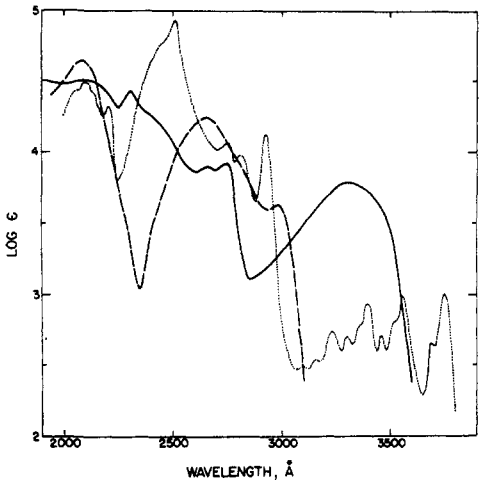

Fig. 1.—Ultraviolet spectra: ———, Ia; . . . . . , phenanthrene; – – – –, 9,10-dihydrophenanthrene.

examination of ultraviolet absorption spectra, because the spectra of aromatic compounds with first-row heteroatoms substituted for carbon are similar to those of the parent hydrocarbons.[1,6] For example, the ultraviolet spectrum of Ib is much like that of phenanthrene.[7] The ultraviolet spectrum of Ia in isooctane shows maxima at (Å. (ϵ)): 3315 (6150), 2745 (8400), 2660 (7920), 2310 (26,400), 2110 (34,000), and 1930 (31,600), and is shown in Fig. 1 with the spectra of phenanthrene and 9,10-dihydrophenanthrene for comparison. The spectrum of Ia bears considerable resemblance to that of phenanthrene, suggesting that only one silicon d-orbital is used, and thus that there is aromatic character in the silicon-containing ring.

2-Lithiobiphenyl (from 2-bromobiphenyl and *n*-butyllithium), when added to excess dimethyldichlorosilane, gave $R(CH_3)_2SiCl$ (R = 2-biphenylyl) which was purified by distillation and refluxed with excess NaN_3 in toluene.[8] The resulting azide, $R(CH_3)_2SiN_3$, was purified by distillation: b.p. 152° (6.5 mm.), $n^{25}D$ 1.5745. *Anal.* Calcd. for $C_{14}H_{15}SiN_3$: C, 66.40; H, 5.93; Si, 11.07; N, 16.60. Found: C, 66.89; H, 6.21; Si, 11.94; N, 14.86; total, 99.80. Pure $R(CH_3)_2SiN_3$ was irradiated with a low-pressure mercury arc, whereupon nitrogen gas was eliminated and ring closure took place. The solid product was separated, sublimed, and recrystallized from heptane to give Ia as large colorless cubes, m.p. 143°, in 35% yield from the azide. *Anal.* Calcd. for $C_{14}H_{15}SiN$: C, 74.60; H, 6.65; Si, 12.42; N, 6.22. Found: C, 74.11; H, 6.89; Si, 12.81; N, 6.50; total, 100.31. The infrared spectrum in benzene shows strong peaks at (cm.$^{-1}$) 3400 (N–H), 1460 (Si–Ph), 1330 (N–Ph), 920 (Si–N), and 1250 (Si–CH_3), together with other identifying bands.

The reactivity of Ia toward nucleophilic reagents is expected to be quite high (hydrolysis in humid air is rapid) because of the availability of four other d-orbitals, in contrast to the behavior of Ib, which has reduced reactivity because the only acceptor orbital is (partially) filled.

(6) L. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 24.

(7) M. J. S. Dewar, V. P. Kubba, and R. Pettit, *J. Chem. Soc.*, 3073 (1958).

(8) J. S. Thayer and R. West, *Inorg. Chem.*, **3**, 406 (1964).

Insertion of Si and other group IV elements into phenanthrene and other aromatic systems is under continuing investigation.[8a]

(8a) NOTE ADDED IN PROOF.—While this work was in press, the synthesis of a heteroaromatic aluminum compound was reported by Eisch and Healy, *J. Am. Chem. Soc.*, **86**, 4221 (1964).

