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The Isolation of Isomeric 5-Oxazolones and the Assignment of Their Structures by Means of NMR Spectroscopy

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In the syntheses of 5-oxazolones (2-isopropenyl-4-alkyl-2-oxazolin-5-ones) from *N*-methacryloyl-α-amino acids, new isomerized oxazolones were obtained. By NMR spectroscopy, the structures of isomerized oxazolones were determined to be pseudoxazolones (2-isopropylidene-4-alkyl-3-oxazolin-5-ones). The NMR spectra of several pseudoxazolones were measured and compared with the normal oxazolones.

Several methods have been reported on the preparation of 5-oxazolones from *N*-acyl-α-amino acids. Two methods were studied for the cyclodehydration of *N*-methacryloyl-DL-α-amino acids (I): a) the action of excess acetic anhydride (Cleaver's method; Method A),[1] and b) the action of an equimolar amount of acetic anhydride in pyridine (Carter's method; Method B).[2] We have previously found that two types of 5-oxazolones—normal and isomerized oxazolones—were obtained in high yields depending on the method of syntheses.[3] By infrared and ultraviolet spectral studies, the structure of III (2-isopropylidene-4-alkyl-3-oxazolin-5-one, pseudoxazolone)[4] was assigned to these isomerized oxazolones. Only a few methods have been known for the preparation of pseudoxazolones containing aromatic substituents; the method reported here is new and unique. In order to obtain a more definite basis for the assigned structures, we have prepared several 5-oxazolones and compared their nuclear magnetic resonance (NMR) spectra. We have found that the assigned structure was correct, and that NMR spectroscopy was the best method to distinguish these isomers.[5] It is the purpose of this paper to make available

1) C. S. Cleaver and B. C. Pratt, *J. Am. Chem. Soc.*, **77**, 1544 (1955).
2) H. E. Carter, P. Handler and C. M. Stevens, *J. Biol. Chem.*, **138**, 619 (1941).
3) F. Toda, *Bulletin of the Tokyo Institute of Technology*, No. 57, 93 (1964).
4) R. C. Elderfield, "Heterocyclic Compounds," Vol. V, John Wiley & Sons, Inc., New York (1957), p. 298; H. E. Carter, "Organic Reactions," Vol. III, John Wiley & Sons, Inc., New York (1962), p. 199; A. R. Katritzky, "Advances in Heterocyclic Chemistry," Vol. IV, Academic Press, New York (1965) p. 75; E. Baltazzi, *Quarterly Reviews*, **9**, 150 (1955).
5) F. Weygand, L. Schmidhammer and W. König, *Angew. Chem.*, **75**, 287 (1963); F. Weygand, W. Steglich and H. Tanner, *Ann.*, **658**, 128 (1962); F. Weygand, W. Steglich, D. Mayer and W. von Philipsborn, *Chem Ber.*, **97**, 2023 (1964).

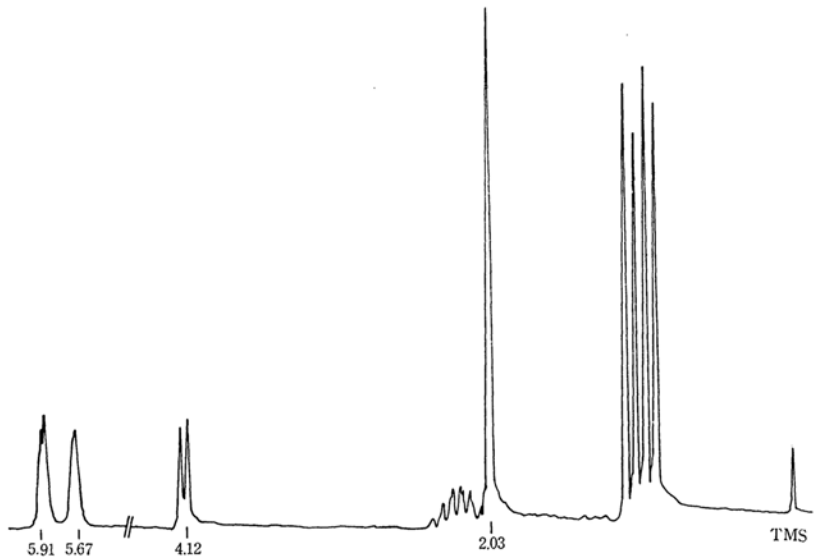
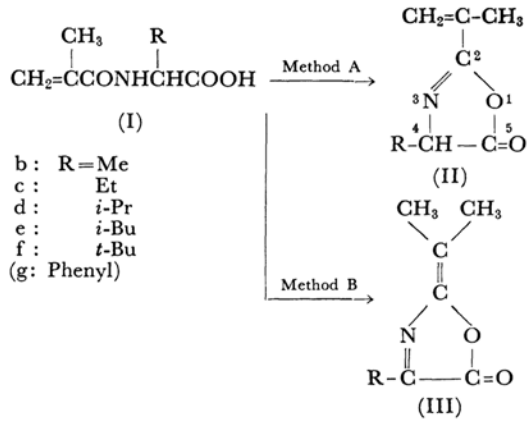


