Table 1. Comparison of cephalosporins and corresponding oxa-β-lactam derivatives (paired ion chromatography (PIC) tetrabutyl ammonium hydroxide (0.005 M) 1% CH_3CN)

Compounds 1A–5A k'O	Compounds 1–5 k'S	k'S/k'O
1A 4.85	1 8.15	1.68
2A 3.23	2 5.15	1.59
3A 1.08	3 2.08	1.93
4A 0.92	4 1.31	1.42
5A 1.54	5 2.85	1.85

Table 2. Comparison of cephalosporins and corresponding oxa-β-lactam derivatives μ NH_2 bonded phase propylamine on 10 μm Silica (Waters) 2/4/7.5/86.5 $HOAc/CH_3OH/CH_3CN/H_2O$

Compounds 1A–5A k'O	Compounds 1–5 k'S	k'S/k'O
1A 14.2	1 20.3	1.43
2A 16.2	2 21.3	1.31
3A 12.0	3 17.1	1.43
4A 13.2	4 17.6	1.33
5A 7.6	5 18.8	2.47

which were not available commercially were distilled in glass before usage.

The data clearly indicate that a consistent trend in k'-values should be expected with nuclear variation in these compounds. In the case of the reversed phase system, changing from sulfur [S] to oxygen [O] derivative gave rise to a nearly linear decrease in k'-values. Table 1 illustrates this relationship and indicates that the ratio k'S/k'O is uniform. The microBondapak NH_2 system also yielded a decrease in k'-values in going from [S] to [O], but the data were not linear (table 2). However, it indicates that the ratio k'S/k'O is uniform in 4 out of 5 cases under these conditions. It is obvious that the presence of the oxygen atom in place of the sulfur atom has significant impact on the polarity of the entire β-lactam compound, and if this property alone is used to consider the chromatography of the derivative, a linear response could be expected. Although, when the additional ion-exchange property is exploited with the microBondapak NH_2 column, non-linearity and change of eluting order indicate that the effect of hetero-atom replacement can have varied effects on the pKa and therefore the retention properties in this system.

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The occurrence of 5-hydroxytryptamine in the holothurian, *Pentacter crassa*

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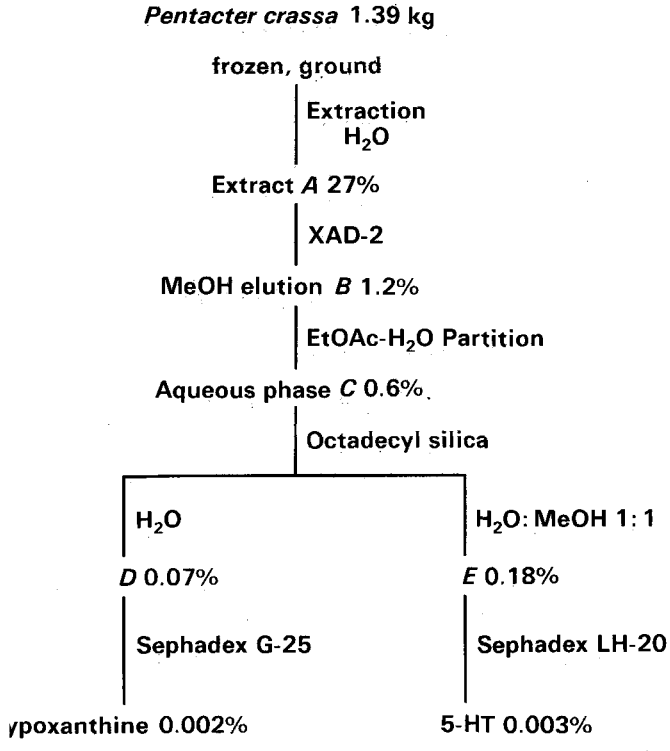
Summary. 5-Hydroxytryptamine (5-HT) and hypoxanthine were isolated chromatographically from the holothurian *Pentacter crassa.* This study was initiated as a result of the observed hypotensive activity of a *P. crassa* extract. This activity was also encountered in extracts of the holothurians *Thelenota ananus* and *Stichopus chloronatus* and can be attributed to 5-HT.

In the marine environment 5-HT has been identified as a constituent of some species of molluscs[1,2], sea anemones[3], annelids[3], tunicates[4,5] and gorgonians[4]. The function of 5-HT in marine invertebrates, particularly molluscs, has been the subject of much physiological and pharmacological research[2,6] and it is now accepted that 5-HT does act as a neurotransmitter and in some cases, e.g. anemones, as a toxin. Few studies on the occurrence of 5-HT in echinoderms have been undertaken. It has been reported[7] that the level of 5-HT in echinoderm nervous tissue is very low and in the case of the sunflower starfish, 5-HT was not detected[8]. The presence of 5-HT in a sea urchin has been indicated by fluorescence[9] and cytochemical analysis indicated its presence in a starfish and a holothurian *Pentacter peterseni*[10]. This report describes the isolation of 5-HT, and hypoxanthine, from the holothurian *Pentacter crassa* (Ekman 1918) (Echinodermata: Holothuroidea)[11]. Hypoxanthine is present in the marine environment in clams, fish and soft corals[1].

