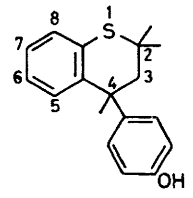
Alteration of Cage Geometry by Systematic Structural Modification of a Clathrate Host Molecule

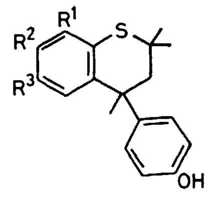
By **Andrew D. U. Hardy, Joseph J. McKendrick,** and **David D. MacNicol,*** Department of Chemistry, University of Glasgow, Glasgow G12 8QQ

A study of compounds structurally related to the versatile host compound, 4-*p*-hydroxyphenyl-2,2,4-trimethylthiachroman (I) is described. The compounds (II)—(IV) which possess an additional methyl group at the 6-, 7-, or 8-position of (I) have been synthesised and found to exhibit an interesting spectrum of behaviour. The previously described 7-methyl analogue (III) forms spontaneously-resolved unsolvated crystals while (II) and (IV) are new hosts. A single-crystal *X*-ray investigation of the trigonal crystals of the cyclo-octane clathrate of the 8-methyl analogue (IV), space group $R\bar{3}$, a = 33.629(9), c = 8.239(3), and Z = 18 (host), has established the formation of a fundamentally new cage-shape. Compound (V) has also been synthesised in the present study, as have analogues (VII) and (VIII) of the host Dianin's compound (VI), but in these three cases no inclusion behaviour has been found.

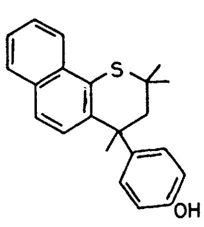
THE importance of clathrate compounds,[1] both from practical and theoretical standpoints, is now widely recognised. In view of the key role of cage geometry in determining guest inclusion, the design and synthesis of new host compounds is of fundamental interest. The present study [2] concerns the systematic structural modification of the known host molecules 4-*p*-hydroxyphenyl-2,2,4-trimethylthiachroman (I) and Dianin's compound (VI), with a view to producing new hosts. A pre-requisite for selecting suitable points of structural alteration was a knowledge of the crystal structures of the parent clathrates. The crystal structures of clathrates of (I) [3] and (VI) [4] have been determined by *X*-ray methods, and in each case sextet-units are present, the hydroxy-groups of six host molecules being linked together by a network of hydrogen bonds such that the oxygen atoms form a hexagon. These sextets are stacked along the *c* axis such that their bulkier parts interlock forming cages. This arrangement gives rise to infinite columns [part of one may be seen, *e.g.* in Figure 2(b), see later], each of which is surrounded by six identical columns, these being related by three-fold screw axes. Since the carbon atoms C(5)—C(8) of the fused aromatic ring of the thiachroman or chroman are situated on the ' outside ' of the columns, modification at these positions may be expected to affect intercolumn packing.



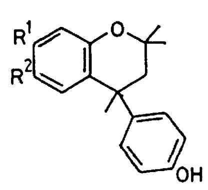
(I)



(II) $R^1 = R^2 = H$; $R^3 = Me$
(III) $R^1 = R^3 = H$; $R^2 = Me$
(IV) $R^2 = R^3 = H$; $R^1 = Me$



(V)



(VI) $R^1 = R^2 = H$
(VII) $R^1 = H$; $R^2 = Me$
(VIII) $R^2 = H$; $R^1 = Me$

We now report the synthesis and properties of the compounds (II), (IV), and (V) which are all related to (I), and the analogues (VII) and (VIII) of Dianin's compound (VI). This work complements our previous clathrate engineering studies concerned with removal of specific methyl groups directly from the cage wall on the ' inside ' of columns,[5] and variation of the hydrogen-bonding functionality in the hexamers which form the top and bottom of each void.[6]

EXPERIMENTAL

Preparation of 4-p-*Hydroxyphenyl*-2,2,4,6-*tetramethylthiachroman* (II).—A mixture of phenol (29.7 g) and 4-methyl-4-(*p*-tolylthio)pentan-2-one (35.0 g), prepared by piperidine-catalysed Michael addition of *p*-thiocresol to mesityl oxide,[7] was saturated (6 h) at 0 °C with dry gaseous hydrogen chloride. The resulting dark red viscous liquid was set aside for 2 months in a flask fitted with a drying tube; the excess of phenol was then extracted with boiling water (5 × 150 ml), leaving a clear yellow glass containing a considerable amount of 2,2-bis-(*p*-hydroxyphenyl)propane which was removed by addition of benzene and chilling the solution. Chromatography on Mallinckrodt silicic acid (ratio 40 : 1, eluant 10% ethyl acetate in benzene) gave a pale yellow oil which defied crystallisation. Final purification was achieved by gel permeation chromatography (200 × 2.5 cm column of Sephadex LH 20 modified with Nedox 1114, elution with methanol). The resulting colourless glass was crystallised by sudden cooling of a hot light petroleum solution. Clathrating properties were exhibited when it was grown from cyclopentane, cyclohexane, and n-pentane (Table 1); cyclopentane gave colourless prisms, m.p. 64—67° (74%). A sample was desolvated by sublimation (60°, 0.01 mmHg) for microanalysis (Found: C, 76.50; H, 7.70. $C_{19}H_{22}OS$ requires C, 76.48; H, 7.43%, *M*, 298); *m*/*e* 298; $\nu_{max.}$ (KBr), cyclopentane adduct, 3 410 cm^{-1} (OH); τ($CDCl_3$) *ca.* 2.8—3.4 (7 H, m), 4.95 (1 H,

