

THE CONFIGURATION OF THE SESQUITERPENOID 4-HYDROXY-MYOPORONE (ATHANAGRANDIONE)

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(Received 11 October 1983)

Key Word Index—*Ipomoea batatas*; Convolvulaceae; *Fusarium solani*; *Athanasia grandiceps*, sweet potato, sesquiterpenoid; configuration; 4-hydroxymyoporone; athanagrandonine; eremoacetal.

Abstract—The conversion of eremoacetal to (–)-1-(furan-3-yl)-4-hydroxy-4,8-dimethylnonane-1,6-dione establishes the configuration of (–)-4-hydroxymyoporone (athanagrandonine) as *R*.

Several papers have appeared concerning the furano-sesquiterpenoid stress metabolites of the sweet potato, including their biosynthesis [1–4]. Although much of the work has been directed towards 4-ipomeanol [1-(furan-3-yl)-4-hydroxypentan-1-one] and other lung toxins the range of constituents which has been isolated has also given considerable information regarding the oxygenation steps required to convert farnesol to the stress metabolites.

4-Hydroxymyoporone (**1**, stereochemistry not defined) was first reported in 1974 as a constituent isolated from sweet potatoes infected by *Fusarium solani* [5]. It was later found to arise [1] from ipomeamarone† and has been shown to be metabolized to the potent, pulmonary toxins [8]. Unfortunately, the optical rotation of 4-hydroxymyoporone was not reported [5] although it has been stated [3] that oxidation of ipomeamarone with *t*-butyl perbenzoate in the presence of cuprous chloride gave 4-hydroxymyoporone with the same (but not recorded) rotation as a sample isolated from sweet potatoes. Now that the absolute configuration of (–)-ngaione (**2**) [6] and (+)-ipomeamarone [7] has been confirmed it is possible to assign the configuration of 4-hydroxymyoporone from infected sweet potatoes as in **1**.

Subsequent to the discovery of 4-hydroxymyoporone, reported in 1974, Bohlmann and Zdero described, in 1978, a substance isolated from *Athanasia grandiceps* Hilliard et Burt and called it athanagrandonine [9]. This sesquiterpene, on the basis of spectral data, was also assigned the structure **1** without stereochemical details. In addition, its optical rotation was reported, $[\alpha]_D - 0.7^\circ$ (CHCl₃; *c* 2.8).

In this communication we report the preparation of (*R*)-1-(furan-3-yl)-4-hydroxy-4,8-dimethylnonane-1,6-

dione [(–)-4-hydroxymyoporone or athanagrandonine] from (+)-eremoacetal (**3**), a substance of established configuration [10]. Hydroboration of eremoacetal with a limited amount of diborane followed by treatment with alkaline hydrogen peroxide is known to give the expected epimeric secondary alcohols [11]. In addition, some of the nonanetriols (**4a** and **5a**), each as a mixture of stereoisomers, were obtained. The use of an excess of diborane and a longer reaction time has now given a high conversion to the nonanetriols. They presumably arise by the known [12] elimination of substituted boranes to generate a double bond followed by hydroboration of the double bond and reduction of the carbonyl group.

The triols (**4a** and **5a**) were easily separated from each other by chromatography of their diacetates (**4b** and **5b**). Reduction of the diacetates (**4b**) to the triols (**4a**) followed by oxidation with Fétizon's reagent [13] gave the diketone, ipomeanine [14], arising from retroaldol cleavage of 4-hydroxymyoporone. This reaction established the structure of the triols (**4a**) because the diketone derived from the triols (**5a**) would not undergo the retroaldol reaction. Oxidation of the triols (**4a**) with pyridinium chlorochromate or dimethylsulphoxide-oxalyl chloride [15] gave a mixture from which 4-hydroxymyoporone could be isolated. This sample had spectral data in agreement with those published [5, 14] and showed an optical rotation of $[\alpha]_D - 1.0^\circ$. Therefore, (–)-4-hydroxymyoporone (athanagrandonine, $[\alpha]_D - 0.7$ [9]) can be assigned the *R* configuration. Although the rotation of 4-hydroxymyoporone from infected sweet potatoes had not been reported its formation from ipomeamarone [3] establishes its configuration as *S* (**1**).

