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Synthesis of 2-Tetrafluoroethyl-pseudooxazolone-(5)

Hiroshi KAYAHARA and Ichiro TOMIDA

Department of Agricultural Chemistry, College of Agriculture, Shinshu University, Ina-shi, Nagano-ken

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There is ample evidence in the literature which indicates the importance of oxazolone intermediates in racemization processes during peptide synthesis. Among the presently known oxazolone intermediates, only the compound of 2-trifluoromethyl substituent[1] has one conjugated double bond and is called pseudo-oxazolone. In our laboratory we also isolated an amino acid pseudooxazolone, 2-tetrafluoroethyl-4-alkyl-pseudooxazolone-(5).

We now wish to report the isolation and structural determination of two pseudooxazolones, namely, 2-tetrafluoroethyl-4-*sec*-butyl-pseudooxazolone-(5) (I) and 2-tetrafluoroethyl-4-isopropylpseudooxazolone-(5)(II).

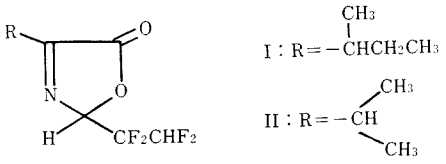

FIG. 1.

We prepared compounds I and II according to the work of Steglich and his associates[2] who had prepared 2-trifluoromethylpseudooxazolone-(5) from DL-amino acids.

Pseudooxazolone I can be obtained from DL-Ileu-OH treated with 2.4 equivalent mole of tetrafluoropropionic anhydride after 3 hr refluxing. The resulting tetrafluoropropionic acid was removed off and I was obtained by careful distillation in 44% yield.

Pseudooxazolone I had bp 71～72°/30 mmHg. ν_{max}^{film} 1800, 1640, 1250, 1120, 1020, 860 and 790 cm^{-1}. The carbonyl absorption appears as a strong band in the 1800 cm^{-1} region characteristic of a conjugated azlactone. The olefinic stretching band appears as a sharp band in the 1640 cm^{-1} region. The position of the double bond is assigned on the basis of NMR evidence, the proton bearing the C-2 of I being observed as a triplet at δ^{CCl_4} 6.15 (J=11.5). The NMR spectrum further supports the presence of a proton of CHF_2CF_2 group which is found as a virtual type splitting pattern at δ^{CCl_4} 5.2, 6.1 and 6.9. The complete absence of the parent peak in the MS spectrum may represent the loss of carbon monoxide, and I displays *m/e* 213 (19%, M^+–CO), 146 (32%, M^+–CO_2–CHF_2) and 112 (52%, M^+–CO–CHF_2CF_2).

Based on the above mentioned evidence, compound I is surely an amino acid pseudooxazolone, 2-tetrafluoroethyl-4-*sec*-butyl-pseudooxazolone-(5).

The treatment of DL-Val-OH with tetrafluoropropionic anhydride afforded compound II in 25% yield, bp 73.5～74°/30 mmHg. A very close similarity of the IR spectrum of II to that of I strongly suggests it to also be a pseudo-type oxazolone. Further, the MS and NMR spectra of II bear an expected similarity to those of I.

Based on the data obtained above, it can readily be shown that the oxazolone derived from DL-valine by using tetrafluoropropionyl N-protecting group is undoubtedly a pseudo-type oxazolone, 2-tetrafluoroethyl-4-isopropyl-pseudooxazolone-(5).

It is of interest to examine the chemistry of I and II from the viewpoint of the asymmetric induction because of their structural relationship to 2-trifluoromethylpseudooxazolone-(5) which was reported by Steglich and his associates.[3,4]

We intend to publish a detailed account of these reactions together with the complete results.

EXPERIMENTAL

Infrared spectra were obtained with a Hitachi EPI-G_2 spectrophotometer by using a sodium chloride liquid film cell. Nuclear magnetic resonance spectra were obtained with a Hitachi R-24 in carbon tetrachloride containing tetramethylsilane as an internal reference. Chemical shifts are expressed in ppm from TMS (δ=0).

