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THE SYNTHESIS OF DENDRODOINE, 5-[3-(N,N-DIMETHYLAMINO-1,2,4-THIADIAZOLYL]-3-INDOLYLMETHANONE, A METABOLITE OF THE MARINE TUNICATE *DENDRODA GROSSULAR*

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Abstract - The cytotoxic natural product dendrodoine has been synthesised by a 1,3-dipolar addition reaction between indolyl-3-carbonyl nitrile and N,N-dimethylaminonitrile sulphide generated in situ through the thermolysis of 5-(N,N-dimethylamino)-1,3,4-oxathiazol-2-one.

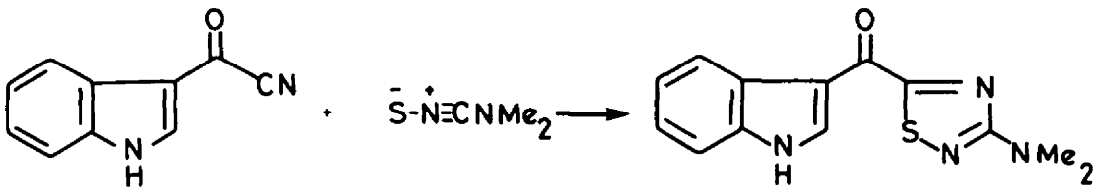
Recently the isolation and structure determination of dendrodoine (3), a metabolite of the marine tunicate Dendroda grossular (Styélidés) indigenous to the North Brittany coast was announced.[1] The constitution of this cytotoxic molecule is unusual for although the indolic ring and the side chain of tryptamine, or an equivalent precursor, appear to be incorporated into dendrodoine, the further biosynthetic elaboration of the side chain into a 1,2,4-thiadiazole unit is very rare, if not unique.

We now report the synthesis of the natural product via a 1,3-dipolar addition between indolyl-3-carbonyl nitrile (1) and N,N-dimethylaminonitrile sulphide (2).

Surprisingly, we can find no mention of indolyl-3-carbonyl nitrile in the chemical literature, although in our hands it is easily prepared by heating indolyl-3-carbonyl chloride[2] with copper(I)cyanide.[3] Indeed, we have devised a 'one pot' synthesis of this compound from indole and oxalyl chloride for it is unnecessary to isolate and purify the intermediate acid chloride prior to its reaction with copper(I)cyanide.

Nitrile sulphides can be generated by thermolysis of 1,3,4-oxathiazol-2-ones[4] and in our case the new starting material (6) was formed by treating N,N-dimethylurea (4) with chlorocarbonylsulphenyl chloride (5).[5] The product was then added slowly to a solution of indolyl-3-carbonyl nitrile (1) in N,N-dimethylformamide maintained at 145-150°, giving the nitrile sulphide (2) and thence dendrodoine (3).

After chromatographic purification, this compound was shown to have identical physical properties to those attributed to the natural product.[1]



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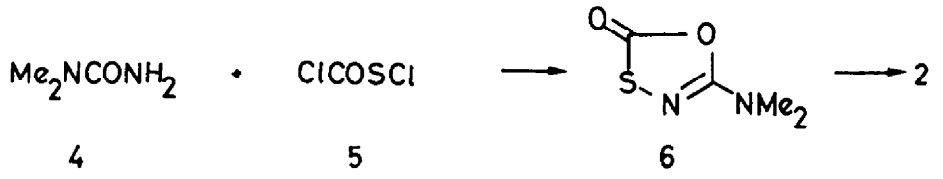

EXPERIMENTAL

Infra red data refer to Nujol mulls unless stated otherwise. ^{1}H N.m.r. spectra were recorded at 100 MHz and ^{13}C n.m.r. spectra at 22.5 MHz; in both instances chemical shift were measured downfield relative to tetramethylsilane as internal standard.

