

experiments permit only *comparison* of the interaction under different conditions. However, this may be done simply and rapidly, and if independent data are available describing the interaction in one environment, then it may be quantitatively evaluated for others.

The enthalpy of the interaction between the amide and polyglycine can be calculated from the temperature dependence of K_a , and will be independent of the concentration of available peptide bonds. For acetamide in dioxane the value obtained was -3600 cal./mole. Klotz and Franzen found an enthalpy of -800 cal./mole for the dimerization of N-methylacetamide in dioxane. The more negative value obtained in the chromatographic experiments suggests that acetamide may bind to polyglycine with more than one peptide hydrogen bond. Since a maximum of three such bonds can be formed by each acetamide molecule, the value of the enthalpy may be as low as -1200 cal./mole of hydrogen bonds. An enthalpy could not be calculated for water, since binding was not observed at either 0 or 40° in this solvent.

These experiments will be extended to evaluate the characteristics of the association in other solvents.

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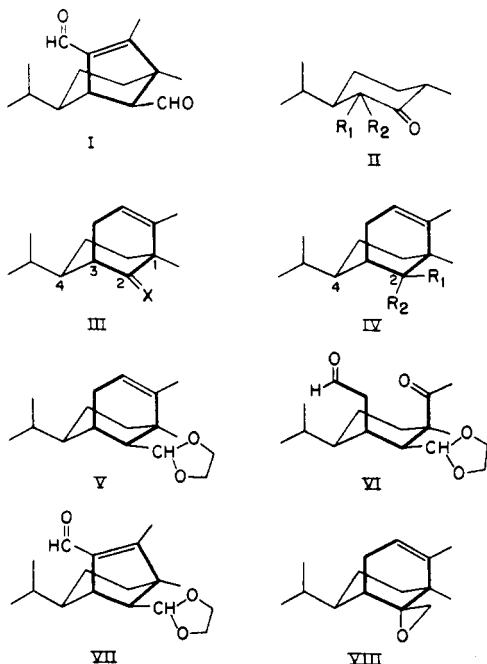
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Total Synthesis of Helminthosporal

Sir:

Recently the constitution of helminthosporal, the important crop-destroying toxin of the fungus *Helminthosporium sativum*, has been demonstrated by an incisive chemical investigation.¹ Subsequent studies on this substance have also permitted the assignment of stereochemistry, exclusive of absolute configuration, as in I.² We report here the total synthesis of helminthosporal by a method which confirms the previous structural conclusions and which additionally allows the designation of absolute configuration.



(1) P. de Mayo, E. Y. Spencer, and R. W. White, *J. Am. Chem. Soc.*, **84**, 494 (1962); P. de Mayo, E. Y. Spencer, and R. W. White, *Can. J. Chem.*, **39**, 1608 (1961).

(2) P. de Mayo, personal communication.

(-)-Carvomenthone^{3,4} (II, $R_1 = R_2 = H$) was converted *via* the known α -hydroxymethylene derivative⁵ to the diketo aldehyde II ($R_1 = CHO$, $R_2 = CH_2CH_2COCH_3$), using methyl vinyl ketone and triethylamine at room temperature (3 days, 71%).⁶ This substance was deformylated by 2% ethanolic potassium carbonate at reflux (16 hr.) to give the diketone II ($R_1 = H$, $R_2 = CH_2CH_2COCH_3$, 70% yield, infrared max. 5.82μ , n.m.r. peaks⁸ at 0.87 – 1.02δ due to three methyl groups and at 2.05δ due to C-acetyl. Treatment of this diketone with boron trifluoride in methylene chloride solution at 25° (16 hr.) afforded in 40% yield the bridged keto olefin III ($X = O$) and its C-4 epimer in a ratio of 4:1. These liquid epimers were purified by v.p.c. or *via* the crystalline semicarbazones. The major isomer has b.p. 66 – 68° (0.06 mm.), infrared absorption at 5.83μ , n.m.r. peaks at 0.80 – 1.01δ due to three methyl groups attached to saturated carbon, at 1.6δ (doublet) due to one methyl attached to unsaturated carbon, and at 5.60δ due to one olefinic proton; both isomers lack ultraviolet absorption characteristic of α,β -unsaturated ketones.⁹

