

# A NEW SYNTHESIS OF THIOPHENES AND THIAPYRANS

## Part III. Hydroxythionaphthenes and Alkoxythionaphthenes

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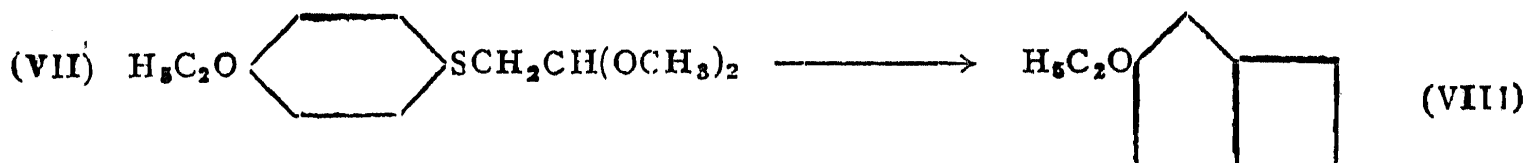
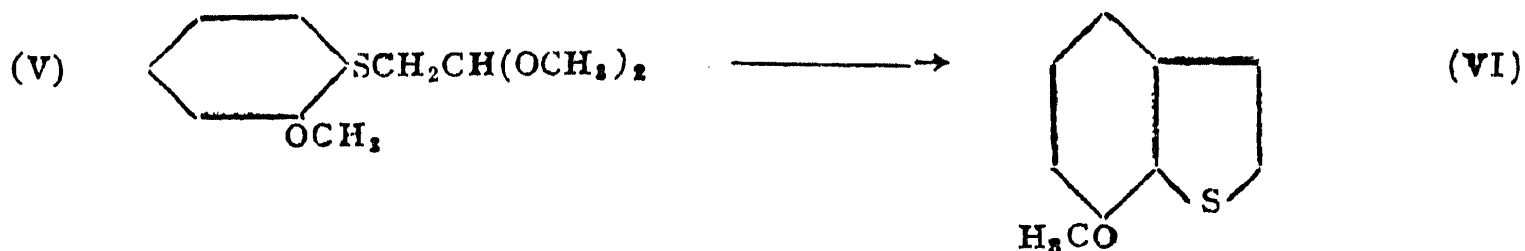
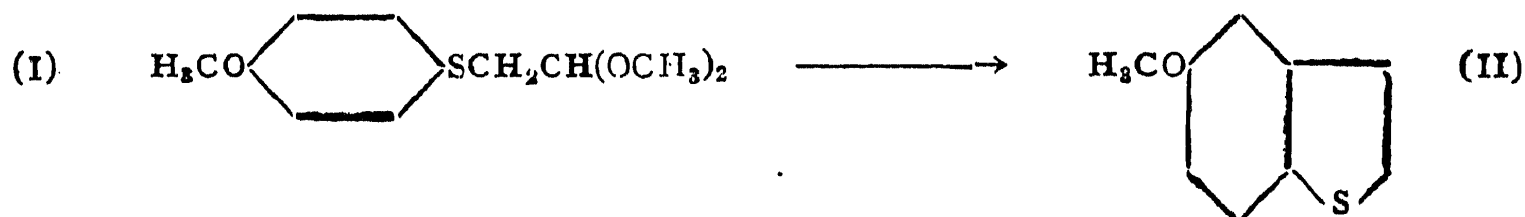
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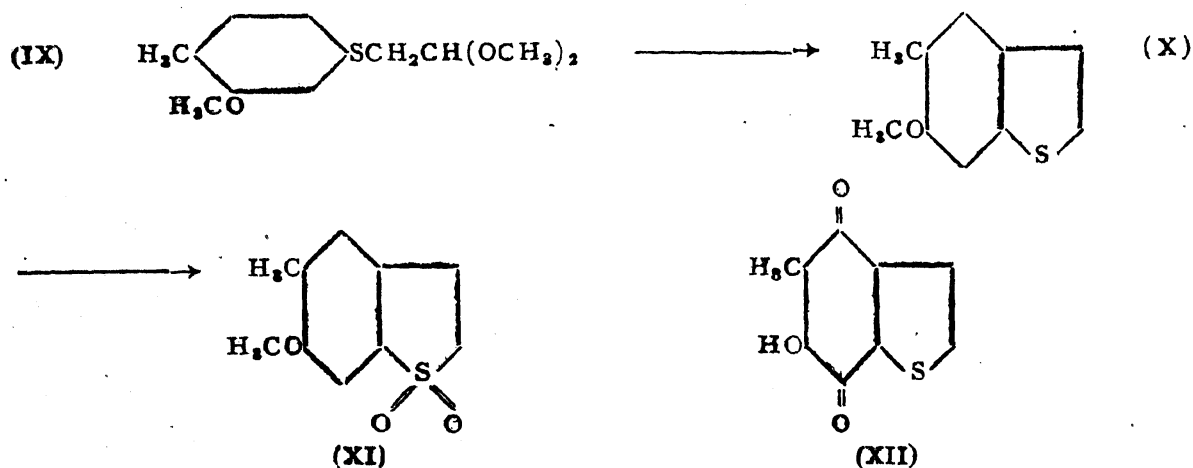
OF the six possible monomethoxythionaphthenes only 3-methoxy-<sup>1</sup> and 5-methoxy-thionaphthenes<sup>2</sup> are known and are obtained by methylation of the corresponding hydroxy derivatives. Out of the remaining four unknown monomethoxythionaphthenes, 6-methoxy- (IV) and 7-methoxy-thionaphthenes (VI) have now been prepared in addition to 5-methoxythionaphthene (II), now prepared by an alternative route. Among the monoethoxythionaphthenes only the 3-ethoxy derivative<sup>3</sup> is reported. 5-Ethoxythionaphthene has now been synthesised.