Fig. 1. The NMR spectrum of compound IId at 100 Mc.

the information obtained in this laboratory by means of NMR spectroscopy.[6]



The NMR spectrum of 2-isopropenyl-4-isopropyl-2-oxazolin-5-one (IId) is shown in Fig. 1. The methyl protons of the isopropenyl group at the 2-position gave a singlet at δ 2.03. The terminal methylene protons were shown to be at δ 5.91 and 5.67. The proton at the 4-position afforded a doublet (δ 4.12, J=4.2 cps) split by the spin-coupling with the tertiary proton of the isopropyl substituent. The fact that the protons of two methyl groups gave two pair of doublets at δ 1.08 and 0.94 (J=7.2 cps) can be explained by the differences in conformational populations, which cause the magnetic nonequivalence of the isopropyl group close to the center of molecular asymmetry.[7] The isomerization of oxazolones was readily detected from the changes in their infrared and ultraviolet spectra. In the cases of IId and IIId,

TABLE 1. THE NMR OF III (ppm FROM TMS)

IIIa, R=H	$(CH_3)_2C$= 2.26, 2.15	H-C-C=O 7.80	
IIIb	$(CH_3)_2C$= 2.10, 2.04	CH_3-C-C=O 2.29	
IIIc	$(CH_3)_2C$= 2.11, 2.02	CH_3- 1.30, J=7.8 triplet	-CH_2- 2.63 quartet
IIIe	$(CH_3)_2C$= 2.12, 2.02	$(CH_3)_2C$ 1.02, J=9.6 doublet	
IIIf	$(CH_3)_2C$= 2.09, 2.01	$(CH_3)_3C$- 1.35	
IIIg	$(CH_3)_2C$= 1.86, 1.63		

the absorption of carbonyl groups ($\nu_{C=O}$)[8,9] and the λ_{max}[10] in cyclohexane were changed from 1825 to 1775 cm^{-1} and from 218 to 305 mμ after isomerization. The NMR spectra of III are listed in Table 1. In Fig. 2, the NMR spectrum of IIId is shown for the sake of comparison. The protons

6) After this manuscript had been submitted to this Bulletin, we found a paper (W. Steglich and R. Hurnaus, *Tetrahedron Letters*, No. 4, 383 (1966)), in which the work similar to ours was described. Their results agreed essentially with ours written in this paper. We presented these results orally at the 17th Annual Meeting of The Chemical Society of Japan (Abstract of 17th Annual Meeting of The Chemical Society of Japan, 3HO5, 182, April (1964)).

7) A. T. Bottini and R. L. VanEtten, *J. Org. Chem.*, **30**, 575 (1965).

8) Y. Shimodoi, K. Matsuda and N. Murata, *Kogyo Kagaku Zasshi (J. Chem. Soc. Japan, Ind. Chem. Sect.)*, **65**, 1664 (1962); R. Filler and E. J. Piasek, *J. Org. Chem.*, **28**, 221 (1963).

9) R. Filler and E. J. Piasek, *ibid.*, **29**, 2205 (1964).

