Chemistry of Hop Constituents. Part 43.[1] Cyclic Polysulphides and a Thiophen from Myrcene, and their Occurrence in the Essential Oil of Hops

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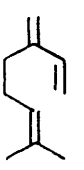
Steam-distilled hop oils (from hops dressed on the bine with sulphur) have been shown to contain 3-(4-methylpent-3-enyl)thiophen (2) and 4-(4-methylpent-3-enyl)-1,2-dithiacyclohex-4-ene (4) together with the corresponding trisulphide (5) and tetrasulphide (6) but not the monosulphide (3). All five compounds are obtainable from myrcene (1) and sulphur and have been characterised, and some alternative syntheses and related work are described.

STUDIES on sulphur compounds present in steam-distilled hop oils have demonstrated the presence of *S*-methyl thioesters,[2,3] dimethyl polysulphides,[4] and sesquiterpene episulphides.[1] Also identified were the cyclic disulphide (4)[5] and the related thiophen (2),[5,6] which appeared to be derived from myrcene (1), a major monoterpene constituent of hop oils. Except for the *S*-methyl thioesters, all these sulphur compounds were found in enhanced amounts in hop oil from hops which had been treated with sulphur during the growing season to combat mildew. *In vitro* experiments showed that myrcene (1) interacted slowly with sulphur at ambient temperature on irradiation with visible or u.v. light, to give a mixture containing *inter alia* the two compounds (2) and (4), which were separated and identified.[5] Indications of the formation of the cyclic sulphide (3) and trisulphide (5) were also obtained and are now confirmed.

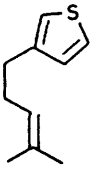
Myrcene-related Sulphur Compounds in Hops.—We now report the recognition in steam-distilled hop oil of the cyclic trisulphide (5) and tetrasulphide (6), in addition to the disulphide (4) and the thiophen (2). Syntheses of these four compounds and of the cyclic monosulphide (3) have been achieved in order to complete the identifications. No evidence was obtained for the presence in hop oil of the cyclic monosulphide (3).

The absence of the sulphide (3) from hop oils suggested that the constituents (2) and (4)—(6) were unlikely to be artefacts formed from myrcene (1) and contaminating sulphur (off the bine) during the extraction of oil from the hops by steam-distillation. This conclusion arose because a mixture of *all* these compounds (2)—(6) was formed when myrcene (1) was deliberately treated with sulphur under a variety of photolysis conditions. Moreover, the formation of compounds (2)—(6) was barely detectable when myrcene and sulphur were subjected to the conditions of steam distillation. In connection with the possible biogenesis of the sulphur compounds (2) and (4)—(6) from myrcene in the hop, it may be significant that mintsulphide (11) is found [7] in peppermint oil, of which the sesquiterpene germacrene D (12) is a major constituent. There may be therefore in certain plants a biogenetic pathway which, in effect, adds sulphur to unsaturated systems.

The new myrcene-related sulphur compounds were first detected in hop oils by g.l.c. with flame photometric sulphur detection. They were then recognised by g.l.c. peak enhancement as low-yield products from irradiation



(1)



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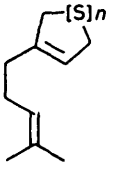
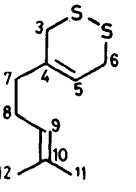
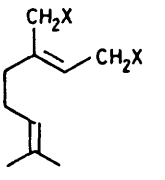


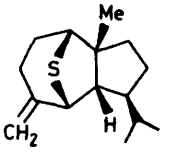
(3) $n = 1$
(5) $n = 3$
(6) $n = 4$



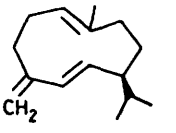
(4)



(7) X = SH
(8) X = S · SO_3^- Na^+
(9) X = Cl
(10) X = SCN



(11)



(12)

of myrcene with sulphur, but the reaction mixtures also contained a component subsequently characterised as the sulphide (3). Preliminary chemical work on the mixtures showed that the sulphur compounds were not thiols,

being unaffected by air. They did not add to naphthoquinone and so lacked the dienoid system of myrcene (1). G.l.c. analysis showed also that with triphenylphosphine in boiling dibutyl ether, the suspected higher polysulphides were removed and at the same time there were increases in the amounts of disulphide (2 ×) and monosulphide (6 ×), and triphenylphosphine sulphide crystalised from the solution. After treatment with aluminium amalgam and water, the di- and higher poly-sulphides were replaced by a single new compound, subsequently recognised as the dithiol (7). These findings, together with g.l.c.–mass spectrometric fragmentation data, provided enough structural evidence to warrant synthesis as a means of fully establishing the identity of the new compounds.

In other experiments, mixtures of myrcene and organic isothiocyanates were irradiated (*cf.* ref. 1). Only traces of the foregoing sulphur compounds were produced, other sulphur compounds being formed in greater amount. These were not investigated in detail, being irrelevant for the immediate purpose. G.l.c.–mass spectrometry indicated that ethyl isothiocyanate, for example, added to myrcene. No evidence emerged for the formation of episulphides [1] in any of the foregoing experiments.

