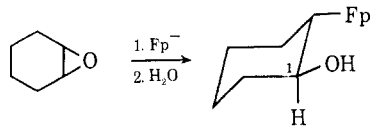
of solutions of either the *cis*- or *trans*-stilbene complex[8] alone or in the presence of iodide gave only the corresponding olefin, while similar decomposition of the *trans*-crotonate complex gave only ethyl *trans*-crotonate, as determined by nmr spectra of the reaction solutions. The sequence therefore provides a synthetically useful complement to the reduction of epoxides through conversion to phosphorus betaines with triphenylphosphine[9] or lithium diphenylphosphide,[10] which results in stereochemical inversion. It constitutes a convenient alternative to the reduction of epoxides by conversion to iodohydrins and reduction of these with zinc or stannous chloride.[11]

The stereochemical result may be readily accounted for by a mechanism involving initial SN2 opening of the epoxide by the complex anion, followed by a trans migration of the organometallic group concerted with the loss of water from the oxonium ion formed on protonation of the alcohol.[12]

The intermediate alcohols may be isolated as labile, air-sensitive yellow solids, by quenching solutions of the alkoxide **3** with water. The nmr spectrum of the alcohol derived from cyclohexene oxide exhibits a broad multiplet (19 Hz at half-height) at τ 6.90 for the proton at C_1, consistent with an axial conformation for this proton resulting from trans opening of the epoxide ring.[13,14]



While the intermediate alcohols are generally unstable, the related alkoxides, which may be precipitated from the initial reaction solution by the addition of ether, are relatively stable. This is most strikingly illustrated by the alcohol derived from *trans*-stilbene oxide which is exceedingly labile in solution and in the solid state. By contrast the corresponding alkoxide is a stable yellow solid which can be stored for prolonged periods of time without apparent decomposition.

The further use of these substances and of the cationic metal–olefin complexes will be reported shortly.

Acknowledgment. This work was supported by grants from the National Science Foundation (GP-27991-X) and by the National Institutes of Health (GM-16395) which are gratefully acknowledged.

(8) The *trans*-stilbene salt decomposes rapidly in nitromethane solutions above 0° to give the nitromethane-complexed cation, $[C_5H_5Fe(CO)_2CH_3NO_2]^+$, as a crystalline orange salt: ir (KBr) 2030, 2080 (C≡O) 1540, 1340 cm^{-1} (NO_2); nmr (CD_3NO_2) τ 4.50 (s, 5, Cp), 5.64 (s, 3, CH_3).

(9) G. Wittig and W. Haag, *Chem. Ber.*, **88**, 1654 (1955).

(10) E. Vedejs and P. L. Fuchs, *J. Amer. Chem. Soc.*, **93**, 4070 (1971).

(11) J. W. Cornforth, R. H. Cornforth, and K. K. Mathews, *J. Chem. Soc.*, 112 (1959).

(12) The stereochemical constraints involved in participation of the complex organometallic substituent in elimination reactions have been examined in a previous report: A. Cutler, R. W. Fish, W. P. Giering, and M. Rosenblum, *J. Amer. Chem. Soc.*, **94**, 4354 (1972).

(13) Alone among these alcohols, that derived from *trans*-ethyl crotonate is a stable yellow-orange crystalline material, mp 64–64.5°. Its nmr spectrum (CD_3NO_2), τ 6.07 (q + m, 3, CH_2 + β-H), 6.75 (d, 1, J = 6 Hz, OH), 7.67 (d, 1, J = 6 Hz, α-H) 8.73 (t, 3, J = 7 Hz, CH_3CH_2), 8.79 (d, 3, J = 6 Hz, CH_3CHOH), indicates that epoxide ring opening has taken place through displacement at the α carbon atom of the ester. It seems likely that it is the electron-withdrawing ester function which is largely responsible for stabilizing the metal–carbon σ bond in this substance.

(14) J. M. Jackman and S. Sternhell, "Applications of NMR Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 288. Jensen, Madann, and Buchanan[7] have recently reported similar results in the reaction of cyclohexene oxide with pyridine[bis-(dimethylglyoximato)]cobalt(I), and have confirmed this assignment through an examination of the spectra of the two epimeric alcohols.

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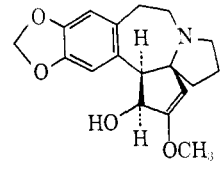
The Total Synthesis of Cephalotaxine

Sir:

Cephalotaxine is the parent member of the Cephalotaxus group of alkaloids, several of which have shown significant inhibitory activity against experimental lymphoid leukemia. Structural elucidation by a combination of chemical and X-ray crystallographic studies has shown cephalotaxine to have the unique structure and stereochemistry indicated in formula **1**.[1–4] In this



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paper we wish to report the first total synthesis of racemic cephalotaxine.