10) D. A. Bassi, V. Deulofeu and F. A. Ortega, *J. Am. Chem. Soc.*, **75**, 171 (1953); F. Weygand and W. Steglich, *Angew. Chem.*, **73**, 433 (1961).

of two methyl groups of the isopropyl substituent at the 4-position afforded a doublet at δ 1.28 (J=6.6 cps), while the tertiary proton afforded a septet at δ 2.97. Two methyl groups of the isopropylidene substituent at the 2-position gave two singlets, at δ 2.11 and 2.02. This results from the magnetic nonequivalence of methyl groups, as the oxazolone ring contains oxygen and nitrogen atoms.

In the cases of *N*-methacryloyl-DL-phenylalanine and *N*-acryloyl-DL-valine, double bonds migrated

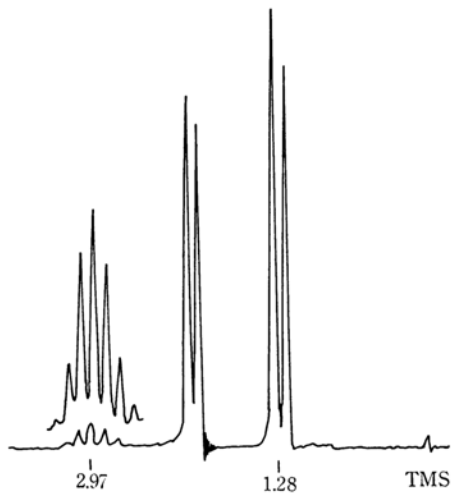
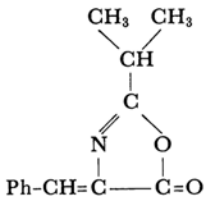
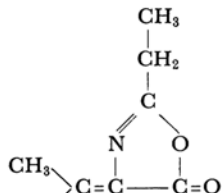


Fig. 2. The NMR spectrum of compund IIId at 60Mc.

further under the treatment of Method B and gave a product which had an *exo*-double bond at the 4-position, as is shown in IV and V (in *N*-acryloyl-DL-valine, about a 1 : 1 mixture of V and VIId was obtained). This phenomena seems to result from the increased conjugate system with the phenyl group in IV and hyperconjugation with two methyl groups in V. The NMR spectra of IV and V are exhibited in Table 2. IIIc and V are thought to be isomers with regard to each other; they can be clearly distinguished by their NMR spectra.

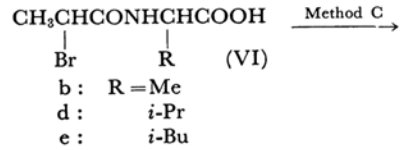


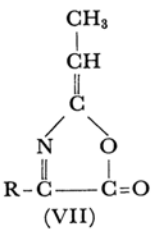
(IV)



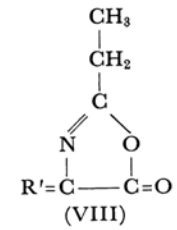
(V)

2-Ethylidene-4-alkyl-3-oxazolin-5-ones (VII) were prepared from *N*-(2-bromopropionyl)-α-amino acids (VI) by Bergmann's method,[11] using benzoic anhydride and sodium acetate as dehydrating agents (Method C).





(VII)



(VIII)

VII was also prepared by Method B from *N*-acryloyl-DL-α-amino acids, but it was accompanied by a small amount of VIII, as has been mentioned above. Bergmann suggested that a dynamic equilibrium existed between normal and pseud-oxazolone, but the resulting mixture of VIId and V obtained by Method B was separated satisfactorily into two fractions, which were distilled at 74.5—78.5°C/11 mmHg and 88.5—91.5°C/11 mmHg respectively.[12] Their infrared spectra resembled each other except that V exhibited new absorptions at 1620, 1275 and 880 cm^{-1}. Characteristic differences were seen in the λ_{max} values of VIId and V in cyclohexane, the former being at 292 mμ, and the latter, at 271 mμ. From the experimental finding that VIId rearranged to V with a small amount of acetic acid in pyridine at an elevated temperature, it may be concluded that rearrangement proceeded to V step by step *via* VIId, since Method B was thought to be a rather drastic reaction in comparison with Method C.