Syntheses.—The cyclic disulphide (4) was best prepared (30%) from myrcene (1) and ' activated ' sulphur in a basic solvent at 110 °C (this method [5] was used previously, however, for preparing trithiolans [8]). Reduction of the disulphide with aluminium amalgam readily gave the dithiol (7). This showed a ^{1}H n.m.r. spectrum similar to that of the disulphide (Table 1) except for the

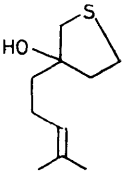
TABLE 1

^{1}H N.m.r. data (at 90 MHz) for the dithiol (7) and the cyclic polysulphides (4)—(6) in $CDCl_3$ containing a trace of $SiMe_4$

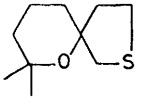
δ_H and multiplicity (J/Hz)				
(7)	(4)	(5)	(6)	Assignment
1.21 t (7)				SH
1.49 t (7)				SH
1.60	1.60 s	1.61 s	1.58 s	*cis*-Me
1.68	1.68 s	1.68 s	1.66 s	*trans*-Me
2.16	2.06 m	2.20 m	2.19 m	CH_2–CH_2
3.17 d (7)	3.19 m		3.60 s	≥C–CH_2–S
3.20 *ca.* t (7.5)	3.31 m	3.45—3.8 m	3.59 d (9.5)	S–CH_2–CH=
5.09 m	5.09 m	5.10 m	5.12 m	Side-chain –CH=
5.39 t (8)	5.74 t (9)	5.57 t (7.9)	5.64 t (9.5)	Ring –CH=

triplet SH signals and the additional splitting of the SCH_2 signals arising from coupling to the thiol protons. Conversion [9] of the dithiol into the bis(sodium thiosulphate) salt (8) and then treatment with disodium sulphide,[10] and with disodium disulphide, afforded the novel cyclic trisulphide (5) and tetrasulphide (6), respectively.

An attempt was made to convert the accessible disulphide (4) with sulphuryl chloride [11] into the dichloride (9) for subsequent conversion with sulphide into the cyclic sulphide (3). However, the reaction with sulphuryl chloride even under very mild conditions gave a mixture of five compounds (as shown by t.l.c.) and no tractable product could be isolated. It was expected that phosphines would abstract one sulphur atom from the molecule of the cyclic disulphide (4) to yield the desired sulphide (3), but triphenylphosphine in boiling dibutyl ether proved quite unreactive. With tris(dimethylamino)phosphine [12] at ambient temperature, on the other hand, the sulphur was completely removed from the disulphide (4) to yield myrcene (1) and the phosphine sulphide. Another possible route to the sulphide (3) comprised treating the disulphide (4) with sodium cyanide, a method [13] by which 3,6-dihydro-1,2-dithiin was converted into Δ^3-thiolene together with 1,2-epithiobut-3-ene. Although the disulphide (4) was consumed and thiocyanate ion formed, g.l.c. analysis showed that only traces of the required monosulphide (3) were produced, the bulk of the product being polymeric. Nevertheless, the result gave valuable support for the structure (3). In a final attempt at bulk synthesis the lead(II) derivative of the dithiol (7) was prepared and treated,[14] in the absence of air, with cyanogen bromide to form the bisthiocyanate (10), for subsequent treatment with disodium sulphide. However, none of the expected product (3) was detected by g.l.c.; moreover the first stage afforded the cyclic disulphide (4) in over 60% yield, presumably with concomitant formation of lead(II) bromide and cyanide. Finally, thiacyclopentan-3-one was treated with 4-methylpent-3-enylmagnesium bromide to produce the 3-hydroxy-3-(4-methylpent-3-enyl)tetrahydrothiophen (13) in the hope of being able to dehydrate



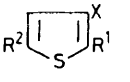
(13)



(14)

RS–CH=CH–C≡CH

(15) R = Bu
(16) R = Me_2C=CH[CH_2]$_2$



(17) R^1 = Me_2C=CH[CH_2]$_2$, R^2 = X = H
(18) R^1 = Me_2C=CH[CH_2]$_2$, R^2 = H, X = Br
(19) R^1 = R^2 = Me_2C=CH[CH_2]$_2$, X = Br

this, at least in part, to the required cyclic sulphide (3). However, attempts at dehydration led to the spirobicyclic compound (14).

Although the thiophen (2) had been obtained, in sufficient quantity for full characterisation, from myr-

cene and sulphur,[5] it had been hoped to prepare some by dehydrogenation of the cyclic sulphide (3). In view of the inaccessibility of the latter, direct synthesis of the thiophen (2) was attempted from 3-bromothiophen by lithiation and then treatment with 4-methylpent-3-enyl bromide. This proved highly unsatisfactory because the 3-thienyl-lithium did not react with the bromide below 0 °C, and it is well known [15] that above 0 °C ring-opening reactions occur as well as metal–halogen exchange processes.[16] Indeed, with ether as reaction medium, the major products were those of ring scission, namely 5-thianon-3-en-1-yne (15) and 9-methyl-5-thiadeca-3,8-dien-1-yne (16), and only traces of monoalkenylthiophens arose. In tetrahydrofuran the situation was reversed: the product comprised a mixture (30%) of the monoalkenylthiophens (2) and (17) along with the bromoalkenylthiophens (18) (37%) and (19) (30%) and only small amounts of the ring-opened products. Liquid chromatography of the mixture provided separate samples of the 3-bromothiophens (18) and (19), but the 3-alkenylthiophen (2) could not be separated from the accompanying dominant amount of 2-isomer (17).

