Table I. Benzophenone-Initiated Photoxidation of Cumene at 62.5° and 3130 A

[Benzophenone], M	[Cumene], M	$I_0 \times 10^8$, einsteins cm^{-2} sec^{-1}	$I_a \times 10^5$, einsteins l.$^{-1}$ sec^{-1}	$-$d[O$_2$]dt $\times 10^6$, moles l.$^{-1}$ sec^{-1}
1.0	1.98	2.14	2.14	4.48
0.3	2.25	1.96	1.96	6.57
0.09	2.34	2.02	2.02	6.88
0.0081	2.38	2.97	2.51	6.52
0.0024	2.38	4.96	2.14	6.67
0.00073	2.38	4.62	0.71	4.55
0.00060	2.38	3.92	0.428	3.64
0.00022	2.38	4.23	0.207	1.86
0.00020	2.38	3.72	0.167	2.02
0.000066	2.38	3.77	0.0566	1.43
0.000060	2.38	3.55	0.049	1.20

Table II. Diethyl Ketone Initiated Photooxidation of Cumene at 62.5° and 3130 A

[Diethyl ketone], M	[Cumene], M	$I_0 \times 10^8$, einsteins cm^{-2} sec^{-1}	$I_a \times 10^5$, einsteins l.$^{-1}$ sec^{-1}	$-$d[O$_2$]dt $\times 10^6$, moles l.$^{-1}$ sec^{-1}
1.03	2.13	3.13	3.28	8.42
0.50	2.25	3.40	2.24	8.26
0.226	2.31	2.06	0.77	4.17
0.10	2.37	2.64	0.494	4.05
0.0503	2.38	2.06	0.208	2.25
0.0224	2.38	3.72	0.171	2.60
0.0104	2.38	4.10	0.088	1.26

of diethyl ketone and of benzophenone sensitized photooxidations thus plotted are seen to be superimposable. The slope of the common line in Figure 1 is simply $k_p(\Phi^T/k_t)^{1/2}$. The rate constant ratio $k_p/k_t^{1/2}$ for cumene oxidation has been found[7] to be 4.5×10^{-3} (l./mole sec)$^{1/2}$, from which we obtained a value of $\Phi^T = 0.0255$ for both systems.

The quantum yield Φ^T is defined as $k_r[RH]/(k_r[RH] + k_q[O_2] + k_d + k_{sol}[sol])$, where k_r, k_q, k_d, and k_{sol} are the rate constants for the hydrogen abstraction, oxygen quenching, decay, and solvent quenching reactions of the triplet state, respectively. The values of these rate constants for benzophenone have been estimated by Hammond, *et al.*:[8] $k_d = 2.6 \times 10^5$ sec^{-1}; $k_q = 10^9$ l. mole^{-1} sec^{-1}; $k_r = 7 \times 10^4$ l. mole^{-1} sec^{-1}; k_{sol}[9] $= 3 \times 10^4$ l. mole^{-1} sec^{-1}. The solubility of oxygen in a 1:2 mixture of cumene and chlorobenzene at 62.5° was determined to be 5.5×10^{-3} mole l.$^{-1}$. Substitution of these values into the definition for the quantum yield gives a value of $\Phi^T = 0.027$ for benzophenone, in agreement with the value of 0.025 found here.

Closer examination of the expression for quantum yield shows that the value of $k_q[O_2]$ is about ten times the sum of the other three terms. Quenching of the triplet state by oxygen has been found to be diffusion limited for many compounds.[11] If one assumes the oxygen quenching of the diethyl ketone triplet state is also diffusion limited and large compared to other triplet decay processes, the reactivities of the triplets states of these ketones can be calculated. The values of the diffusion-limited quenching rate constants were first obtained from known relationships.[15] These are $(k_q)_{BP} = 1.2 \times 10^9$ l. mole^{-1} sec^{-1} and $(k_q)_{DEK} = 1.4 \times 10^9$ l. mole^{-1} sec^{-1}. From these values, the triplet state of diethyl ketone is found to be about 20% more reactive than the benzophenone triplet state, with values of k_r estimated to be 8×10^4 l. mole^{-1} sec^{-1} and 7×10^4 l. mole^{-1} sec^{-1}, respectively. Even though the absolute values of these rate constants are subject to some uncertainty, it is safe to conclude that *the triplet states of diethyl ketone and benzophenone abstract hydrogen with comparable reactivities.*

Experiments were also carried out at 3650 A for benzophenone-sensitized photooxidations. The quantum yields of initiation at this wavelength are found to be indistinguishable from the results obtained at 3130 A.

