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ALPHA-OXYGENATED FATTY ACIDS OCCURRING AS AMIDES OF 2-METHYLENE-β-ALANINE IN A MARINE SPONGE

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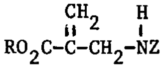
In 1973 Kashman *et al.*[2] reported the isolation of a new amino acid 2-methylene-β-alanine (**1a**) from the Red Sea sponge *Fasciospongia cavernosa*. It occurs as the methyl ester (**1b**) and its amino group is acylated by five or more C_{16}-C_{20} fatty acids (**1c**, n = 13-17). We have encountered four sets of N-acyl derivatives of the same amino acid in an unidentified black sponge from Hawaiian waters.[3] In our case, the amino acid occurs free or as the methyl ester. More remarkably, the amide linkage in two groups of compounds is formed with three C_{14}-C_{16} fatty acids that bear unprecedented *alpha* keto or *alpha* hydroxy functions.



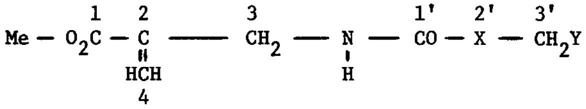
$$RO_2C\text{-}\overset{\overset{CH_2}{\|}}{C}\text{-}CH_2\text{-}\overset{\overset{H}{|}}{N}Z$$

1 **a** R = Z = H   **b** R = Me, Z = H
c R = Me, Z = $OC\text{-}CH_2\text{-}(CH_2)_n\text{-}CH_3$
d R = Me, Z = $OC\text{-}CO\text{-}(CH_2)_n\text{-}CH_3$
e R = Me, Z = $OC\text{-}CHOH\text{-}(CH_2)_n\text{-}CH_3$
f R = H, Z = $OC\text{-}CH_2\text{-}(CH_2)_n\text{-}CH_3$

Continuous pentane extraction of the freeze dried sponge followed by silica gel and Sephadex chromatography of the pentane residue yielded the major group of compounds, **1d** (n = 11, 12, 13), as an amorphous white wax, mp 36.5-37°. High resolution mass spectrometry showed this solid to be a mixture of three homologs predominantly, $C_{19}H_{33}NO_4$, $C_{20}H_{35}NO_4$, and $C_{21}H_{37}NO_4$, differing only in length of the aliphatic chain. The ir spectrum indicated presence of a secondary amide (3400 sh, 3420, 1665, 1520 and 1260), an ester (1720), and a terminal methylene (950 cm^{-1}). We made no attempt to separate this or the analogous (*vide infra*) amide mixtures. Comparison of our ^1H nmr data with those of Kashman *et al.*[2] (Table 1) demonstrated close correspondence of the 2-methylenepropanoic acid moiety, but substantial downfield shifts of the amide proton and of the methylene protons *alpha* to the acyl function.

^{13}C nmr data supported the 2-methylene-β-alanine (C-1 166.0, C-2 135.5, C-3 40.2, C-4 127.4) as well as the amide function (C-1' 159.8 ppm), but also revealed an additional carbonyl function (C-2') resonating at 198.7 ppm. The ^1H chemical shift data (Table 1) demand that this carbonyl be placed next to the amide carbonyl. This unusual structural feature is further substantiated by a uv maximum at 244 nm (ε 2900, dioxane), in reasonable agreement with a literature value of 241 nm (ε 2456, EtOH).[4] Mass spectral fragmentation is in full accord with the postulated structure. The three main parent peaks at m/e 367, 353, and 339 undergo facile cleavage between the

Table 1. Proton Chemical Shift Data (δ) for Our Compounds **1d** (n = 11-13) and Kashman's **1c** (n = 13-17); Y = $(CH_2)_nCH_3$



$$\mathrm{Me - O_2\overset{1}{C} - \underset{\underset{4}{HCH}}{\underset{\|}{\overset{2}{C}}} — \overset{3}{CH_2} — \underset{\underset{H}{|}}{N} — \overset{1'}{CO} — \overset{2'}{X} — \overset{3'}{CH_2}Y}$$

Our **1d**, X = CO	3.74	6.25	5.77	4.09	7.35	--	--	2.85
Kashman's **1c**, X = CH_2	3.74	6.22	5.79	4.06	6.12	--	2.17	--

carbonyls, leading to the base peak at m/e 142 ($C_6H_8NO_3$) and acyl fragments at m/e 225 ($C_{15}H_{29}O$) and corresponding lower homologs at m/e 211 and 197.

The polar fractions of the original silica gel chromatography were rechromatographed on Sephadex to remove high molecular weight material, and again on silica gel, which yielded the second most abundant group of compounds, **1e**, (n = 11-13) and a mixture of **1c** and **1f**. This mixture was separable on Sephadex LH-20. The **1c** amides were identical by ^{1}H and tlc comparison as well as by ms -- except of course for chain length -- with a sample provided by Professor Kashman. The ^{1}H nmr spectrum of the **1f** amides was virtually superimposable on that of **1c** except for the absence of the methyl ester and the presence of a D_2O exchangeable proton signal at δ10.12. Mass spectral parent peaks occurred at 14 mass units below those of **1c**, as did the base peak, now at m/e 128. Esterification of **1f** with ethereal diazomethane yielded a group of compounds identical with **1c** by tlc, ms, and ^{1}H nmr. The attempted reverse reaction, mild acid or base hydrolysis of **1c**, failed and led only to decomposition of the β-alanine portion of the molecule.

The **1e** amides were characterized by a broad ir band at 3300 cm^{-1}, an exchangeable proton in the ^{1}H nmr spectrum at about δ3.7, and a 3H signal at δ4.07 assigned to the C-3 methylene alpha to the NH (dd, J_{3NH} = 6Hz, J_{34} < 1Hz) and to a secondary alcohol methine (m). The ^{1}H nmr spectrum further showed the absence of a 2H triplet between δ2 and 3, characteristic of a methylene next to a carbonyl. The likely surmise that **1e** is the alcohol corresponding to **1c** was proven by oxidizing the hydroxyamides **1e** with chromium trioxide dipyridine complex to a group of ketoamides identical with **1c** by tlc, ^{1}H nmr, and ms.

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REFERENCES

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2. Y. Kashman, L. Fishelson, and I. Néeman, Tetrahedron 29, 3655 (1973).
3. The sponge was collected near the Blowhole, Oahu. It is purple to black on the outside and off-white inside. Pending identification we are keeping specimens and photographs on file.
4. E. W. Colvin, J. Martin, W. Parker, R. A. Raphael, B. Shroot, and M. Doyle, J. Chem. Soc. Perkin Trans I, 860 (1972).

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