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Cyclo-(L-valyl-L-ornithyl-L-leucyl-D-phenylalalanylglycyl)$_2$, an Active Analog of Gramicidin S

Sir:

Certain of the peptide antibiotics,[1] such as gramicidin S, cyclo-(L-valyl-L-ornithyl-L-leucyl-D-phenylalanyl-L-prolyl)$_2$, possess several features in common. These include a cyclic structure, D-amino acid residues, and basic character due to the presence of diamino acid residues. The efficacy of a cyclic structure for antibacterial activity is indicated by the finding that the activity of a synthetic open-chain decapeptide, with the same sequence of amino acid residues as are found in gramicidin S, is decreased markedly from that of gramicidin S.[2] We synthesized some 12 dipeptide anhydrides such as L-ornithyl-D-phenylalanine anhydride, because a dipeptide anhydride is the simplest cyclic peptide which has the structural features mentioned above. These compounds, however, showed no antibacterial activities.[3] Furthermore, we found that a synthetic cyclic hexapeptide, cyclo-L-valyl-L-ornithyl-L-leucyl-D-phenylalanyl-L-prolylglycyl, showed no activity,[4] and a decapeptide, cyclo-(glycyl-L-ornithyl-L-leucyl-D-phenylalanylglycyl)$_2$, showed very weak activity.[5] It has also been reported that certain cyclic decapeptides such as homogramicidin S exhibited antibacterial activities.[6]

We wish to report the synthesis of a highly active analog of a gramicidin S in which a glycine residue has replaced the proline residue. This analog, cyclo-(L-valyl-L-ornithyl-L-leucyl-D-phenylalanylglycyl)$_2$, has been synthesized as follows. Carbobenzoxy-D-phenylalanylglycine ethyl ester (I),[7] m.p. 109–110°, $[\alpha]^{25}D$ +19.5° (*c* 2, methanol), was prepared by coupling carbobenzoxy-D-phenylalanine with glycine ethyl ester by the dicyclohexylcarbodiimide procedure. I was converted to oily D-phenylalanylglycine ethyl ester hydrochloride (II) by catalytic hydrogenation in a yield of 97%. Reaction of carbobenzoxy-L-leucine with II by the dicyclohexylcarbodiimide method gave carbobenzoxy-L-leucyl-D-phenylalanylglycine ethyl ester, yield 66%, m.p. 113–115°, $[\alpha]^{25}D$ +13° (*c* 2, methanol) (*Anal.* Calcd. for $C_{27}H_{35}O_6N_3$: C, 65.17;

(1) R. O. Studer and K. Vogler, *Helv. Chim. Acta*, **45**, 394 (1962).

(2) B. F. Erlanger and L. Goode, *Nature*, **174**, 80 (1954); *Science*, **131**, 669 (1960).

(3) N. Izumiya and M. Winitz, presented in part at the 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April, 1960; N. Izumiya, T. Kato, Y. Fujita, M. Ohno, and M. Kondo, *Bull. Chem. Soc. Japan*, in press.

(4) T. Kato, M. Kondo, M. Ohno, and N. Izumiya, *ibid.*, in press.

(5) T. Kato, M. Ohno, M. Kondo, Y. Fujita, and N. Izumiya, 6th International Congress of Biochemistry, New York, N. Y., 1964 p. 159.

(6) (a) R. Schwyzer and P. Sieber, *Helv. Chim. Acta*, **41**, 1582 (1958); (b) German Patent; *Chem. Abstr.*, **57**, 949 (1962).

(7) O. K. Behrens, D. G. Doherty, and M. Bergmann, *J. Biol. Chem.*, **136**, 61 (1940).