The NMR spectra of VII at 60 Mc are shown in Table 3. The methyl group of the ethylidene substituent at the 2-position of VIIb was exhibited

TABLE 2. THE NMR SPECTRA OF IV AND V

IV	$(CH_3)_2C$	$(CH_3)_2CH$-	Ph-CH=C-C=O
	1.34, J=7.2 doublet	2.87 septet	7.24, 6.99
V	CH_3-	-CH_2-	$(CH_3)_2C$=
	1.27, J=7.8 triplet	2.54 quartet	2.32, 2.22

11) M. Bergmann and F. Stern, *Ann.*, **448**, 20 (1926).

12) 2-Isopropyl-4-isopropylidene-2-oxazolin-5-one was prepared by a similar method to that of Simonsen (G. R. Ramage and J. L. Simonsen, *J. Chem. Soc.*, **1935**, 532) from *N*-isobutyrylglycine and acetone in low yield. The product was decided to be the above compound by NMR: $(CH_3)_2$ isopropyl, δ 1.28, J= 6.6 cps, doublet; Me_2CH δ 2.81, septet; $(CH_3)_2C$= δ 2.32, 2.22, two singlets. $\nu_{C=C}$ was also observed in the infrared spectrum at 1610 cm^{-1}.

Table 3. The NMR spectra of VII

VIIb	CH_3-C=		CH_3-CH=		CH_3-C-C=O	
	2.02,	1.96	5.51,	5.43	2.31	
	doublet	doublet	quartet	quartet		
	34%	66%[a]	J=7.8			
VIId	CH_3-C=		CH_3-CH=		$(CH_3)_2$C-	$(CH_3)_2$CH-
	2.10,	2.01	5.55,	5.48	1.31	3.04
	doublet	doublet	quartet	quartet	doublet	septet
	28%	72%[a]	J=7.8		J=7.8	
VIIe	CH_3-C=		CH_3-CH=		$(CH_3)_2$C-	
	2.08	2.01	5.51	5.44	1.00	
	doublet	doublet	quartet	quartet	doublet	
			J=7.8		J=7.8	

a) Content of isomers concerning the *exo*-double bond.

in two doublets,[13] at δ 2.02 and 1.96, while the proton attached to the *exo*-double bond gave two pair of quartets, at δ 5.51 and 5.43 (J=7.8 cps), as is shown in Fig. 3.

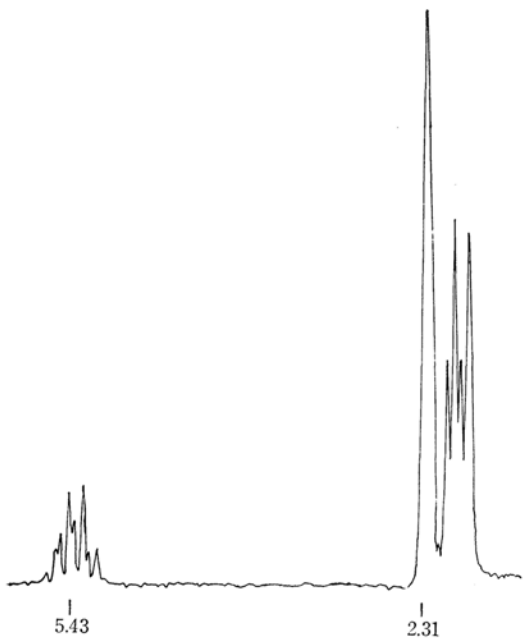


Fig. 3. The NMR spectrum of compound VIIb at 60 Mc.

These observations show that VII is composed of two geometric isomers concerning the *exo*-double bonds (the isomer ratios were approximately 2 : 1), as has been suggested in the literature.[14]

In the spectrum of VIIb at 100 Mc, shown in Fig. 4, the methyl protons at δ 2.31 were divided into two large peaks. The finding that their relative intensities are roughly 2 : 1 may be elucidated as follows: each geometric isomer would exert different chemical shifts even on the methyl protons at the 4-position. The fact that each peak exhibits fine structures indicates the existence of long-range interaction in these compounds between the methyl protons at the 4-position and the protons in the ethylidene group at the 2-position. When the infrared spectrum of VIIb was compared with that of IIIb, VIIb gave absorptions at 3078 and 3062 cm^{-1} (in chloroform; -CH=C< stretching) and at 820 and 812 cm^{-1} (in carbon disulfide; out-of-plane deformation). However, it was not certain that these absorptions corresponded to geometric isomers concerning the *exo*-double bond at the 2-position. An attempt to isolate each isomer from the mixture by distillation and gas chromatography was unsuccessful.