The assignment of configuration at C-4 to III ($X = O$) and its 4-epimer rests partly on the fact that reduction with lithium aluminum hydride produces a mixture of secondary alcohols from the former (ratio 4:1) but only a single alcohol from the latter. That the predominating course of reduction of both III ($X = O$) and its C-4 epimer is (as it is expected to be) that which produces an hydroxyl with axial orientation of the cyclohexane ring (IV, $R_1 = H$, $R_2 = OH$, and the C-4 epimer) is indicated by n.m.r. data. The n.m.r. peak due to the $-CH-O$ proton is at 3.54δ

for IV ($R_1 = H$, $R_2 = OH$) and at 3.48δ for the C-4 epimer; the corresponding proton in the spectrum of the minor alcohol from III ($X = O$) (IV, $R_1 = OH$, $R_2 = H$) shows a peak at 3.10δ .¹⁰

Reaction of the unsaturated ketone III ($X = O$) with methoxymethylene triphenylphosphorane in dimethyl sulfoxide¹¹ at 40° (12 hr.) gave a 90% yield of the Wittig product III ($X = CHOCH_3$) which was further transformed into the ethylene acetal V (together with minor amounts of the C-2 epimer) with ethylene glycol-benzene-*p*-toluenesulfonic acid at reflux (1 hr., 86% yield). Hydroxylation of V with osmium tetra-

(3) Prepared by hydrogenation of (+)-carvone; see E. S. Rothman and A. R. Day, *J. Am. Chem. Soc.*, **76**, 111 (1954).

(4) Formal total syntheses of both (-)- and (+)-carvomenthone are provided by the terpene literature. For example; a route for the (-) isomer appears in the series (a) W. H. Perkin, Jr., *J. Chem. Soc.*, **85**, 654 (1904); K. Alder and W. Vogt, *Ann.*, **564**, 109 (1949); (b) A. T. Fuller and J. Kenyon, *J. Chem. Soc.*, **125**, 2304 (1924); (c) K. Fujita and T. Matsuura, *J. Sci. Hiroshima Univ.*, **18A**, 455 (1955) [*Chem. Abstr.*, **50**, 10582 (1956)]; (d) M. G. Vavon, *Compt. rend.*, **153**, 70 (1911).

(5) V. S. Kora, J. Černý, V. Herout, and F. Šorm, *Collection Czech. Chem. Commun.*, **19**, 566 (1954).

(6) R. B. Turner, D. E. Nettleton, Jr., and R. Ferebee, *J. Am. Chem. Soc.*, **78**, 5923 (1956).

(7) Satisfactory analytical data were obtained for this and the other major intermediates in this synthesis. All the assigned structures are supported by spectral data though these are not extensively reported here.

(8) Expressed as parts per million shift (δ) downfield from tetramethylsilane.

(9) The formation of bridged-ring products such as III ($X = O$), as a side reaction in the Robinson annulation process, has been discussed recently by W. S. Johnson, J. J. Korst, R. A. Clement, and J. Dutta, *J. Am. Chem. Soc.*, **82**, 614 (1960); S. Julia, *Bull. Soc. Chim. France*, **21**, 780 (1954). In the present instance the conditions are such as to render the normal Robinson reaction mode almost insignificant. Further, the ratio of C-4 epimers of III ($X = O$) can also be altered markedly by varying reaction conditions.

(10) The carbonyl proton resonance in IV ($R_1 = OH$, $R_2 = H$) can be expected to occur at higher field than that in the epimeric IV ($R_1 = H$, $R_2 = OH$) by ca. 0.5 p.p.m. See, e.g., A. H. Lewin and S. Winstein, *J. Am. Chem. Soc.*, **84**, 2464 (1962); R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).