The method described above can be extended to determine the reactivities of other ketones, for example, the derivatives of benzophenone. The values of diffusion-limited k_q's for these derivatives should be closely similar; ratios of k_r's can be obtained with good accuracy. Those results will be reported shortly.

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[7] J. C. W. Chien, *J. Am. Chem. Soc.*, **89**, in press.

[8] G. S. Hammond, W. P. Baker, and W. M. Moore, *ibid.*, **83.** 2795 (1961).

[9] This value was given for toluene. Even though chlorobenzene is expected to quench benzophenone triplet with somewhat higher efficiency[10] than toluene and cumene, the three were assumed here to have equal efficiencies. The error thus introduced would not be appreciable because solvent quenching is small compared to oxygen quenching.

[10] S. K. Lower and M. A. El-Sayed, *Chem. Rev.*, **66**, 208 (1966).

[11] Examples are acetone triplet,[12] anthracene triplet,[13] biacetyl triplet,[14] and benzophenone triplet.[5]

[12] H. J. Groth, Jr., G. W. Luckey, and W. A. Noyes, Jr., *J. Chem. Phys.*, 21, 115 (1953).

[13] R. Livingston and D. W. Tanner, *Trans. Faraday Soc.*, **54**, 765 (1958).

[14] H. L. J. Backstrom and K. Sandros, *J. Chem. Phys.*, **23**, 2197 (1955).

[15] See references cited by Hammond, *et al.*[5]

James C. W. Chien
Research Center, Hercules Incorporated
Wilmington, Delaware 19899

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Inner-Sphere Reduction of an Azidocobalt(III) Complex by Vanadium(II). Kinetics of Formation and Decomposition of the Metastable Monoazidovanadium(III) Ion[1]

Sir:

The question of whether vanadium(II) reductions of cobalt(III) complexes proceed by inner-sphere or outer-sphere mechanisms has been considered previously by several workers.[2-6] The evidence has been indirect, however, with arguments based largely on comparisons of reactivity patterns toward different complexes. This situation stands in contrast to that for chromium(II) reductions, where the very slow decomposition of the metastable monosubstituted chromium(III) complex, primary product of the inner-sphere pathway, permits its isolation and identification. The high rate at which vanadium(III) substitution processes come to equilibrium has hitherto prevented the finding of similar direct evidence for vanadium(II).

Consider the alternate mechanisms for reduction of the cobalt(III) complex CoL_5X^{2+} by V(II). In an outer-sphere process (eq 1), the immediate product is the stable

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[1] Work performed in the Ames Laboratory under the auspices of the U. S. Atomic Energy Commission. Contribution No. 2007.

[2] J. Candlin, J. Halpern, and D. Trimm, *J. Am. Chem. Soc.*, **86**, 1019 (1964).

[3] H. Diebler and H. Taube, *Inorg. Chem.*, 4, 1029 (1965).

[4] P. Dodel and H. Taube, *Z. Physik. Chem.* (Frankfurt), 44, 92 (1965).

[5] R. T. M. Fraser, *J. Am. Chem. Soc.*, **84**, 3436 (1962).

[6] N. Sutin, *Ann. Rev. Phys. Chem.*, **17**, 119 (1966).

$$CoL_5X^{2+} + V^{2+} \longrightarrow Co^{2+} + 5L + X^- + V^{3+} \qquad (1)$$

aquovanadium(III) cation, whereas the inner-sphere mechanism first produces the metastable vanadium(III) complex VX^{2+} (eq 2), which subsequently decomposes

$$CoL_5X^{2+} + V^{2+} \longrightarrow Co^{2+} + 5L + VX^{2+} \qquad (2)$$

to the aquo ion (eq 3). These mechanisms cannot

$$VX^{2+} \longrightarrow V^{3+} + X^- \qquad (3)$$

be distinguished in the limit that the rate of decomposition of the VX^{2+} complex approaches its rate of production.