Structural Evidence.—In the mass spectrum of the thiophen (2), the base peak at *m/z* 97 is characteristic of alkyl- and alkenyl-thiophens.[17] In the i.r. spectrum, the pair of strong bands at 699 and 774 cm^{-1} together with the pair of weak bands at 984 and 1 080 cm^{-1} provided support for the 3-substituted thiophen structure (2).[18] The ^1H n.m.r. spectrum of (2), already reported in outline,[5] was fully diagnostic,[19] as also was the ^1H n.m.r. spectrum of the 2-isomer (17). The latter spectrum was readily obtained from the synthetic mixture of the two isomers at low gain, the spectrum of the minor component (2) then being lost in the base-line noise.

For the first member (4) of the cyclic sulphide series to be isolated, the ^1H and ^{13}C n.m.r. chemical shifts were correlated. Thus two ^{13}C spectra were acquired with off-resonance ^1H decoupling respectively at δ_H 0.0 and 7.0. This provided two sets of reduced $^1J_{CH}$ values,[20] the ordering of which led unambiguously to the correlations in Table 2. The singlets from quaternary carbons were assigned from terpene data,[21] and the ordering of the $-S-CH_2$ signals [22] was decided by a specific ^1H decoupling experiment. Irradiation at the frequency of the ^1H triplet signal at δ 5.74, necessarily from H-5, caused collapse of the ^1H signal at δ 3.31, which therefore arose from H-6: the associated ^{13}C signal was at δ 29.4, whence the assignment to C-6 (Table 2). The decoupling experiment also demonstrated that the two methine protons were unconnected so that the disulphide molecule necessarily contained two trisubstituted double bonds. This agreed with compound (4) being formally derived by addition of S_2 across the conjugated diene bonds in myrcene (1). These various observations thus made structure (4) certain. As a result it was relatively straightforward to confirm the structures of the cyclic sulphides (5) and (6), which had ^1H n.m.r. spectra similar to that of the disulphide (4). In the series (4)—(6), the chemical shifts of the methylene groups which flanked the sulphur moved to lower field with increase in the number of sulphur atoms (Table 1). This was reminiscent of the methyl shift trend in the dimethyl polysulphides.[23] With the cyclic trisulphide (5), specific ^1H irradiation at the resonance frequency of either the side chain or the ring $-CH=$ proton confirmed the assignments of the pairs of methylene signals made by comparison with the data from (4). In the conformationally more mobile tetrasulphide (6), the two $S-CH_2$ groups gave separate first-order proton signals, enabling immediate assignment.

TABLE 2

N.m.r. (^{13}C and ^1H) correlations for the cyclic disulphide (4)

Carbon-13 data		Proton data		
δ	Multiplicity	δ	Multiplicity	Assignment
17.7	q	1.60	s	12
25.7	q	1.68	s	11
26.6	t	2.06	approx. s	8
39.9	t			7
29.4	t	3.31	m	6
31.4	t	3.19	m	3
119.5	d	5.74	approx. t	5
123.2	d	5.09	m	9
132.3	s			10
136.5	s			4

[a] See structure for numbering.

None of the sulphides (4)—(6) showed i.r. absorption in the 2 550—2 600 cm^{-1} region, and none showed strong bands near 1 600, 995, and 895 cm^{-1}, consistent respectively with the compounds not being thiols and being devoid of the conjugated diene system of myrcene.

The mass spectrum of the cyclic disulphide (4) showed [5] prominent peaks from fragment ions at *m/z* 167, 136, 135, 93, and 69. The first three peaks arose from the molecular ion by loss of SH, S_2, and S_2H, respectively; the last neutral fragment is stated to be particularly characteristic of 1,2-dithiacyclohexanoid compounds.[17] The last two peaks (69 is the base peak) appeared also in the spectrum of myrcene [24] (1), indicating similar fragmentation in (4) subsequent to the loss of sulphur, and hence a common skeleton from that point on. Analogously, in the mass spectra of the cyclic tri- and tetra-sulphides, (5) and (6), there were peaks corresponding to the molecular ion less SH, S_2, S_2H, S_3, and S_3H, as well as S_4 and S_4H in the case of compound (6). Also in each mass spectrum, the base peak had *m/z* 69 and there was a prominent ion at *m/z* 93, both indicative of the fragmented myrcene skeleton.

For the cyclic monosulphide (3), an accurate mass determination for the molecular ion defined the elemental composition, and the methods of formation pointed to the structure (3) which was strongly supported by the mass fragmentation pattern. Of the moderately prominent ion peaks at *m/z* 135, 93, and 69, the first was attributable to loss of SH from the molecular ion and the others to the myrcene skeleton.[24] The most prominent ions arose from the ring system as it fragmented from the side chain, being at *m/z* 99 and 85, corresponding to

$C_5H_7S^+$ and $C_4H_5S^+$, the last ion providing the base peak. Good confirmatory evidence that the compound had structure (3) and thus was the lowest member of the homologous series (4)—(6) came from a plot of the Kovats retention indices [25] against number of sulphur atoms, which was linear for the known di-, tri-, and tetrasulphides (4)—(6). The intercept from the Kovats number for the ' unknown ' gave 1.0 *S*, in conformity with the homologous monosulphide structure (3).

EXPERIMENTAL

I.r. maxima were taken from spectra recorded with a Perkin-Elmer 157G spectrophotometer. N.m.r. spectra (^1H and ^{13}C) were obtained with a Bruker WH90 Fourier-transform instrument operating at 90 or 22.6 MHz (nominal), respectively: solutions at 25 °C contained $SiMe_4$ or $Me_3Si[CH_2]SO_3Na$ as appropriate. An A.E.I. MS12 instrument or a Varian CH 5D double-focussing spectrometer provided mass spectral data. Gas chromatography was performed using a Pye GCV apparatus equipped with synchronous flame ionisation and flame photometric detection: the glass columns (1.5 m) were packed with Chromosorb W AW DMCS (80—100 mesh) or Diatomite CQ (100—120 mesh), with stationary phases of 3% OV1 or 3% OV17. For column chromatography, silicic acid (Mallinckrodt 2847, 100 mesh) and redistilled solvents were employed.