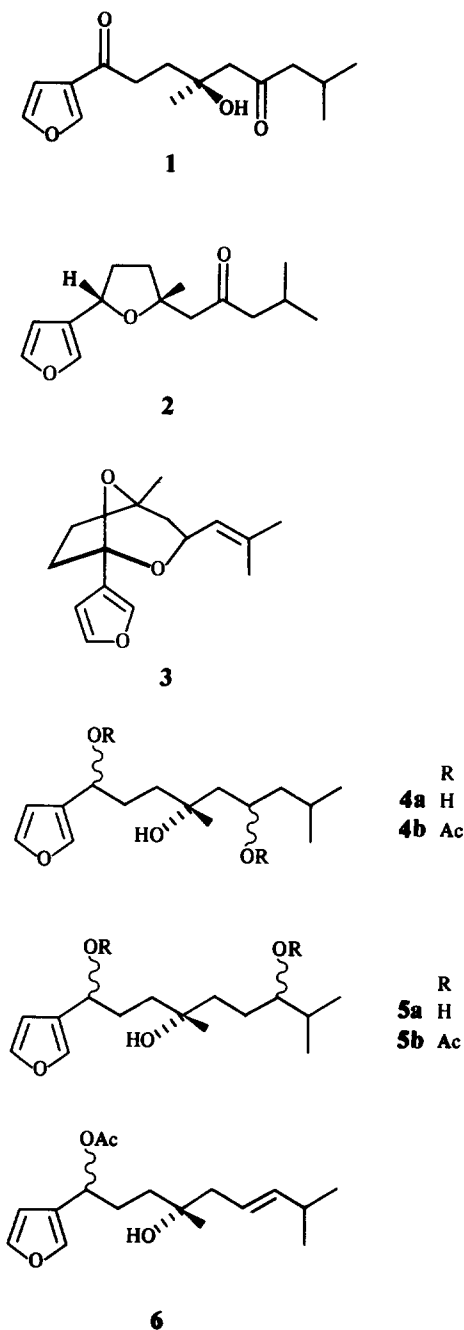
EXPERIMENTAL

¹H NMR spectra were recorded in CCl₄ at 60 MHz with TMS as internal standard.

Treatment of eremoacetal (3) with diborane. Eremoacetal (**3**) (2.48 g, 10 mmol) in dry THF (30 ml) under N₂ was treated with diborane (14 mmol, 0.9 M in THF) at 0° for 1 hr, followed by standing at room temp for 48 hr. NaOH soln (15 ml, 10%) and H₂O₂ (10 ml, 30%) were added and the mixture stirred for 1 hr. The aq. layer was separated and extracted with Et₂O (3 × 20 ml). The combined organic fractions were washed with brine, dried

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†Although the name ngaione should have priority [6] in the chemical literature ipomeamarone is in common use for its enantiomer [7]. Similarly, 4-hydroxymyoporone should have priority over athanagrandonine (its enantiomer). However, both ipomeamarone and athanagrandonine are used here because of their acceptance in the literature



and the solvents removed under red. pres. to yield a viscous oil (3 g). TLC showed the mixture to consist mainly of two polar components. The mixture was acetylated with Ac_2O and pyridine and the crude acetates were chromatographed on silica gel with mixtures of petrol and Et_2O .

The least polar fractions contained the acetates of the epimeric secondary alcohols (15%) expected from the hydroboration-oxidation sequence [11]. The next product eluted was 1-(furan-3-yl)-4-hydroxy-4,8-dimethylnon-6-enyl acetate (**6**) (9%). (Found: C, 69.4; H, 8.8. $\text{C}_{17}\text{H}_{26}\text{O}_4$ requires C, 69.4; H, 8.9%). IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 3500, 1740, 1380, 1245, 1030, 880, 800. ^1H NMR: δ 0.9–1.1 (9H, m), 2.0 (3H, s), 5.4 (2H, m), 5.6 (1H, t, $J = 7$ Hz), 6.3 (1H, m), 7.3 (2H, m).