TABLE 1

Inclusion compounds formed by (II) and (IV)

Host	Guest	Ratio *
(II)	n-Pentane	6 : 1
	Cyclopentane	6 : 1
	Cyclohexane	6 : 1
(IV)	Carbon tetrachloride	6 : 1
	Benzene	5 : 1
	Toluene	4 : 1
	Cyclopropane	6 : 1
	Cyclopentane	6 : 1
	Cyclohexane	6 : 1
	Cycloheptane	4 : 1
	Cyclo-octane	4.5 : 1

* Mole ratio host : guest, determined by multiple integration of the ^{1}H n.m.r. spectrum ($CDCl_3$ solution) except for the CCl_4 clathrate of (IV) which was analysed by microanalysis for chlorine. All adducts were prepared by recrystallisation of unsolvated material from the appropriate pure solvent, a sealed tube being employed for cyclopropane.

s), 7.76 (2 H, AB$_q$, δ_{AB} 0.32 p.p.m. J 14 Hz), and 7.78, 8.26, 8.61, and 8.91 (each 3 H, s).

Recrystallisation from most solvents (*e.g.* benzene and ethanol) was unsuccessful on account of the high solubility of (II).

Preparation of 4-p-*Hydroxyphenyl*-2,2,4,8-*tetramethylthiachroman* (IV).—A mixture of phenol (7.7 g) and 4-methyl-4-(*o*-tolylthio)pentan-2-one [7] (9.0 g) was saturated (4 h) at 0 °C with dry gaseous hydrogen chloride and gave a dark red viscous liquid. After 21 months excess of phenol was removed with boiling water (6 × 50 ml) to give a thick yellow gum. After chromatography on Mallinckrodt silicic acid (ratio 25 : 1, eluant 10% chloroform in light petroleum), the solution was set aside to give a pale yellow solid (15%). Recrystallisation from cyclo-octane gave solvated colourless hexagonal crystals, m.p. 110—111 °C, *M*, 298; *m*/*e* 298; $\nu_{max.}$ (KBr) 3 275 cm^{-1} (OH); τ($CDCl_3$) *ca.* 2.8—3.4 (7 H, m), 5.38 (1 H, s), 7.70 (3 H, s), 7.74 (2 H, AB$_q$, δ_{AB} 0.31 p.p.m. J 14 Hz), 8.24, 8.59, and 8.90 (each 3 H, s).

Desolvated (IV) was obtained by melting crystals of the cyclopentane clathrate under vacuum (Found: C, 76.7; H, 7.65. $C_{19}H_{22}OS$ requires C, 76.48; H, 7.43%).

Inclusion compounds of (IV) are listed in Table 1.

Preparation of 4-p-*Hydroxyphenyl*-2,2,4-*trimethyl*-7,8-*benzothiachroman* (V).—A mixture of phenol (4.0 g) and 4-methyl-4-(1-naphthylthio)pentan-2-one [7] (5.0 g) was saturated (6 h) at 0 °C with dry gaseous hydrogen chloride. The resulting dark green viscous liquid changed to a pale brown solid within 24 h; removal of excess of phenol with boiling water (6 × 30 ml) left a pale yellow glass which solidified when set aside. Three recrystallisations from benzene gave (V) as white needles, m.p. 152—154 °C (52%) (Found: C, 78.9; H, 6.7. $C_{22}H_{22}OS$ requires C, 79.01; H, 6.63%; *M*, 334); *m*/*e* 334; $\nu_{max.}$ (KBr) 3 535 and 3 420 cm^{-1} (OH); τ($CDCl_3$) *ca.* 1.6—1.9 and 2.2—3.5 (10 H), 5.23 (1 H, s), 7.64 (2 H, AB$_q$, δ_{AB} 0.26 p.p.m. J 14 Hz), 8.14, 8.50, and 8.77 (each 3 H, s).

Preparation of 4-p-*Hydroxyphenyl*-2,2,4,6-*tetramethylchroman* (VII).—Methyl iodide (140.8 g) in anhydrous diethyl ether (200 ml) was added dropwise over 1.5 h to magnesium turnings (24.4 g) in ether (250 ml) under a dry atmosphere.[8] 4,6-Dimethylcoumarin (54.0 g), prepared according to ref. 9, in ether (2 l) was introduced with stirring over 2 h to give a pale yellow precipitate. After stirring overnight at room temperature the excess of Grignard reagent was destroyed by use of 22% acidified ammonium chloride solution (500 ml) and the ether layer separated and dried. After solvent evaporation a pale yellow solid (57%) remained and was recrystallised from light petroleum to give 2-(2-hydroxy-5-methylphenyl)-4,4-dimethylbut-2-en-4-ol as white prisms, m.p. 94—96 °C (Found: C, 75.5; H, 8.85. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80%); $\nu_{max.}$ (KBr) 3 350 and 3 110 cm^{-1} (OH); τ($CDCl_3$) *ca.* 2.9—3.4 (3 H, m), 4.23 (1 H, q, J 1.5 Hz), 7.75 (3 H, s), 8.06 (3 H, d, J 1.5 Hz), and 8.78 (6 H, s).