Sulphur Compounds in Hop Oil.—G.l.c. analysis of hop oil (on OV1 on Diatomite), as previously described,[1] revealed peaks (amongst others) with retention times (*A*) 17.8, (*B*) 31.6, (*C*) 39.6, and (*D*) 46.8 min. These also appeared amongst other peaks, *e.g.* (*E*) 14.8 min, in the similarly obtained chromatograms from reaction mixtures obtained by irradiation of myrcene (1) (10 g) and sulphur (2 g) in cyclohexane (100 ml) at ambient temperature with a medium-pressure mercury lamp (125 W) for 22 h, or with sunlight for several weeks, or at 58 °C with a tungsten photoflood lamp (500 W) for 2 weeks. Eventually, using authentic specimens (below), the unknown compounds were identified by g.l.c. peak enhancement [1] as (*A*) the thiophen (2), (*B*) the cyclic disulphide (4), (*C*) the trisulphide (5), (*D*) the tetrasulphide (6), and (*E*) the cyclic monosulphide (3).

Samples of the reaction solutions [standardised at *ca.* 10 mg of component (*B*)] were treated as follows. (i) Myrcene (10 μl), tetradecane (10 μl), and ethanol (2 ml) were added and the solution was heated under reflux with 1,4-naphthoquinone (52 mg) for 3 h. G.l.c. analysis (OV1 on Diatomite), before and after refluxing, showed that only the peak ascribed to myrcene diminished (by 80%). (ii) Triphenylphosphine (100 mg) and dibutyl ether (2 ml) were added and the solution was refluxed for 1.4 h. G.l.c. analysis as before showed that peaks (*C*) and (*D*) disappeared while (*B*) and (*E*) increased (2×; 6×). When cold the reaction solution deposited triphenylphosphine sulphide, m.p. 156.5—157 °C (lit.,[26] 158 °C). (ii) Ether (15 ml) was added, followed by thin strips of amalgamated aluminium (2.5 g) and water (1 ml) in portions during 3 h: the mixture was then filtered. G.l.c. analysis as before showed that peaks (*B*), (*C*), and (*D*) had been replaced by a new peak (*F*), with t_R 29.9 min, characteristic of the dithiol (7), in amount *ca.* 2× that expected from the disulphide (4) present [peak (*B*)].

Preparation of a Mixture of the Thiophen (2) *and the Disulphide* (4).—Myrcene (1) (340 g) and powdered sulphur (20 g) in cyclohexane (2.5 l) at 58 °C under nitrogen were irradiated for 14 days with a photoflood tungsten lamp (500 W) using the apparatus previously described.[27] The mixture was filtered free from sulphur and evaporated under reduced pressure to remove myrcene and solvent, and the viscous red-brown residue (30 ml) was further freed from sulphur by application to a column (115 × 25 mm) of charcoal and elution with light petroleum (b.p. 60—80 °C). The eluate was concentrated and chromatographed on a silicic acid column (120 × 25 mm) using light petroleum (b.p. 60—80 °C). Evaporation of the eluate provided a brown oil (20 ml), which was subjected to fractional short-path distillation (bath temp. 70 °C) at 0.05 mmHg. Chromatography of the first fraction (0.3 ml) in light petroleum on a silicic acid column (350 × 20 mm) and removal of solvent afforded 3-(4-methylpent-3-enyl)thiophen (2) (10 mg) as a colourless pungent oil with definitive characteristics as reported [5] and $\nu_{max.}$ (film) 3 108, 2 970s, 2 925s, and 2 860s (C–H), 1 674, 1 452s, 1 378s, 1 288, 1 237, 1 104, 1 080, 984, 873, 839s, 774s, and 699s cm^{-1}. The second and third fractions were combined and similarly chromatographed (3×) on silicic acid columns (350 × 20 mm) to afford the cyclic disulphide (4) (100 mg) as an oil with a terpenoid odour and the reported characteristics.[5]

Preparation of the Cyclic Disulphide (4).—Sulphur (5.1 g) in dimethylformamide (3 ml) and pyridine (57 ml) was ' activated ' by passing in ammonia gas for 30 s. Myrcene (1) (11 g) was added slowly with stirring and then the mixture was heated at 100—105 °C for 2 h, cooled, poured into hydrochloric acid (*ca.* 1M; 400 ml), and extracted with ether (2 × 200 ml). The extract was washed (*ca.* 1M-HCl, 2 × 200 ml; 2.5% Na_2CO_3, 200 ml; H_2O, 100 ml), and dried ($CaCl_2$), and evaporated, and the residue was chromatographed in light petroleum (b.p. 60—80 °C) on a silicic acid column (180 × 25 mm). Finally, vacuum distillation at 110 °C and 0.05 mmHg afforded a distillate and a still-pot residue.

The distillate was pale yellow 4-(4-methylpent-3-enyl)-1,2-dithiacyclohex-4-ene (4) (5.2 g, 30%), with the reported characteristics [5] and $\nu_{max.}$ (film) 2 968s, 2 915s, 2 885s, and 2 850s (C–H), 1 655 (C=CH), 1 445s, 1 400s, 1 378s (Me_2C=), 1 264, 1 159, 1 105, 983, 834 (C=CH), and 775 cm^{-1}, which polymerised during 2—3 weeks if stored in light.