Further elution gave 6-acetoxy-1-(furan-3-yl)-4-hydroxy-4,8-

dimethylnonyl acetate (**4b**), a mixture of stereoisomers, as a viscous oil (1.44 g, 40%). (Found. m/z 294.184. $\text{C}_{19}\text{H}_{30}\text{O}_6 - \text{HOAc}$ requires 294.183.) IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 3500, 1730, 1500, 1240, 1150, 1130, 1020, 940, 870. ^1H NMR: δ 0.93 (6H, d, $J = 6$ Hz), 1.12 (3H, s), 2.00 and 2.04 (each 3H, s), 2.5 (1H, br s, D_2O exch.), 5.18 (1H, m), 5.75 (1H, t, $J = 6$ Hz), 6.44 (1H, m), 7.4 (2H, m).

Continued elution gave 7-acetoxy-1-(furan-3-yl)-4-hydroxy-4,8-dimethylnonyl acetate (**5b**), a mixture of stereoisomers as a viscous oil (0.60 g, 17%). (Found. m/z 294.184. $\text{C}_{19}\text{H}_{30}\text{O}_6 - \text{HOAc}$ requires 294.183.) IR $\nu_{\text{max}}^{\text{film}} \text{cm}^{-1}$: 3500, 1735, 1500, 1240, 1150, 1020, 940, 860. ^1H NMR: δ 0.91 (6H, d, $J = 7$ Hz), 1.12 (3H, s), 2.04 (6H, s), 2.5 (1H, br s, D_2O exch.), 4.67 (1H, m), 5.77 (1H, t), 6.47 (1H, m), 7.45 (2H, m).

Oxidation of triols (4a). (i) Reduction of the diacetate (**4b**) with LiAlH_4 gave the triol (**4a**) which was used directly for the oxidation. A mixture of silver carbonate (200 mg) on celite (1 g) and the triols (**4a**, 45 mg) in C_6H_6 (20 ml) was heated under reflux for 3 hr. Filtration through celite and removal of the solvent under red. pres. gave 1-(furan-3-yl)pentane-1,4-dione (ipomeanine [14]) (20 mg, 72%) as a yellow oil, bp $90^\circ/0.05$ mm (block) (lit. [16] $74\text{--}79^\circ/0.001$ mm). The product had IR and ^1H NMR spectra identical with those reported [14].

(ii) The triols (**4a**, 250 mg, 0.94 mmol) in CH_2Cl_2 (5 ml) were added to a suspension of pyridinium chlorochromate (1.4 g, 6.7 mmol) and dry NaOAc (0.3 g) in dry CH_2Cl_2 (60 ml) at room temp. TLC showed the presence of four new products and no starting material. After isolation, the crude mixture was separated by prep. TLC (Et_2O -petrol, 3:2). The highest R_f , UV active compound was (*R*)-(-)-1-(furan-3-yl)-4-hydroxy-4,8-dimethylnonane-1,6-dione [(*-*)-4-hydroxymyoporone or athanagrandione] (40 mg, 17%) isolated as a yellow oil [$[\alpha]_D^{20} + 2.7^\circ$, $[\alpha]_D^{600} - 0.8^\circ$, $[\alpha]_D^{20} - 1.0^\circ$, $[\alpha]_{377}^{20} - 0.8^\circ$, $[\alpha]_{346}^{20} - 1.7^\circ$, $[\alpha]_{436}^{20} > +85^\circ$ (CHCl_3 ; c 2.0) [lit. [9] for athanagrandione $[\alpha]_D - 0.7^\circ$ (CHCl_3 ; c 2.8)]. The IR, ^1H NMR and mass spectra were identical with those recorded [5, 9]. The other products were mainly mono-ketones and their cyclic acetals, including dihydroeremoacetal [10]. Oxidation of the triols (**4a**) with dimethylsulphoxide-oxalyl chloride [15] gave a similar result.

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