This diol (18.0 g) was added to phenol (19.9 g) at 45 °C, and dry gaseous hydrogen chloride passed in for 4 h; the resulting dark red viscous liquid was set aside in an oven at 45 °C for 6 days. Excess of phenol was extracted with boiling water (5 × 50 ml); ethanol (25 ml) introduced and the gum allowed to crystallise. Recrystallisation from ethanol gave (VII) as large white single prisms, m.p. 135—136 °C (52%) (Found: C, 81.0; H, 7.9. $C_{19}H_{22}O_2$ requires C, 80.81; H, 7.85%; *M*, 282); *m*/*e* 282; $\nu_{max.}$ (KBr) 3 385 cm^{-1} (OH); τ(deuterioacetone) 1.92 (1 H, s), *ca.* 2.8—3.4 (7 H), 7.75 (3 H, s), 7.81 (2 H, AB$_q$, δ_{AB} 0.41 p.p.m. J 14 Hz), 8.36, 8.71, and 9.12 (each 3 H, s).

Preparation of 4-p-*Hydroxyphenyl*-2,2,4,7-*tetramethylchroman* (VIII).—Methyl iodide (85.3 g) in anhydrous diethyl ether was added dropwise over 1 h to magnesium turnings (14.7 g) in ether (100 ml), under nitrogen.[8] 4,7-Dimethylcoumarin (30.0 g), prepared according to ref. 9, in dry (Na) benzene (1 l) was introduced with stirring over 2.5 h, then stirred for a further 17 h at room temperature. Standard work-up gave a yellow solid which was twice recrystallised from ethanol to give 2-(2-hydroxy-4-methylphenyl)-4,4-dimethylbut-2-en-4-ol as white prisms, m.p. 114—115 °C (45%) (Found: C, 75.80; H, 8.65. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80%); $\nu_{max.}$ (KBr) 3 330 and 3 055 cm^{-1} (OH); τ($CDCl_3$) *ca.* 3.0—3.4 (3 H), 4.24 (1 H, q, J 1.5 Hz), 7.74 (3 H, s), 8.06 (3 H, d, J 1.5 Hz), and 8.79 (6 H, s).

The diol (3.54 g) was added to phenol (4.0 g) at 48 °C and dry gaseous hydrogen chloride passed in for 6 h. The resulting dark red viscous liquid was set aside at 55 °C for 6 days. Excess of phenol was removed with boiling water (4 × 50 ml), and methanol (10 ml) added. The solution was boiled to remove solvent to give a solid (81%) with a persistent grey colour which was not eliminated by successive recrystallisations from toluene and cyclohexane. Sublimation (98 °C, 0.01 mmHg) gave (VIII) as colourless prisms, m.p. 129—130 °C (Found: C, 80.95; H, 8.0. $C_{19}H_{22}O_2$ requires C, 80.81; H, 7.85%; *M*, 282); *m*/*e* 282; $\nu_{max.}$ (KBr) 3 382 cm^{-1} (OH); τ($CDCl_3$) *ca.* 2.8—3.4 (7 H), 4.91 (1 H, s), 7.68 (3 H, s), 7.83 (2 H, AB$_q$, δ_{AB} 0.28 p.p.m. J 14 Hz), 8.35, 8.66, and 9.10 (each 3 H, s).

Selectivity Experiments on Clathrate Hosts (I), (II), *and* (IV).—4-*p*-Hydroxyphenyl-2,2,4-trimethylthiachroman (I) (61.3 mg) was sealed in a tube at atmospheric pressure with an equimolar mixture of cyclopentane, cyclohexane, and cycloheptane (*ca.* 3 ml), and the tube heated to 120 °C. The tube was then allowed to cool to room temperature over several h. The crystalline product was removed after 1 day, dried for 1 h at room temperature and 0.01 mmHg and its ^{1}H n.m.r. spectrum recorded with benzene or deuteriobenzene as solvent. Similarly (IV) (54.5 mg) and (II) (130.0 mg) were each recrystallised from *ca.* 5 and 2 ml of the equimolar mixture. Recoveries were 62.5, 40.8, and 38.4 mg respectively. When the recrystallisations were repeated identical incorporation of cycloalkanes resulted.

X-*Ray Crystal Structure Analysis of the Cyclo-octane Adduct of Compound* (IV).—*Crystal data.* $C_{19}H_{22}OS$.

$C_8H_{16} \times 2/9$, $M = 323.4$, $a = 33.629(9)$, $c = 8.239(3)$ Å, $Z = 18$ (host plus 4 molecules C_8H_{16}), $U = 8\,069.0$ Å^3, $D_c = 1.21$ g cm^{-3}, $F(000) = 3\,136$. Trigonal space group $R\bar{3}$ (or $R3$) referred to hexagonal cell. Mo-K_α radiation, $\lambda = 0.710\,7$ Å, μ(Mo-K_α) = 1.80 cm^{-1}. M.p. 110—111 °C. Host : guest (cyclo-octane) ratio 4.5 : 1 found by ^{1}H n.m.r. for a $CDCl_3$ solution. The crystal used was an extended hexagon of *ca.* 0.55 × 0.40 × 0.375 mm.

