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Phytochemistry, Vol. 21, No. 1, pp. 243–244, 1982.
Printed in Great Britain.

0031-9422/82/010243-02 $03.00/0

HELIPYRONE FROM *ANAPHALIS ARANEOSA* AND ITS SYNTHESIS*

ESAHAK ALI, DEBASIS BAGCHI and SATYESH C. PAKRASHI†

Indian Institute of Experimental Medicine, Calcutta-32, India

(*Received* 8 *May* 1981)

Key Word Index—*Anaphalis araneosa*; Compositae; helipyrone; NMR spectra; synthesis; β-sitosterol; stigmasterol; anisic acid.

Abstract—The dimeric 4-hydroxy-2-pyrone, heliopyrone, was isolated from *Anaphalis araneosa* and its structure confirmed by spectral analysis and synthesis.

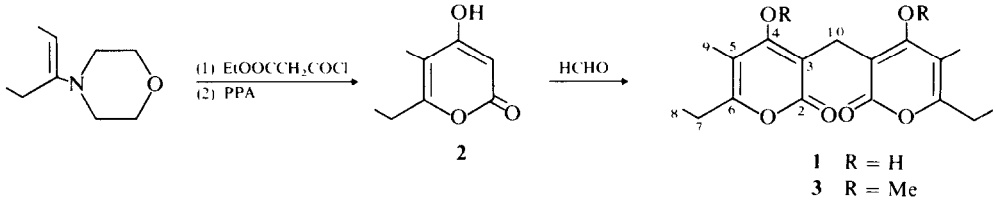
We earlier reported two new flavones from *Anaphalis araneosa* [1]. The petrol extract of the same plant yielded another crystalline compound, mp 218–220°, in addition to anisic acid and a mixture of β-sitosterol and stigmasterol. From extensive spectral data, the compound was identified as helipyrone (**1**), a dimeric 4-hydroxy-2-pyrone, isolated previously from *Helichrysum italicum* [2]. Helipyrone and several other derivatives containing the same pyrone unit have since been reported from a number of other *Helichrysum* species [3,4].

The ^{13}C NMR spectra of helipyrone was studied in detail. The assignments (see Experimental) were made on the basis of chemical shift rules and selective proton decoupling. It may be noted that the methylene bridge protons show long-range coupling to both C-3 ($^2J_{C,CH_2}$ = 6.1 Hz) and C-2 ($^3J_{C,CH_2}$ = 5.5 Hz). Consequently, the recent assignment [4] of C-3 and C-5 resonances in helipyrone and its derivatives needs to be interchanged.

The compound showed moderate *in vitro* antitumor activity against L5178Y cell culture carried out by Dr. T. Ikekawa, National Cancer Center Research Institute, Tokyo. Therefore, although a synthesis of helipyrone has already been reported [5] we accomplished the same result by a different route. Condensation of malonic ester half acid chloride with morpholine enamine of diethyl ketone followed by PPA cyclization of the crude reaction product yielded 6-ethyl-4-hydroxy-5-methyl-α-pyrone (**2**) [5]. Condensation of **2** with formaldehyde [5] furnished helipyrone (**1**).

EXPERIMENTAL

Flowering plants of *Anaphalis araneosa* DC (1.5 kg) were extrd with petrol as previously reported [1]. The extract was concd and extrd with 5% NaOH soln. The alkali-insol. part on chromatography over Si gel gave a mixture of β-sitosterol and stigmasterol (230 mg), mp 154°; M^+ *m/z* 414, 412. The alkali-



2

1 R = H
3 R = Me

* Part 65 in the series "Studies on Indian Medicinal Plants". For Part 64, see Dutta, P. K., Chakravarty, A. K., Chaudhury, U. S. and Pakrashi, S. C., *Indian J. Chem.* (in press).

† To whom all correspondence should be addressed.

soluble part on chromatography over Si gel yielded, in order of elution, helipyrone (220 mg), araneosol (30 mg), araneol (50 mg) and anisic acid (20 mg).

