

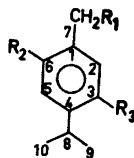
New Thymol Derivatives from *Inula salicina* L.

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From root extracts of *Inula salicina* L. we have isolated two aromatic esters of isobutyric acid, 7-isobutyryloxythymol methyl ether (1) and 7-isobutyryloxythymohydroquinone dimethyl ether (2), and a vinylpentaacetylene.

Thymol methyl ether (3) and thymohydroquinone dimethyl ether (4) have been isolated from a number of plants belonging to the Compositae family.<sup>1</sup> Recently also isobutyrylates of thymol derivatives have been found in *Gailardia* and *Helenium* species of the same family.<sup>2</sup> We now wish to report the finding of two isobutyrylates in root extracts of another member of the Compositae family, *Inula salicina* L. The esters, which are difficultly separable oils, were



1.  $R_1 = O\text{-isobut.}$ ,  $R_2 = H$ ,  $R_3 = OMe$ . 2.  $R_1 = O\text{-isobut.}$ ,  $R_2 = R_3 = OMe$ . 3.  $R_1 = R_2 = H$ ,  $R_3 = OMe$ . 4.  $R_1 = H$ ,  $R_2 = R_3 = OMe$ . 5.  $R_1 = OH$ ,  $R_2 = H$ ,  $R_3 = OMe$ . 6.  $R_1 = OH$ ,  $R_2 = R_3 = OMe$ . 7.  $R_1 = R_3 = H$ ,  $R_2 = OMe$ .

purified by column and thin-layer chromatography followed by vacuum distillation. Their molecular formulae were determined by accurate mass measurements as being  $C_{15}H_{22}O_3$  and  $C_{16}H_{24}O_4$ .

The isobutyryloxy group was revealed by an absorption in the infrared spectrum at  $1735\text{ cm}^{-1}$  and a six proton doublet at  $\tau\ 8.85$  ( $J = 6.9\text{ Hz}$ ) coupled to a one proton septet at 7.47 in the NMR spectrum. That the isobutyric acid was present as an ester of a primary, more specifically benzylic, alcohol was indicated by the hydrolysis products. In the NMR spectrum (Table 1) of the

Table 1. NMR spectra in  $\text{CCl}_4$  solution of the compounds treated in this communication. For numbering, see formulas 1–7.

Compound	5	6	2	3	8	9, 10	7
$\text{C}_{15}\text{H}_{22}\text{O}_3$ (1)	2.88	3.19	3.24	6.21	6.70	8.81	4.98
$\text{C}_{16}\text{H}_{24}\text{O}_4$ (2)	3.20	6.21	3.28	6.21	6.69	8.81	4.91
Thymol methyl ether (3)	3.03	3.41	3.49	6.27	6.75	8.81	7.71
Thymohydroquinone dimethyl ether (4)	3.38	6.23	3.41	6.23	6.72	8.81	7.81
$\text{C}_{11}\text{H}_{16}\text{O}_3$ (5)	2.93	3.27	3.24	6.22	6.72	8.81	5.53
$\text{C}_{12}\text{H}_{18}\text{O}_3$ (6)	3.22	6.21	3.33	6.21	6.71	8.83	5.49
Carvacrol methyl ether (7)	3.41	6.22	3.05	3.38	7.18	8.80	7.89

alcohol (5), formed on hydrolysis of the isobutyrate 1, the signals from the isobutyryl group are replaced by a one proton singlet at  $\tau$  7.70, due to a hydroxy group.

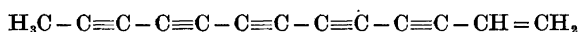
Moreover, a sharp two proton singlet at  $\tau$  4.98 in the spectrum of the ester 1 is shifted upfield to 5.53.

The NMR spectra of the two esters 1 and 2 show that they are 1,2,4-trisubstituted and 1,2,4,5-tetrasubstituted benzene derivatives, respectively. The spectrum of the ester 1 shows two protons in *ortho* position to each other ( $J=8.0$  Hz) at  $\tau$  2.88 and 3.19, the latter in turn further split into a double doublet ( $J=1.6$  Hz), due to coupling to a proton in its *meta* position, which appears as a narrow doublet at  $\tau$  3.24. The spectrum of the ester 2 has in the same region only two singlets at  $\tau$  3.20 and 3.28 diagnostic of two protons in *para* position to each other and not further coupled.

