

INEUPATORIOL, A THIOPHENE ANALOGUE OF ICHTHYOTHEREOL, FROM *INULA EUPATORIODES*

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Abstract—Ineupatoriol, a thiophene analogue of ichthyothereol, was isolated from *Inula eupatorioides*. The absolute stereochemistry is that of ichthyothereol.

INTRODUCTION

An earlier article by some of us [1] concerned itself with the structure determination of several germacranolides from the CHCl_3 extract of *Inula eupatorioides* DC. We now describe the isolation and structure determination of the acetylenic 3-hydroxytetrahydropyran **1a** from the non-polar part of the extract. **1a**, which we have named ineupatoriol, is a thiophene analogue of the potent fish poison ichthyothereol **4a** [2–4].

RESULTS AND DISCUSSION

Ineupatoriol (**1a**), $\text{C}_{14}\text{H}_{16}\text{O}_2\text{S}$ (high resolution mass spectrometry), was a relatively unstable noncrystalline secondary alcohol which furnished a monoacetate **1b**, $\text{C}_{16}\text{H}_{18}\text{O}_2\text{S}$ (IR bands at 3590 and 3450 replaced by carbonyl band at 1730 cm^{-1} , paramagnetic shift of a one-proton multiplet from δ 3.39 to 4.63). Recognition that **1a** was a methyl 2-thienylacetylene came from a comparison of its ^1H NMR spectrum (Table 1) with that of its hexahydro derivative **2** and from the ^{13}C NMR spectrum (see Experimental). As a result of the reduction, the group $\text{MeC}\equiv\text{C}-$ (very weak IR band at 2240 cm^{-1} , ^1H NMR signal at δ 2.07, ^{13}C NMR signals at δ 4.66 q, 90.97 s and 73.28 s [5]) was transformed into $\overset{1}{\text{CH}_3}\overset{2}{\text{CH}_2}\overset{3}{\text{CH}_2}-$ (numbering as in final structure) with the chemical shift of H-3 indicating that it was allylic. Simultaneously, a *trans* double bond of type $\overset{8}{\text{CH}}=\overset{9}{\text{CH}}-\overset{10}{\text{CHR}_2}$ ($J_{8,9} = 16\text{ Hz}$) which because of the chemical shift of H-8 and H-9 (δ 6.74 and 6.06) had to be part of a conjugated system was reduced to $\text{CH}_2\text{CH}_2\text{CHR}_2$. These changes were particularly evident in the NMR spectrum (C_6D_6) of the Jones oxidation product **3** which was used for extensive decoupling experiments. In **3** (but not in **1a** or **1b**), H-3 and H-8 were allylically coupled to two mutually coupled protons H-5 and H-6 ($J_{5,6} = 3\text{ Hz}$) whose signals (δ 6.52 and 6.59) appeared somewhat upfield from their position in **1a**, **b** and were identified with

two β -hydrogens on a thiophene ring. The upfield shift was ascribed to saturation of the conjugated double and triple bonds. Consequently, ineupatoriol was a 2,5-disubstituted thiophene. H-10 of ineupatoriol was further coupled to the proton on the carbon carrying the secondary hydroxyl group (H-11). The chemical shift of H-10 (δ 3.59) indicated that C-10 also carried the second, remaining oxygen atom of ineupatoriol in the form of an ether bridge which was in turn attached to a methylene (carbon triplet at δ 67.56). As only one methyl group was present (^1H and ^{13}C NMR spectra), ineupatoriol was a 2-substituted 3-hydroxytetrahydropyran of formula **1a**. This was verified by deriving the sequence H-12–H-14 in **3** through decoupling (Table 1). The carbon chemical shift changes accompanying the conversion of **1a** to **1b** (see Experimental) also agreed with this formulation. The magnitude of $J_{10,11}$ (9 Hz in **1a**, 10 Hz in **1b**) was comparable to that reported for **4b** (9 Hz) [3, 4], hence the relative stereochemistries were the same (H-10, H-11 *trans*). The absolute configuration of ichthyothereol, first deduced from the negative Cotton effect of the saturated ketone **5** [2, 3], was confirmed [4] by degradation of **4b** to the enantiomer **6** of a substance derived from D-glucose. As the CD spectrum of hexahydroketone **3** also exhibited a negative Cotton effect ($\Delta\epsilon_{298} = -0.682$) the absolute configuration of ineupatoriol was the same as that of ichthyothereol and was correctly represented by **1a**.

Ichthyothereol and its acetate have so far been found in *Ichthyothere terminalis* [2, 3], in various *Dahlia* [2, 4, 7] and *Clibadium* species [8, 10] and in some Anthemidae [11–13], but not in Inuleae and the combination of a thiophene ring with a 3-hydroxy-pyranoid end-group appears to be new.