The involatile still-pot residue was evidently the *polymeric disulphide* [Found: C, 59.5; H, 8.0; S, 32.0. $(C_{10}H_{16}S_2)_n$ requires C, 59.95; H, 8.05; S, 32.0%], $\nu_{max.}$ (film) 2 972s, 2 930s, and 2 860s (C–H), 1 670, 1 655, 1 445s, 1 378s, 1 212s, 1 107, 983, 892, and 830 cm^{-1}, which with aluminium amalgam and water in ether afforded the dithiol (7) (95% yield) as shown by g.l.c. (OV17 on Chromosorb W).

Interaction of the Disulphide (4) *with Phosphines.*—The disulphide (4) (200 mg) and triphenylphosphine (260 mg) were heated together in dibutyl ether (10 ml) under reflux for 2 h. G.l.c. (OV17 on Chromosorb W) indicated that no reaction had occurred.

To the disulphide (4) (200 mg) in benzene (5 ml) was added tris(dimethylamino)phosphine (200 mg). After 24 h, g.l.c.–mass spectrometry indicated that myrcene had been formed [24] together with tris(dimethylamino)phosphine sulphide, *m/z* 197 $(M + 2)^+$, 196 $(M + 1)^+$, 195 M^+, 152, 151 $(M - NMe_2)^+$, 119 $[P(NMe_2)_2]^+$, 108, 107 $(Me_2NPS)^+$, 76 $(Me_2NS)^+$, 63 $(PS)^+$, 60, and 44 $(Me_2N)^+$.

Formation of the Monosulphide (3).—The disulphide (4) (200 mg) in dimethylformamide (10 ml) was stirred with potassium cyanide (130 mg) in water (2 ml) for 6 h and the mixture was then poured into water (10 ml). Extraction with light petroleum (b.p. 40—60 °C) left an aqueous phase

which gave a positive reaction in a test [with Fe^{III}] for thiocyanate anion. Examination of the dried extract (Na_2SO_4) by g.l.c.[1] (OV1 on Diatomite) revealed a trace component with retention time 14.8 min, identical with the monosulphide component (*E*) in the myrcene–sulphur reaction product. 2,5-*Dihydro*-3-(4-*methylpent*-3-*enyl*)*thiophen* (3) (Found: M^+, 168.0951. $C_{10}H_{16}S$ requires M^+, 168.0972) had *m/z* 170 [$(M + 2)^+$, 8], 169 [$(M + 1)^+$, 10], 168 (M^+, 87), 153 (40), 135 [$(M - SH)^+$, 20], 121 (34), 119 (32), 111 (34), 107 (28), 100 (46), 99 [$(C_5H_7S)^+$, 60], 93 (44), 91 (29), 87 (54), 85 [$(C_4H_5S)^+$, 100], 81 (36), 79 (30), and 67 (isoprenyl cation, 50%).

Reduction of the Disulphide (4) *to the Dithiol* (7).—The cyclic disulphide (4) (5.3 g) in ether (700 ml) was warmed with thin, twisted strips of aluminium amalgam (6 × 0.5 g), while water (6 × 100 μl) was added to maintain effervescence. When g.l.c. analysis (OV17 on Chromosorb W) showed that the disulphide (4) had largely gone (>98%), the mixture was filtered, and the ether layer was washed (H_2O), dried ($MgSO_4$), and evaporated. Distillation of the pale yellow oil (4.96 g) gave colourless 2-(4-*methylpent*-3-*enyl*)*but*-2-*ene*-1,4-*dithiol* (4.21 g, 78%), b.p. 64—66 °C at 0.2 mmHg (Found: C, 59.2; H, 9.1. $C_{10}H_{18}S_2$ requires C, 59.4; H, 8.9%), *m/z* 202 (M^+, 44), 200 [$(M - H_2)^+$, 10], 185 (18), 168 [$(M - SH_2)^+$, 18], 154 [$(M - MeSH)^+$, 48%; *m** 117.4], 152 (38), 143 (23), 139 (25), 119 (14), 115 (27), 108 (22), 107 [$(154 - CH_2SH)^+$, 100%; *m** 74.3], 106 (23), 99 (24), 91 (26), 79 (62), 78 (64), 77 (90), and 69 (36%); $\nu_{max.}$ (film) 2 982s, 2 920s, and 2 858s (C–H), 2 715w, and 2 550w cm^{-1} (SH). The dithiol was stable under nitrogen: air oxidised it to the disulphide, as shown by g.l.c. (OV17 on Chromosorb W).

Preparation of the Bis(*thiosulphate*) *Salt* (8).—Freshly distilled chlorosulphonic acid (0.95 g) in dry ether (30 ml) was added dropwise to a stirred solution of the dithiol (7) (2.5 g) in ether (40 ml) at 0 °C during 1 h. The temperature was allowed to rise to ambient during 1 h, and then sodium hydroxide (0.5 g) in methanol (20 ml) was added. The precipitate was collected and dissolved in water (250 ml), and the solution stirred with Amberlite XAD-2 (50 g) for 2 h. The resin was collected and stirred with methanol (100 ml) for 30 min, and the aqueous phase was re-treated (2×) with Amberlite, which was then washed as before. The combined methanol extracts were evaporated under reduced pressure to give crystals (2.3 g), m.p. 150 °C (decomp.), of *disodium* 2-(4-*methylpent*-3-*enyl*)*but*-2-*ene*-1,4-*diyl bis*-(*thiosulphate*) (8) *monohydrate* (Found: C, 28.4; H, 4.1. $C_{10}H_{16}Na_2O_6S_4,H_2O$ requires C, 28.3; H, 4.25%); δ (D_2O) 1.61 and 1.68 (each s, Me), 2.21 (4 H, m, CH_2–CH_2), 3.74 (2 H, s, S–CH_2–C≤), 3.87 (2 H, m, S–CH_2–CH=), 5.18 (1 H, m, C*H*=Me_2), and 5.65 (1 H, t, =C*H*–CH_2S, *J* 8 Hz). The hydrate was hygroscopic and had to be stored in a desiccator.

