

## The Crystal Structure of Methyl 1-Thio- $\alpha$ -D-ribofuranoside

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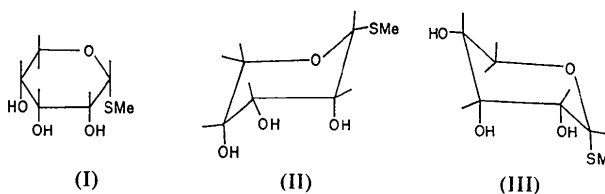
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The crystal structure of methyl 1-thio- $\alpha$ -D-ribofuranoside,  $C_6H_{12}O_4S$ , has been determined by direct methods. The space group is  $P2_12_12_1$ , with four molecules in a unit cell,  $a=8.696(2)$ ,  $b=12.83(3)$ ,  $c=7.335(2)$  Å. The structure was refined to  $R=0.028$  for 830 independent reflections measured with Ni-filtered Cu  $K\alpha$  radiation. The absolute configuration was confirmed. The molecule has the  ${}^1C_4$  chair conformation, thereby permitting the formation of a *syn-axial* intramolecular hydrogen bond with an  $H\cdots O$  distance of 2.1 Å and  $O-H\cdots O$  angle of  $142^\circ$ . The intermolecular hydrogen-bonding forms buckled ribbons extending in the  $c$  direction which link the molecules into columns, separated by van der Waals interactions.

### Introduction

Originally isolated as comparatively rare natural products (Horton & Hutson, 1963), the thiosugars have recently become more important as synthetic intermediates (Paulson & Todt, 1968), possible precursors of nucleosides (Whistler, Nayak & Perkins, 1970), and potential enzymatic inhibitors (Claeyssens & De Bruyne, 1965). Methyl 1-thio- $\alpha$ -D-ribofuranoside (I) is a member of a series of mono and dithiosubstituted ribofuranosides prepared and supplied in the crystalline form by Dr N. A. Hughes of the University of Newcastle upon Tyne, England. The  $\alpha$ -D-ribofuranoses are conformationally interesting because both the  ${}^1C_4$  (II) and  ${}^4C_1$  (III) chair conformers give rise to *syn-axial* interactions which are believed to play an important role in determining conformational stability. Theoretical calculations and experimental observations by p.m.r. on  $\alpha$  and  $\beta$ -D-ribofuranose indicate that both conformers are present in aqueous solution (Stoddart, 1971). The influence of intramolecular hydrogen bonding on the con-

formational equilibrium in solution of a related compound, methyl 2-deoxy- $\alpha$ -ribofuranoside, has been discussed recently by Lemieux (1971).



The object of this investigation was primarily to determine the molecular conformation in the crystalline state of (I) and it is the first of a systematic study of the structural and conformational characteristics of several mono- and dithioribofuranosides. The influence of configuration, the anomeric effect, and intramolecular hydrogen bonding on the conformation of the pyranosides has been reviewed recently by Stoddart (1971); this study is aimed at examining to what degree these various conformational determining factors are influenced by the substitution of the ring or anomeric oxygen by a sulfur atom.

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Table 1. Atomic positional and thermal parameters with *e.s.d.*'s for methyl 1-thio- $\alpha$ -D-ribofuranoside

Positional parameters are expressed as fractions of the lattice translations. Thermal parameters are defined by the expression:  $T = \exp [-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + 2hk\beta_{12} + 2hl\beta_{13} + 2kl\beta_{23})]$ . Non-hydrogen parameters  $\times 10^4$ , hydrogen parameters  $\times 10^3$ .

	$x$	$y$	$z$	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$
S(1)	1398 (1)	1924 (8)	9541 (1)	163 (1)	68 (1)	138 (2)	-7 (1)	24 (2)	11 (1)
C(1)	2638 (5)	2333 (3)	7716 (5)	120 (7)	55 (3)	108 (7)	3 (3)	4 (6)	6 (4)
C(2)	2811 (5)	3523 (3)	7747 (5)	114 (6)	53 (2)	107 (7)	-5 (3)	-18 (5)	-7 (3)
C(3)	3748 (5)	3866 (3)	6094 (5)	114 (5)	50 (2)	132 (6)	-1 (4)	18 (6)	2 (3)
C(4)	3020 (4)	3447 (3)	4345 (5)	112 (5)	61 (3)	112 (8)	-1 (3)	15 (6)	0 (4)
C(5)	2906 (5)	2274 (3)	4509 (6)	156 (7)	57 (3)	118 (3)	-3 (4)	19 (7)	-19 (4)
C(6)	1884 (8)	552 (4)	9598 (11)	234 (12)	68 (3)	381 (17)	5 (5)	91 (13)	68 (7)
O(2)	1356 (4)	4033 (2)	7831 (4)	118 (4)	59 (2)	116 (5)	15 (3)	15 (4)	-7 (3)
O(3)	3921 (5)	4963 (2)	6127 (4)	198 (6)	49 (2)	121 (5)	-15 (3)	8 (5)	3 (3)
O(4)	1516 (4)	3867 (2)	4151 (4)	143 (5)	71 (2)	112 (6)	12 (2)	-7 (5)	24 (3)
O(5)	1976 (2)	1948 (2)	6030 (3)	130 (4)	49 (2)	107 (4)	-12 (2)	-2 (3)	-11 (2)



There were 143 reflections less than two standard deviations above background and these were considered unobserved. The data were corrected for Lp (Shiono, 1970) and absorption (Craven, 1963; Busing & Levy, 1957), and reduced to structure amplitudes.

