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A NOVEL PREPARATION OF PSEUDOXAZOLONES

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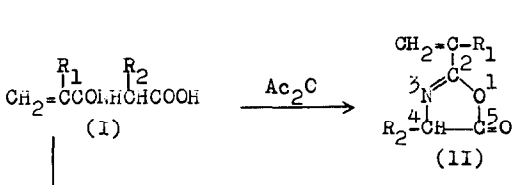
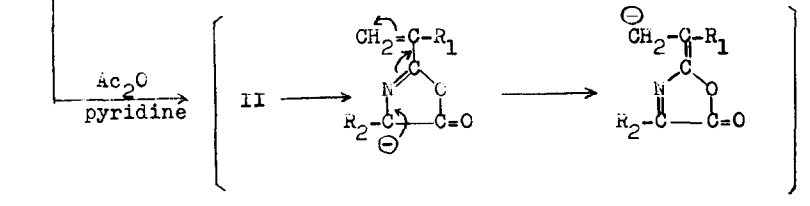
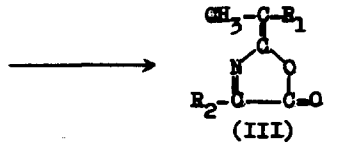
The several methods were reported on the preparation of 5-oxazolones (azlactones) from α-acylamino acids (1). We adopted two methods for the cyclodehydration of N-acryloyl- and N-methacryloyl-DL-α-amino acids (I): a) the action of an excess amount of acetic anhydride (Cleaver's method)(2); b) the action of acetic anhydride in pyridine (Carter's method)(3). We have found that two types of 5-oxazolones---the normal oxazolones (II) and the pseudoxazolones (III)---were obtained in the high yields by these two methods.



(I) (II)

IIa; R_1=H, R_2=i-Pr
IIb; R_1=Me, R_2=i-Pr
IIc; R_1=n-Bu, R_2=i-Pr
IId; R_1=Me, R_2=i-Bu
IIe; R_1=Me, R_2=Benzyl





(III)

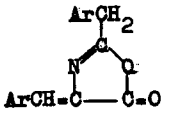
IIIa; R_1=Me, R_2=Me
IIIb; R_1=Me, R_2=i-Pr
IIIc; R_1=Me, R_2=i-Bu
IIId; R_1=Me, R_2=t-Bu
IIIe; R_1=Me, R_2=Phenyl
IIIf; R_1=n-Bu, R_2=i-Pr

2-Vinyl-4-isopropyl-2-oxazolin-5-one (IIa, b.p. 53-5°/3mmHg., 20%), IIb (101-3°/20mmHg., 51%), IIc (95-6°/2mmHg., 47%), IId (70°/2mmHg., 50%) and IIe (110°/1mmHg., 20%) were synthesized from the corresponding N-acyl derivatives of DL-valine (4), DL-leucine and DL-phenylalanine by heating in a large amount of acetic anhydride for five minutes at 100°. The structure of II was decided to be 2-oxazolin-5-one from the assignment of infrared and n.m.r. spectra. The compounds absorbed at 1825 (νC=O), 1655 (νC=N) and 1610-15cm^{-1} (νC=C) in liquid film. N.m.r. spectrum of IIb shows that the methyl protons of the isopropenyl group at 2-position and the terminal methylene protons were shown at δ=2.03, 5.91 and 5.67. The proton at 4-position gave a doublet (δ=4.12, J=4.2cps) and the protons of two methyl groups of the isopropyl substituent afforded two pairs of doublets at δ=0.98 and 1.11 (J=7.2cps). Difference in the conformational populations caused magnetic nonequivalence of the isopropyl group close to the center of molecular asymmetry (5). The II type compounds were not obtained from N-acryloylalanine, N-acryloylphenylalanine and N-methacryloylalanine by the same treatment.

