

NATURAL AND SYNTHETIC MATERIALS WITH THE INSECT  
HORMONE ACTIVITY. XIII.\*

AROMATIC TERPENIC THIOETHERS

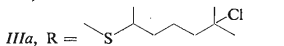
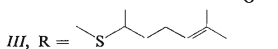
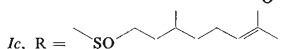
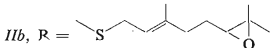
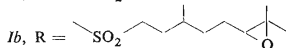
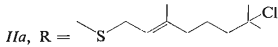
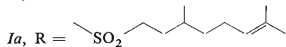
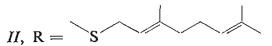
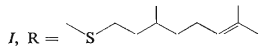
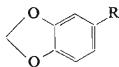
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Received January 20th, 1972

The preparation of several aromatic thioethers containing a monoterpene component is described. Some of them display a low biological activity.

In connection with the study of the compounds of aromatic character, imitating the effect of insect juvenile hormone, we prepared several phenylthioether derivatives which are the analogues of compounds derived from phenyl ethers prepared some time ago by Bowers<sup>1</sup>. The aromatic component of these thioethers was in all instances 3,4-methylenedioxybenzene, while the terpenic part was represented by residues (radicals) derived from citronellol and geraniol on the one hand, and 2-methylhept-2-en-6-ol on the other. The starting methylenedioxybenzene was transformed to 3,4-methylenedioxy-1-bromobenzene, and this to 3,4-methylenedioxythiophenol. Under the effect of sodium hydride on the preceding compound (in dimethylformamide)



\* Part XII: This Journal 37, 1755 (1972).

sodium thiophenolate was prepared which was alkylated directly by citronellyl bromide<sup>2</sup>, geranyl bromide<sup>3</sup>, 6,7-epoxygeranyl bromide, and methylheptenyl bromide<sup>4</sup> to thioethers *I*, *II*, *IIb*, and *III*. Thioether *I* was oxidised by monopero-phthalic acid and the mixture obtained was separated by thin-layer chromatography on silica gel to oxidation products *Ia*, *Ib*, and *Ic*. Thus it was established that the isopropylidene bond is not oxidised selectively to epoxide, but that under the working conditions employed an oxidation of the sulfidic sulfur atom to sulfoxide or the sulfone group takes place simultaneously. Thioethers *II* and *III* were transformed under the effect of hydrogen chloride and anhydrous conditions to compounds *IIa* and *IIIa*. The prepared substances were tested for their juvenile hormone activity on several species of insects and they had only a low effect.

## EXPERIMENTAL

### 3,4-Methylenedioxyphenyl Thioether of Citronellol (*I*)

To a solution of 3,4-methylenedioxythiophenol (2 g, 13 mmol) in dimethylformamide (6.5 ml) sodium hydride (0.323 g, 13.5 mmol) was added at 0°C under stirring. After 30 min standing in an ice bath citronellyl bromide (2.85, 13 mmol) was added dropwise and the mixture was heated at 80°C for 5 h. After cooling it was extracted three times with ether and the combined extracts were washed with 10% KOH, three times with water, and then dried over anhydrous magnesium sulfate. After evaporation of the solvent a yellow oil was obtained which was distilled. The main fraction distilled at 165–166°C/Torr (1.656 g) which was identified as compound *I*. In the mass spectrum an intensive molecular peak of mass 292 occurs as well as the characteristic fragment ions of *m/e* 167, 154, 153, and 69. For C<sub>17</sub>H<sub>24</sub>O<sub>2</sub>S (292.3) calculated: 69.82% C, 8.27% H, 10.97% S; found: 69.86% C, 8.14% H, 11.08% S.

*Oxidation*: Thioether *I* (0.292 g, 1 mmol) was oxidised with monopero-phthalic acid (0.201 g, 3.3 mmol) in ethereal solution (1 ml of the solution contained 4.07 mg of the acid) at 0°C for 24 h. Then the ethereal solution was washed with 10% potassium hydroxide solution and water, and dried over magnesium sulfate. After evaporation of ether a yellow oil remained in which a mixture of three substances was detected chromatographically. Using thin layer chromatography on silica gel and a mixture of 10% of ether in benzene as solvent sulfone *Ia* was isolated (0.068 g) of *R<sub>F</sub>* 0.63. In its mass spectrum the following characteristic strong peaks were observed: 324 (M<sup>+</sup>), 186, 169, 138. From the residual oil sulfone epoxide *Ib* (0.075 g) of *R<sub>F</sub>* 0.64 was isolated by repeated chromatography in a solvent system containing 45% of benzene in ether, the mass spectrum of which contained the following peaks: 340 (M<sup>+</sup>), 188, 187, 169*m/e*, and sulfoxide *Ic* (0.055 g) of *R<sub>F</sub>* 0.48 and *m/e* 308 (M<sup>+</sup>), 291, 170, 169, 122, 69; *m* = 87; 170<sup>+</sup> → 122<sup>+</sup> + 64.

### 3,4-Methylenedioxyphenyl Thioether of Geraniol (*II*)

On reaction of sodium hydride (0.308 g, 12.8 mmol) with 3,4-methylenedioxythiophenol (1.96 g, 12.3 mmol) in dimethylformamide and subsequent alkylation with geranyl bromide (2.67, 12.3 mmol), under the conditions as in the case of thioether *I*, 2.3 g of thioether *II* were obtained, b.p. 160–161°C/Torr, *m/e* 290 (M<sup>+</sup>), 154, 153, 136, 81, 69. For C<sub>17</sub>H<sub>22</sub>O<sub>2</sub>S (290.2) calculated: 70.21% C, 7.64% H, 11.05% S; found: 69.87% C, 7.47% H, 11.18% S.