Crystallographic measurements. Least-squares best cell dimensions were obtained by a treatment of the θ, χ, ϕ setting angles of twenty-two reflections measured on a Hilger and Watts automatic diffractometer. Intensities were measured by the θ—2θ step-scan procedure with Zr-filtered Mo-K_α radiation. Background counts were taken at each end of the scan range. The intensities of three reflections were monitored after every 40 intensity measurements, and the results used to place the reflections on a common scale; the changes in the standard intensities during data collection were small (<4%). Reflections were surveyed out to $\theta \leqslant 27°$, with an option whereby those intensities with $I \lesssim 2\sigma(I)$ were not measured. The intensity values were corrected for Lorentz-polarisation effects, but not for absorption, and 1 451 independent reflections, with $I > 2\sigma(I)$, were obtained.

Structure analysis. The structure was solved in the centrosymmetric space group $R\bar{3}$ (this choice was justified by the success of the analysis), by direct phase-determining methods with MULTAN [10] and the 185 reflections having the largest $|E|$ magnitudes. An E map computed with that set of phases which gave the highest figure-of-merit and the lowest residual revealed 15 of the host non-hydrogen atom positions. A subsequent difference electron-density distribution revealed the remaining six non-hydrogen atom positions of the host molecule. The atomic parameters of these 21 atoms were adjusted by several cycles of full-matrix least-square calculations by use of the program CRYLSQ from the '*X*-RAY '72 ' system,[11] and for anisotropic temperature factors R was reduced to 14.6%.

TABLE 2

Atom co-ordinates ($\times 10^4$)

	X	*Y*	*Z*
S(1)	2 396(1)	1 907(1)	2 857(4)
C(2)	2 296(3)	1 364(3)	2 077(10)
C(3)	2 594(3)	1 442(3)	0 592(9)
C(4)	2 526(2)	1 670(3)	−0 918(9)
C(5)	2 641(4)	2 446(4)	−1 725(16)
C(6)	2 679(6)	2 855(5)	−1 421(30)
C(7)	2 584(6)	2 959(5)	−0 019(41)
C(8)	2 514(4)	2 668(5)	1 377(26)
C(9)	2 490(3)	2 236(3)	1 113(17)
C(10)	2 562(3)	2 120(3)	−0 487(12)
C(11)	2 083(2)	1 346(2)	−1 823(8)
C(12)	1 784(3)	1 494(2)	−2 328(9)
C(13)	1 390(3)	1 207(2)	−3 231(9)
C(14)	1 300(2)	0 770(2)	−3 645(8)
C(15)	1 585(3)	0 613(2)	−3 127(9)
C(16)	1 974(3)	0 902(3)	−2 250(9)
C(17)	2 928(3)	1 748(4)	−2 108(12)
C(18)	1 783(3)	1 046(3)	1 757(11)
C(19)	2 444(5)	1 144(5)	3 440(13)
O(20)	0 921(2)	0 487(2)	−4 571(7)
C(21)	2 442(6)	2 794(6)	3 119(27)

At this stage several difference electron-density distributions were calculated; the 22 hydrogen atoms of the host molecule were located but it proved impossible to allow effectively for the guest molecules of cyclo-octane. When the host hydrogen atoms were included in the least-squares calculations (with isotropic temperature factors) the R value converged to a final value of 10.6% (R' 15.1%). The weighting scheme employed in the last cycles of the least-squares calculations was $w = (-19.06 + 1.67\,|F|)^{-1}$.

Calculations were carried out on an IBM 370/158 computer at Edinburgh and an IBM 370/168 at Newcastle. Observed and calculated structure factors, anisotropic temperature factors,* and hydrogen atom co-ordinates and thermal parameters are listed in Supplementary Publication No. SUP 22512 (24 pp., 1 microfiche).† Scattering factors for non-hydrogen atoms were taken from ref. 12, those for hydrogen from ref. 13. The anomalous dispersion was allowed for in the least-squares calculations, with values of $\Delta f'$ and $\Delta f''$ for sulphur taken from ref. 14. Atomic fractional co-ordinates are listed in Table 2, and various parameters connected with the clathrate's molecular geometry are listed in Tables 3—6.

TABLE 3

Interatomic distances (Å) and valency angles (°), with standard deviations in parentheses

(*a*) Bond lengths

S(1)–C(2)	1.80(1)	C(6)–C(7)	1.29(4)
S(1)–C(9)	1.74(1)	C(7)–C(8)	1.45(3)
C(2)–C(3)	1.52(1)	C(8)–C(9)	1.43(2)
C(2)–C(18)	1.53(1)	C(8)–C(21)	1.55(3)
C(2)–C(19)	1.56(1)	C(9)–C(10)	1.43(2)
C(3)–C(4)	1.54(1)	C(11)–C(12)	1.39(1)
C(4)–C(10)	1.50(1)	C(11)–C(16)	1.39(1)
C(4)–C(11)	1.53(1)	C(12)–C(13)	1.40(1)
C(4)–C(17)	1.58(1)	C(13)–C(14)	1.38(1)
C(5)–C(6)	1.34(2)	C(14)–C(15)	1.37(1)
C(5)–C(10)	1.42(1)	C(14)–O(20)	1.38(1)
C(15)–C(16)	1.38(1)		