Condensation of prolinol[5] with 3,4-methylenedioxyphenylacetyl chloride[6] in acetonitrile solution at −20° in the presence of suspended potassium carbonate gave the alcohol **2** as a viscous oil (82% yield). Oxidation of **2** with dicyclohexylcarbodiimide, dichloroacetic acid, and dimethyl sulfoxide[7] gave the oily aldehyde **3**, isolated by chromatography in 70% yield [nmr peaks ($CDCl_3$) at δ 9.50 (1 H, d, J = 1.5 Hz); ir max (film) 1720 cm^{-1}]. Cyclization of aldehyde **3** to tetracyclic enamide **4**, mp 122–123°, was accomplished in 85% yield by stirring at room temperature in chloroform solution in the presence of boron trifluoride etherate [nmr peaks ($CDCl_3$) at δ 6.65 (1 H, s), 6.52 (1 H, s), 5.96 (1 H, s, vinyl), 5.90 (2 H, s), 3.68 (2 H, t, J = 3 Hz), 3.26 (2 H, s), 2.74 (2 H, t, J = 3 Hz), 1.90 (2 H, m); ir max ($CHCl_3$) 1650 cm^{-1}]. Enamide **4** upon reduction with lithium aluminum hydride in refluxing tetrahydrofuran gave enamine **5** (100%), mp 82–83° [nmr peak (C_6D_6) at δ 5.00 (1 H, s)].

Treatment of enamine **5** with 2-acetoxypropionyl chloride[8] in refluxing acetonitrile in the presence of

(1) W. W. Paudler, G. I. Kerley, and J. McKay, *J. Org. Chem.*, **28**, 2194 (1963).

(2) (a) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and I. A. Wolff, *Tetrahedron Lett.*, 4081 (1969); (b) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and W. Rohwedder, *ibid.*, 815 (1970); (c) K. L. Mikolajczak, R. G. Powell, and C. R. Smith, Jr., *Tetrahedron*, **28**, 1995 (1972); (d) R. E. Perdue, Jr., L. A. Spetzman, and R. G. Powell, *Amer. Hort. Mag.*, **49**, 19 (1970).

(3) D. J. Abraham, R. D. Rosenstein, and E. L. McGandy, *Tetrahedron Lett.*, 4085 (1969).

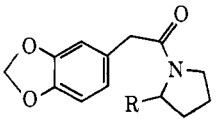
(4) For speculative proposals concerning the biogenetic origin of these alkaloids, see: (a) V. A. Snieckus in "The Alkaloids," Vol. 1, The Chemical Society Specialist Reports, 1971, p 149; (b) R. G. Powell, *Phytochemistry*, **11**, 1467 (1972).

(5) O. Vogl and M. Pohm, *Monatsh. Chem.*, **83**, 541 (1952).

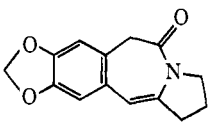
(6) E. R. Shepard, H. D. Porter, J. F. Noth, and C. K. Simmans, *J. Org. Chem.*, **17**, 568 (1952).

(7) J. G. Moffatt in "Oxidation," Vol. 2, R. L. Augustine and D. J. Trecker, Ed., Marcel Dekker, New York, N. Y., Chapter 1.

(8) E. B. Reid and G. Denny, Jr., *J. Amer. Chem. Soc.*, **81**, 4632 (1959).



2, R = CH_2OH
3, R = CHO



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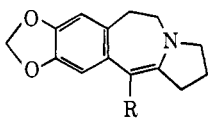
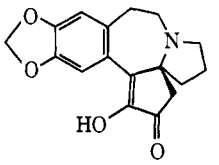


5, R = H
6, R = $COCH(OAc)CH_3$
7, R = $COCHOHCH_3$
8, R = $COCOCH_3$



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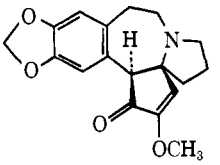

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suspended sodium bicarbonate gave the crystalline vinylogous amide **6**, mp 132–133° (75%) [nmr peaks ($CDCl_3$) at δ 1.12 (3 H, d, J = 7 Hz), 2.09 (3 H, s), 5.60 (1 H, q, J = 7 Hz); ir max ($CHCl_3$) 1740 and 1650 cm^{-1}]. Hydrolysis of **6** with potassium carbonate in aqueous methanol afforded alcohol **7**, mp 139–141°, in 95% yield [nmr peaks ($CDCl_3$) at δ 0.85 (3 H, d, J = 7 Hz), 4.75 (1 H, q, J = 7 Hz); ir max ($CHCl_3$) 3300 cm^{-1}]. Alcohol **7** was converted to the oily yellow α-dicarbonyl compound **8** (80%) upon brief refluxing with lead dioxide in toluene [nmr peak ($CDCl_3$) at δ 2.22 (3 H, s)].[9,9a]

Without purification **8** was treated with magnesium methoxide in methanol[10] resulting in formation of crystalline pentacyclic desmethylcephalotaxinone (**9**),[11,12] mp 104–107°, upon recrystallization from methanol (52%) [found for **9**: nmr ($CDCl_3$) δ 1.8 (4 H, m), 2.60 (2 H, s), 2.9–3.6 (6 H, m), 5.10 (1 H, br s, OH), 6.00 (2 H, s), 6.75 (1 H, s), 7.00 (1 H, s); uv max (C_2H_5OH–HCl) 324 nm (ε 8700), 262 (8500), 232 (7800); uv max (C_2H_5OH–KOH) 341 nm (ε 13,100); ir max ($CHCl_3$) 3475, 3300, 1700, and 1645 cm^{-1}; m/e 299.1158].