5-Methoxythionaphthene (II) was prepared starting from *p*-mercaptoanisole by condensation with bromoacetaldehyde dimethyl acetal to give *p*-methoxyphenyl  $\omega$ -dimethoxyethyl sulphide (I) followed by ring-closure of the latter to (II). 6-Methoxythionaphthene (IV) was prepared similarly by the cyclization of *m*-methoxyphenyl  $\omega$ -dimethoxyethyl sulphide (III). 7-Methoxythionaphthene (VI) was likewise obtained from *o*-methoxyphenyl



$\omega$ -dimethoxyethyl sulphide (V). Cyclization of *p*-ethoxyphenyl  $\omega$ -dimethoxyethyl sulphide (VII) gave 5-ethoxythionaphthene (VIII). The yield of the latter was more than that of 5-methoxythionaphthene (II). The yield of (IV) (62%) was more than that of (VI) (18%), because of the activation of the cyclization position due to the *p*-methoxy group.

6-Methoxy-5-methylthionaphthene (X) was prepared by the cyclization of 3-methoxy-4-methylphenyl  $\omega$ -dimethoxyethyl sulphide (IX) as an intermediate in the synthesis of the sulphur isoster (XII) of the physiologically active 3-hydroxy-2-methyl-1:4-naphthoquinone ("phthiacol") and also with the view to illustrate the application of the new synthesis to disubstituted derivatives of thionaphthene. Oxidation of (X) with hydrogen peroxide in acetic acid gave 6-methoxy-5-methylthionaphthene-1-dioxide (XI).



Among the monohydroxythionaphthenes, 2-hydroxy-<sup>4</sup>, 3-hydroxy-(thioindoxyl),<sup>5</sup> 4-hydroxy-<sup>6</sup> and 5-hydroxy-thionaphthenes <sup>2,6</sup> are known. Demethylation of 7-methoxythionaphthene (VI) by treatment with pyridine hydrochloride<sup>7</sup> at 180° for 8 hours gave 7-hydroxythionaphthene (XIII) in 88% yield. Even after repeated distillations under reduced pressure, the hydroxy derivative did not give correct elementary analysis. It distills as a colourless liquid which solidifies on cooling to a white solid and darkens on keeping. It dissolves in aqueous alkali, couples with benzenediazonium chloride giving a chocolate-coloured dye. The hydroxythionaphthene crystallized from *n*-hexane in colourless fluffy needles, m.p. 67–68°, which on keeping in an evacuated desiccator overnight changed to a colourless oil. The hydroxy derivative is being investigated further.



Demethylation of (X) gave 6-hydroxy-5-methylthionaphthene (XIV) in 85% yield. The hydroxythionaphthene coupled with benzenediazonium chloride giving a reddish-brown dye.

### EXPERIMENTAL

(Analyses are by Drs. Weiler and Strauss and by Mr. T. S. Gore. M.ps. are uncorrected.)

The condensation of alkoxyphenylthiols with bromoacetaldehyde dimethyl acetal, the subsequent cyclization of *S*-alkoxyphenylthioglycollic-aldehyde dimethyl acetals to the corresponding alkoxythionaphthenes and the characterization of the intermediate acetals as 2:4-dinitrophenylhydrazones have been carried out according to the general method outlined earlier.<sup>8</sup> The thionaphthenes were characterised as the picrates.

