

Synthesis of some new 2-Tetrafluoroethyl-pseudo-oxazolones-(5) from the Tfp-Amino acids

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In the series of our investigations on the racemization in the peptide synthesis,^{1~4)} it was demonstrated that Tfp- (tetrafluoropropionyl-) group, a new N-protecting group, possessed properties similar to that of the well known Tfa-group. As a part of these studies, the isolation⁵⁾ and the application⁶⁾ of the 2-tetrafluoroethyl-pseudooxazolone-(5) derivatives, which contain α -branched alkyl substituents at C-4 such as *sec*-butyl-(I) or isopropyl group (II), was recently reported.

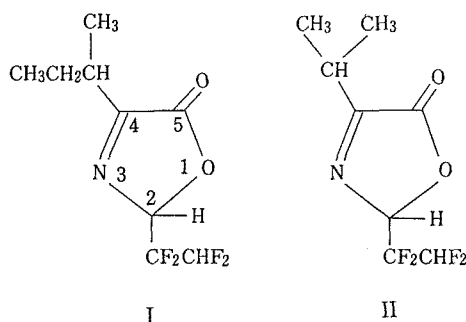


Fig. 1

In the asymmetrically inducing reactions of the compounds I and II with L-proline, it was shown that the tetrafluoroethyl-group bound at C-2 had caused no effect different from that in the case of Tfa-group on the ratio of the both diastereomeric (LL and DL) dipeptide derivatives and it was also suggested that the magnitude of the alkyl substituents at C-4 have an influence on such induction.

In order to investigate further the effect of the substituents at C-4 in the pseudo-oxazolone ring on the asymmetric induction, we intended to synthesize a series of the corresponding compounds.

The present report deals with the systematic synthesis of some new 2-tetrafluoroethyl-pseudooxazolones-(5) with α -disubstituted alkyl group at C-4 such as: 2-tetrafluoroethyl-4-methyl-(III), -ethyl-(IV), -n-propyl-(V), -n-butyl-(VI), -isobutyl-(VII) and -benzyl-pseudooxazolone-(5) (VIII).

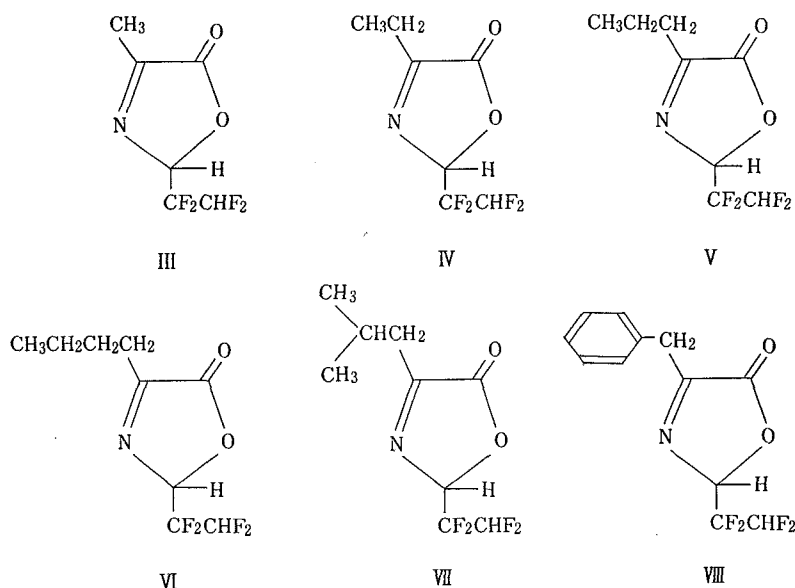


Fig. 2

It was found that the formation of the oxazolone ring from the amino acids having α -disubstituted side chain was not so easy as in the case of I and II (which had been prepared from isoleucine and valine having the bulky side chain), unless the reaction conditions were strictly controlled as written in the following experimental section. This observation was consistent with the view that the large space of the substituent at C-4 in the oxazolone ring can be favorable for its stabilization after the ring closure, as discussed by W. König⁷⁾ and also by us.⁴⁾

Each oxazolone (III~VIII) was obtained from DL-alanine, DL- α -amino-n-butyric acid, DL-norvaline, DL-norleucine, DL-leucine and DL-phenylalanine respectively in the treatment with ca. 3 equivalent moles of tetrafluoropropionic anhydride. In every case, the reflux-time must be exactly controlled as depicted in Table 1.