EXPERIMENTAL

The extraction of *I. eupatorioides* has been described [1]. Fractions 5 and 6 (C_6H_6 –EtOAc, 9 : 1) and 7–9 (C_6H_6 –EtOAc, 4 : 1) which exhibited one major spot on TLC were combined (2 g from 1.5 kg of above-ground parts) and rechromatographed over 100 g Si gel (60–120 mesh, BDH India),

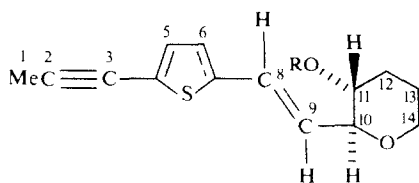
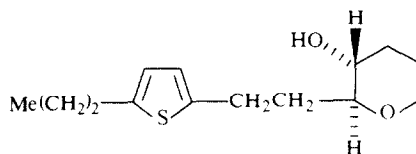
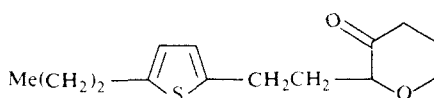
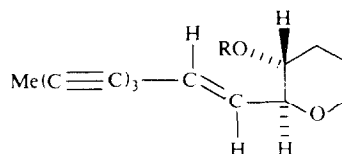
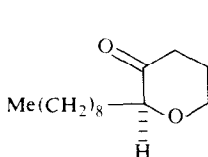
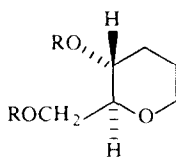
Table 1. ^1H NMR data for compounds **1–3** (270 MHz, CDCl_3 , TMS as internal standard)*

	1a	1b	2	2 (C_6D_6)	3 (C_6D_6)
H-1†	2.07 <i>s</i>	2.07 <i>s</i>	0.95 <i>t</i> (7)	0.83 <i>t</i> (7.5)	0.82 <i>t</i> (7)
H-2‡	—	—	1.67 <i>sext</i> (7)	1.56 <i>sext</i> (7)	1.55 <i>sext</i> (7)
H-3‡	—	—	2.71 <i>t(br)</i> (7)	2.58 <i>t(br)</i> (7)	2.56 <i>t(br)</i> (7)
H-5	6.94 <i>d</i> (3)	6.94 <i>d</i> (3)	6.39 <i>d(br)</i> (3)	6.64 <i>d(br)</i> (3)	6.52 <i>d(br)</i> (3)
H-6	6.79 <i>d</i> (3)	6.78 <i>d</i> (3)	6.56 <i>d(br)</i> (3)	6.54 <i>d(br)</i> (3)	6.59 <i>d(br)</i> (3)
H-8	6.74 <i>d</i> (16)	6.67 <i>d</i> (16)	2.9 <i>m</i> ‡	3.58 <i>s</i> ‡‡	2.93 <i>m</i> ‡
H-9a	6.06 <i>dd</i> (16, 6)	5.95 <i>dd</i> (16, 7)	2.19 <i>m</i>	2.27 <i>m</i>	2.30 <i>dtd</i> (15, 8, 3.5)
H-9b	—	—	2.10 <i>m</i>	1.87 <i>m</i>	2.04 <i>dtd</i> (15, 7, 9)
H-10	3.59 <i>dd</i> (9, 7)	3.80 <i>dd</i> (10, 7)	3.03 <i>td</i> (9, 2.5)	3.0 <i>m</i>	3.50 <i>dd</i> (9, 3.5)
H-11	3.39 <i>m</i>	4.63 <i>td</i>	3.31 <i>m</i>	3.1 <i>m</i>	—
H-12a	—	2.21 <i>m</i>	—	—	2.14 <i>m</i> [§]
H-12b {	undetermined	1.55 <i>s</i>	{ undetermined	{ undetermined	1.76 <i>m</i>
H-13a {	undetermined	2.05 <i>m</i>	{ undetermined	{ undetermined	1.55 <i>m</i> **
H-13b {	undetermined	1.74 <i>m</i>	{ undetermined	{ undetermined	1.25 <i>m</i> ††
H-14a	3.95 <i>dm</i> (11)	3.98 <i>m</i> (11)	3.90 <i>dm</i> (12)	3.71 <i>dd(br)</i> (11, 5)	3.58 <i>dddd</i> **
H-14b	3.39 <i>m</i>	3.45 <i>td</i> (11, 4)	3.31 <i>m</i>	3.0 <i>m</i>	3.07 <i>ddd</i>

*Coupling constants (Hz) in parentheses.

†Intensity three protons.

‡Intensity two protons.

