It should be noted that the resonance frequencies are in the same order as those of the corresponding monosubstituted pyridines and differ by about the same quantity. All this would agree with Bray and coworkers' opinion[5-7] that the decrease of the frequency of a chlorine attached to a carbon atom which is adjacent in the ring to a nitrogen atom is due to the increase of the double-bond character of the C–Cl bond.

While writing this paper, we had been informed that a communication concerning the same study was to be given by E. A. C. Lucken and C. Mazeline of the Cyanamid European Research Institute, Geneve, Switzerland, at the XIIIth Colloque Ampère, to be held in Leuven, Belgium, on September 1–5, 1964. We report their results for comparison in Table III.[8]

Table III

	Dichloropyridine	
	3,5-	2,6-
Frequency, Mc.p.s.	34.79	33.86
η	0.07 ± 0.02	0.09 ± 0.02
Angle between the two C–Cl bonds	122° 30′ ± 30′	113° ± 30′

Acknowledgment. We are indebted to Dr. Margherita Landucci for help in preparing the single crystals, to Professor Eolo Scrocco for encouragement, and to the C.N.R. for sponsoring this research.

(5) P. J. Bray, *et al.*, *J. Chem. Phys.*, **25**, 1286 (1956).
(6) P. J. Bray, *et al.*, *ibid.*, **28**, 99 (1958).
(7) H. O. Hooper and P. J. Bray, *ibid.*, **30**, 957 (1959).
(8) On this subject we have contacted Drs. Lucken and Mazeline. Considering the respective techniques, we all feel that there is not a real disagreement between the two sets of results. On the other hand, on the basis of our experience, it seems to us that the error indicated in Table I is a fair estimate of the standard error in the present case.

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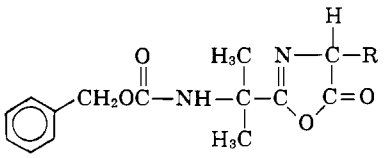
Optically Active Peptide Oxazolones. Preliminary Racemization Studies under Peptide-Coupling Conditions

Sir:

There is ample evidence in the literature to indicate the importance of oxazolone intermediates in racemization processes during peptide synthesis.[1,2] In our laboratory we isolated and studied the racemization of the amino acid oxazolone, 2-phenyl-L-4-benzyl-5-oxazolone.[3]

We now wish to report the isolation of the first optically active, crystalline peptide oxazolones, namely, 2-(1′-benzyloxycarbonylamino-1′-methyl)ethyl-L-4-benzyloxazolone (I) and 2-(1′-benzyloxycarbonylamino-1′-methyl)ethyl-L-4-methyloxazolone (II).

We undertook to prepare compounds I and II after noting the work of Kenner and his associates[4] who



I, R = CH_2–C$_6$H$_5$

II, R = CH_3

prepared the crystalline optically inactive oxazolone 2-(1′-benzyloxycarbonylamino-1′-methyl)ethyl-4,4-dimethyloxazolone. They synthesized this oxazolone by heating the peptide acid Z-Aib-Aib-OH[5] in acetic anhydride at 110–120° for 15 min.

In order to prepare the dipeptide acids from which compounds I and II were derived we employed the technique of Mazur,[6] who observed the acceleration of the *p*-nitrophenyl ester coupling reaction by imidazole. The amino acid derivative Z-Aib-ONp was allowed to react separately with the ester hydrochlorides HCl-Phe-OCH_3 and HCl-Ala-OCH_3 in the presence of NEt_3 and excess imidazole in DMF solvent. Excellent yields of the optically pure dipeptide esters were obtained. These esters were converted to the corresponding free acids under careful, dilute acidic hydrolysis conditions. Physical data on the key compounds are recorded in Table I.