The reaction mixture was then dissolved in ether, washed several times with ice-cold saturated sodium hydrogen carbonate solution in order to remove the liberated tetrafluoropropionic acid and dried over sodium sulfate. After removal of the ether, each product was obtained as an oily substance in good yield.

The structure of the individual products was elucidated on the basis of their IR and NMR spectra. Their IR spectra showed the same absorption bands of the CO-group at 1805 cm^{-1} characteristic of the conjugated azlactone moiety and the bands at 860 and 780 cm^{-1} due to the CHF_2CF_2 -group. Their NMR spectra showed also the same characteristic pattern in virtual type splitting at 5.2, 6.1 and 6.9 ppm due to the presence of the CHF_2CF_2 -group and also in triplet at 6.15 ppm ($J=11.5\text{ Hz}$) attributable to a proton at C-2 of the azlactone ring. These were equivalent to the previously described data.⁶⁾

Based on the above mentioned evidence, each product was 2-tetrafluoroethyl-4-alkyl-pseudooxazolone-(5) derivatives.

It is planned to examine the influence of the different alkyl substituents at C-4 on the ratio of LL- and DL- diastereomeric dipeptide derivatives.

Experimental

Infrared spectra were obtained with a Hitachi EPI-G₂ spectrophotometer by using a sodium chloride liquid film cell. Nuclear magnetic resonance spectra were obtained with a Hitachi R-24 in deuteriochloroform. Chemical shifts were expressed in ppm from TMS ($\delta=0$).

Tetrafluoropropionic acid;

The mixture of tetrafluoropropyl alcohol (74g, 0.56 mole), chromium trioxide (210g, 2.1 mole) and water (1 l) was stirred vigorously, and conc. sulfuric acid (100ml) was added. After the reaction temperature was raised to 70~75°C, the additional sulfuric acid (350ml) was added gradually. Then, a solution of chromium trioxide (210g, 2.1 mole) in water (500ml) was added into it in about 50ml portions over a period of 2 hr. with vigorous stirring. The solution was poured into an ice water, extracted with ether and the ether solution was dried over anhydrous sodium sulfate. After removal of the ether followed by distillation in vacuo, pure tetrafluoropropionic acid (65.4g) was obtained in 80% yield (B. p 133°C/700mmHg).

Tetrafluoropropionic anhydride;

This reagent was prepared from tetrafluoropropionic acid according to the previously reported manners.

General synthesis of 2-tetrafluoroethyl-4-alkyl-pseudooxazolone-(5);

A mixture of DL-amino acid (6~10mmole) and tetrafluoropropionic anhydride (2.6~3.5 eq.) was refluxed for the required times such as depicted in Table 1 at 135°C. After the reaction mixture was dissolved in ether, the etherate was washed several times with ice-cold saturated sodium hydrogen carbonate solution in order to remove the tetrafluoropropionic acid and dried over sodium sulfate. After removal of the ether, the corresponding pseudooxazolones were obtained as oil. Lability of the products under distillation made the further purification difficult. Their purity was checked by means of NMR analysis and the characteristic data were listed in Table 1.