H, 7.09; N, 8.45. Found: C, 64.75; H, 7.07; N, 8.33), which was hydrogenated to produce oily L-leucyl-D-phenylalanylglycine ethyl ester hydrochloride (III) in a yield of 100%. Oily *p*-methoxybenzyloxycarbonyl-L-valine (IV) was prepared from *p*-methoxybenzyloxycarbonyl azide[8] and L-valine, yield 72%. *p*-Methoxybenzyloxycarbonyl-L-valyl-δ-carbobenzoxy-L-ornithine ethyl ester, yield 66%, m.p. 140–144°, $[\alpha]^{25}D$ −7.8° (*c* 1, acetic acid) (*Anal.* Calcd. for $C_{29}H_{39}O_8N_3$: C, 62.46; H, 7.05; N, 7.54. Found: C, 62.22; H, 6.96; N, 7.61), which was obtained by condensation of IV with δ-carbobenzoxy-L-ornithine ethyl ester *p*-toluenesulfonate[3,9] by the mixed anhydride method, was treated with hydrazine to afford *p*-methoxybenzyloxycarbonyl-L-valyl-δ-carbobenzoxy-L-ornithine hydrazide (V), yield 91%, m.p. 211–213°, $[\alpha]^{20}D$ −4.2° (*c* 1, dimethylformamide) (*Anal.* Calcd. for $C_{27}H_{37}O_7N_5$: C, 59.65; H, 6.86; N, 12.88. Found: C, 59.57; H, 6.87; N, 12.77). V was converted into *p*-methoxybenzyloxycarbonyl-L-valyl-δ-carbobenzoxy-L-ornithine azide (VI). Condensation of VI with III gave *p*-methoxybenzyloxycarbonyl-L-valyl-δ-carbobenzoxy-L-ornithyl-L-leucyl-D-phenylalanylglycine ethyl ester (VII), yield 80%, m.p. 206–208°, $[\alpha]^{25}D$ −23.5° (*c* 1, acetic acid) (*Anal.* Calcd. for $C_{46}H_{62}O_{11}N_6$: C, 63.14; H, 7.14; N, 9.61. Found: C, 63.02; H, 7.15; N, 9.94), R_f[10] 0.87. A portion of VII was saponified with alkali to *p*-methoxybenzyloxycarbonyl-L-valyl-δ-carbobenzoxy-L-ornithyl-L-leucyl-D-phenylalanylglycine (VIII), yield 84%, m.p. 214–215°, $[\alpha]^{25}D$ −21° (*c* 1, acetic acid) (*Anal.* Calcd. for $C_{44}H_{58}O_{11}N_6$: C, 62.39; H, 6.90; N, 9.92. Found: C, 61.95; H, 6.88; N, 10.00), R_f[10] 0.82. Removal of the *p*-methoxybenzyloxycarbonyl group from VIII by an exposure to trifluoroacetic acid[8] and subsequent neutralization with triethylamine yielded L-valyl-δ-carbobenzoxy-L-ornithyl-L-leucyl-D-phenylalanylglycine (IX), yield 76%, m.p. 191–192°, $[\alpha]^{25}D$ −4.2° (*c* 1, acetic acid) (*Anal.* Calcd. for $C_{35}H_{50}O_8N_6 \cdot 0.5H_2O$: C, 60.76; H, 7.43; N, 12.15. Found: C, 60.96; H, 7.37; N, 12.05), R_f[10] 0.85. Another portion of VII was treated with hydrazine to give *p*-methoxybenzyloxycarbonyl-L-valyl-δ-carbobenzoxy-L-ornithyl-L-leucyl-D-phenylalanylglycine hydrazide (X), yield 87%, m.p. 217–219°, $[\alpha]^{25}D$ −20° (*c* 1, acetic acid) (*Anal.