[§] $J_{12a,12b} = 16$, $J_{12a,14a} = 1.5$ Hz.^{||} $J_{12b,13a} = 10.5$, $J_{12b,13b} = 6.5$ Hz.** $J_{13a,14b} = 5.5$, $J_{13a,14b} = 11$ Hz.†† $J_{13b,14a} = 4$, $J_{13b,14b} = 3.5$ Hz.‡‡ J_{14a} , $J_{14b} = 11$ Hz.**1a** R = H**1b** R = Ac**2****3****4a** R = H**4b** R = Ac**5****6** R = 3,5 — dinitrobenzoyl

100 ml fractions being collected as follows: fractions 1–9 (C_6H_6), 10–15 (C_6H_6 –EtOAc, 9 : 1), 16–20 (C_6H_6 –EtOAc, 4 : 1), 21–25 (C_6H_6 –EtOAc, 2 : 1). Fractions 6–9 which did not crystallize were combined to give **1a** (0.5 g): UV λ_{max}^{EtOH} nm: 211, 244, 273 (sh), 310, 322 (sh) ($\log \epsilon$ 4.06, 3.69, 3.70, 4.29, 4.18) (ϵ 3.79×10^{-5}); IR $\nu_{max}^{CHCl_3}$ cm^{-1} (after rechromatography): 3590 (OH), 3450 (bonded OH), 3070 (weak), 2940, 2860, 2240 (weak, $C \equiv C$), 1650, 1620, 1530 (weak), 1470, 1455, 1445, 1100, 1035, 970. [Calc. for $C_{14}H_{15}O_2S$: MW, 248.0870. Found: MW(MS), 248.0865 (41.2%). Other significant peaks in the high resolution MS were at m/z (rel. int.): 230 [$C_{14}H_{14}OS$]⁺ (11.4), 178 [$C_{10}H_{10}OS$]⁺ (28.4), 177 [$C_{10}H_9OS$]⁺ (55.9), 149 [C_9H_9S]⁺ (28.4), 148 [C_9H_8S]⁺ (48.6), 147 [C_9H_7S]⁺ (33.2), 135 [C_8H_7S]⁺ (23.4), 100 [$C_8H_6C_2$]⁺ (41.8, A) and 71 [C_4H_7O]⁺ (100, B); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 4.66 (q, C-1), 25.43 (t, C-13), 32.03 (t, C-12), 67.56 (t, C-14), 70.17 (d, C-10), 73.28 (s, C-3), 83.05 (d, C-11), 90.97 (s, C-2), 123.34 (s, C-4), 126.04 (d), 126.08 (d), 127.30 (d), 131.40 (d) (C-5, C-6, C-8 and C-9), 141.86 (s, C-7).

Acetylation of 30 mg **1a** with Ac_2O –pyridine at room temp. overnight followed by the usual work-up and TLC gave 30 mg **1b** as a gum, IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2230 (weak), 1730, 1660, 1640, 1230, 1075, 1030, 950; MS (after repurification) m/z : 290 [M]⁺, 248, 230, 100(A), 71(B); ^{13}C NMR ($CDCl_3$): δ 4.70 (s, C-1), 21.12 (q, Me of acetate), 24.89 (t, C-13), 29.21 (t, C-12), 67.47 (t, C-14), 71.58 (d, C-10), 73.29 (s, C-3), 89.87 (t, C-11), 90.97 (s, C-2), 123.15 (s, C-4), 125.45 (s), 125.70 (d), 126.47 (d), 131.20 (d, C-5, C-6, C-8 and C-9); 141.74 (s, C-7), 169.87 (s, C=O).

A soln of 35 mg **1a** in 25 ml EtOAc was hydrogenated over 10% Pd/C for 1 hr and worked-up in the usual manner. Separation of the major product by prep. TLC (EtOAc– C_6H_6 , 1 : 9) gave 30 mg **2** as gum, IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3300–3600 (bonded OH), 1600, 1080, 1025 and 925; MS m/z 254 [M]⁺, 236, 100(A), 71(B).

A soln of 30 mg **2** in 10 ml Me_2CO was cooled to 0° and allowed to stand with 0.1 ml of Jones reagent at 5° for 0.5 hr.

Excess reagent was destroyed by addition of 5 ml MeOH. The mixture was dil. with H_2O and extracted with $CHCl_3$. The washed and dried extract was evapd and the residue purified by prep. TLC (C_6H_6 –EtOAc, 15 : 1) to give 20 mg **3** as a gum; IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1710, 1100, 1025, 915; CD curve (EtOH, c 2.99×10^{-4}) $\Delta\epsilon_{298}$ –0.682 (min), $\Delta\epsilon_{262}$ –0.110 (max), $\Delta\epsilon_{240}$ –0.410 (min); [Calc. for $C_{14}H_{20}O_2S$: MW 252.1184. Found: MW(MS), 252.1159 (16.9%).] Other significant peaks in the high resolution MS were at m/z (rel. int.) 153 [$C_9H_{13}S$]⁺ (35.4), 152 [$C_9H_{12}S$]⁺ (35.7), 139 [$C_8H_{11}S$]⁺ (71.3), 140 [$C_8H_{12}S$]⁺ (30.6), 123 [C_7H_7S]⁺ (68.4), 111 [C_6H_7S]⁺ (30.4), 110 [C_6H_6S]⁺ (16.3), 100 (C_5H_8O)⁺ (100, A by H transfer). As expected peak B was absent.

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