From the disodium salt in water with silver nitrate, the orange-yellow anhydrous *silver sodium double salt* was precipitated (Found: C, 24.8; H, 3.2. $C_{10}H_{16}AgNaO_6S_4$ requires C, 24.45; H, 3.3%).

Conversion of the Bis(*thiosulphate*) *Salt* (8) *into the Cyclic Trisulphide* (5).—To the bis(thiosulphate) salt (8) (0.98 g) in 0.25M-phosphate buffer at pH 8 (60 ml) containing formalin (2 ml), a solution of disodium sulphide dihydrate (1.0 g) in water (25 ml) was added dropwise, with stirring, during 30 min, while pH 8 was maintained (by adding 0.5M-HCl). After 4 h, the pH of the solution was adjusted to 3 (with aqueous HCl) and the solution was extracted with chloroform (4 × 20 ml). The extract was washed (H_2O; 20 ml), dried ($MgSO_4$), and evaporated and the residual red oil applied to a column (135 × 25 mm) of silicic acid and eluted with light petroleum (b.p. 60—80 °C) (250 ml), followed by 19 : 1 light petroleum–diethyl ether (150 ml) to afford 5-(4-*methylpent*-3-*enyl*)-1,2,3-*trithiacycloheptene* as a pale yellow oil (18 mg) (Found: C, 53.0; H, 7.2. $C_{10}H_{16}S_3$ requires C, 51.7; H, 6.9%); *m/z* 234 [$(M + 2)^+$, 5], 232 (M^+, 11), 201 (4), 200 [$(M - S)^+$, 14], 199 [$(M - SH)^+$, 10], 169 (10), 168 [$(M - S_2)^+$, 51], 167 [$(M - S_2H)^+$, 44], 166 (6), 143 (9), 136 [$(M - S_3)^+$, 39], 135 [$(M - S_3H)^+$, 71], 121 (34), 111 (19), 107 (37), 99 (28), 97 (65), 93 (61), 91 (50), 77 (56), 70 (25), and 69 (100%).

Conversion of the Bis(*thiosulphate*) *Salt* (8) *into the Cyclic Tetrasulphide* (6).—The bis(thiosulphate) salt (0.81 g) was treated similarly with disodium disulphide [28] (0.9 g) at 10 °C and the mixture (after 2 h) was extracted to afford a semi-crystalline product (445 mg), which was applied to a column (400 × 25 mm) of silicic acid and eluted with light petroleum (b.p. 60—80 °C) and then 1 : 50 chloroform–light petroleum (350 ml). The last fractions (250 ml) were evaporated to give 6-(4-*methylpent*-3-*enyl*)-1,2,3,4-*tetrathiacyclo-oct*-6-*ene* as a mobile pale yellow oil (61 mg) (Found: C, 45.1; H, 6.25. $C_{10}H_{16}S_4$ requires C, 45.45; H, 6.1%; *m/z* 266 [$(M + 2)^+$, 3], 265 [$(M + 1)^+$, 3], 264 (M^+, 24), 232 [$(M - S)^+$, 8], 200 [$(M - S_2)^+$, 26], 199 [$(M - S_2H)^+$, 4], 168 [$(M - S_3)^+$, 4], 167 [$(M - S_3H)^+$, 13], 136 [$(M - S_4)^+$, 14], 135 [$(M - S_4H)^+$, 77], 93 (48), and 69 (100%).

3-(4-*Methylpent*-3-*enyl*)*thiacyclopentan*-3-*ol* (13).—Thiacyclopentan-3-one [29] (3.6 g) in diethyl ether (20 ml) was added during 15 min to the Grignard solution prepared from 1-bromo-4-methylpent-3-ene [30] (7.5 g), ether (22 ml), and magnesium (1.05 g), and the mixture was refluxed for 45 min. Ammonium chloride (4 g) in the minimum of water was stirred in for 1 h. Extraction with ether gave, after the ether had been washed (0.5M-HCl, 20 ml; saturated aqueous NaCl, 20 ml), dried (K_2CO_3), and evaporated, an oil (4.58 g). This was applied to a silicic acid column (200 × 25 mm), which was eluted with 1 : 19 ether–light petroleum (50 ml fractions). Evaporation of fractions 18—30 afforded 3-(4-*methylpent*-3-*enyl*)*thiacyclopentan*-3-*ol* (3.15 g) as a pale yellow liquid, n_D^{25} 1.5105 (Found: C, 64.5; H, 9.7. $C_{10}H_{18}OS$ requires C, 64.5; H, 9.7%); $\nu_{max.}$ (film) 3 440s cm^{-1} (OH); *m/z* 186 (M^+), 170, 169, and 168 [$M - H_2O$]$^+$ δ ($CDCl_3$) 1.63 and 1.69 (s, s, Me_2C=), 2.28 (s, OH), *ca.* 2.9 (m, CH_2–S–CH_2), and 5.15 (t sept, =CH, *J* 9 and 1 Hz).