* Calcd. for $C_{44}H_{60}O_{10}N_8$: C, 61.38; H, 7.02; N, 13.02. Found: C, 60.84; H, 7.15; N, 12.89), R_f[10] 0.91 (after catalytic hydrogenation R_f[10] 0.76), which was converted to *p*-methoxybenzyloxycarbonyl-L-valyl-δ-carbobenzoxy-L-ornithyl-L-leucyl-D-phenylalanylglycine azide (XI). Reaction of XI with IX gave *p*-methoxybenzyloxycarbonyl-L-valyl-δ-carbobenzoxy-L-ornithyl-L-leucyl-D-phenylalanylglycyl-L-valyl-δ-carbobenzoxy-L-ornithyl-L-leucyl-D-phenylalanylglycine (XII), yield 75%, m.p. 253–257°, $[\alpha]^{25}D$ −48° (*c* 0.5, acetic acid) (*Anal.* Calcd. for $C_{79}H_{106}O_{18}N_{12} \cdot H_2O$: C, 62.02; H, 7.12; N, 10.99. Found: C, 61.77; H, 7.18; N, 10.94), after catalytic hydrogenation R_f[10] 0.60. Treatment of XII with 10 equiv. of di-*p*-nitrophenyl sulfite[11] gave amorphous *p*-methoxybenzyloxycarbonyl-L-valyl-δ-carbobenzoxy-L-ornithyl-L-leucyl-D-phenylalanylglycyl-L-valyl-δ-carbobenzoxy-L-ornithyl-L-leucyl-D-phenylalanylglycine *p*-nitrophenyl ester (XIII); the active ester content was estimated spectrophotometrically to be 71%. The *p*-methoxybenzyloxycarbonyl group of XIII was removed by the action of trifluoroacetic acid and the decapeptide *p*-nitrophenyl ester trifluoroacetate obtained was treated with a large amount of hot pyridine.[11] Purification of the aqueous methanolic solution of the crude product through columns of Dowex 50 (H^+ form) and Dowex 1 (OH^- form) gave cyclo-(L-valyl-δ-carbobenzoxy-L-ornithyl-L-leucyl-D-phenylalanylglycyl)$_2$ (XIV), yield 55%, m.p. 248–250°, $[\alpha]^{25}D$ −132° (*c* 1, acetic acid) (*Anal.* Calcd. for $C_{70}H_{96}O_{14}N_{12} \cdot 3H_2O$: C, 60.76; H, 7.43; N, 12.15. Found: C, 60.62; H, 7.40; N, 12.25), R_f[10] 0.93. The molecular weight of a dried sample of XIV was determined by a Model 301 A osmometer, Mechrolab Inc. (solvent ethanol)[12] (Calcd.: 1330. Found: 1230). XIV was also obtained in a yield of 14% by a dimerization reaction[13] of L-valyl-δ-carbobenzoxy-L-ornithyl-L-leucyl-D-phenylalanylglycine *p*-nitrophenyl ester. Removal of the carbobenzoxy group from XIV by catalytic hydrogenation in the presence of equivalent hydrogen chloride in methanol provided cyclo-(L-valyl-L-ornithyl-L-leucyl-D-phenylalanylglycyl)$_2$ dihydrochloride (XV), yield 92%, m.p. 227–230°, $[\alpha]^{25}D$ −194° (*c* 0.5, ethanol), −143° (*c* 0.5, 50% ethanol) (*Anal.* Calcd. for $C_{54}H_{86}O_{10}N_{12}Cl_2 \cdot 6H_2O$: C, 52.20; H, 7.95; N, 13.53. Found: C, 52.06; H, 7.98; N, 13.28). Two moles of water of crystallization was lost when XV was left in a desiccator with calcium chloride; six moles was lost on drying at 120° under vacuum for 2 hr. Homogeneity of XV was established by chromatography (R_f 0.77[10] and 0.90[14]). Quantitative amino acid determination gave the following molar ratio: val, 1.0; orn, 0.9; leu, 1.0; phe, 1.0; gly, 1.0.[15] XV was treated with dinitrofluorobenzene in the usual manner. The hydrolysate of dinitrophenylated XV gave only one DNP-amino acid, δ-DNP-ornithine (R_f[14] 0.63).

