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N-METHYLMUREXINE - A NATURALLY-OCCURRING MARINE COMPOUND?

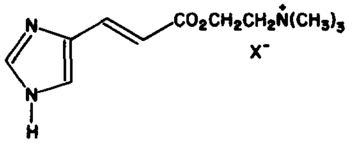
Colin C. Duke, John V. Eichholzer and John K. MacLeod*

Research School of Chemistry, Australian National University,

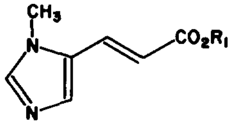
Canberra, ACT 2600, Australia

Murexine (1) has been found in many widely distributed species of marine gastropod molluscs.[1] Recently an N-methylmurexine was reported[2] to occur in Nucella emarginata found off the California coast and was tentatively assigned structure (3).

We report here the unambiguous synthesis of the two possible N-methylmurexines (2) and (3), neither of which correspond to the compound extracted from Nucella emarginata. Also, mass spectral results on synthetic murexine (1) show that the preliminary identification by one of us of an N-methylmurexine from Dicathais orbita[3] by mass spectrometry requires correction. Ions characteristic of an N-methylimidazolyl moeity are present in the mass spectrum of (1) due to thermal intermolecular methyl transfer from the quaternary ammonium group[4] to the imidazole ring and this had lead to the initial incorrect assignment. Subsequent purification of the natural product via recrystallisation of the stable iodide salt gave murexine (1) which was identical with the corresponding synthetic compound.[5]



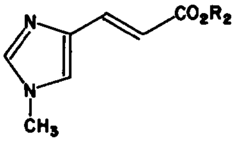
(1)



(2) $R_1 = CH_2CH_2\overset{+}{N}(CH_3)_3X^-$

(4) $R_1 = H$

(6) $R_1 = CH_2CH_2Cl$



(3) $R_2 = CH_2CH_2\overset{+}{N}(CH_3)_3X^-$

(5) $R_2 = CH_3$

(7) $R_2 = CH_2CH_2Cl$

The compounds (2) and (3) were prepared as follows: 3-[5-(1-Methyl)imidazolyl]-2-chloropropanoic acid, prepared regiospecifically from 4-(5)-imidazolyl-2-chloropropanoic acid,[6] was converted to trans-β-[5-(1-methyl)imidazolyl]acrylic acid (4) on reaction with aq.$(CH_3)_3N$ in a sealed tube at 60°. Methylation of methyl trans-β-[4-imidazolyl]acrylate[7] with $(CH_3)_2SO_4$ and K_2CO_3 in acetone gave methyl trans-β-[4-(1-methyl)imidazolyl]acrylate (5) as the only mono N-methylated product. Comparison of the physical and spectroscopic (^{1}H-NMR, UV) properties of (5) with those of the methyl ester of (4) established the 1,4-disubstitution pattern[8] of (5). The two compounds (4) and (5) were each treated with 2-chloroethanol/HCl at 20° overnight to give the chloroethylesters (6) and (7) which on further treatment with $(CH_3)_3N$/DMF in a sealed tube at 80° for 24 hrs gave the respective N-methylmurexine chloride salts (2) and (3). After conversion of the chlorides of (2) and (3) to the iodides using Dowex 1 (I^-) the compounds were crystallised from methanol.[9]

Compound (2)($X^- = I^-$) m.p. 224°, analyses for $C_{12}H_{20}IN_3O_2$. ^{1}H-NMR δ(D_2O, ext. TMS) 3.70, s, $^{+}N(CH_3)_3$; 4.20, s, CH_3; 4.26, m, CH_2; 5.14, m, CH_2; 6.86, d, J 16 Hz, C=CH; 8.08, br d, J 16 Hz, C=CH; 7.86-8.46, v br s, 2H imidazolyl.

Compound (3)($X^- = I^-$) m.p. 224-5°, analyses for $C_{12}H_{20}IN_3O_2$. ^{1}H-NMR δ(D_2O, ext. TMS) 3.70, s, $^{+}N(CH_3)_3$; 4.14, s, CH_3; 4.26, m, CH_2; 5.10, m, CH_2; 6.82, d, J 16 Hz, C=CH; 7.89, br s, 1H imidazolyl; 8.04, d, J 16 Hz, C=CH; 8.12, br s, 1H imidazolyl.

A comparison of the ^{1}H-NMR spectra of (2) and (3) with that reported for the proposed N-methylmurexine from N. emarginata showed that the latter did not correspond to either of the synthetic compounds. The most obvious difference was between the chemical shifts of the imidazolyl N-methyl group in (2) and (3)(δ 4.20 and 4.14 respectively) and that (δ 3.83) reported for a three-proton signal assigned to an imidazolyl N-methyl group in the compound from N. emarginata.

The identity of the natural product from N. emarginata must therefore be regarded as uncertain and requires re-investigation.

References

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(9) All compounds mentioned have been fully characterised and their structures are consistent with UV, NMR, mass spectral data and analyses.

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