Table 1. Synthesis of 2-Tetrafluoroethyl-4-alkyl-pseudooxazolones-(5) and their characterizations

Pseudooxazolone from	Molar ratio of reagent	Reaction time (min.)	Yield (%)	IR(cm^{-1}) and NMR (ppm) data
DL-Alanine (III)	3.0	3	80	ν^{film} : 1805(CO), 1660(double bond), 1250, 1120, 1010, 860, 830, 780, 750 δ^{CDCl_3} : 2.3(<i>s</i> , CH_3), 6.15(<i>t</i> , $J=11.5$ Hz, $\text{C}_2\text{-H}$) 5.2, 6.1 and 6.9 (each <i>t</i> , $J=6$ Hz, CHF_2CF_2)
DL-Amino-n-butyric acid (IV)	2.9	30	59	ν^{film} : 1805(CO), 1650(double bond), 1250, 1120, 1010, 860, 830, 780, δ^{CDCl_3} : 1.3 (<i>t</i> , $J=8$ Hz, CH_3CH_2), 2.7 (<i>q</i> , $J=8$ Hz, CH_2), 6.15(<i>t</i> , $J=11$ Hz, $\text{C}_2\text{-H}$), 5.2, 6.1 and 6.9 (each <i>t</i> , $J=6$ Hz, CHF_2CF_2)
DL-Norvaline (V)	3.3	30	76	ν^{film} : 1805(CO), 1650(double bond), 1260, 1130, 1010, 865, 780, δ^{CDCl_3} : 1.0(<i>t</i> , CH_3CH_2), 1.8(<i>m</i> , $\text{CH}_3\text{CH}_2\text{CH}_2$), 2.65(<i>t</i> , $J=7$ Hz, $\text{CH}_3\text{CH}_2\text{CH}_2$), 6.15 (<i>t</i> , $J=11.5$ Hz, $\text{C}_2\text{-H}$), 5.2, 6.1 and 6.9(each <i>t</i> , $J=6$ Hz, CHF_2CF_2)
DL-Norleucine (VI)	3.4	30	65	ν^{film} : 1805(CO), 1650 (double bond), 1245, 1120, 1010, 860, 780, δ^{CDCl_3} : 0.92 (nearly <i>t</i> , $J=6$ Hz, CH_3CH_2), 1.6(<i>m</i> , $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$), 2.68 (nearly <i>t</i> , $J=8$ Hz, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$), 6.1(<i>t</i> , $J=11$ Hz, $\text{C}_2\text{-H}$), 5.2, 6.1 and 6.9(each <i>t</i> , $J=6$ Hz, CHF_2CF_2)
DL-Leucine (VII)	2.6	5	96	ν^{film} : 1805(CO), 1640(double bond), 1390, 1375, 1250, 1120, 1010, 860, 780, δ^{CDCl_3} : 1.05(<i>d</i> , $J=6$ Hz, isopropyl group), 2.3 (<i>m</i> , CH_3CHCH_3), 2.6 (<i>d</i> , $J=6$ Hz, CH_2 -isopropyl), 5.2, 6.1 and 6.9 (each <i>t</i> , $J=6$ Hz, CHF_2CF_2), 6.15 (<i>t</i> , $J=11.5$ Hz, $\text{C}_2\text{-H}$)
DL-Phenylalanine (VIII)	3.3	2	78	ν^{film} : 1805(CO), 1650(double bond), 1500, 1255, 1120, 1010, 865, 780, 760, 710 δ^{CDCl_3} : 4.0 (<i>s</i> , CH_2), 7.3(<i>s</i> , C_6H_5), 6.1 (<i>t</i> , $J=11$ Hz, $\text{C}_2\text{-H}$), 5.2, 6.1 and 6.9 (each <i>t</i> , $J=6$ Hz, CHF_2CF_2)

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Tfp-アミノ酸からの新しい数種の 2-テトラフロロエチル-シュードオキサゾロン-(5)の合成

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要 約

我々のグループでペプチド合成における新しいN-保護基を開発中であるが、その一環として既に Tfp (テトラフロロプロピオニル) 基の性質およびその応用を報告し、ラセミ化を伴う際の反応中間物であるシュードオキサゾロンを単離、同定した。今回、オキサゾロンに L-アミノ酸又はジペプチドを作用させる場合の不斉誘導因子を究明する目的で一連のオキサゾロンを Tfp-アミノ酸から系統的に合成し、それらの構造決定を行なった。合成されたオキサゾロンは4位の置換基がメチル、エチル、n-プロピル、n-ブチル、イソブチル、ベンジルの各物質であり、それらはいずれもシュード型オキサゾロンであることを確認した。