#### *p*-Methoxyphenyl $\omega$ -dimethoxyethyl sulphide (I)

*p*-Mercaptoanisol<sup>9</sup> (7.6 g.), sodium (1.2 g.), sodium iodide (1.25 g.), bromoacetal (9.3 g.) and absolute alcohol (25 c.c.) were boiled for 2 hours. The crude sulphide after distillation, gave a colourless liquid, b.p. 170–80° (bath temp.)/2.5–3 mm. (8.6 g.; yield 70%). After three redistillations it was collected at 155–60° (bath temp.)/2.5–3 mm. (Found: C, 58.2; H, 7.0.  $C_{11}H_{16}O_3S$  requires C, 57.9; H, 7.0%). 2:4-Dinitrophenylhydrazone crystallized from alcohol in lustrous flat orange needles, m.p. 106–07° (Found: N, 16.1.  $C_{15}H_{14}N_4O_5S$  requires N, 15.5%).

#### 5-Methoxythionaphthene (II)

The sulphide (I) (6.1 g.) was added to phosphorus pentoxide (30 g.) and phosphoric acid (18 c.c.) at 150–60°/0.34 mm. 5-Methoxythionaphthene was isolated through the picrate and distilled when it was obtained as a white solid having a pleasant smell, m.p. 42–43°; b.p. 85–90° (bath temp.)/0.52 mm. Fries *et al.*<sup>2</sup> give m.p. 44° (Found: C, 66.0; H, 4.9. Calc. for  $C_9H_8OS$ : C, 65.9; H, 4.9%). The yield of 5-methoxythionaphthene was poor.

#### *m*-Methoxyphenyl $\omega$ -dimethoxyethyl sulphide (III)

*m*-Mercaptoanisol<sup>10</sup> (6.1 g.), sodium (1.0 g.), sodium iodide (1.0 g.), bromoacetal (7.4 g.) and absolute alcohol (30 c.c.) were boiled for 3 hours. The sulphide gave a colourless liquid, b.p. 120–60° (bath temp.)/2.5 mm. (7.31 g.; yield 74%). After three redistillations it was finally collected at 125–30° (bath temp.)/2.5 mm. (Found: C, 57.2; H, 7.0.  $C_{11}H_{16}O_3S$  requires C, 57.9; H, 7.0%). 2:4-Dinitrophenylhydrazone gave small yellow

rods (alcohol-benzene, m.p. 123–24° (Found: N, 15.2.  $C_{15}H_{14}N_4O_5S$  requires N, 15.5%).

#### 6-Methoxythionaphthene (IV)

The sulphide (VII) (4.13 g.) was added to a mixture of phosphorous pentoxide (20 g.) and phosphoric acid (12 c.c.) at 160–70°/2.5 mm. Crude 6-methoxythionaphthene (1.84 g., yield 62%) was isolated through the picrate and the purified product (0.88 g.) was finally distilled twice when it gave a colourless liquid, b.p. 153–56° (bath temp.)/16 mm. (Found: C, 65.8; H, 5.1.  $C_9H_8OS$  requires C, 65.9; H, 4.9%). The *picrate* crystallised in yellow needles from alcohol, m.p. 105–06° (Found: N, 11.3.  $C_{15}H_{11}N_3O_8S$  requires N, 10.7%).

#### *o*-Methoxyphenyl $\omega$ -dimethoxyethyl sulphide (V)

*o*-Mercaptoanisole (6 g.), prepared from *o*-anisidine (*cf.*, preparation of *m*-thiocresol),<sup>11</sup> sodium (1 g.), bromoacetal (7.5 g.) and absolute alcohol (30 c.c.) were boiled for 6 hours. The crude sulphide after distillation, gave a pale yellow liquid, b.p. 150–80° (bath temp.)/15 mm. (8.0 g; yield 82%). After three redistillations it was collected at 175–80° (bath temp.)/15 mm. (Found: C, 57.4; H, 6.8.  $C_{11}H_{16}O_3S$  requires C, 57.9; H, 7.0%). 2:4-Dinitrophenylhydrazone crystallized from alcohol in orange needles, m.p. 135–36° (Found: N, 15.3.  $C_{15}H_{14}N_4O_5S$  requires N, 15.5%).