Our approach has been to seek a particularly reactive cobalt(III) complex and a relatively slow reacting VX^{2+} system. The complex *cis*-$Co(en)_2(N_3)_2^+$ seemed best suited for this study.[7] Kinetic measurements were carried out on the oxidation–reduction reaction at 25.0°, 0.10 M H^+, and ionic strength 1.0 M (maintained with lithium perchlorate).

The electron-transfer rate was studied in a series of conventional spectrophotometric rate studies using relatively low concentrations of vanadium(II) ($2–20 \times 10^{-4}$ M). (On this time scale, reaction 3 would be essentially at equilibrium.) The rate expression found in these experiments is given by eq 4, with $k_{ox} = 32.9 \pm 0.7$ M^{-1} sec^{-1}.

$$-d[Co(III)]/dt = k_{ox}[V^{2+}][cis\text{-}Co(en)_2(N_3)_2^+] \qquad (4)$$

A number of kinetic experiments on the same reaction were carried out at substantially higher vanadium(II) concentrations (*ca.* 0.1 M)[8] using a stopped-flow apparatus[9] with spectrophotometric detection to follow the progress of the reaction. The reaction followed pseudo-first-order kinetics when studied at 5200 A, where any VN_3^{2+} present would make only a negligible contribution to the absorbance; the calculated rate constants for oxidation agreed with that found in the conventional studies at lower $[V^{2+}]$. The same solutions were studied also at 3500 A, an absorption maximum for VN_3^{2+}. At this wavelength the kinetic behavior was complex; the first-order rate plots were curved especially in the early stages of reaction. The spectral data in these runs were resolved into two components using known extinction coefficients assuming the kinetic data for the same solutions at 5200 A represented the true rate of oxidation–reduction.

Absorbance contributions of the stable reactants and products were quantitatively accounted for; an excess light absorption at 3500 A remained, and it was attributed to the presence of the VN_3^{2+} intermediate. The excess absorption intensity rose with time, passed through a maximum, and finally fell at still longer times. Figure 1 illustrates the formation and decay of VN_3^{2+} in a typical experiment.

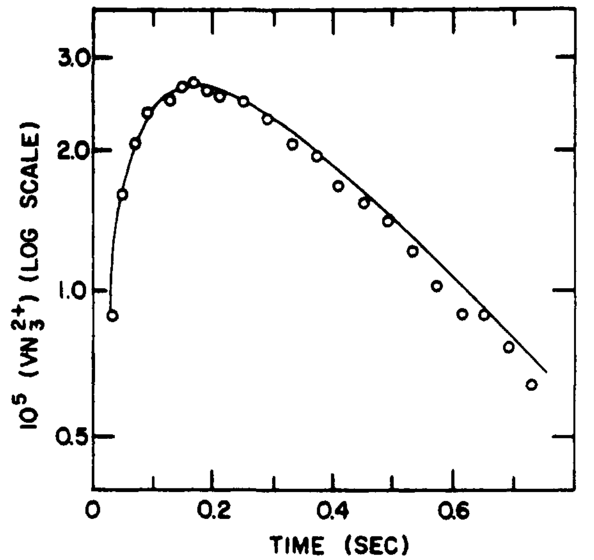

Figure 1. The formation and decay of the VN_3^{2+} intermediate seen at 3500 A in a typical experiment. The points are the observed concentrations obtained from the excess absorption intensity and the line is calculated from the known rate parameters.[11] Concentrations in this run are $[Co(III)]_0 = 1.5 \times 10^{-4}$ M, $[H^+] = 0.10$ M, $[V^{2+}] \cong 0.1$ M; $k_{ox}[V^{2+}] = 2.96$ sec^{-1}. The intermediate, presuming it is VN_3^{2+}, builds up to a maximum concentration of 2.7×10^{-5} M at 0.17 sec; calculated,[11] 2.74×10^{-5} M at 0.173 sec.

The inner-sphere reaction sequence (eq 5) allows one

$$cis\text{-}Co(en)_2(N_3)_2^+ \xrightarrow{k_{ox}[V^{+2}]} VN_3^{2+} \xrightarrow{k_{aq}} V^{3+} + N_3^- \qquad (5)$$

to calculate the presumed rate of formation and decay of VN_3^{2+} from known values of the rate parameters.[10,11] The agreement of calculated and observed values is generally quite satisfactory; the solid line in Figure 1 was calculated on this basis and it fits quite closely the observed absorbance changes. This quantitative agreement of the data with the inner-sphere model constitutes a *direct proof* for its operation in this instance.