(11) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

oxide followed by oxidation of the diol with lead tetraacetate led to the keto aldehyde VI (80%), infrared max. 5.78, 5.87 μ , and this was cyclized by dilute base in ethanol to the unsaturated aldehyde VII (50% yield); infrared max. 3.67, 5.98, 6.17 μ ; n.m.r. peaks at 0.75–1.10 δ (three methyls), 2.00 δ ($\text{C}=\text{C}-\text{CH}_3$), 4.47 δ (doublet, one acetal proton), and 9.90 δ (CHO), ultraviolet max. 266 m μ (ϵ 9900). Hydrolysis of the acetal function in VII was accomplished using 1.5% sulfuric acid in aqueous tetrahydrofuran to give synthetic helminthosporal (I), m.p. 55–58°, $[\alpha]_{\text{D}}^{18} -47.8^\circ$ (c 1.00, chloroform) having infrared, n.m.r., and ultraviolet spectra identical with those of the natural substance. Reduction of synthetic I with lithium aluminum hydride followed by reaction with 3,5-dinitrobenzoyl chloride afforded a bisdinitrobenzoate, m.p. 148–149.5°, alone or admixed with a sample, m.p. 148–149.5°, derived from natural helminthosporal.

Since the absolute configuration of (–)-carvomenthone is as shown in II ($R_1 = R_2 = \text{H}$), the absolute stereochemistry of helminthosporal (I) follows from the synthesis. The orientation of the formyl group at C-2 in helminthosporal as shown in I is indicated by n.m.r. data and the resistance of this substance to isomerization in acid solution.

An alternative approach to helminthosporal consists of the reaction of the ketone III ($\text{X} = \text{O}$) with the methylene transfer agent dimethylsulfonium methylide¹² to give the oxirane VIII (95% yield, configuration at C-2 tentative), subsequent treatment with zinc bromide–benzene (30% yield) to form a mixture of C-2 epimeric aldehydes, and conversion to V (and the C-2 epimer) with ethylene glycol under acid catalysis.¹³

(12) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 867 (1962).

(13) We thank Dr. Paul de Mayo for an authentic sample of tetrahydrohelminthosporal bis-3,5-dinitrobenzoate and for helpful discussions. This research was supported by the National Institutes of Health.

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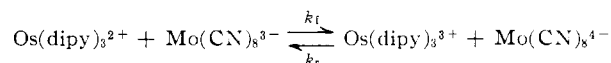
The Rate of the Tris-(2,2'-dipyridine)-osmium(II)-Octacyanomolybdate(V) Electron-Transfer Reaction¹

Sir:

The application of the temperature-jump method to the study of rapid bimolecular electron-transfer reactions requires that the equilibrium constant for the reaction be of the order of unity. Consequently, the standard entropy change for the electron-transfer reaction should be fairly large, so that the change in the equilibrium produced by the temperature jump may be readily measurable. One way in which this can be achieved is by the use of oppositely charged reactants. Halpern, Legare, and Lumry² have successfully used this method to measure the rate of electron transfer between tris-(4,7-dimethyl-1,10-phenanthroline)-iron(II) and hexachloroiridate(IV). We report here the results of a study of the rate of the tris-(2,2'-dipyridine)-osmium(II)-octacyanomolybdate(V) reaction.

The temperature-jump apparatus is of similar design to that of Czerlinski and Eigen³ and Diebler⁴ except that we have used a single light beam instead of a dual beam. This modification improves the signal-to-noise ratio by a factor of two.⁵ A Bausch and Lomb grating

monochromator equipped with a 30-w. tungsten filament lamp was used as the light source. The temperature jump of about 10° was produced by discharging a 0.02 μf . condenser, charged to 80 kv., through the solution, and the resulting change in the equilibrium was measured by recording the absorbance of $\text{Os}(\text{dipy})_3^{2+}$ at 480 m μ as a function of time. The values of k_f and k_r defined by the equation



were found to be $2.0 \times 10^9 F^{-1} \text{ sec.}^{-1}$ and $4.0 \times 10^9 F^{-1} \text{ sec.}^{-1}$, respectively, at 10° and ionic strength 0.50 (0.45 F KNO_3 + 0.05 F HNO_3). These rate constants are even somewhat higher than those found for the $\text{Fe}(\text{DMP})_3^{2+}$ – IrCl_6^{2-} system under comparable conditions.²

