Tetrahedron Letters Vol. 21, pp 1125 -1128 0040-4039/80/0315-1125$02.00/0

SYNTHESIS OF α-METHYLENE-β-ALANINE AND ONE OF ITS NATURALLY OCCURRING α-KETOAMIDES

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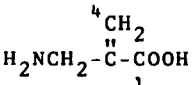
Abstract -- α-Methylene-β-alanine (1) has been synthesized from t-butyl bisbromomethyleneacetate by successively generating the α-methylene, then the β-amino function from a bromomethylene. Hydrolysis or methanolysis completes the synthesis of 1·HCl, and of its methyl ester (3)·HCl, from which the α-ketopalmitic acid amide of I was prepared.

Kashman et al.[2] first reported isolation of a new toxic amino acid, α-methylene-β-alanine, from a Red Sea sponge Fasciospongia cavernosa. This presumed antimetabolite occurs in the sponge as its methyl ester, which is N-acylated by a series of C_{16}-C_{20} fatty acids.



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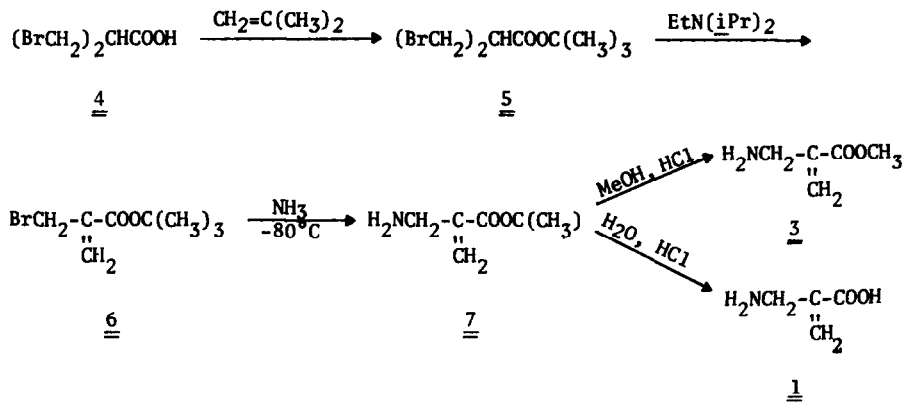
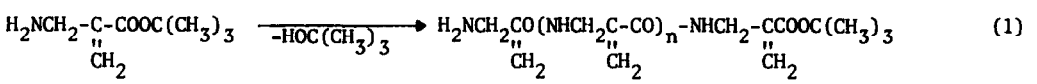
Yunker and Scheuer[3] subsequently isolated three sets of N-acyl derivatives of the same amino acid methyl ester from a black Hawaiian sponge Spongia cf. zimocca.[4] The amide linkage in two groups of their compounds is formed with fatty acids which, remarkably, bear alpha keto[5] or alpha hydroxy functions [$RNCH_2$-$\overset{CH_2}{\overset{\|}{C}}$-COOMe; R = $COCHOH(CH_2)_nCH_3$ (2a); R = $COCO(CH_2)_nCH_3$ (2b), n = 11-13]. We now report the first synthesis of α-methylene-β-alanine and of one of its naturally occurring derivatives (2b, n = 13).

α-Methylene-β-alanine (1) and its methyl ester (3) were prepared by a sequence of reactions shown in the Chart. Compound 5[6] was obtained from 4[7] (0.2 mol) and isobutylene[8] (1 mol) in a mixture of benzene (40 mL), diethyl ether (20 mL), and conc H_2SO_4 (1 mL). After stirring for 60 h under Hg seal, the solution was washed with satd sodium bicarbonate solution. Evaporation of the solvent gave 5 in 90% yield (mp 47-48°C, 50°C[9]), from which 6 was prepared according to the published method.[9] Compound 7,[10] obtained by treatment of 6 with ammonia, is surprisingly

Chart



reactive and on attempted isolation at room temperature a white wax, mp 70-78°C, was obtained. According to mass spectral data the wax is a composite of polycondensates (Eq. 1).



(1)

However, in the synthesis of 1 or 3 from 7, the polycondensation may be suppressed under the following conditions. Compound 6 (1.2 g) was added to ammonia (20 mL) at -80°C and left with stirring but without external cooling for 2 h. More ammonia may be added. The mixture was poured onto a mixture of ice (30 g) and methylene chloride (3 mL) and the aqueous phase was washed with methylene chloride (2 × 3 mL). After washing with ice water and drying at 0°C, a solution of HCl in MeOH (2 mL) was added, followed by removal of the solvents in vacuo. The remaining product was dissolved in a solution of HCl in MeOH (10 mL) and left at room temperature overnight. The solvent was removed in vacuo to give an oil which was dissolved in dry acetone (2 mL) and cooled in Dry Ice-acetone to give crystalline 3 as the hydrochloride (27% yield, mp 107-8°C[11] (recrystallized by dissolving in MeOH, followed by addition of 5 volumes of acetone).[12] ^{1}H-NMR (D_2O) δ 4.23 (OCH_3), 4.28 (NCH_2), 6.52 (=CH_2), 6.97 (=CH_2); ^{13}C-NMR (D_2O) ppm, C-1 167.9, C-2 133.0, C-3 41.2, C-4 133.8, OCH_3 53.8; mass spectrum m/e 115 ($M^{+\cdot}$).[13]