Another source of the VN_3^{2+} intermediate must be considered: oxidation of an azidovanadium(II) complex (eq 6–8). This mechanism is eliminated as a

$$V^{2+} + HN_3 \rightleftharpoons VN_3^+ + H^+ \text{ (rapid ?)} \qquad (6)$$

$$VN_3^+ + Co(en)_2(N_3)_2^+ \longrightarrow VN_3^{2+} + Co^{II} + 2en + 2N_3^- \qquad (7)$$

$$VN_3^{2+} \longrightarrow V^{3+} + N_3^- \qquad (8)$$

possibility on the basis of the following arguments and observations. Since $[HN_3]$ increased manyfold during a run, to 3×10^{-5} M at equilibrium, $[VN_3^+]$ would increase, leading to a rate of cobalt(III) disappearance not following pseudo-first-order kinetics, in violation of the observations. A series of runs was also performed with added HN_3 at low concentration, $\sim 5 \times 10^{-4}$ M. These runs gave kinetic behavior at 3500 and 5200 A identical with experiments without added

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[7] Cobalt complexes containing azide ion generally react with reducing agents, including vanadium(II), relatively rapidly, and the dissociation rates of the monoazidometal(III) complexes are generally among the lowest for a particular metal ion. The *cis*-diazido complex chosen does, however, suffer from the disadvantage that a double-bridged reaction could possibly occur: R. Snellgrove and E. L. King, *J. Am. Chem. Soc.*, **84**, 4609 (1962); A. Haim, *ibid.*, **88**, 2324 (1966). In addition, the absorption of the cobalt(II) complex must not obscure that of VN_3^{2+}. The molar extinction coefficients at 3500 A of *cis*-$Co(en)_2(N_3)_2^+$ and VN_3^{2+} are 3.1×10^3 and 2.0×10^3 M^{-1} cm^{-1}, respectively.

[8] At $[V^{2+}] \cong 0.1$ M the first-order rate constant for production of VN_3^{2+} in inner-sphere reaction 2 with $k_{ox} = 33$ M^{-1} sec^{-1} would be $\cong 3.3$ sec^{-1}.

[9] D. W. Carlyle and J. H. Espenson, to be published.

[10] The kinetic and equilibrium properties of VN_3^{2+} have been studied: J. H. Espenson, unpublished experiments. The apparent first-order rate constant for aquation of VN_3^{2+} is 6.0 sec^{-1} at 25.0°, 0.10 M H^+, and unit ionic strength. Establishment of equilibrium in eq 3 is catalyzed slightly by V^{2-}, however, and at $[V^{2+}] = 0.1$ M the specific rate for aquation of VN_3^{2+} is 10.0 ± 0.7 sec^{-1} under these conditions.

[11] According to the reaction sequence in eq 5 the concentration of VN_3^{2+} follows the equation

$$[VN_3^{2+}] = [Co(III)_0]\{k_{ox}[V^{2+}]/(k_{aq} - k_{ox}[V^{2+}])\}\{e^{-k_{ox}[V^{2+}]t} - e^{-k_{aq}t}\}$$

The precise value of $k_{ox}[V^{2+}]$ is obtained from the experiment at 5200 A, and $k_{aq} = 10$ sec^{-1}.

HN_3, indicating that the sequence of reactions 6–8 is not an important path for VN_3^{2+} formation under these conditions.[12]

Finding direct evidence for inner-sphere reaction in the case of V^{2+} and *cis*-$Co(en)_2(N_3)_2^+$ should not be regarded as proof that V(II) reductions in general, or even other V(II)–Co(III) reactions, proceed by inner-sphere mechanisms. Halpern and co-workers[13] have shown that $Co(CN)_5^{3-}$ can act by both mechanisms and that the balance in that instance can be tipped in favor of one or the other pathway by seemingly minor changes.

V(II) and Cr(III) are isoelectronic; substitution reactions of $V(OH_2)_6^{2+}$ are expected to be slow relative to other divalent metal ions, as Cr(III) substitutions are relative to trivalent ions. A barrier to the inner-sphere reaction 2 is the replacement of H_2O by X in the primary coordination sphere of V(II). In the case of the relatively slow cobalt(III) reactions this does not seem likely to provide a barrier to an inner-sphere process, but faster reactions could be forced outer sphere.