Table I

Compound[a]	M.p., °C.	$[\alpha]^{25}D$, deg. (*c*, dioxane)
Z-Aib-L-Phe-OCH_3	94.2–94.8	+27.2 (2.2)
Z-Aib-L-Phe-OH	60–65	+34.2 (2.5)
Z-Aib-L-Ala-OCH_3	68.6–69.6	−5.5 (4.5)
Z-Aib-L-Ala-OH	139–140	+5.9 (4.5)
Oxazolone from Z-Aib-L-Phe-OH	96.0–97.4	−131.3 (2.2)
Oxazolone from Z-Aib-Ala-OH	115–119	−52.1 (1.5)

[a] The microchemical analyses of C, H and N for compounds listed fall within accepted limits.

The optically active oxazolone I can be obtained from the free acid after 8–10 hr. room-temperature treatment with a 2:1 dioxane–acetic anhydride solution using a concentration of approximately 60 mg./ml. of peptide. The solvent is removed by careful distillation when the negative rotation of the solution reaches a maximum value.

The oxazolone I, which can be obtained optically pure by fractional crystallization, has m.p. 96.0–97.4°; $[\alpha]^{25}D$ −131.3° (*c* 2.2, dioxane) (*Anal.* Calcd. for $C_{21}H_{22}N_2O_4$: C, 68.85; H, 6.01; N, 7.65. Found: C, 68.85; H, 6.22; N, 7.72); ν_{max} 3280, 1825, 1717, 1662, 1529, 1380, 1262, 1099, 1080, 1040, and 698 cm.$^{-1}$. All are intense peaks. The peak at 1825 cm.$^{-1}$ is characteristic for the oxazolone carbonyl group.

Some difficulty was encountered in obtaining the optically active compound II. Using the dioxane–acetic anhydride treatment for 4 hr. at room temperature an optically impure oxazolone was obtained, m.p. 109–115°; $[\alpha]^{25}D$ −43.3° (*c* 1.0, dioxane).

(1) M. W. Williams and G. T. Young, *J. Chem. Soc.*, 3701 (1964).
(2) M. Goodman and K. C. Stueben, *J. Org. Chem.*, **27**, 3409 (1962).
(3) M. Goodman and L. Levine, *J. Am. Chem. Soc.*, **86**, 2918 (1964).
(4) M. T. Leplawy, D. S. Jones, G. W. Kenner, and R. C. Sheppard, *Tetrahedron*, 11, 39 (1960).
(5) The residue Aib refers to the α-aminoisobutyryl residue.
(6) R. H. Mazur, *J. Org. Chem.*, **28**, 2498 (1963).

Table II. Rate Constants for the Racemization of Oxazolone I

Reagent causing racemization	Concn., M	$k_1 \times 10^{-2}$ min.$^{-1}$	k_2, l. mole^{-1} min.$^{-1}$	$t_{1/2}$, min.
Pyridine	3.74	1.837 ± 0.043	0.012	2711
	4.30	2.480 ± 0.015		
	4.87	3.175 ± 0.014		
DL-Phe-OCH_3	6.15×10^{-2}	4.438 ± 0.070	0.75	43.8
	9.23×10^{-2}	6.992 ± 0.077		
	12.3×10^{-2}	8.978 ± 0.066		
p-Nitrophenylate ion	2.789×10^{-4}	1.410 ± 0.022	68.42	0.48
	5.579×10^{-4}	3.255 ± 0.012		
	8.368×10^{-4}	5.237 ± 0.031		

Table III. Rate Constants for Ring Opening of Oxazolone I

Reagent causing ring opening	Concn., M	$k_1 \times 10^{-2}$ min.$^{-1}$	k_2, l. mole^{-1} min.$^{-1}$	$t_{1/2}$, min.
DL-Phe-OCH_3	2.132×10^{-1}	1.443 ± 0.022	0.065	505
	3.780×10^{-1}	2.632 ± 0.044		
	7.590×10^{-1}	4.803 ± 0.072		
p-Nitrophenylate ion	1.16×10^{-2}	1.984 ± 0.040	1.60	20.5
	1.74×10^{-2}	3.101 ± 0.055		
	2.32×10^{-2}	4.155 ± 0.086		

We prepared a more optically pure oxazolone using dicyclohexylcarbodiimide in ether to ring close the dipeptide acid; m.p. 115–119°; $[\alpha]^{25}D$ −52.1° (*c* 1.5, dioxane) (*Anal.* Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.20; N, 9.31. Found: C, 62.58; H, 6.43; N, 9.60); ν_{max} 3260, 1823 (characteristic for oxazolone carbonyl group), 1715, 1662, 1540, 1308, 1262, 1112, 1079, and 1008 cm.$^{-1}$. All are intense peaks. Fractional crystallization of the optically active oxazolone II is difficult because it appears to have only a slightly lower melting point than the racemic compound.