Indolyl-3-carbonyl nitrile (1). Oxalyl chloride (8.5 cm^3) was added dropwise to a vigorously stirred solution of indole (10 g) in diethyl ether (200 cm^3) maintained at ~0°. After 1 h, copper(I)cyanide (14.2 g), acetonitrile (8 cm^3) and toluene (150 cm^3) were introduced and the reaction mixture heated so that the diethyl ether distilled off. The residual material was maintained at 110° for 6 h, the solids were then removed by filtration and washed with acetonitrile. The filtrate and washings were combined, boiled with charcoal, again filtered and finally evaporated under reduced pressure to yield a pale yellow solid which was purified by chromatography over silica gel using dichloromethane as eluent. Indolyl-3-carbonyl nitrile prepared in this way is a colourless solid, m.p. ~190° (dec.), yield 53%. ν_{max} cm^{-1} 3200 br, 1615; δ_H (d^6-DMSO) 12.95 (1H, bs, NH), 9.60 (1H, s, H-2), 8.05 (1H, m, H-4), 7.82 (1H, m, H-7), 7.20 (2H, m, H-5, H-6); δ_C (d^6-DMSO) 158.6 (s, CO), 137.6 (s, C-7a), 124.8 (d, C-2, C-5), 124.3 (s, CN), 123.7 (d, C-4), 121.0 (d, C-6), 116.3 (s, C-3a), 114.3 (s, C-3), 113.3 (s, C-2, C-7)[6] m/z (EI), 170 (M$^+$, 77%), 144 (100%) [Found: C, 71.0; H, 3.4; N, 16.3 $C_{10}H_6N_2O$ requires; C, 70.6; H, 3.55; N, 16.5].

5-(N,N-Dimethylamino)-1,3,4-oxathiadiazol-2-one (6). Chlorocarbonylsulphenyl chloride (11.5 g)[7] in acetonitrile (20 cm^3) was added in portions to a suspension of N,N-dimethylurea (25 g) in acetonitrile (200 cm^3). The reaction mixture was stirred for 1 h and then filtered. Methanol was added to the filtrate in order to decompose excess chlorocarbonylsulphenyl chloride and the solvents then evaporated off at 40° in the presence of silica (100 g). The residue was added to the top of a column of silica and eluted with 3:1 dichloromethane, 60-80° petrol thus affording a yellow oil (9.6g, 74.5%) of the title compound. ν_{max} (liquid) cm^{-1} 2920, 1755, 1620; δ_H ($CDCl_3$) 3.05 2.85 (2 x S, 2 x 3H, 2 x NCH_3); m/z (EI) 146 (M$^+$, 23%), 72 (100%). On heating to ~60° this compound began to decompose and consequently it was used directly in the next step without further purification.

5-[3-(N,N-Dimethylamino)-1,2,4-thiadiazolyl]-3-indolylmethanone (3). Indolyl-3-carbonyl nitrile (100 mg) in N,N-dimethylformamide (1 cm^3) was heated to 145 - 150° and 5-(N,N-dimethylamino)-1,3,4-oxathiadiazol-2-one (0.8 cm^3) added in portions. After a few minutes the reaction mixture was cooled and added to the top of a column of neutral alumina. Elution with chloroform 60-80° petrol mixtures (1:1 — 2:1) afforded the title compound as yellow prisms (20 mg) m.p. 280-282°; mixed m.p. 280-283° (with authentic dendrodoine), lit.[1] 280-285°; ν_{max}cm^{-1} 3225, 1630w, 1598; δ_H (d^6-DMSO) 12.2 (1H, br, NH), 9.05 (1H, s, H-2), 8.42 (1H, m, H-4), 7.66 (1H, m, H-7), 7.41 (2H, m, H-5, H-6), 3.30 (6H, s, 2 x NCH_3); δ_H (d^6-Me_2CO) 9.35 (1H, d, H-2), 8.50 (1H, m, H-4), 7.65 (1H, m, H-7), 7.40 (2H, m, H-5, H-6), 3.25 (6H, s, 2 x NCH_3); δ_C (d^6-Me_2CO), 187.8 (s, CO), 175.7 (s, C-5'), 172.4 (s, C-3'), 138.3 (d, C-2), 136.6 (s, C-7a), 126.3 (s, C-3), 123.7 (d, C-5), 122.8 (d, C-6), 121.4 (d, C-4), 112.8 (d, C-4), 112.4 (s, C-3a), 38.6 (s, $N(CH_3)_2$. m/z 314 (M$^+$ 56%), 144 (100%), 129 (14), 102 (28) [Found: C, 57.2; H, 4.6; N, 20.7 calculated for $C_{13}H_{12}N_4OS$ C, 57.35; H, 4.4; N, 20.6%].

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