The presence in the NMR spectra of a one proton septet ( $J=6.9$  Hz) at  $\tau$  6.70 and a six proton doublet at 8.81 indicated a further isopropyl group and thus that the esters were thymol derivatives, or more specifically *p*-cymol derivatives, with one (6.21 3H) and two (6.21 6H) methoxy groups, respectively.

Hydrogenolysis of the ester 1 with hydrogen on palladized alumina<sup>3</sup> furnished an oily product in the NMR spectrum, of which signals from the benzylic ester group were replaced by a three proton singlet at  $\tau$  7.71 diagnostic of an aromatic methyl group. This compound was shown to be identical with thymol methyl ether (3) in chromatographic and spectroscopic properties and definitely different from carvacrol methyl ether (7) (see Table 1).

In addition to the two aromatic isobutyrate we have isolated trace amounts of a polyacetylene with UV spectrum diagnostic of an enepentyne. This compound is probably identical with the most widely distributed polyacetylene in the Compositae family,<sup>4</sup> the explosive hydrocarbon



In small amounts were also present  $\beta$ -sitosterol, friedelin, and two triterpenoids,  $\text{C}_{30}\text{H}_{52}\text{O}$  and  $\text{C}_{32}\text{H}_{52}\text{O}_2$ . No further attempts were done to identify them.

## EXPERIMENTAL

The following instruments were used for recording the spectral data: IR, Perkin Elmer 257; NMR, Varian A-60A; and MS, AEI MS 902. The solvents used for NMR spectroscopy, carbon tetrachloride and tetramethylsilane, and the silica gel and silica gel G for column and thin-layer chromatography were supplied by Merck.

Dried, finely ground roots of *Inula salicina* L. (150 g) were extracted in a Soxhlet extractor with ethyl acetate for 5 h. This extract on evaporation gave a dark, viscous oil (11 g) which was dissolved in chloroform and applied to a dry silica column. On elution with petroleum ether-ether mixtures, and finally methanol, a number of fractions were collected. The monoterpene fraction, obtained on elution with petroleum ether-ether (3:1) was evaporated to give a yellow oil (1.0 g, 6.7 % of dry weight). This oil was resubjected to column chromatography on alumina grade II, and the esters 1 and 2 occurred in the fraction obtained on elution with petroleum ether-ether (4:1).

Further purification was undertaken by TLC (silica gel G: 0.5 mm, eluted twice with 10 % ether in petroleum ether). The esters 1 and 2 occurred admixed in the two main zones. Distillation and redistillation resulted in the isolation of virtually pure 1 (b.p. 70–75°/0.1 mm, 0.27 g, 0.18 % of dry weight; MW 250.1570, calc. for  $C_{15}H_{22}O_3$ , 250.1569), and 2 (b.p. 95–105°/0.1 mm, 0.16 g, 0.11 % of dry weight; MW 280.1674 as calc. for  $C_{18}H_{24}O_4$ ).

Alkaline hydrolysis of 1 was accomplished by heating on steam bath at 80°C for 2 h with KOH in MeOH (ca. 10 %) and gave isobutyric acid and 5 (MW 180.1152, calc. for  $C_{11}H_{18}O_2$ , 180.1150), while similar treatment of 2 yielded isobutyric acid and some impure 6 (MW 210.1253, calc. for  $C_{12}H_{18}O_3$ , 210.1256).

Hydrogenolysis over palladium/activated alumina (10 % Pd) (Fluka) in 5 % acetic acid in methanol for 7 h at 20°C resulted in the quantitative conversion of 1 to 3 and of 2 to 4. 4 and 3 were identified by comparison of their NMR spectra and TLC behaviour as compared with those of synthetic samples of 3, 4 and 7. The methyl ethers of thymol, thymohydroquinone, and carvacrol 3, 4, and 7 were prepared by methylation with dimethyl sulphate and potassium carbonate of the corresponding phenols.

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