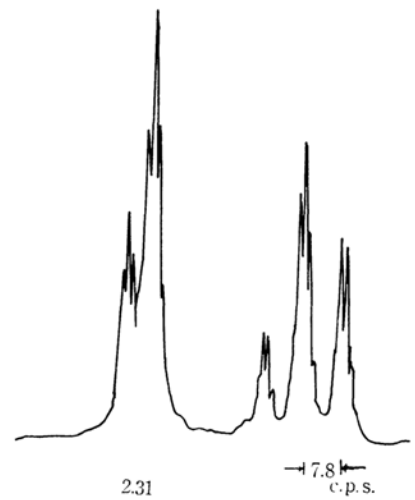


Fig. 4. The NMR spectrum of compound VIIb at 100 Mc.

Experimental

NMR Spectra Measurement. The proton magnetic resonance spectra were taken with Varian DP-60, HR-100, HA-100 and JEOL 3H-60 on 10—20% (W/V) solutions of the samples in carbon tetrachloride containing tetramethylsilane as an internal standard, at 60 Mcps and 100 Mcps and at room temperature.

13) E. Sturm and K. Haner, *Angew. Chem.*, **76**, 862 (1964).
14) A. R. Katritzky, "Advances in Heterocyclic Chemistry," Vol. IV, Academic Press, New York (1965), p. 98.

The chemical shifts are expressed as ppm from tetramethylsilane.

The Preparation of 2-Isopropenyl-4-isopropyl-2-oxazolin-5-one (IId). Method A. About 200 m*l* of acetic anhydride was heated to 100°C in an oil bath; into the preheated acetic anhydride, 25 g of *N*-methacryloyl-DL-valine was then added as quickly as possible, after which the mixture was held at 100°C for an additional five minutes. Acetic acid and excess acetic anhydride were removed under reduced pressure, and the residue was fractionated *in vacuo*. The yield of the product boiling at 100—103°C/20 mmHg was 11.5 g (51%).

The Preparation of 2-Isopropylidene-4-isopropyl-3-oxazolin-5-one (IIId). Method B. A mixture of 37 g of *N*-methacryloyl-DL-valine and 100 m*l* of pyridine was heated to 90—100°C in an oil bath. Then 21 g of acetic anhydride was vigorously stirred in. The mixture was kept at the same temperature for two hours. After pyridine and acetic acid were distilled off under reduced pressure, the fraction boiling at 74—76°C/1 mmHg was collected as pure material; it weighed 21 g (64%).

Found (for IIId): C, 64.16; H, 7.93; N, 7.92%. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.78; N, 8.38%. By analogous procedures, IIIb (bp 54—56°C/1.5 mmHg; mp 31—32°C; 41%), IIIc (bp 66—68°C/1 mmHg), IIIe (bp 84—86°C/1 mmHg; 78%), IIIf (bp 73—74°C/1 mmHg; 69%), IIIg (mp 138°), IV (bp 130°C/1 mmHg; 80%) and V (bp 89—92°C/11 mmHg) were prepared.

The Preparation of 2-Ethylidene-4-isopropyl-3-oxazolin-5-one (VIId). Method C. A mixture of 14 g of *N*-(2-bromopropionyl)-DL-valine, 4.6 g of sodium acetate, and 18.8 g of benzoic anhydride was ground in a mortar. The solid mixture was then heated on an oil bath at 11 mmHg; the distillate boiled at 74.5—78.5°C was collected. The yield was 4.8 g (51%).

Found (for VIId): C, 62.83; H, 7.36; N, 9.12%. Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.14%. By the same method, VIIb (bp 57—60°C/5 mmHg; 75%), VIIe (bp 75°C/4 mmHg; 30%) and IIIa (R=H, bp 63—64°C/4 mmHg; 47%) were synthesized.

The authors were indebted to Dr. Tsuneo Yoshino, Basic Research Laboratories, Toyo Rayon Company and Miss Kikuko Hayamizu, Government Chemical Industrial Research Institute of Tokyo, for the measurements of the spectra, and to Dr. Yuzuru Fujiwara, Department of Chemistry, The University of Tokyo, for his helpful discussions.