3,4-Methylenedioxyphenyl Thioether of 7-Chloro-3,7-dimethyloct-2-en-1-ol (*Ila*)

Dry hydrogen chloride was introduced at  $-10^{\circ}\text{C}$  into a solution of thioether *II* (0.109 g, 0.38 mmol) in ether (2 ml) and methanol (8 ml) until saturated. The mixture was allowed to stand at room temperature for several hours and the excess hydrogen chloride was neutralised with solid sodium hydrogen carbonate. The mixture was extracted thrice with ether and the combined ethereal extracts were washed with saturated sodium hydrogen carbonate solution, three times with water, and dried over magnesium sulfate. The oily residue (0.129 g) was chromatographed on a thin layer of silica gel in a mixture of 50% of benzene in light petroleum, affording 0.106 g of pure product. For  $\text{C}_{17}\text{H}_{23}\text{ClO}_2\text{S}$  (326.7) calculated: 62.44% C, 7.10% H, 10.85% Cl, 9.81% S; found: 62.21% C, 7.28% H, 11.14% Cl, 10.02% S.

3,4-Methylenedioxyphenyl Thioether of 6,7-Epoxygeraniol (*Iib*)

To a solution of 3,4-methylenedioxythiophenol (0.222 g, 1.45 mmol) in dimethylformamide (2 ml) sodium hydride (0.036 g, 1.5 mmol) was added at  $0^{\circ}\text{C}$  and after 30 min standing mono-epoxygeranyl bromide (0.359 g, 1.45 mmol) was added to it dropwise. The latter was prepared on reaction of 1.1 equivalent of monoperphthalic acid with 1 equivalent of geranyl bromide under the conditions given for substances *Ia*–*Ic*. After 10 h heating at  $80^{\circ}\text{C}$  the reaction mixture was extracted three times with ether and the extracts were washed with 1% KOH and water, and dried over anhydrous magnesium sulfate. After evaporation of ether the residual oil (0.386 g) was chromatographed on a thin layer of silica gel in a mixture of 10% of ether in benzene. Yield 0.170 g of substance *Iib*,  $R_F$  0.65 and  $m/e$  306 ( $\text{M}^+$ ), 154, 153, 71. For  $\text{C}_{17}\text{H}_{22}\text{O}_3\text{S}$  (306.2) calculated: 66.61% C, 7.24% H, 10.47% S; found: 66.32% C, 7.28% H, 10.34% S.

3,4-Methylenedioxyphenyl Thioether of 2-Methylhept-2-ene-6-ol (*III*)

Taking 3,4-methylenedioxythiophenol (0.298 g, 1.93 mmol), sodium hydride (0.048 g, 2 mmol), and methylheptenyl bromide (0.369 g, 1.93 mmol) in dimethylformamide (2 ml) 0.466 g of a product were obtained under conditions as in the case of thioether *I*, which was purified by thin-layer chromatography on silica gel in the system 5% ether in light petroleum. Yield 0.288 g of substance *III*,  $R_F$  0.8 and  $m/e$  264 ( $\text{M}^+$ ), 154, 153, 69. For  $\text{C}_{15}\text{H}_{20}\text{O}_2\text{S}$  (264.2) calculated: 68.12% C, 7.63% H, 12.13% S; found: 67.91% C, 7.58% H, 11.87% S.

3,4-Methylenedioxyphenyl Thioether of 6-Chloro-6-methylheptan-2-ol (*IIIa*)

From thioether *III* (0.132 g, 0.5 mmol) in ether (0.5 ml) and methanol (15 ml) an oil was obtained when a procedure was applied as in the case of thioether *Ila*. This oil was purified by thin-layer chromatography on silica gel in 30% ether in light petroleum. Yield 0.115 g,  $R_F$  0.73. For  $\text{C}_{15}\text{H}_{21}\text{ClO}_2\text{S}$  (300.7) calculated: 59.86% C, 7.04% H, 11.79% Cl, 10.64% S; found: 60.10% C, 7.37% H, 11.58% Cl, 9.98% S.

## Biological Properties

The substances were applied in an acetonic solution (1  $\mu\text{l}$ ) on the body surface of freshly emerged larvae of the last instar of the red bug *Dysdercus cingulatus* (*Pyrrhocoridae*) and *Graphosoma italicum* (*Pentatomidae*), as well as on the body surface of freshly emerged pupae of *Tenebrio molitor*. The activity was evaluated after the next sloughing on the basis of the inhibition of metamorphosis of external morphological structures; it is given in hormonal units ID-50, meaning the amount of substance in micrograms eliciting one half of the morphological effect. Substances

*Ia—Ic* had no effect on any of the species even in the concentration of 1 000  $\mu\text{g}$ . On *T. melitor* only substance *Ib* had activity 5, other substances activity 1 000; substance *II* did not display any activity on *G. italicum*, substance *Ib* had activity 10, other substances 500. On *D. apterus* the substances had the following activities: *I* 5, *II* 10, *IIa* 0.3, *Ib* 3, *III* 50, *IIIa* 1. Substance *Ib* was also tested on *Triatoma infestans* and had activity 0.8  $\mu\text{g}$ .

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Translated by Ž. Procházka.