Attempted Dehydration of the Alcohol (13).—The alcohol (13) (0.25 g) was heated at 170—180 °C in dry dimethyl sulphoxide (3 ml) for 8 h. The cooled solution was poured into water (20 ml), extracted with ether (10 ml), and evaporated. The same product (g.l.c. peak enhancement) resulted from the alcohol (13) (0.5 g) when heated in boiling benzene (8 ml) containing toluene-*p*-sulphonic acid (140 mg) under a Dean–Stark head for 5 h. Evaporation of the solution, application of the residue to a silicic acid column (100 × 25 mm), and elution with 1 : 39 ether–light petroleum gave 7,7-*dimethyl*-6-*oxa*-2-*thiaspiro*[5.4]*decane* (14) as a pale yellow liquid (0.33 g), n_D^{25} 1.4999; *m/z* 186 (M^+, 100), 171 (14), 159 (13), 139 (19), 131 (17), 123 (25), 99 (18), 83 (18), and 69 (55%); δ ($CDCl_3$) 1.20 (s, Me_2C), 1.35—2.35 (m, 4-, 8-, 9-, 10-H_2), and 2.50—3.00 (m, CH_2–S–CH_2).

Formation of 2- *and* 3-(4-*Methylpent*-3-*enyl*)*thiophen and Open-chain Products*.—Under nitrogen at low pressure, the solvent was stripped from 1.5M-butyl-lithium in hexane (55

ml) and replaced by oxygen-free, dry diethyl ether (50 ml). The resulting solution was added slowly to a stirred solution of 3-bromothiophen (8.9 g) in dry ether (25 ml) at −72 °C (acetone–solid CO_2) under nitrogen. To the solution of thienyl-lithium at −72 °C, an oxygen-free solution of 1-bromo-4-methylpent-3-ene [30] (8.9 g) in dry ether (25 ml) was added, at such a rate that the temperature was kept below −60 °C. While the mixture was allowed to warm to room temperature during 48 h, samples (2 ml) were withdrawn through a septum by syringe; each was hydrolysed (aqueous HCl) and the ethereal layer was analysed by g.l.c. (OV17 on Chromosorb W). Below 0 °C, only 3-bromothiophen (*ca.* 5%), and much thiophen and 4-methylpent-3-enyl bromide, were detected. Above 0 °C, appreciable amounts of ring-opened products appeared, with only a small amount of mixed alkenylated thiophens (retention times relative to 3-bromothiophen): *5-thianon-3-en-1-yne* (15), t_R 2.98, *m/z* 140 (M^+), 125 (M − Me)$^+$, 111 (M − Et)$^+$, 97 (M − Pr)$^+$, 84 (C_4H_4S)$^+$, 69, 58 (C_2H_2S)$^+$, and 57 (C_4H_9)$^+$; (4-methylpent-3-enyl)thiophens (2) and (17), t_R 3.38; *m/z* 166 M^+; *9-methyl-5-thiadeca-3,8-dien-1-yne* (16), t_R 4.03; *m/z* 166 (M^+), 138 (M − C_2H_4)$^+$, 123, 97 (M − isoprenyl)$^+$, 83 (M − $Me_2C{=}CHCH_2CH_2$)$^+$, 82, and 69.

Repetition of the reaction, employing purified tetrahydrofuran as solvent, afforded relatively small amounts of the ring-opened products. G.l.c. analysis was performed after hydrolysis, as before: 5-thianon-3-en-1-yne (15), t_R 3.20; mixed alkenylthiophens (2) and (17), t_R 3.38; 9-methyl-5-thiadeca-3,8-dien-1-yne (16), t_R 4.38; *3-bromo-2-(4-methylpent-3-enyl)thiophen* (18), t_R 5.68; *m/z* 244 and 246 (M^+), 175 and 177 (M − isoprenyl)$^+$, 165 (M − HBr)$^+$, 98, 97, and 69 (base peak); δ ($CDCl_3$) 1.58 and 1.69 (s, s, $Me_2C{=}$), 2.35 (m, $=CH{-}CH_2{-}CH_2$), 2.79 (m, 2-CH_2), 5.17 (m, $=CH{-}$), and 6.90 and 7.10 (d, d, 4-H and 5-H, *J* 5 Hz); *3-bromo-2,5-bis(4-methylpent-3-enyl)thiophen* (19), t_R 6.30; *m/z* 326 and 328 (M^+), 257 and 259 (M − isoprenyl)$^+$, 202 and 204, 189 and 191, 188 and 190 [(M − (2 × isoprenyl)]$^+$ 109 (C_6H_5S)$^+$, and 69; δ ($CDCl_3$) 1.51 and 1.61 (s, s, 2 × $Me_2C{=}$), *ca.* 2.2 (m, 2 × $CH_2{-}CH{=}$), *ca.* 2.6 (m, 2-, 5-CH_2), 5.05 (m, 2 × $=CH{-}$), and 6.51 (s, 4-H).