Kinetic Studies. The rates of racemization of oxazolone I using certain nucleophiles in dioxane have already been observed. These nucleophiles were, in order of decreasing racemization rates: *p*-nitrophenylate ion, DL-phenylalanine methyl ester (DL-Phe-OCH_3), and pyridine. Second-order rate constants were calculated from three pseudo-first-order rate constants for each nucleophile. Ring-opening reactions were studied by following the disappearance of the intense oxazolone peak at 1825 cm.$^{-1}$. The same concentration of oxazolone, namely, 3.045×10^{-2} *M*, was used in both the racemization and ring-opening studies.

Our kinetic data support the concept that under peptide-coupling conditions a small steady-state concentration of oxazolone can form which subsequently racemizes much faster than it can ring open. Racemization depends on the concentration and basicity of the nucleophiles present in the reaction mixture. From the data in Tables II and III it can readily be shown that *p*-nitrophenylate ion can racemize the oxazolone 40 times faster than it can react with it to give ring-opened product. A weaker nucleophile such as DL-Phe-OCH_3 causes racemization to occur 11 times faster than ring opening.

In the course of our efforts to synthesize these oxazolones we uncovered some interesting chemistry in connection with the coupling of hindered peptides. We intend to publish a detailed account of these reactions together with complete results from kinetic studies on the racemization of peptide oxazolones in the near future.

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Book Reviews

Energetics of Propellant Chemistry. By BERNARD SIEGEL, Head, High Temperature Chemistry Section, and LEROY SCHIELER, Head, Chemical Propulsion Dept., Aerospace Corporation, Los Angeles, Calif. John Wiley and Sons, Inc., 605 Third Ave., New York, N. Y. 1964. xiii + 240 pp. 15.5 × 23.5 cm. $10.00.

"The Energetics of Propellant Chemistry" is stated by the authors to be an introduction to propellant chemistry for chemists or advanced chemistry students. This is an appropriate description of the level of difficulty of the contents. References throughout the book to "the student" indicate that the author had use as a textbook in mind. For this purpose the instructor would be forced to provide his own problem assignments as there are no exercises given. However, there are in the appendices and in Chapter 5 fairly extensive tables of data suitable for calculating specific impulse and rocket engine performance, with suggestions for using them.

The function of a propellant is to power a rocket. This function is in the background of the discussion of particular substances or classes of substances throughout the book, and the discussion of every topic turns ultimately to its relationship to specific impulse or other rocket performance parameter. Nevertheless the book is not primarily a propellant engineer's textbook or handbook. It is primarily a book of physical chemistry limited in scope to the gross measurable properties (thermodynamics) and the theoretical molecular interpretation of these properties (principally in terms of binding energies) of a selected group of elements of low atomic weight and their compounds. A background equivalent at least to a good course in physical chemistry will be necessary for the reader to follow the arguments readily.

The main body of the book is a detailed analysis of binding energies and other molecular properties that lead to desirable propellants. Beginning with Chapter 2, the authors deal with energies of formation of combustion products, the energetics of working fluid gases, and the binding energies of fuels and oxidizers, to each of which a chapter is devoted. The final chapter of text is a discussion of real propellant systems. The customary limitation to elements of low atomic weight is strictly adhered to. All the reactive elements up to and including potassium are considered. In the discussion of products, the major emphasis is on oxides, fluorides, and hydrogen compounds. Bond types of typical molecules are discussed and a rationale for comparative strengths of bonds