Means:	C(sp^3)–H	1.0
	C(sp^2)–H	1.0
	O–H	0.9

(*b*) Valency angles

C(9)–S(1)–C(2)	103.5(5)	C(3)–C(2)–S(1)	109.8(6)
C(18)–C(2)–S(1)	110.1(6)	C(19)–C(2)–S(1)	106.3(7)
C(8)–C(9)–S(1)	114.9(12)	C(10)–C(9)–S(1)	125.9(7)
C(18)–C(2)–C(3)	113.4(7)	C(19)–C(2)–C(3)	108.9(7)
C(4)–C(3)–C(2)	119.3(6)	C(19)–C(2)–C(18)	108.0(8)
C(10)–C(4)–C(3)	110.7(7)	C(11)–C(4)–C(3)	111.9(6)
C(17)–C(4)–C(3)	104.9(6)	C(11)–C(4)–C(10)	113.3(6)
C(17)–C(4)–C(10)	110.3(7)	C(5)–C(10)–C(4)	119.9(9)
C(9)–C(10)–C(4)	123.8(8)	C(17)–C(4)–C(11)	105.2(6)
C(12)–C(11)–C(4)	120.7(6)	C(16)–C(11)–C(4)	121.9(6)
C(10)–C(5)–C(6)	122.9(15)	C(7)–C(6)–C(5)	122.3(18)
C(9)–C(10)–C(5)	116.1(8)	C(8)–C(7)–C(6)	120.4(15)
C(9)–C(8)–C(7)	118.1(17)	C(21)–C(8)–C(7)	123.1(15)
C(21)–C(8)–C(9)	118.7(15)	C(10)–C(9)–C(8)	119.2(12)
C(16)–C(11)–C(12)	117.3(6)	C(13)–C(12)–C(11)	121.0(7)
C(15)–C(16)–C(11)	122.5(7)	C(14)–C(13)–C(12)	119.5(7)
C(15)–C(14)–C(13)	120.4(7)	O(20)–C(14)–C(13)	120.3(6)
O(20)–C(14)–C(15)	119.3(6)	C(16)–C(15)–C(14)	119.3(7)

Means:	C(sp^2)–C(sp^2)–H	119
	C(sp^2)–C(sp^3)–H	100
	C(sp^3)–C(sp^3)–H	109
	H–C(sp^3)–H	106
	C(sp^2)–O–H	116

DISCUSSION

In contrast to 4-*p*-hydroxyphenyl-2,2,4,7-tetramethylthiachroman (III) which forms unsolvated orthorhombic crystals,[15] the isomeric compounds (II) and (IV)

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* Anisotropic thermal parameters are of the form $\exp[-2\pi^2(h^2a^{*2}U_{11} + \ldots 2hka^*b^*U_{12} + \ldots)]$.

† For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1978, Index issue.

TABLE 4

Torsion angles (°), with standard deviations in parentheses

C(9)–S(1)–C(2)–C(3)	35.3(7)
C(9)–S(1)–C(2)–C(19)	152.9(7)
C(2)–S(1)–C(9)–C(10)	−11.5(10)
C(18)–C(2)–C(3)–C(4)	61.5(9)
C(2)–C(3)–C(4)–C(10)	54.4(9)
C(2)–C(3)–C(4)–C(17)	173.3(7)
C(3)–C(4)–C(10)–C(9)	−22.6(11)
C(11)–C(4)–C(10)–C(9)	104.1(10)
C(17)–C(4)–C(10)–C(9)	−138.2(9)
C(3)–C(4)–C(11)–C(16)	−50.4(9)
C(10)–C(4)–C(11)–C(16)	−176.4(7)
C(17)–C(4)–C(11)–C(16)	63.0(9)
C(6)–C(5)–C(10)–C(4)	−179.8(13)
C(5)–C(6)–C(7)–C(8)	11.5(32)
C(6)–C(7)–C(8)–C(21)	174.5(19)
C(7)–C(8)–C(9)–C(10)	3.6(20)
C(21)–C(8)–C(9)–C(10)	−179.1(12)
S(1)–C(9)–C(10)–C(5)	−178.9(8)
C(8)–C(9)–C(10)–C(5)	−1.9(15)
C(16)–C(11)–C(12)–C(13)	−0.1(11)
C(12)–C(11)–C(16)–C(15)	−0.4(11)
C(12)–C(13)–C(14)–C(15)	2.3(11)
C(13)–C(14)–C(15)–C(16)	−2.8(11)
C(14)–C(15)–C(16)–C(11)	1.9(11)
C(9)–S(1)–C(2)–C(18)	−90.3(7)
C(2)–S(1)–C(9)–C(8)	171.4(9)
S(1)–C(2)–C(3)–C(4)	−62.1(8)
C(19)–C(2)–C(3)–C(4)	−178.2(8)
C(2)–C(3)–C(4)–C(11)	−73.1(9)
C(3)–C(4)–C(10)–C(5)	162.2(8)
C(11)–C(4)–C(10)–C(5)	−71.1(10)
C(17)–C(4)–C(10)–C(5)	46.6(11)
C(3)–C(4)–C(11)–C(12)	133.1(7)
C(10)–C(4)–C(11)–C(12)	7.0(10)
C(17)–C(4)–C(11)–C(12)	−113.5(8)
C(10)–C(5)–C(6)–C(7)	−9.8(27)
C(6)–C(5)–C(10)–C(9)	4.7(18)
C(6)–C(7)–C(8)–C(9)	−8.3(29)
C(7)–C(8)–C(9)–S(1)	−179.1(13)
C(21)–C(8)–C(9)–S(1)	−1.8(18)
S(1)–C(9)–C(10)–C(4)	5.8(14)
C(8)–C(9)–C(10)–C(4)	−177.3(10)
C(4)–C(11)–C(12)–C(13)	176.6(7)
C(4)–C(11)–C(16)–C(15)	−177.1(7)
C(11)–C(12)–C(13)–C(14)	−0.8(11)
C(12)–C(13)–C(14)–O(20)	−178.2(6)
O(20)–C(14)–C(15)–C(16)	177.7(7)

