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ENTADAMIDE C, A SULPHUR-CONTAINING AMIDE FROM *ENTADA PHASEOLOIDES**

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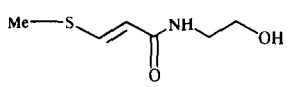
Key Word Index—*Entada phaseoloides*; Leguminosae; sulphoxide; entadamide C; (*R*)-(+)-*trans*-*N*-(2-hydroxyethyl)-3-methylsulphinylpropenamide; isolation; synthesis; absolute configuration.

Abstract—A third new sulphur-containing amide, entadamide C, has been isolated from the leaves of *Entada phaseoloides* together with entadamide A. The stereostructure including the absolute configuration of entadamide C was established as (*R*)-(+)-*trans*-*N*-(2-hydroxyethyl)-3-methylsulphinylpropenamide, the sulphoxide form of entadamide A, by spectroscopic methods and physical properties. Chemical synthesis of (±)-entadamide C was achieved in three steps from propiolic acid.

INTRODUCTION

In our recent papers [1, 2], we reported the isolation and structural elucidation of two new sulphur-containing amides, named entadamide A (**1**) and entadamide B, from the dry seed kernels of *Entada phaseoloides* Merr. Further studies on the basic components in the leaves of *E. phaseoloides* led to the isolation of a third new sulphur-containing amide, named entadamide C (**2**). In this paper we describe the isolation, structure, including the absolute configuration, and synthesis of a racemic modification of this new compound (**2**).



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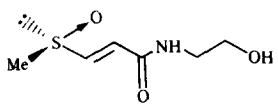

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RESULTS AND DISCUSSION

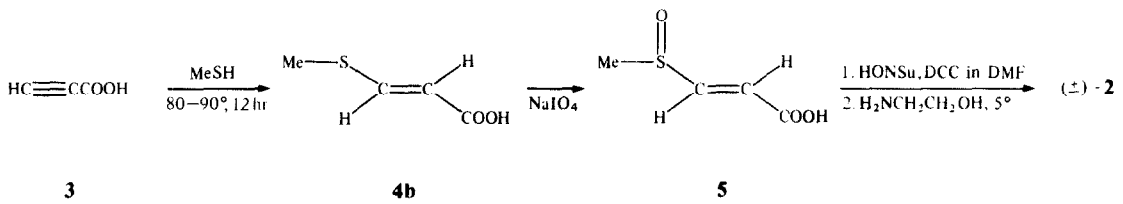
The basic fraction obtained from the 75% ethanolic extract of the air-dried leaves of *E. phaseoloides* was subjected to silica gel CC followed by preparative TLC according to the procedure described before [1] to afford a new sulphur-containing amide, named entadamide C (**2**, 27 mg, 0.004% of dry wt) together with entadamide A (**1**, 37 mg, 0.005% of dry wt) which was previously found in the seeds of the same plant [1].

Entadamide C (**2**) was recrystallized from acetone and obtained as colourless needles, mp 144–145° and $[\alpha]_D^{24}$ +186° (MeOH). It behaved like **1** with chromogenic reagents. The molecular formula of **2** was determined to be $C_6H_{11}NO_3S$ ($[M]^+$ *m/z* 177.0471, calcd 177.0460) by high resolution EIMS measurement. The IR spectrum (KBr) of **2** like that of **1** showed bands at 3400 cm^{-1} (OH), 3300 cm^{-1} (NH), 1655 cm^{-1} (amide CO) and 1620 cm^{-1} (C=C). However, an additional band was present at 1040 cm^{-1} (S=O).

The ^1H NMR spectrum in CD_3OD revealed the signals for a *trans*-disubstituted olefin [δ7.61 and 6.70 (each 1H, *d*, *J* = 14.6 Hz)], one isolated methyl group (δ2.75, 3H, *s*) and two methylene groups connected to each other [δ3.64 and 3.40 (each 2H, *t*, *J* = 5.8 Hz)].

The ^1H NMR spectrum measured in DMSO-d_6 showed the presence of an amide NH group (δ8.50, *br*, disappears on addition of D_2O) and an OH group (δ4.7, *br*, disappears on addition of D_2O). These assignments were supported by the ^{13}C NMR data (Table 1). The most marked difference in the ^{13}C NMR spectrum of **2** compared with that for **1** was the downfield shift of the methyl signal from δ14.7 to 40.0 (Table 1). This downfield shift suggested that the methyl group must connect to a more electronegative substituent than that of **1**. Furthermore, the molecular formula of **2** differed from **1** in composition by the increment of one oxygen atom, suggesting a sulphoxide form of entadamide A (**1**). The CD spectrum of **2** showed a positive Cotton effect ($[\theta]_{252}$ +6500), indicating that the absolute configuration of **2** should be *R* in comparison with those of the authentic compounds (*R*)-1-(4-methylsulphinyl-3(*E*)-butenyl)-thiourea ($[\theta]_{248}$ +6900) and its *N*-phenyl derivative ($[\theta]_{250}$ +7100) [3]. From the above results, the absolute stereostructure of

*Parts of this work were presented at the 108th Annual Meeting of the Pharmaceutical Society of Japan at Hiroshima, 4 April 1988 (Abstracts p. 291).



Synthesis of (±)-entadamide C (**2**)

Scheme 1.