XV was found to be much more active than gramicidin S against *B. subtilis* in a synthetic medium. The results of the inhibitory activity on the microorganisms are shown in Table I.[16]

The present study shows that the replacement of the proline residue by glycine residues in the sequence of gramicidin S does not reduce the activity, demonstrating that not all the structural features of the natural peptide are necessary for the full activity: *e.g.*, the side chain of proline is not required. It should be noted that a bradykinin analog wherein the serine residue is replaced by a glycine residue exhibits nearly

(8) F. Weygand and K. Hunger, *Chem. Ber.*, **95**, 1 (1962).

(9) T. Kato, S. Makisumi, M. Ohno, and N. Izumiya, *J. Chem. Soc. Japan*, **83**, 1151 (1962).

(10) The R_f of the thin layer chromatography with Merck silica gel G refers to the system 1-butanol–acetic acid–pyridine–water (4:1:1:2, v./v.). Compounds possessing a free amino group were detected by spraying with ninhydrin and those with blocked amino groups by spraying with 47% hydrobromic acid, followed by ninhydrin.

(11) R. Schwyzer and P. Sieber, *Helv. Chim. Acta*, **40**, 624 (1957).

(12) We are greatly indebted to Dr. W. C. Alford, National Institutes of Health, for the molecular weight determination.

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

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

(15) We are greatly indebted to Dr. E. Gross, National Institutes of Health, for the amino acid analyses.

(16) We are greatly indebted to Dr. M. Shibata, Research Laboratories, Takeda Chemical Industries, Ltd., Japan, for the biological assays.

TABLE I

	Amt. compd. nec. for complete inhibition of growth, μg./ml.			
	Stephenson–Whetham's synthetic medium (modified)		—Bouillon agar medium—	
	E. coli[a]	*B. subtilis*[b]	*E. coli*[a]	*B. subtilis*[b]
Gramicidin S sulfate[c]	>100	10	>100	10
XV	>100	1	>100	20

[a] *Escherichia coli* IFO 3044. [b] *Bacillus subtilis* PCI 219. [c] A product of Astra Co., Worcester, Mass. This contains 8 moles of water of crystallization.

equal activity to that of the natural bradykinin.[17]

(17) M. Bodanszky, J. T. Sheehan, M. A. Ondetti, and S. Lande, *J. Am. Chem. Soc.*, **85**, 991 (1963).

On the other hand, it appears that the valine residues in gramicidin S are of importance for the activity because the cyclo-(glycyl-L-ornithyl-L-leucyl-D-phenylalanylglycyl)$_2$ showed very weak activity.[5] To clarify this point, a synthesis of cyclo-(glycyl-L-ornithyl-L-leucyl-D-phenylalanyl-L-prolyl)$_2$ will be the subject of a subsequent publication.

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BOOK REVIEWS

Vapor Pressure of the Chemical Elements. By A. N. NESMEYANOV, Director, Institute of Elemento-Organic Compounds, U. S. S. R. Academy of Sciences, Moscow. Edited by ROBERT GARY, National Bureau of Standards, Washington, D. C. American Elsevier Publishing Co., Inc., 52 Vanderbilt Ave., New York 17, N. Y. 1963. 462 pp. 17 × 25 cm. Price, $17.50.

An incredible and inexcusable mistake has been made by the editor and the publisher: the author of the book has been misidentified! The man deserving the credit is Andrey (abbreviated An.) N. Nesmeyanov, not his brother Aleksandr N. Nesmeyanov, the organic chemist and former president of the U. S. S. R. Academy of Sciences. In two lines on the title page that do not appear in the Russian original, the institutional affiliation of the wrong man is listed; and on the printed dust jacket, the birth date and achievements of the organic chemist are advertised. The author is at Moscow State University where he has engaged in many vaporization studies and radiochemical investigations. He is therefore able to write from practical experience, and the book is far more authoritative than if it had been written by his brother.

The book itself can be divided into six parts: (1) a large Chapter I entitled "Methods for Measuring Vapor Pressure"; (2) Chapters II–IX containing data and discussions on the vapor pressures of the elements arranged according to the periodic table groups; (3) a short, misnamed Chapter X entitled "Theoretical Vapor Pressures and Heats of Sublimation of Elements"; (4) 695 references; (5) 39 pages of reference tables; and (6) a subject index. A serious shortcoming is the lack of an author index.