#### 7-Methoxythionaphthene (VI)

The sulphide (V) (6.25 g.) was added to a mixture of phosphorus pentoxide (31 g.) and phosphoric acid (20 c.c.) at 160–70°/15 mm. when a pale yellow liquid (0.8 g.; yield 18%) was obtained. It was treated with picric acid (1.2 g.) and the picrate was decomposed by passing a benzene solution through a column of activated alumina. The fraction which gave blue fluorescence in ultra-violet light, was collected and gave the thionaphthene as a colourless liquid. The liquid was redistilled thrice and finally collected at 140–45° (bath temp.)/15 mm. (Found: C, 65.9; H, 4.9.  $C_9H_8OS$  requires C, 65.9; H, 4.9%). The *picrate* crystallised in elongated orange needles from absolute alcohol, m.p. 110–11° (Found: N, 10.4;  $C_{15}H_{11}N_3O_8S$  requires N, 10.7%).

#### *p*-Ethoxyphenyl $\omega$ -dimethoxyethyl sulphide (VII)

*p*-Mercaptophenetol (10.7 g.), prepared from *p*-phenetidine (*cf.*, preparation of *m*-thiocresol),<sup>11</sup> sodium (1.6 g.) bromoacetal (13.4 g.) and absolute alcohol (50 c.c.) were refluxed for 3 hours. The sulphide gave a pale yellow

liquid, b.p. 180–85°/16 mm. (14.2 g.; yield 85%). After three redistillations, it was collected at 180° (bath temp.)/12 mm. (Found: C, 59.5; H, 7.4.  $C_{12}H_{18}O_3S$  requires C, 59.5; H, 7.4%). 2:4-Dinitrophenylhydrazone crystallized from alcohol with one molecule of alcohol of crystallization in orange needles, m.p. 84–85° (Found: N, 13.5.  $C_{16}H_{16}N_4O_5S$ ,  $C_2H_5OH$  requires N, 13.3%).

#### 5-Ethoxythionaphthene (VIII)

The sulphide (VII) (8.5 g.) was added to a mixture of phosphorus pentoxide (42 g.) and phosphoric acid (25.5 c.c.) at 180–200°/12 mm. The yellow liquid (0.96 g.; yield 15.4%) was treated with picric acid (1.25 g.) in absolute alcohol. The picrate was dissolved in benzene and the solution passed through an activated alumina column using benzene for developing the chromatogram. The fraction, which exhibits a bluish-green fluorescence in ultra-violet light, was collected and gave the thionaphthene as a liquid possessing a fruity smell. The liquid was redistilled four times and finally collected at 145° (bath temp.)/12 mm. (Found: C, 67.3; H, 5.7.  $C_{10}H_{10}OS$  requires C, 67.4; H, 5.6%). The picrate crystallized in yellow needles from absolute alcohol, m.p. 93° (Found: N, 10.6.  $C_{16}H_{13}N_3O_8S$  requires N, 10.3%).

4-Nitro-2-methoxytoluene was prepared from 4-nitro-*o*-toluidine (Fast Scarlet G Base) by Sandmeyer reaction and methylation of the resulting *p*-nitro-*o*-cresol. 4-Nitro-2-methoxytoluene (20 g.) was dissolved in absolute alcohol (100 c.c.), Raney nickel (2 g.) was added and the mixture shaken in a Parr hydrogenator with hydrogen for 4–5 hours at 42 lb. per sq. inch. Removal of Raney nickel and evaporation of alcohol, gave 4-amino-2-methoxytoluene, as a dark brown solid (14 g.), m.p. 54–56°, which was converted to *o*-methoxy-*p*-thiocresol, b.p. 130° (bath temp.)/12 mm. (*cf.*, preparation of *m*-thiocresol from *m*-toluidine).<sup>11</sup> The thiol has been prepared earlier by Shah, *et al.* by reduction of 2-methoxytoluene-4-sulphonyl chloride.

#### 3-Methoxy-4-methylphenyl $\omega$ -dimethoxyethyl sulphide (IX)

*o*-Methoxy-*p*-thiocresol (8.5 g.), sodium (1.3 g.), bromoacetal (9.5 g.) and absolute alcohol (50 c.c.) were boiled for four hours. The crude sulphide after distillation gave a liquid, b.p. 190–95°/15 mm. (11.2 g.; yield 84%). After four redistillations it was collected at 185° (bath temp.)/15 mm. (Found: C, 59.4; H, 7.6.  $C_{12}H_{18}O_3S$  requires C, 59.5; H, 7.4%), 2:4-Dinitrophenylhydrazone gave orange needles from benzene-*n*-hexane, m.p. 123–24° (Found: N, 15.1.  $C_{16}H_{16}N_4O_5S$  requires N, 14.9%).