Tetrafluoropropionic acid

Sodium tetrafluoropropionate* (200 g) was dissolved in conc. sulfuric acid (40 g) and after direct distillation, 156.4 g of tetrafluoropropionic acid was obtained in 90% yield, (132°/700 mmHg), d 1.563.

Tetrafluoropropionic anhydride

A mixture of tetrafluoropropionic acid (156.4 g) and phosphorus pentoxide (40 g) was refluxed at 135° for 3 hr, then the mixture was distilled. The distillate at the range of 121～125°C was redistilled over phosphorus pentoxide and pure tetrafluoropropionic anhydride was obtained (90 g) in 80% yield, 121°/700 mmHg, d 1.585.

2-Tetrafluoroethyl-4-sec-butyl-pseudooxazolone-(5)(I)

A mixture of DL-isoleucine (9.8 g, 75 mM) and tetrafluoropropionic anhydride (30.4 cc, 2.4 eq) was

refluxed for 3 hr at 135°C, then the reaction mixture was distilled *in vacuo* and the fraction of 71~72°/30 mmHg was dissolved in ether, washed several times with ice-cold saturated sodium hydrogn carbonate to remove tetrafluoropropionic acid and dried over sodium sulfate. After removal of ether, 7.87 g of I was obtained in 44% yield. Found: C, 44.81; H, 4.56; N, 5.80. Calcd. for $C_9H_{11}NO_2F_4$: C, 44.53; H, 4.40; N, 5.63%. IR ν_{max}^{film} 1800, 1640, 1250, 1020, 860 and 790 cm^{-1} NMR δ^{CCl_4} 0.98 (3H, t, J=7.2 Hz, $\underline{CH_3}CH_2$–), 1.35 (2H, d, J=7.0 Hz, $\underline{CH_3}CH$–), 1.8 (2H, m, $CH_3CH\underline{CH_2}CH_3$), 2.95 (1H, m, $CH_3\underline{CH}CH_2CH_3$), 6.15 (1H, t, J=11.5 Hz, C_2–H), 5.2, 6.1 and 6.9 (1H, each t, J=5.9 Hz, CHF_2CF_2–). MS *m/e*, 213 (19%, M^+–CO), 198 (20%), 146 (32%, M^+–CO_2–CHF_2), 112 (52%, M^+–CO–CF_2CHF_2), 101 (41%), 90 (29%), 84 (47%), 82 (26%), 68 (47%), 57 (61%), 51 (66%), 41 (100%), 39 (56%).

2-Tetrafluoroethyl-4-isopropyl-pseudooxazolone-(5)(II)

DL-Valine (8.75 g, 75 mM) and tetrafluoropropionic anhydride (27 cc) were reacted in the same manner as for I. The resulting 2-tetrafluoroethyl-4-isopropyl-pseudooxazolone-(5) was obtained (4.12 g, 25%), 73.5~74°/30 mmHg. Found: C, 42.13; H, 3.74; N, 6.26. Calcd. for $C_8H_9NO_2F_4$: C, 42.29; H, 3.96; N, 6.17%. IR ν_{max}^{film} 1800, 1640, 1250, 1120, 1010, 860, 840 and 790 cm^{-1} NMR δ^{CCl_4} 1.35 (6H, d, J=7.0 Hz, isopropyl) 3.15 (1H, m, $CH_3\underline{CH}CH_3$), 6.15 (1H, t, J=11.5 Hz, C_2–H), 5.2, 6.1 and 6.9 (1H, each t, J=5.9 Hz, CHF_2CF_2). MS *m/e*, 199 (18%, M^+–CO), 184 (28%), 183 (26%), 132 (55%, M^+–CO_2–CHF_2), 101 (39%), 98 (50%, M^+–CO–CF_2CHF_2), 90 (44%), 82 (37%), 70 (66%), 55 (67%), 51 (72%), 43 (100%), 41 (77%), 39 (70%).

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