In the first chapter of 121 pages, the author describes the various experimental methods of vapor pressure measurement. He is to be commended for the excellent and comprehensive coverage of the literature, with some very old and some very new methods receiving attention. The Russian literature is emphasized. Many good drawings of apparatus are given, and several of the author's own experimental apparatuses are described. The great desirability of the use of radioactive tracers in several different types of measurements is very appropriately emphasized. The isotopic exchange method of vapor pressure measurement, which was developed by the author but which has not been extensively used as yet, is discussed at length. Anyone wishing a summary of vapor pressure methods or ideas for attacking particular vapor pressure studies should find this chapter rewarding.

The most serious shortcoming in the first chapter is the treatment of subjects that are not yet fully understood. Twice on page 52 and on pages 104 and 116, there are declarative statements concerning vaporization coefficients and orifice size, residual gas effect, surface condition, and absolute pressure measurements by mass spectrometry which are directly contradictory to sentences in preceding paragraphs. It would have been far better to put the ideas in adjacent sentences and simply to state that the problems are not resolved.

The Knudsen method is properly evaluated as "the most reliable one for measuring low vapor pressures"; but the evaluation of the so-called "differential" Knudsen method is too harsh. The introduction to the Langmuir method contains some misleading statements, and the mass spectrometric technique is probably underestimated on page 117. The flow method is capable of great precision, contrary to the statement on page 35, and the treatment of the diffusion correction at low flow rates in this technique is inadequate. Specific errors occur on page 73 in eq. 63 which does not contain K and on page 68 where it is stated that log $I\sqrt{T}$ (rather than log IT) plotted against $1/T$ is parallel to log P *vs.* $1/T$.

The table of contents concerning Chapter I is confusing. For example, mass spectrometry is discussed partially in a sub-subsection entitled "Determination of Vapor Pressure from the Density of the Molecular Beam" in a subsection entitled the "Knudsen Effusion Method," and also in a sub-subsection entitled "Vapor Composition and Methods for Measuring It" in an unlettered subsection entitled "Influence of the Langmuir Coefficient and the Molecular Composition of the Vapor on the Results of Vapor Pressure Measurements." This last section is worthwhile reading, but little that is definitive appears.

In the following chapters on the vapor pressures of the elements, the author has considered practically all the published work except for H, N, O, and the noble gases. Numerous tables of published measurements are given and several vapor pressure graphs are included. One hopes that in a book of this kind he can find a critical and definitive discussion of all the work, ultimately a choice of a value for the property in question, and an estimate of the reliability of the chosen value. In this regard the book is a disappointment. Nowhere is the reliability of the chosen value given, and the discussions are not sufficiently clear, definite, and critical to command confidence in the value. Controversy exists at the present time concerning the vapor pressures of boron and uranium, and the book contributes little to the solution of either problem. Entirely properly and at numerous places, the author notes the desirability of additional work.

The reference tables near the end of the book will probably be used most. In the first a most useful set of references, which were considered in the preparation of the book, is arranged according to the elements.

The chosen vapor pressure data are presented in five different ways in Tables II–XXVI. The methods that were used for the evaluation of published data and for the preparation of the tables are almost hidden on pages 393–397, but these should certainly be read by one wishing to use the tables.

Table II contains computed coefficients for a four-term vapor pressure equation, of use perhaps to engineers. Table III contains a summary of gaseous species, melting point, heat of fusion, the computed boiling point, the chosen $\Delta H°_{298}$, and the values of this last quantity from Honig[1] and Stull and Sinke.[2] Appreciable differences exist for Au, B, Al, Y, Ce, Gd, Lu, Si, Hf, As, Bi, Pa, Fe, Co, Ni, and Os. The usefulness of this table will

(1) R. E. Honig, *RCA Rev.*, **18**, 195 (1957).

(2) D. R. Stull and G. C. Sinke, "Thermodynamic Properties of the Elements," Advances in Chemistry Series, No. 18, American Chemical Society, Washington, D. C., 1956.