both possess inclusion properties. The host : guest ratios of adducts formed by hosts (II) and (IV) are given in Table 1.

A comparison of crystal data of 4-*p*-hydroxyphenyl-2,2,4-trimethylthiachroman (I) and Dianin's compound (VI) with those for related compounds (II)—(IV), and (VII) and (VIII) is given in Table 7.

The cyclopentane clathrate of (II) forms trigonal crystals, space group $R\bar{3}$, with lattice parameters similar to those of the thiachroman parent (I), the modest increase in the *a* dimension indicating only minor changes in intercolumn interactions.

Most significantly, the trigonal cyclo-octane clathrate of (IV) has markedly different lattice parameters from those of (I). The increased *a* dimension corresponds to a greater intercolumn distance, and this, together with the reduced *c* spacing, indicates that the introduction of the methyl group *ortho* to sulphur results in a fundamental change in the shape of the cavity.

TABLE 5

Displacement (Å) of atoms from planes through various sets of atoms

Plane (*A*): C(5)—C(10)

C(5) 0.016, C(6) −0.049, C(7) 0.049, C(8) −0.010, C(9) 0.003, C(10) −0.005, S(1) −0.046, C(4) 0.067, C(21) −0.024

Plane (*B*): C(11)—C(16)

C(11) −0.004, C(12) 0.002, C(13) 0.006, C(14) −0.012, C(15) 0.012, C(16) −0.003, C(4) −0.086, O(20) −0.046

Plane (*C*): S(1), C(4), C(9), C(10)

S(1) −0.001, C(4) 0.007, C(9) 0.032, C(10) −0.023, C(2) 0.236, C(3) −0.454

TABLE 6

Some short intermolecular contacts

$C(17) \cdots C(17^{I})$	3.65	$C(17) \cdots C(21^{II})$	3.94
$O(20) \cdots O(20^{III})$	2.78	$O(20) \cdots H(20^{III})$	1.85

Roman numeral superscripts refer to the following transformations of the atomic co-ordinates relative to the reference molecule at x, y, z:

I $\frac{2}{3} - x, \frac{1}{3} - y, -z - \frac{2}{3}$ II $\frac{2}{3} - y, \frac{1}{3} + (x - y), z - \frac{2}{3}$
III $y, y - x, -z - 1$

A dramatic difference in the selective clathration properties of (I) and (IV) was observed (see Experimental section): the parent host (I) exhibits a very strong preference for cyclopentane, the relative percentages for cyclopentane, cyclohexane, and cycloheptane being 85, 10, and 5%, whereas (IV) shows a relatively increased tendency to include the larger cycloalkanes, corresponding values being 20, 50, and 30% and reflecting the altered cavity shape. Nevertheless, a large alteration in cavity geometry as found for (IV) (*vide infra*) may not be required to effect marked changes in selective clathration behaviour, since ratios of 12, 57, and 31% were

TABLE 7

A comparison of crystal data for compounds (I)—(IV) and (VI)—(VIII)

Host	Guest (host : guest ratio)	Space group	Lattice parameters [a]
(I)	2,5,5-Trimethylhex-3-yn-2-ol (6 : 1) [b]	$R\bar{3}$	$a = 27.91$, $c = 10.99$ Å, $Z = 18$ (host)
(II)	Cyclopentane (6 : 1) [c]	$R\bar{3}$	$a = 29.22(4)$, $c = 10.82(1)$ Å, $Z = 18$ (host)
(III)	*d, e*	$P2_12_12_1$	$a = 11.777(1)$, $b = 16.501(2)$, $c = 8.479(1)$ Å, $Z = 4$
(IV)	Cyclo-octane (4.5 : 1) [c]	$R\bar{3}$	$a = 33.629(9)$, $c = 8.239(3)$ Å, $Z = 18$ (host)
(VI)	Chloroform (6 : 1) [f]	$R\bar{3}$	$a = 27.116(3)$, $c = 11.023(2)$ Å, $Z = 18$ (host)
(VII)	*c, d*	$P2_1/c$	$a = 14.25(3)$, $b = 6.52(1)$, $c = 18.67(4)$ Å, $\beta = 113.0°$, $Z = 4$
(VIII)	*c, d*	$P2_1/n$	$a = 12.91(2)$, $b = 12.11(2)$, $c = 9.79(1)$ Å, $\beta = 90.3°$, $Z = 4$

[a] For $R\bar{3}$ the values of *a* and *c* given are referred to a hexagonal unit cell. [b] Ref. 3*b*. [c] Present work. [d] Unsolvated form. [e] Ref. 15. [f] Ref. 4*a*.

found for (II), the cavity shape of which is probably not greatly different from that of (I), according to the preliminary *X*-ray evidence.