Table 1. ^{13}C NMR spectral data for compounds **1** and **2**

C	**1** ($CDCl_3$)*	**2** (CD_3OD)
1	165.9 (*s*)	165.3 (*s*)
2	115.7 (*d*)	129.5 (*d*)
3	143.4 (*d*)	147.5 (*d*)
NH–CH_2	42.6 (*t*)	43.3 (*t*)
CH_2–OH	62.2 (*t*)	61.4 (*t*)
S–Me	14.7 (*q*)	40.0 (*q*)

*Data are based on ref. [1].

entadamide C (**2**) was established as (*R*)-(+)-*trans*-*N*-(2-hydroxyethyl)-3-methylsulphinylpropenamide.

The gross structure of **2** was also confirmed by direct comparison of the physical properties and spectral data with those of a synthetic compound, which was prepared by an addition reaction of methane thiol to propiolic acid (**3**), followed by oxidation and condensation of *trans*-3-methylsulphinylacrylic acid (**5**) with ethanolamine in a satisfactory yield (Scheme 1). The synthetic compound was found to be a racemic form of **2** by the comparison of its physical properties with those of the natural product.

EXPERIMENTAL

General. Mps uncorr. High and low resolution EIMS: 70 eV, direct inlet system; Optical rotations: MeOH; CD: MeOH; ^1H NMR and ^{13}C NMR: CD_3OD or DMSO-d_6 with TMS as internal standard. TLC: silica gel $60F_{254}$ pre-coated plates (0.25 mm, Merck) using CH_2Cl_2–MeOH (8:1) as a solvent, unless otherwise indicated; spots were visualized by exposing to UV light (254 nm) or I_2 vapour and by spraying with iodoplatinate reagent. All other chemicals used were of the highest commercial grade available.

Plant material. The leaves of *Entada phaseoloides* Merr. were collected in May 1986 in the suburbs of Chiang Mai, Thailand. Air-dried leaves (700 g) were used for this study.

Extraction and isolation of entadamide A (**1**) *and entadamide C* (**2**) were performed by the procedures of ref. [1]. Pure **1** (37 mg) was obtained as a colourless syrup; spectral data: see ref. [1]. The new compound **2** (27 mg), on recrystallization from Me_2CO, was obtained as colourless needles, Mp 144–145°; $[\alpha]_D^{24}$ +186° (MeOH; *c* 0.13); CD (*c* 1.4×10^{-2}; MeOH; 20°): $[\theta]_{252}$ +6500; UV λ_{max}^{EtOH} nm (log ε): 256 (3.87); IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 3300 (NH), 1655 (amide CO), 1620 (C=C), 1040 (S=O); ^{13}C NMR (67.8 MHz, CD_3OD, TMS): see Table 1; ^1H NMR (270 MHz, CD_3OD, TMS) δ: 7.61 (1H, *d*, $J = 14.6$ Hz, CH=CH–CO), 6.70 (1H, *d*, $J = 14.6$ Hz, CH=CH–CO), 3.64 (2H, *t*, $J = 5.8$ Hz, CH_2–OH), 3.40 (2H, *t*, $J = 5.8$ Hz, NH–CH_2), 2.75 (3H, *s*, Me–SO); ^1H NMR (270 MHz, DMSO-d_6, TMS) δ: 8.50 (1H, *br*, CONH, disappears on addition of D_2O), 7.67 (1H, *d*, $J = 15$ Hz, CH=CH–CO), 6.63 (1H, *d*, $J = 15$ Hz, CH=CH–CO), 4.7 (1H, *br*, OH, disappears on addition of D_2O), 3.44 (2H, *t*, $J = 5.8$ Hz, CH_2–OH), 3.21 (2H, *m*, NH–CH_2), 2.68 (3H, *s*, Me–SO); EIMS *m/z* (rel. int.): 177 [M^+] (5), 160 (19), 146 (33), 117 (52), 101 (75), 64 (100), 63 (63), 47 (79), 45 (97).

Synthesis of (±)-*entadamide C* (**2**). A mixture of propiolic acid (**3**, 5.0 g, 0.07 mol), methanethiol (6.8 g, 0.14 mol) and triethylenediamine (80 mg) was heated at 80–90° in a sealed tube for 12 hr to yield 3-methylthioacrylic acid (**4**) according to a modified method of refs [2, 4]. Since **4** was obtained as the mixture of *cis*-(**4a**) and *trans*-isomers (**4b**), it was refluxed in xylene for 24 hr. After removal of xylene, the residue was subjected to silica gel CC eluted with EtOAc to give *trans*-3-methylthioacrylic acid (**4b**), which was finally recrystallized from EtOAc to yield colourless needles (5.4 g, 64.3%). Pure **4b** was then allowed to oxidize with $NaIO_4$ (1.1 equiv.) to give (±)-*trans*-3-methylsulphinylacrylic acid (**5**), which was finally recrystallized from MeOH as a crystalline powder (5.1 g, 82%). To the cold mixture of **5** (1 g) and *N*-hydroxysuccinimide (HONSu, 0.98 g) in a small amount of DMF, a cold soln of DCC (1.5 g) was slowly added with stirring. The mixture was allowed to stand at 5° overnight, and then ethanolamine (0.76 g) in DMF (10 ml) was added dropwise [5]. After being stirred for 24 hr at 5°, the ppt. was filtered off and the filtrate evapd *in vacuo* to dryness. The residue was finally subjected to silica gel CC eluted with CH_2Cl_2–MeOH (8:1) to afford entadamide C (**2**), which was finally recrystallized from Me_2CO to yield (±)-*trans*-*N*-(2-hydroxyethyl)-3-methylsulphinylpropenamide as colourless needles (695 mg, 52.5%) (Scheme 1); mp 122–123°; $[\alpha]_D^{23}$ 0° (MeOH; *c* 0.12); IR: differed slightly from that of the natural one, 1020 cm^{-1} (S=O); other spectral data for ±**2** identical with those of natural **2** (see above).

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