was shown to occur only on prolonged irradiation or on prolonged heating at 130°.

[6] (a) H. Ono, Ph.D. Dissertation, University of California, Berkeley, Calif., 1969; (b) G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, **70**, 231 (1970).

[7] Solutions (10^{-2} *M*) were irradiated in the nmr tube in the presence of oxygen with a Hanovia 450-W medium-pressure mercury lamp, Pyrex filter. The oxaziridines remained unchanged under these conditions of irradiation. Nmr spectra were recorded on a Varian 220-MHz spectrophotometer; uv spectra on a Cary-14 spectrophotometer.

[8] K. Koyano and H. Suzuki, *Tetrahedron Lett.*, 1859 (1968); *Bull. Chem. Soc. Jap.*, **42**, 3306 (1969). These authors presented nmr evidence which was used to distinguish *cis-* and *trans*-nitrone isomers.

[9] According to the assignment of D. Jerina, D. Boyd, L. Paolillo, and E. Becker, *Tetrahedron Lett.*, 1483 (1970).

[10] *trans*-IVa: α-CH, τ 1.82; $-CH_3$, τ 8.49 (t). *cis*-IVa: α-CH, τ 1.75; $-CH_3$, τ 8.46 (t).

isomerized thermally to *trans*-IVa at room temperature. The thermal stability of *cis*-IIIa and -IVa was found to be concentration dependent. They were relatively stable when formed by irradiation at room temperature in alcoholic solvents in 10^{-4} *M* ($t_{1/2} \sim$ 24 hr). The uv spectrum of the photostationary mixture of IVa was similar to that obtained by dilution of the concentrated solution irradiated in the nmr tube to the photostationary state at −60°. The uv spectrum of *cis*-IVa[11] was determined from the photoequilibrium composition and the isosbestic point for cis → trans thermal isomerization.

The ratio of *cis*- and *trans*-IVa at the photostationary state is very different from the ratio of *cis*- and *trans*-IVb formed at the end of the photocyclization reaction. For this reason the quantum yields of the photoreactions for each isomer were determined at 23° (10^{-4} *M*) and are reported in Table I. From the quantum yields of formation of *trans*- and *cis*-IVa[12] and of IVb formation from *cis*- and *trans*-IVa, the calculated ratio of IVb isomers formed after the photostationary state was reached, assuming stereospecificity, is 68% cis:32% trans. After the IVa photostationary state was reached on irradiation at −60°, the ratio of IVb isomers found by nmr was 71% cis:29% trans. Therefore, these results indicate stereospecificity in the nitrone photocyclization reaction.

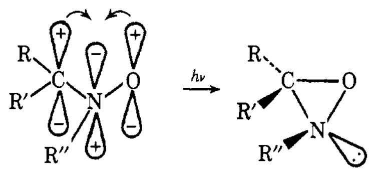
Table I. Quantum Yields for Products at 23° [a]

Reaction	Solvent	ϕ
trans-Ia → *trans*-Ib	Isopropyl alcohol	0.26
trans-IVa → IVb[b]	Methanol	0.016
trans-IVa → *cis*-IVa[c]	Methanol	0.18
cis-IVa → *trans*-IVa[d]	Methanol	0.46
cis-IVa → IVb[b]	Methanol	0.087

[a] Wavelength, 366 nm; concentration, 10^{-4} *M;* ferrioxalate actinometry. [b] Determined by decrease in optical density at 327 nm, isosbestic point of the nitrone isomers. [c] Determined by change in ratio of optical density at 357 and 317 nm. [d] Calculated from the photostationary state relation, $\phi_{t\rightarrow c}\epsilon_t X_t^{\infty} = \phi_{c\rightarrow t}\epsilon_c X_c^{\infty}$, where X_t^{∞} and X_c^{∞} are the mole fractions of the isomers at photoequilibrium.

For the reverse thermal cleavage of oxaziridine to nitrone, Ib in CD_3OD gave a 50:50 mixture of *cis*- and *trans*-Ia with a first-order rate constant, 6.8 × 10^{-4} sec^{-1} at −8°, by nmr spectroscopy.[13] The first-order rate constant for *cis*- → *trans*-Ia under these conditions was 2.9 × 10^{-5} sec^{-1} at 23°. Only in alcoholic solvents was the rate of the thermal *cis*- → *trans*-Ia isomerization slower than the rate of the Ib ring-opening reaction.[14] The photostationary state composition of Ia was confirmed to be 100% *trans*-Ia.