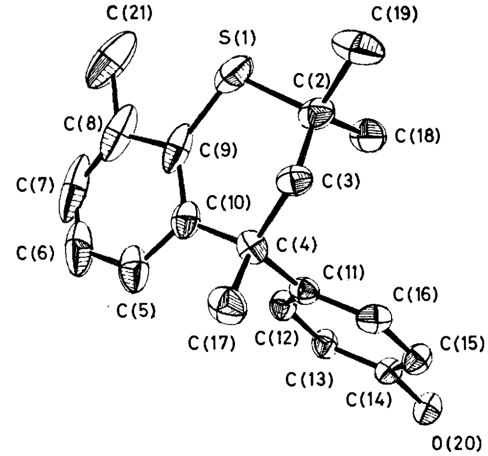

FIGURE 1 An ORTEP drawing (25% probability plot) showing a general view of the molecular structure of host (IV). Hydrogen atoms have been omitted for clarity

Compound (V), which corresponds to fusion of an additional bulky benzene ring at the 7- and 8-positions of (I), was found to crystallise unsolvated from a range of solvents (see Experimental section). Interestingly, the 6- and 7-methyl homologues of Dianin's compound itself, (VII) and (VIII) form monoclinic crystals (see Table 7) without inclusion of solvent.

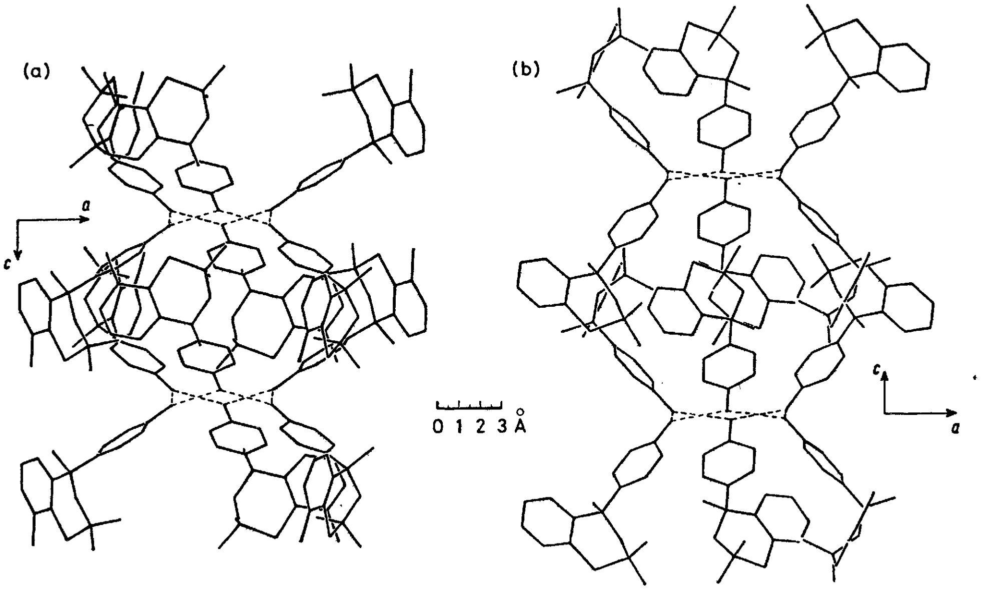

FIGURE 2 Comparative views looking on the *ac* plane for (a) the cyclo-octane clathrate of (IV) and (b) the 2,5,5-trimethylhex-3-yn-2-ol clathrate of (I). The guest molecules are not shown. Hydrogen bonds are denoted by broken lines

Structural Properties of the Cyclo-octane Clathrate of (IV).—An interesting feature of the molecular structure of (IV) is the distorted half-chair conformation of the sulphur-containing ring (see Figure 1 and Table 5). Atoms C(2) and C(3) are displaced from the mean-plane defined by atoms S(1), C(9), C(10), and C(4) by 0.24 and —0.45 Å respectively, the corresponding displacements in the parent (I) [3b] being 0.38 and —0.34 Å.

Pronounced thermal motion is observed for atoms C(5)—(9), and C(21) (see ellipsoids in Figure 1) and this results in unrealistic bond lengths involving these atoms (see Table 3). This high thermal anisotropy may reflect the relatively inefficient column packing in (IV) compared to that in (I).

The overall similarity between the molecular packing arrangements of (IV) and (I) is shown in Figure 2, both views being on the *ac* plane. Both structures embody groups of six molecules, the hydroxy-groups of which are linked by hydrogen bonds such that the oxygen atoms form a distorted hexagon, alternate molecules lying on opposite sides of its plane. Two such sextets are stacked in each *c*-axis repeat and their bulkier parts interlock to form cages. The major differences between the two structures is the marked contraction in the *c* spacing, and hence the cavity length, of (IV) compared to that in (I). The $O \cdots O$ hexamer dimension in (IV) is 2.78(1) Å, compared with 3.03(1) Å for the 2,5,5-trimethylhex-3-yn-2-ol clathrate of (I); [3b] the $O \cdots H$ distance and the $O\text{–}H \cdots O$ angle for (IV) are 1.85(13) Å and 173(8)°. A pronounced increase in the degree of puckering of the oxygen hexagon is observed for (IV) compared with (I), the corresponding mean-plane displacements being ± 0.35 and ± 0.22 Å.