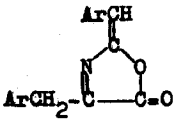
2-Isopropylidene-4-methyl-3-oxazolin-5-one (IIIa, b.p. 54-6°/1.5mmHg., m.p. 31-2°, 41%), IIIb (74-6°/1mmHg., 64%), IIIc (84-6°/1mmHg., 78%), IIId (73-4°/1mmHg., 69%), IIIe (m.p. 138°, 14%) and IIIf (86-8°/0.7mmHg., 58%) were obtained by the dehyd-

ration of the I type compounds with an equimolar amount of acetic anhydride in pyridine at about 100° for 2 hrs. in consequence of the migration of the double bonds from the substituent of 2-position to the 5-oxazolone ring system. The fact that the II type compounds were obtained in the absence of basic solvents instead of III suggests that these solvents may participate in abstraction of the proton attached to the 4-position of 5-oxazolone (6). The reaction proceeded quite readily and gave relatively high yields comparing with the cyclization of N-haloacyl-α-amino acids by benzoic anhydride (Bergmann's method)(7).

Bergmann suggested, indeed, that a dynamic equilibrium probably existed between 4-arylalkylidene-2-oxazolin-5-one (IV) and 2-arylalkylidene-3-oxazolin-5-one (V), but in the compounds reported here, only the pseudoxazolones were obtained as stable isomers, which were identified by the infrared, ultraviolet and n.m.r. spectra (8). The products obtained from N-acryloyl-DL-



(IV)



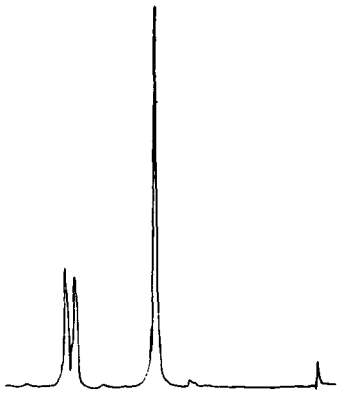
(V)

α-amino acids by the same treatment were found to be composed of pseudoxazolone and normal oxazolone similar to formula IV, in which the double bonds migrated further to the exo-direction at 4-position.

All the compounds gave satisfactory analyses for C, H and N. Infrared frequencies of νC=O and νC=N were exhibited in the region of 1775 and 1680cm^{-1} (9) because of the increased conjugate system and νC=C became very weak in intensity for an improved symmetry.

The 4-alkyl derivatives of III showed the characteristic ultraviolet absorption at 305mμ (ε=1.7×10^4 in cyclohexane), while in II the absorption was observed near at 220mμ (ε=1.9×10^4).

The n.m.r. spectrum of IIId is shown in FIG. 1. Two methyl groups of the isopropylidene substituent at 2-position give a pair of singlets at δ=2.09 and 2.01 because of the different chemical shifts of ring system to each methyl group. The methyl protons of the t-butyl substituent are found at δ=1.35 as a strong singlet. Geometric isomers concerning the exo-double bond in IIIf were detected by n.m.r. in the ratio of about 3/1 calculated from the relative absorption intensities of each methyl group attached to the exo-double bond at 2-position (10).

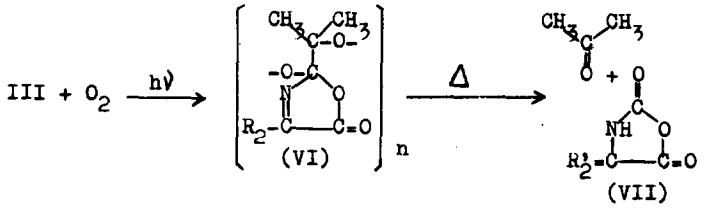


(60Mc, 10% in CCl_4, 20°)
The n.m.r. spectrum of IIId

IIIa was also synthesized by Bergmann's method from N-(α-bromoisobutyryl)-DL-alanine (m.p. 113-5°) in the yield of 65% for a confirmation of the structure and the infrared absorption and boiling point were perfectly identical to those of IIIa. IIIb was hydrolyzed by heating with alkali to give isobutyramide and 3-methyl-2-oxobutyric acid (2,4-dinitrophenylhydrazone, m.p. 191-2°(11)) in 9% and 93% yields respectively.

It was reported that the pseudoxazolones were photo-dimerized by light (12), but IIIe did not show a tendency to dimerize

under the irradiation of ultraviolet light in solid state. III (except for IIIe) afforded the 1:1 alternative copolymers with oxygen in the air by radical chain mechanism. The copolymerization was also accelerated by light. The copolymers (VI) could be cast to transparent film (IIIa, $[\eta]$=0.21 in chloroform, 20°) and decomposed thermally with explosion above 50-60° and gave acetone and N-carboxy-dehydro-α-amino acid anhydrides (VII)(13).



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