The *trans*-Ib thermal cleavage to *cis*- and *trans*-Ia is clearly in accordance with the predictions of the orbital symmetry rules. The observed stereospecificity in the nitrone photocyclization is consistent with the symmetry of the nitrone antibonding molecular orbital. As the carbon–oxygen σ bond forms in disrotatory motion, the nitrogen π orbital rehybridizes to a lone-pair sp^3-hybridized orbital in the opposite direction, giving an oxaziridine with the same configuration as the initial nitrone.



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(11) *trans*-IVa: λ_{max}^{MeOH} 338 nm (ε 14,800). *cis*-IVa: λ_{max}^{MeOH} 325 nm (ε 13,750). Although the uv of the IIIa photostationary state was similar to that of IVa, the photostationary state composition could not be determined because of the lesser solubility of IIIa in CD_3OD.

(12) The combined $\phi_{t\rightarrow c}$ and $\phi_{c\rightarrow t}$ suggest, in addition to oxaziridine formation, the efficient formation of a common twisted state analogous to the twisted state in the stilbene direct photoisomerization: (a) D. Gegiou, K. A. Muszkat, and E. Fischer, *J. Amer. Chem. Soc.*, **90**, 3907 (1968); (b) J. Saltiel and E. D. Megarity, *ibid.*, **91**, 1265 (1969); **90**, 4759 (1968).

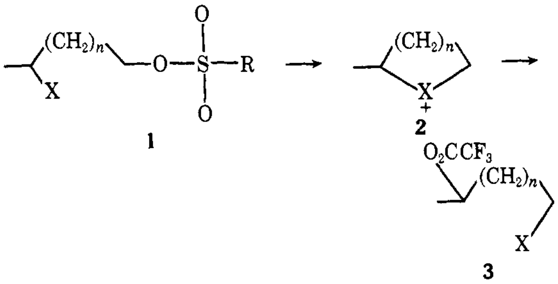
(13) *trans*-Ia: α-CH, τ 2.19; NCH_3, τ 6.27. *cis*-Ia: α-CH, τ 1.94; NCH_3, τ 6.15. No *cis*-Ia was detected in the partial irradiation of *trans*-Ia.

(14) At 23° in isopropyl alcohol (10^{-4} *M*) the ring cleavage rate was 3.4 × 10^{-4} sec^{-1}; the *cis*- → *trans*-Ia thermal rate was 4.0 × 10^{-7} sec^{-1}.

1,3-Halogen Shifts Occurring *via* Four-Membered Ring Halonium Ion Intermediates in the Solvolyses of 3-Halo-1-butyl Trifluoromethanesulfonates

Sir:

The trifluoroacetolysis of primary sulfonate–secondary halides has proved[1] to be an especially advantageous reaction for observing halogen shifts presumed to result from ring opening of halonium ion intermediates (eq 1). According to our analysis of the products and rates of *p*-nitrobenzenesulfonate solvolyses (eq 1, R = *p*-$NO_2C_6H_4$), 1,2, 1,4, and 1,5 participations predominate over competing normal solvolyses by the ratios (k_Δ/k_s) 2000, 760, and 7.1, respectively.[1] In contrast with the postulated intermediacy in these reactions of halonium ions consisting of three-, five-, and six-membered rings, evidence was lacking for formation of a four-membered chloronium ion ring.[1] We now report that the 1,3-halogen shift occurs in the trifluoromethanesulfonates **1** (n = 1, R = CF_3).[2] Participation tendencies decrease in the sequence I > Br > Cl, the amount of Cl shift being no more than a few per cent. These results complement those of Reineke and McCarthy,[3] who have reported a 1,3-bromine migration



(1)

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(1) (a) P. E. Peterson and J. F. Coffey. *Tetrahedron Lett.*, 3131 (1968); (b) J. F. Coffey, Ph.D. Thesis, St. Louis University, 1969; P. E. Peterson and J. F. Coffey, *J. Amer. Chem. Soc.*, in press; (c) see G. A. Olah and P. E. Peterson, *ibid.*, **90**, 4675 (1968), for references to observation by nmr to three-membered and five-membered ring halonium ions.

(2) For applications of the enhanced reactivity of triflates see T. M. Su, W. F. Sliwinski, and P. Schleyer, *ibid.*, **91**, 5386 (1969), and references cited therein.

(3) C. E. Reineke and J. R. McCarthy, Jr., *ibid.*, **92**, 6376 (1970).