This study was undertaken as a result of the biological activity displayed by an aqueous extract of *P. crassa,* which was trawled from N.E. of Cape Peron, Shark Bay, Western Australia and frozen upon collection. The frozen material (1.39 kg) was ground cryogenically, extracted with water and the aqueous extract **A** was subjected to a variety of pharmacological and microbiological bioassays. Potent hypotensive activity was observed when **A** was administered i.v. to pentobarbitone-sodium anaesthetized, deoxycorticosterone acetate-salt, hypertensive rats. Fractionation of **A** was guided by monitoring each separation for hypotensive activity. A solution of **A** (350 g) in water (3 l) was pumped through a column (52 × 45 cm) of Amberlite XAD-2 resin which was then washed with water (5 l) and methanol (9 l). Evaporation of the methanolic fraction gave **B** (16 g) which was partitioned between ethyl acetate and water to give an active, aqueous fraction **C** (9 g). An aqueous solution of **C** (9 g) was chromatographed on a column (7 × 10 cm) of octadecyl silica which was eluted with a water then water-methanol gradient. The material eluted in water **D** (1 g) was inactive, however, it was chromatogaphed on Sephadex G-25, fine, and a colourless solid (22 mg) obtained at V_R/V_M 2.57–2.94 which was

shown to be hypoxanthine by comparison (HRMS, ^{13}C NMR) with an authentic sample. Elution of the octadecyl silica column with water: methanol (1:1) afforded an active fraction E (2.5 g) which was chromatographed on Sephadex LH-20 in methanol to yield potent material at V_R/V_M 2.20–2.53. Rechromatography on Sephadex LH-20 afforded the active constituent (44 mg) which was shown to be identical with 5-HT by ^{13}C NMR, ^1H NMR and bioassay. The pure material caused the well known triphasic response on blood pressure after i.v. administration and this effect was abolished by predosing with methysergide[12], a specific inhibitor of 5-HT. The concentration of 5-HT present (30 µg/1 g dry organism) in *P. crassa* was confirmed by HPLC analysis of butanol extracts of whole organisms.

Aqueous extracts of the holothurians *Thelenota ananus* Jaeger (1833) and *Stichopus chloronatus* Brandt (1835) almost certainly contain 5-HT as they exhibited very similar hypotensive activities, which were abolished by methysergide, to the *P. crassa* extract. Although we were unable to examine neuronal tissue of these holothurians, the isolation of 5-HT from *P. crassa*, and its apparent presence in *T. ananus* and *S. chloronatus*, means that 5-HT should be of primary importance when considering the neurotransmitters, and cardiovascular effects, of holothurians.



Separation scheme for the isolation of the anti-hypertensive constituent from the holothurian, *Pentacter crassa*.

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Hashish: Synthesis of (±)-2′,11-dihydroxy-Δ^9-tetrahydrocannabinol (THC), a metabolite of Δ^9-THC[1]

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Summary. The synthesis of (±)-2′,11-dihydroxy-Δ^9-THC, a difunctionalized metabolite of Δ^9-THC, is presented.

In recent years a great deal of attention has been focused on the biotransformation of cannabinoids. Metabolism has been studied in several species: man, mouse, monkey, rabbit and guinea-pig among others[2–4]. In the case of Δ^9-THC, the active constituent of marihuana, these studies have identified primary metabolites that are hydroxylated within the terpene portion at the allylic positions, C-8 and C-11 and/or the aromatic side chain as shown in **1**. Some of these metabolites are pharmacologically equi-active with Δ^9-THC, and still others are active to greater and lesser degrees. This has complicated the understanding of marihuana activity in man[2,3].

Synthetic methods have been developed which have provided metabolites of Δ^9-THC functionalized either in the terpene portion[5] or the aromatic side chain[6–9]. Until now, the metabolites with a functionalization both in the terpene portion and the aromatic side chain have not been synthesized. In this communication we wish to report the synthesis of (±)-2′,11-dihydroxy-Δ^9-THC **(2)**, the first example of a metabolite belonging to this class. Compound **2** was shown by Harvey et al.[10] by GC-MS to be a major metabolite of Δ^9-THC in the guinea-pig, although it does not appear to be a major metabolite in man.