Although the acetylenic alcohol guest in (I) has been located,[3b] attempts to find the cyclo-octane in (IV) have not been successful. This difficulty is due to disorder and possible high thermal motion of the guest.*

Changes in the interlocking pattern of columns (IV) and (I) can readily be appreciated from the views down the *c* axis (Figure 3). These changes may be attributed

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* In the final difference map, only one significant electron-density peak (1.1 $eÅ^{-3}$) was found in the cage region.

directly to the introduction of the additional methyl group at the 8-position.

The fundamental changes in cavity shape are most clearly seen from the sections through the van der Waals surface (Figure 4). As can be seen, the waist of (I) has been completely eliminated and, indeed, the central section of the new cavity of (IV) is now the widest. This change may be described as a transformation of the ' hour-glass ' surface of (I) into the ' chinese-lantern ' shape of (IV).

In summary, substitution of the 6- and 8-positions of (I) has yielded new clathrate hosts, and it has been established that the 8-methyl homologue (IV) has a fundamentally altered cavity, and selective inclusion properties. Although the clathrates of the thiachroman (I) [3] and Dianin's compound (VI) [4] are isomorphous and structurally very similar, it is noteworthy that their 6-methyl analogues (II) and (VII) pack in totally different ways. This highlights the critical role of crystal packing forces in determining the structures of apparently very closely related systems.

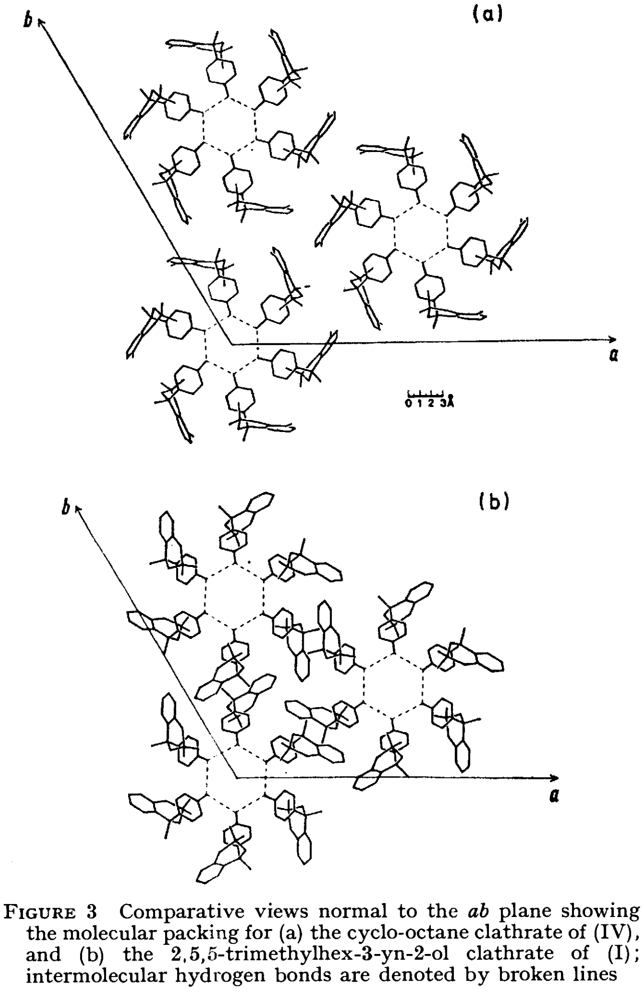

FIGURE 3 Comparative views normal to the *ab* plane showing the molecular packing for (a) the cyclo-octane clathrate of (IV), and (b) the 2,5,5-trimethylhex-3-yn-2-ol clathrate of (I); intermolecular hydrogen bonds are denoted by broken lines

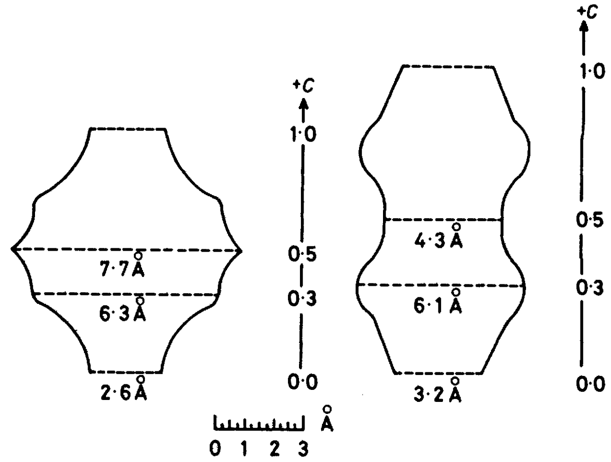

FIGURE 4 Sections through the van der Waals surface of the cavity for (a) compound (IV), and (b) parent compound (I)

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