Cpd 1 is obtained in a manner similar to that of 3 by slowly adding the above methylene chloride solution to conc HCl (10 ml) at 0°C. After separation of the phases the aqueous solution was left overnight at room temperature. Concentration in vacuo gave crystalline 1 as the

hydrochloride (31% yield, mp 153-54° (dec), from MeOH followed by addition of acetone. ^{1}H-NMR (D_2O) δ 4.25 (NCH_2), 6.49 (=CH_2), 6.91 (=CH_2); ^{13}C-NMR (D_2O) ppm, C-1 169.2, C-2 133.2, C-3 41.3, C-4 133.7; mass spectrum m/e 101 ($M^{+\cdot}$). Anal. Calcd: C, 34.92; H, 5.86; N, 10.18%. Found: C, 35.17; H, 5.94, N, 10.03%.

Cpd 2b was prepared by adding 3 as the hydrochloride (1.2×10^{-3} mole) to an equivalent amount of NaOMe in MeOH (1 mL) at 0°C. After stirring for 2 min the solvent was removed in vacuo at 0°C and equivalent methylene chloride solutions of first dicyclohexylcarbodiimide (1.5 mL) and then 2-oxopalmitic acid (215 mL)[14] were added at 0°C. After standing overnight at room temperature the solution was filtered and the amide 2b isolated in 21% yield after column chromatography (25 g Bio-Sil A 200-400 mesh, CH_2Cl_2) (Mp 59.5-60°C, hexane); ^{1}H-NMR ($CDCl_3$) δ 7.36 (NH), 6.32 (=CH_2), 5.84 (=CH_2), 4.15 d (NCH_2 J = 7), 3.82 (OCH_3), 2.92 t ($COCH_2$, J = 7), 1.26 bs $(CH_2)_n$), 0.88 t (CH_3, J = 7); ^{13}C-NMR ($CDCl_3$) ppm, C-1 not observed, C-2 135.8, C-3 40.5, C-4 127.7, CONH 160.1, COCONH 198.9; mass spectrum m/e 367 $M^{+\cdot}$ $C_{21}H_{37}NO_4$ (Calcd: 367.2723. Found: 367.2732) 142 base peak ($C_6H_8NO_3$, Calcd: 142.050. Found: 142.048) 225 ($C_{15}H_{29}O$). The spectral data are thus identical with those found by Yunker and Scheuer[3] for the mixture of fatty acid amides 2b (vide supra).

Acknowledgments. We are grateful to the National Science Foundation for partial support of this work and to the Danish National Science Foundation for financial aid to A.H.

References and Notes

1. A. Holm on sabbatical leave from the University of Copenhagen, 1979.

2. Y. Kashman, L. Fishelson, and I. Ne'eman, Tetrahedron 29, 3655-3657 (1973).

3. M. B. Yunker and P. J. Scheuer, Tetrahedron Lett. 4651-4652 (1978).

4. We are indebted to Dr. Klaus Ruetzler, National Museum of Natural History for identification of the sponge.

5. The =NCOCO- functionality has since been demonstrated in the antibiotic rapamycin [D. C. Neil Swindells, Peter S. White, and John A. Findlay, Can. J. Chem. 56, 2491-2492 (1978).]

6. This procedure which incidentally furnishes 5 in higher yield is slightly modified from that in ref. 8 to avoid the use of an autoclave.

7. A. F. Ferris, J. Org. Chem. 20, 780-787 (1955).

8. H. S. Davis, J. Am. Chem. Soc. 50, 2769-2780 (1928).

9. R. Lattrell and G. Lohaus, Justus Liebigs Ann. Chem. 870-900 (1974).

10. The in situ use of methylene-β-alanine tert. butylester has been briefly described for a single reaction, but isolation was not attempted.[8]

11. Kashman et al. (2) had obtained small amounts of low-melting HCl salt of 3 (mp 93-95°C) by methanolysis of the naturally occurring amides.

12. Crystallization of the HCl salt of 6 may fail to take place if the crude mixture contains a larger amount of polycondensate as evidenced by additional ^{1}H-signals around δ 6.66 ($=CH_2$) and 7.05 ($=CH_2$).

13. NMR spectra on a Varian XL-100 and mass spectra on a Varian MAT 311 instrument. Combustion data by Berkeley Analytical Services, University of California.

14. T. Kuwata, J. Am. Chem. Soc. 60, 559-560 (1938).

(Received in USA 20 December 1979)