*6-Methoxy-5-methylthionaphthene (X)*

The sulphide (IX) (8 g.) was added to a mixture of phosphorus pentoxide (40 g.) and phosphoric acid (25 c.c.) at 200–05°/12 mm. when a colourless liquid (3.6 g.; yield 64%) distilled over which solidified on cooling to room temperature. The product was crystallized from *n*-hexane and then further purified by three redistillations, being finally collected at 160° (bath temp.)/12 mm., m.p. 62–63° (Found: C, 66.9; H, 5.4.  $C_{10}H_{10}OS$  requires C, 67.4; H, 5.6%). The *picrate* gave long orange-red needles from absolute alcohol, m.p. 107–8° (Found: N, 10.3.  $C_{16}H_{13}N_3O_8S$  requires N, 10.3%).

*6-Methoxy-5-methylthionaphthene -1-dioxide(XI)*

The thionaphthene (X) (0.45 g.) was treated with glacial acetic acid (7 c.c.) and hydrogen peroxide 120 vols. (3 c.c.) on water-bath at 85° for 6 hours. The reaction mixture was poured into crushed ice, and neutralized with potassium carbonate. 6-Methoxy-5-methylthionaphthene-1-dioxide was isolated by means of ether, and crystallized from aqueous alcohol when it gave colourless elongated needles, m.p. 187° (Found: C, 57.1; H, 5.2.  $C_{10}H_{10}O_3S$  requires C, 57.1; H, 4.8%).

*7-Hydroxythionaphthene (XII)*

7-Methoxythionaphthene (0.62 g.) and pyridine hydrochloride (5 g.) were heated at 180° for 9 hours. The mixture was diluted with ice-cold water and extracted with ether. The ether solution was extracted with 10% caustic soda solution to remove 7-hydroxythionaphthene from the unreacted 7-methoxythionaphthene. The alkaline extract was acidified and the hydroxythionaphthene isolated by means of ether. The ether extract was washed with saturated sodium sulphate solution till free from acid and dried ( $Na_2SO_4$ ). Removal of ether gave the thionaphthene as a pale straw-coloured liquid (0.5 g; yield 88%). The liquid was distilled four times and finally collected at 135° (bath temp.)/8 mm. as a colourless oil which slowly solidifies, darkens on keeping and does not give correct analysis. The hydroxythionaphthene crystallised from *n*-hexane in colourless fluffy short needles, m.p. 67–68°. On keeping the crystalline product in an evacuated desiccator overnight, a pale yellow-coloured liquid was obtained, which was not analytically pure. A mixture of hydroxythionaphthene (30 mg.) and picric acid (55 mg.) was boiled in absolute alcohol and cooled. The *picrate* separated in elongated orange needles, m.p. 184–86° (Found: C, 44.6; H, 2.7; N, 10.7.  $C_{14}H_9N_3O_8S$  requires C, 44.3; H, 2.4; N, 11.1%).

## 6-Hydroxy-5-methylthionaphthene (XIV)

6-Methoxy-5-methylthionaphthene (0.73 g.) and pyridine hydrochloride (5 g.) were refluxed for 10 hours at 180°. The solution was then diluted with ice-cold water (20 c.c.) and extracted with ether. The ether extract was shaken with 10% caustic soda solution to remove the hydroxythionaphthene. The alkaline extract was acidified and the hydroxy derivative isolated by means of ether. The ether extract was washed with saturated sodium sulphate solution and dried ( $\text{Na}_2\text{SO}_4$ ). Removal of ether gave 6-hydroxy-5-methylthionaphthene (0.57 g.; yield 85%) which on distillation gave a colourless liquid, b.p. 160-65° (bath temp.)/10 mm. (0.325 g.) which solidifies at room temperature. The hydroxythionaphthene was crystallized four times from aqueous alcohol when it gave colourless broken plates, m.p. 146-47° (Found: C, 65.6; H, 4.9.  $\text{C}_9\text{H}_8\text{OS}$  requires C, 65.8; H, 4.9%).

## SUMMARY

5-Methoxythionaphthene (II) and the hitherto unknown 6-methoxy- (IV), 7-methoxy- (VI) and 5-ethoxy-thionaphthenes (VIII) have been prepared by the new synthesis. 6-Methoxy-5-methylthionaphthene (X) was also prepared similarly and gave 6-methoxy-5-methylthionaphthene-1-dioxide (XI) on oxidation. Demethylation of (VI) and (X) gave 7-hydroxythionaphthene (XIII) and 6-hydroxy-5-methylthionaphthene (XIV).

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