Desmethylcephalotaxinone (**9**), upon refluxing in methanol–dioxane solution with excess 2,2-dimethoxypropane in the presence of 3 equiv of *p*-toluenesulfonic acid, was converted to naturally occurring cephalotaxinone (**10**) (40%), mp 180–183°.[4b,13,14] Reduction of **10** with sodium borohydride in methanol at room temperature was stereospecific and gave racemic cephalotaxine (**1**) (80%).[13]

Acknowledgment. This investigation was supported by the Research Corporation and the National Cancer Institute, National Institutes of Health (Grant No. CA12568).

(9) H. H. Inhoffen, K. Radscheit, U. Stache, and V. Koppe, *Justus Liebigs Ann. Chem.*, **684**, 24 (1965).

(9a) NOTE ADDED IN PROOF. Enamine **5** can be converted to α-dicarbonyl compound **8** in a single step in 80% yield by treatment with the mixed anhydride prepared from pyruvic acid and ethyl chloroformate using a modification of the procedure of R. A. Raphael, *et al. J. Chem. Soc., Perkin Trans. 1*, 860 (972). We are grateful to Professor Raphael for bringing this procedure to our attention and to Mr. R. Cvetovich for carrying out this experiment.

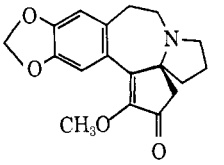
(10) H. Muxfeldt, M. Weigele, and V. Van Rheenen, *J. Org. Chem.*, 30, 3573 (1965).

(11) Mr. R. G. Powell and Mr. K. L. Mikolajczak, USDA, Peoria, Ill., have informed us that they recently isolated desmethylcephalotaxinone (**9**) from *Cephalotaxus harringtonia*. Comparison of our synthetic material with their natural material indicated that the two are identical. As part of their structure proof, these workers have converted desmethylcephalotaxinone to cephalotaxine. Their borohydride reduction of the intermediate cephalotaxinone was stereospecific. We are indebted to Mr. Powell and Mr. Mikolajczak for their cooperation and for making information available to us in advance of publication.

(12) By this sequence of reactions it is possible to prepare gram quantities of **9**.

(13) This compound was identical in ir, nmr, mass spectrum, and tlc with authentic material of natural origin kindly supplied by Mr. R. G. Powell.

(14) This step also produced some other, as yet unidentified, products but surprisingly did not give any of the isomeric vinyl ether i. Desmethylcephalotaxinone (**9**), upon treatment with diazomethane, forms i in high yield.



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(15) Postdoctoral Research Associate, 1971–present.

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Coordinated Nitrene Formation by the Photolysis of Azido Pentaammine Complexes of Rhodium(III) and Iridium(III)

Sir:

Investigations of the photolysis of several different azido–metal complexes suggest the formation of azido radical which then reacts with itself to generate nitrogen.[1] However, this is not the photochemical behavior of the azido group for hydrozoic acid and for organic azides. The photolysis of hydrozoic acid yields the active intermediate nitrene (NH),[2] and organic azides react photochemically to produce substituted nitrenes (NR).[3] We wish to report that the photochemical reactions of $[M(NH_3)_5N_3]^{2+}$, where M = Ir(III) and Rh(III), result in the decomposition of the azido group *via* a coordinated nitrene (M–NH) intermediate.

Photolysis experiments with aqueous solutions of $[Ir(NH_3)_5N_3](ClO_4)_2$ were performed using a Hanovia 8A36 medium-pressure mercury arc lamp and a 270-nm cutoff filter solution (5% benzene in methanol solution). $[Ir(NH_3)_5N_3](ClO_4)_2$ (1 g) was dissolved in 250 ml of 0.1 *M* HCl, and the solution was irradiated. Irradiation was stopped when the uv spectrum of the solution showed that the absorption band at 258 nm

(1) (a) S. A. Penkett and A. S. Adamson, *J. Amer. Chem. Soc.*, **87**, 2514 (1965); (b) J. F. Endicott, M. Z. Hoffman, and L. S. Beres, *J. Phys. Chem.*, **74**, 1021 (1970); (c) C. Bartocci and F. Scandola, *Chem. Commun.*, 531 (1970); (d) W. Beck and K. Scharpp, *Angew. Chem., Int. Ed. Engl.*, **9**, 735 (1970); (e) A. Vogler, *J. Amer. Chem. Soc.*, **93**, 5912 (1971); (f) R. F. Ziolo, J. A. Thich, and Z. Dori, *Inorg. Chem.*, **11**, 626 (1972).

(2) K. H. Welge, *J. Chem. Phys.*, **45**, 4373 (1966); I. Burak and A. Tremin, *J. Amer. Chem. Soc.*, **87**, 4031 (1965).

(3) E. Wasserman, G. Smolinsky, and W. A. Yager, *ibid.*, **86**, 3166 (1964); E. Koch, *Tetrahedron*, **23**, 1747 (1967).