The tetrahydrofuran solution of reaction products was evaporated, and the mixture was chromatographed on silicic acid (40 × 2.5 cm) in light petroleum (b.p. 60—75 °C) to yield three main fractions, which were identified by ^{1}H n.m.r. as (i) a mixture (*ca.* 8 : 1) of 2- and 3-(4-methylpent-3-enyl)-thiophens (17) and (2), (ii) the bromothiophen (18), and (iii) the bromodialkenylthiophen (19). At low gain, the ^{1}H n.m.r. spectrum of the mixture (i) showed only the spectrum of 2-(4-methylpent-3-enyl)thiophen (17), δ ($CDCl_3$) 1.50 and 1.60 (s, s, $Me_2C{=}$), 2.28 (m, $CH_2{-}CH{=}$), 2.73 (t, 2-CH_2, *J* 6.5 Hz), 5.01 (t, $-CH{=}$), and 6.92—7.15 (m, 3-, 4-, 5-H).

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REFERENCES

[1] Part 42, T. L. Peppard, F. R. Sharpe, and J. A. Elvidge, *J. Chem. Soc., Perkin Trans. 1*, 1980, 311.
[2] R. G. Buttery and L. C. Ling, *Brewers Digest*, 1966, **8**, 71.
[3] J. A. Pickett, J. Coates, and F. R. Sharpe, Proc. European Brewery Conv. Congress, Nice, 1975, p. 123; J. A. Pickett, T. L. Peppard, and F. R. Sharpe, *J. Inst. Brewing*, 1976, **82**, 288.
[4] T. L. Peppard and F. R. Sharpe, *Phytochemistry*, 1977, **16**, 2020; T. L. Peppard and D. R. J. Laws, Proc. European Brewery Conv. Congress, Berlin (West), 1979, p. 91.
[5] T. L. Peppard and J. A. Elvidge, *Chem. Ind.*, 1979, 552.
[6] A. Suggett, M. Moir, and J. C. Seaton, Proc. European Brewery Conv. Congress, Berlin (West), 1979, p. 79.
[7] T. Yoshida, S. Muraki, K. Takahashi, T. Kato, C. Kabuto, T. Suzuki, T. Uyehara, and T. Ohnuma, *J. Chem. Soc., Chem. Commun.*, 1979, 512; K. Takahashi, S. Muraki, and T. Yoshida, *Agric. Biol. Chem.*, 1981, **45**, 129.
[8] J. Emsley, D. W. Griffiths, and G. J. J. Jayne, *J. Chem. Soc., Perkin Trans. 1*, 1979, 228.
[9] Cf. T. Tanaka, H. Nakamura, and Z. Tamura, *Chem. Pharm. Bull.*, 1974, **22**, 2725.
[10] Cf. B. Milligan and J. M. Swan, *J. Chem. Soc.*, 1965, 2901; S. Kabuss, A. Luttringhaus, H. Friebolan, and R. Meeke, *Z. Naturforsch.*, 1966, **21b**, 320.
[11] Cf. G. H. Elliot and J. B. Speakman, *J. Chem. Soc.*, 1940, 641.
[12] D. N. Harpp, J. G. Gleason, and J. P. Snyder, *J. Am. Chem. Soc.*, 1968, **90**, 4181; D. N. Harpp and J. G. Gleason, *ibid.*, 1971, **93**, 2437.
[13] R. H. Everhardus, F. Gräfing, and L. Brandsma, *Recl. Trav. Chim. Pays-Bas*, 1976, **95**, 153.
[14] Grasselli Chemical Co., Brit. P. 431 064/1935.
[15] H. J. Jakobsen, *Acta Chem. Scand.*, 1970, **24**, 2663.
[16] B. J. Wakefield, 'The Chemistry of Organo-Lithium Compounds,' Pergamon, Oxford, 1974.
[17] Q. N. Porter and J. Baldas, 'Mass Spectrometry of Heterocyclic Compounds,' Wiley–Interscience, New York, 1971.
[18] H. D. Hartough, 'The Chemistry of Heterocyclic Compounds—Thiophene and its Derivatives,' Interscience, New York, 1952, ch. 4.
[19] *Cf.* T. J. Batterham, 'NMR Spectra of Simple Heterocycles,' Wiley–Interscience, New York, 1973.
[20] R. R. Ernst, *J. Chem. Phys.*, 1966, **45**, 3845.
[21] F. Bohlmann and R. Zeisberg, *Org. Magn. Reson.*, 1975, **7**, 426.
[22] J. B. Stothers, 'Carbon-13 NMR Spectroscopy,' Academic Press, New York, 1972, p. 158.
[23] D. Grant and J. R. van Wazer, *J. Am. Chem. Soc.*, 1964, **86**, 3012; G. R. Pettit, I. B. Douglass, and R. A. Hill, *Can. J. Chem.*, 1964, **42**, 2357.
[24] R. Rhyage and E. von Sydow, *Acta Chem. Scand.*, 1963, **17**, 2025.
[25] J. Janak, J. Jonas, and M. Kratochvil, *Collect. Czech. Chem. Commun.*, 1965, **30**, 265; E. Kovats, *Helv. Chim. Acta*, 1958, **41**, 1915.
[26] D. B. Denney and M. J. Boskin, *J. Am. Chem. Soc.*, 1960, **82**, 4736.
[27] B. J. Clarke and R. P. Hildebrand, *J. Inst. Brewing*, 1965, **71**, 26.
[28] F. G. Mann and B. C. Saunders, 'Practical Organic Chemistry,' Longmans, London, 4th edn., 1970, p. 167.
[29] M. A. Gianturco, P. Friedal, and A. S. Giammarino, *Tetrahedron*, 1964, **20**, 1763; H. Wynberg, A. Logothetis, and D. Ver Ploeg, *J. Am. Chem. Soc.*, 1957, **79**, 1972.
[30] M. Julia, S. Julia, and R. Guegan, *Bull. Soc. Chim. Fr.*, 1960, 1072.