The diffusion-limited rate constants for the $\text{Os}(\text{dipy})_3^{2+}$ – $\text{Mo}(\text{CN})_8^{3-}$ and $\text{Os}(\text{dipy})_3^{3+}$ – $\text{Mo}(\text{CN})_8^{4-}$ reactions calculated from the Debye equation⁶ are $1 \times 10^{10} F^{-1} \text{ sec.}^{-1}$ and $2 \times 10^{10} F^{-1} \text{ sec.}^{-1}$, respectively, at 10° and zero ionic strength. The values will be somewhat lower at the ionic strength used in these studies. It will be seen that the observed rate constants lie within one order of magnitude of the diffusion-controlled limits, as do the rate constants obtained by Halpern, Legare, and Lumry.²

Since the observed rates are close to the diffusion-controlled limits, the energy required to reorganize the inner and outer coordination shells of the reactants and products cannot be very large. The Marcus theory⁷ may be used to calculate the rate constants for the electron-exchange reactions related to this oxidation–reduction reaction, and one may then compare these calculations with the observed rates. According to this theory the rate constant for an electron-transfer reaction is given by

$$k = Z e^{-(w + m^2\lambda)/RT} \quad (1)$$

where Z is the collision frequency between two uncharged molecules in solution ($10^{11} \text{ l. mole}^{-1} \text{ sec.}^{-1}$), w is the work required to bring the two reactants together, and $m^2\lambda$ is the energy required to reorganize the inner and outer coordination shells of the reactants. Substitution of $k = 2.0 \times 10^9 F^{-1} \text{ sec.}^{-1}$ in eq. 1 gives $m^2\lambda = 3 \pm 1 \text{ kcal. mole}^{-1}$ at 10°. The energy required to reorganize the coordination shells of $\text{Os}(\text{dipy})_3^{2+}$ and $\text{Mo}(\text{CN})_8^{3-}$ prior to the electron transfer thus appear to be much lower than the values calculated for many other reactants.^{9,10} Since the reorganization energies are small and probably not too different in other electron-transfer reactions involving $\text{Os}(\text{dipy})_3^{2+}$, $\text{Mo}(\text{CN})_8^{3-}$, $\text{Os}(\text{dipy})_3^{3+}$, and $\text{Mo}(\text{CN})_8^{4-}$ (provided $K \approx 1$), the rate constants for the $\text{Os}(\text{dipy})_3^{2+}$ – $\text{Os}(\text{dipy})_3^{3+}$ and $\text{Mo}(\text{CN})_8^{3-}$ – $\text{Mo}(\text{CN})_8^{4-}$ exchange reactions may be estimated from the rate constant for the $\text{Os}(\text{dipy})_3^{2+}$ – $\text{Mo}(\text{CN})_8^{3-}$ reaction merely by correcting for the differences in the electrostatic work required to bring the various pairs of reactants together, and assuming the reorganization terms to be the same, for all three reactions in the first approximation. When these corrections are made, estimates of $1 \times 10^7 F^{-1} \text{ sec.}^{-1}$ and $3 \times 10^4 F^{-1} \text{ sec.}^{-1}$ are obtained for the rate constants for the $\text{Os}(\text{dipy})_3^{2+}$ – $\text{Os}(\text{dipy})_3^{3+}$ and

(5) G. G. Hammes and J. I. Steinfeld, *J. Am. Chem. Soc.*, **84**, 4639 (1962).

(6) P. Debye, *Trans. Electrochem. Soc.*, **82**, 265 (1942).

(7) R. A. Marcus, *J. Phys. Chem.*, **67**, 853 (1963).

(8) The upper and lower limits of $m^2\lambda$ were calculated on the assumption that $w = z_1 z_2 e^2 / DR$ and $w = z_1 z_2 e^2 [\exp(-\kappa R)] / DR$, respectively. The mean value of w was used in calculating the electron-exchange rates.

(9) N. Sutin, *Ann. Rev. Nucl. Sci.*, **12**, 285 (1962).

(10) B. M. Gordon, L. L. Williams, and N. Sutin, *J. Am. Chem. Soc.*, **83**, 2061 (1961).

(1) Research performed under the auspices of the U. S. Atomic Energy Commission.

(2) J. Halpern, R. J. Legare, and R. Lumry, *J. Am. Chem. Soc.*, **85**, 680 (1963).

(3) G. Czerlinski and M. Eigen, *Z. Elektrochem.*, **63**, 652 (1959).

(4) H. Diebler, Ph.D. Thesis, Georg-August-University, Göttingen, Germany, 1960.