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(12) At much higher [HN_3], >0.01 *M*, there is a noticeable effect of added HN_3. This may correspond to eq 6–8, or it may be a consequence of substances generated in the reduction of V(II) by HN_3 which is important at the higher concentrations.

(13) J. P. Candlin, J. Halpern, and S. Nakamura, *J. Am. Chem. Soc.*, **85**, 2517 (1963).

James H. Espenson
Department of Chemistry and Institute for Atomic Research
Iowa State University, Ames, Iowa 50010

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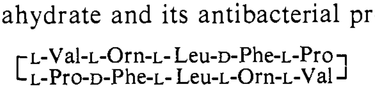
Cyclosemigramicidin S[1]

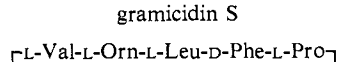
Sir:

Schwyzer and Sieber synthesized *cyclo*-[L-Val-L-Orn-(δ-Tos)-L-Leu-D-Phe-L-Pro-]$_2$, the ditosyl derivative of gramicidin S, by dimerization of H-Val-Orn(δ-Tos)-Leu-D-Phe-Pro-ONp in the presence of large amount of pyridine; their preparation showed no production of *cyclo*-[Val-Orn(δ-Tos)-Leu-D-Phe-Pro-], the monotosyl derivative of cyclosemigramicidin S.[2,3] We wish to report the synthesis of cyclosemigramicidin S monohydrochloride tetrahydrate and its antibacterial properties.



L-Val-L-Orn-L-Leu-D-Phe-L-Pro
L-Pro-D-Phe-L-Leu-L-Orn-L-Val

gramicidin S



L-Val-L-Orn-L-Leu-D-Phe-L-Pro

cyclosemigramicidin S

H-Leu-D-Phe-Pro-OEt·HCl (I), mp 225–228° dec, $[\alpha]^{18}\mathrm{D}$ −30.9° (*c* 0.5, AcOH) (*Anal.* Calcd for $C_{22}H_{33}O_4N_3\cdot HCl\cdot 0.25H_2O$: C, 59.44; H, 7.82; N, 9.46. Found: C, 59.47; H, 7.83; N; 9.57), was prepared in 93% yield by hydrogenation of Z-Leu-D-Phe-Pro-OEt.[4] Condensation of the azide derived from Z(OMe)-Val-Orn(δ-Z)-$NHNH_2$[5] with I gave Z(OMe)-Val-Orn(δ-Z)-Leu-D-Phe-Pro-OEt (II), 81%, mp 149–150°, $[\alpha]^{24}\mathrm{D}$ −26.8° (*c* 2, DMF). *Anal.* Calcd for $C_{49}H_{66}O_{11}N_6\cdot H_2O$: C, 63.07; H, 7.35; N, 9.01. Found: C, 63.04; H, 7.18; N, 9.29. II was saponified with alkali to give Z(OMe)-Val-Orn(δ-Z)-Leu-D-Phe-Pro-OH (III), 84%, mp 143–145°, $[\alpha]^{20}\mathrm{D}$ −18.2° (*c* 2, DMF). *Anal.* Calcd for $C_{47}H_{62}O_{11}N_6\cdot 1.5H_2O$: C, 61.75; H, 7.17; N, 9.20. Found: C, 61.85; H, 6.87; N, 9.42. Treatment of III with 5 equiv of di-*p*-nitrophenyl sulfite[6] gave amorphous acyl pentapeptide *p*-nitrophenyl ester (IV); the active ester content was estimated spectrophotometrically[7] to be 106%. The *p*-methoxybenzyloxycarbonyl group of IV was removed by the action of trifluoroacetic acid and the pentapeptide *p*-nitrophenyl ester trifluoroacetate (V) so obtained was treated with a large amount of pyridine at 60° for the cyclization reaction. The concentration of V in pyridine was 3×10^{-4} *M*. The residue obtained after cyclization was dissolved in aqueous methanol, and the solution was passed through columns of Dowex 50 (H^+ form) and Dowex 1 (OH^- form). It was observed that the effluent contains two compounds with the character of benzyloxycarbonyl-substituted cyclic peptide. The product less soluble in aqueous methanol was isolated by fractional crystallization (the mother liquor was set aside for the isolation of the more soluble product), and it was assigned as *cyclo*-[Val-Orn(δ-Z)-Leu-D-Phe-Pro-]$_2$ (VI), 12% from III, mp 250–252° dec, $[\alpha]^{20}\mathrm{D}$ −275° (*c* 0.3, AcOH). *Anal.* Calcd for $C_{76}H_{104}O_{14}N_{12}\cdot 2H_2O$: C, 63.13; H, 7.53; N, 11.62. Found: C, 62.98; H, 7.72; N, 11.46.[8] The molecular weight of VI was determined on a Hitachi Type 115 osmometer (solvent, methanol): calcd, 1446; found, 1420. Catalytic hydrogenation of VI in the presence of 2 equiv of hydrogen chloride in methanol yielded gramicidin S dihydrochloride octahydrate, 91%, mp 274–276° dec, $[\alpha]^{20}\mathrm{D}$ −269° (*c* 0.1, EtOH) (*Anal.* Calcd for $C_{60}H_{92}O_{10}N_{12}\cdot 2HCl\cdot 8H_2O$: C, 53.04; H, 8.16; N, 12.37. Found: C, 52.80; H, 8.03; N, 12.05), R_f 0.95[9] and 0.76.[10] The more soluble product was isolated as follows. The mother liquor was evaporated, and the residue was fractionated into two compounds with a column of Sephadex LH-20 using methanol as a developing solvent. Two peaks were observed on the chromatogram. The faster eluting fraction yielded VI, 8% from III, mp 250–252° dec. Total yield of VI was 20% from III. The slower elution fraction yielded the product more soluble in the pure state, assigned as *cyclo*-[Val-Orn(δ-Z)-Leu-D-Phe-Pro-] (VII),[11] 16% from III, dec pt above 240°, $[\alpha]^{20}\mathrm{D}$ −49.7° (*c* 0.1, AcOH). *Anal.* Calcd for $C_{38}H_{52}O_7N_6\cdot H_2O$: C, 63.13; H, 7.53; N, 11.62; mol wt, 723. Found: C, 62.83; H, 7.49; N, 11.23; mol wt, 710. Hydrogenation of VII yielded cyclosemigramicidin S monohydrochloride tetrahydrate, 88%, mp 223–225° dec, $[\alpha]^{20}\mathrm{D}$ −76.1° (*c* 0.06,