Helipyrone (**1**). Crystallized from petrol–$CHCl_3$ as colourless prisms, mp 218–220°; IR (nujol) cm^{-1}: 3300–2500 (bonded OH), 1680 (CO) 1610, 1560; UV λ_{max}^{EtOH} nm: 217 *sh* (log ε 4.67), 287 (log ε 4.17), 305 *sh* (log ε 4.18); ^1H NMR (60 MHz, $CDCl_3$): δ 11.13 (OH), 3.53 ($-CH_2-$), 2.57 *q* ($-C\underline{H}_2-CH_3$), 1.20 *t* ($-CH_2-C\underline{H}_3$), 1.98 (5-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.29 *q* (C-9, ^1J = 130 Hz), 11.43 *qt* (C-8, ^1J = 129.4 Hz, ^2J = 5.5 Hz), 19.26 *t* (C-10, ^1J = 130 Hz), 24.32 *qt* (C-7, ^1J = 128 Hz, ^2J = 4.3 Hz), 101.59 *t* (C-3, ^2J = 6.1 Hz), 108.59 *m* (C-5), 160.97 *m* (C-6), 168.32 *m* (C-4), 169.16 *t* (C-2, ^3J = 5.5 Hz); MS: *m/z* (rel. int.) 320 (M^+, 36), 291 (7), 263 (4), 207 (18), 180 (27), 166 (62), 154 (67), 137 (72), 126 (71), 113 (34), 111 (33), 83 (100), 57 (87); (Found: C, 63.80; H, 6.67%; $C_{17}H_{20}O_6$ requires: C, 63.74; H, 6.29%.) Identical in all respects with an authentic sample of helipyrone [2].

Di-O-methyl helipyrone (**3**). Helipyrone (20 mg) was treated with excess of CH_2N_2–Et_2O. Usual work-up yielded the dimethyl ether **3** as an oil (15 mg). IR (film) cm^{-1}: 1715, 1680, 1595; ^1H NMR (60 MHz, $CDCl_3$): δ 1.21 *t* ($C\underline{H}_3$ CH_2), 1.92 (5-CH_3), 2.44 *q* ($C\underline{H}_2-CH_3$), 3.54 ($-CH_2-$), 3.84 ($-OCH_3$); MS: *m/z* (rel. int.) 348 (M^+, 97), 333 (56), 315 (8), 305 (36), 277 (46), 245 (41), 221 (100), 193 (13), 182 (23), 181 (27), 167 (20), 113 (19), 57 (42).

Synthesis of helipyrone (**1**) *and 6-ethyl-4-hydroxy-5-methyl-α-pyrone* (**2**). Ethylmalonyl chloride (0.015 mol, 2.25 g) was added dropwise to a soln of morpholine enamine and diethyl ketone [6] (0.0298 mol, 4.62 g) in 5 ml of dry C_6H_6 over a period of 15 min. The mixture was stirred for 2 hr and then kept overnight. To the cooled reaction mixture was added 5 ml C_6H_6, 5 ml of H_2O and 5 ml of HCl–H_2O (1:1) and the mixture stirred for 1 hr. The C_6H_6 layer was sepd, washed with 0.1 N HCl, followed by H_2O, dried and distilled to yield 900 mg of an oil. Without further purification, 300 mg of this oil was allowed to react with polyphosphoric acid (prepared from 3 g of P_2O_5 and 2 ml orthophosphoric acid) at 120° for 1.5 hr. Usual work-up followed by chromatography of the product yielded 150 mg of **2** as colourless needles, mp 155° (lit. [3] 156–157°); IR (nujol) cm^{-1}: 3340 *br*, 1655, 1635 *sh*, 1610, 1565; UV λ_{max}^{EtOH} nm: 282 (log ε 4.15); ^1H NMR (100 MHz, $CDCl_3$): δ 1.21 *t* ($-CH_2-C\underline{H}_3$), 1.98 (5-CH_3), 2.58 *q* ($-C\underline{H}_2-CH_3$), 5.7 (H-3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.72 (C-2), 167.68 (C-4), 163.61 (C-6), 108.20 (C-5), 89.76 (C-3), 24.48 (C-7), 11.39 (C-8), 8.98 (C-9); MS: *m/z* (rel. int.) 154 (M^+, 100), 126 (90), 111 (58), 83 (94), 69 (51), 57 (64). *Helipyrone* (**1**). To a soln of **2** (70 mg) in EtOH (3 ml) was added conc HCl (1 drop) and HCHO (0.4 ml) and the mixture heated at 100°. After 1 hr, another 0.4 ml of HCHO was added and the mixture evapd to dryness. The residue on crystallization yielded 60 mg of helipyrone identical (IR, TLC and mp) with the natural product.

Acknowledgements – The authors are indebted to Professor R. Hänsel, Free University, Berlin, for an authentic sample of helipyrone and Dr. J. Uzawa, Institute of Physical and Chemical Research, Saitama, Japan, for some of the ^{13}C NMR data.

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