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(1) The nomenclature of cyclosemigramicidin S has been introduced by E. Schröder and K. Lübke in their monograph (*Peptides*, **2**, 429 (1966)) for *cyclo*-(L-Val-L-Orn-L-Leu-D-Phe-L-Pro-).

(2) R. Schwyzer and P. Sieber, *Helv. Chim. Acta*, **41**, 2186 (1958).

(3) The abbreviations followed are from *Biochemistry*, **5**, 2485 (1966); Z-, benzyloxycarbonyl; Z(OMe)-, *p*-methoxybenzyloxycarbonyl; Mz-, *p*-methoxyphenylazobenzyloxycarbonyl; -ONp, *p*-nitrophenoxy; Dbu, L-α,γ-diaminobutyric acid residue.

(4) M. Ohno, *et al.*, *Bull. Chem. Soc. Japan*, **39**, 1738 (1966); *J. Am. Chem. Soc.*, **88**, 376 (1966).

(5) T. Kato, M. Kondo, M. Ohno, and N. Izumiya, *Bull. Chem. Soc. Japan*, **38**, 1202 (1965).

(6) R. Schwyzer and P. Sieber, *Helv. Chim. Acta*, **43**, 1760 (1960).

(7) R. Schwyzer and P. Sieber, *ibid.*, **41**, 1582 (1958).

(8) The same product was obtained by benzyloxycarbonylation of the native gramicidin S, 80%, mp 250–251° dec, $[\alpha]^{20}\mathrm{D}$ −273° (*c* 0.3, AcOH).

(9) The R_f on paper chromatography refers to the system 1-butanol–acetic acid–pyridine–water (4:1:1:2, v/v).

(10) The R_f on thin layer chromatography with Merck silica gel refers to the same solvent system described.[9]

(11) It would be of interest to note that the solubility of *cyclo*-[Val-Orn(δ-Z)-Leu-D-Phe-Sar- or -Gly-] in any of the solvents tested is smaller than that of *cyclo*-[Val-Orn(δ-Z)-Leu-D-Phe-Sar- or -Gly-]$_2$.