### Structure determination and refinement

The structure factors were scaled and normalized by the use of a Wilson plot. Additional renormalization of special groups of  $E$ 's to assist in phase determination was carried out using a program by Shiono (1970). Several sets of three origin-defining and one enantiomorph-determining reflection were selected and used in a tangent-refinement procedure (Hall, 1967). The resulting  $E$  maps, calculated from the 132 highest  $E$  values, failed to reveal the structure, but the addition of a fifth phase to the tangent refinement gave an  $E$  map with peaks corresponding to all but one non-hydrogen atom. The initial structure-factor agreement,  $R=0.29$ , was reduced to 0.05 by the addition of the missing atom and anisotropic refinement, using a block-diagonal least-squares program on an IBM 1130 (Shiono, 1970). At this stage, all the hydrogen atoms were unambiguously located from a difference map. Anomalous dispersion corrections (Cromer & Liberman, 1970) for S and O atoms were added and a full-matrix least-squares refinement of all heavy atoms anisotropically and hydrogen atoms isotropically gave a final  $R$  of 0.028 and  $wR$  of 0.023, where  $w=1/(\sin \theta/\lambda)$ . The weighting approximates in this case to the average  $1/\sigma F$  for a given range of  $\sin \theta$ , thus the strong reflections, which are subject to multiple reflection and extinction effects, are not overweighted. The function minimized was  $\sum w(|F_o| - K|F_c|)^2$  where  $K$  is a single scale factor. No observed data point was removed or 'weighted' zero during the refinement.

The absolute configuration of the sugar was determined by two methods; a Bijvoet pair comparison, and a refinement of D and L isomers for  $+h+k+l$  data (Ibers & Hamilton, 1964). The intensities of the Bijvoet pairs were recorded by hand-centering the reflections and counting for 20 sec at the maximum peak height. The ratio of the observed and calculated intensities below clearly indicates the D isomer.

$h$	$k$	$l$	$\frac{I(hkl)}{I(\bar{h}\bar{k}\bar{l})}$ Obs.	$\frac{I(hkl)}{I(\bar{h}\bar{k}\bar{l})}$ Calc. for D isomer
7	7	1	0.72	0.79
4	10	2	0.66	0.76
4	6	1	0.85	0.78
3	1	2	1.27	1.31
3	11	1	0.73	0.74
2	10	3	0.68	0.76
1	3	4	0.69	0.71
1	4	1	1.31	1.54
1	5	1	1.18	1.22

Refinement of  $+h+k+l$  reflections for the D ( $R=0.028$ ) and L ( $R=0.035$ ) isomers rejected the L at greater than 99.5% confidence level using Hamilton's (1965)  $R$ -value significance test. The final atomic positional and thermal parameters are given in Table 1 and the structure factors in Table 2. The atomic numbering and thermal ellipsoids are shown in Fig. 1.

### Description of the structure

The molecule (I), shown in Fig. 1, has the  ${}^1C_4$ , or  $1C$ , ring conformation (II) with the two axial oxygen atoms O(2), O(4), linked by an intramolecular hydrogen bond, as previously reported by Girling & Jeffrey (1971). Although there may be other factors involved, the preference over the more usual  ${}^4C_1$  conformer (III) can therefore be ascribed simply to the greater strength of

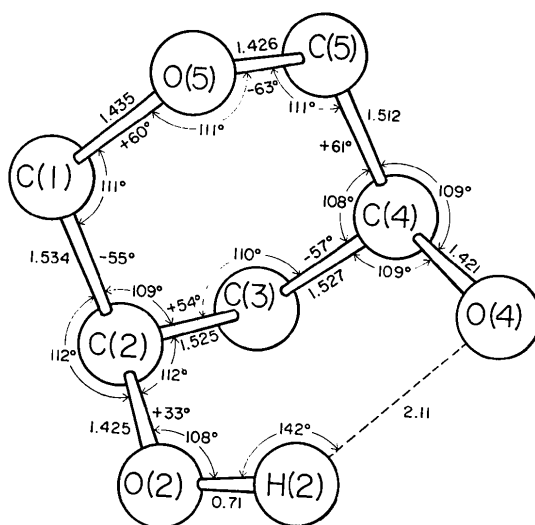


Fig. 2. Fused-ring system formed by the intramolecular hydrogen bond; it consists of two six-membered rings in the chair conformation and an eight-membered ring in the 'tub' form. Torsion angles and valence angles are in  $^\circ$ , distances are in Å. The standard deviations are 0.005 Å and 0.5 $^\circ$ , except for those involving hydrogens, where they are 0.1 Å and  $\sim 5^\circ$ .

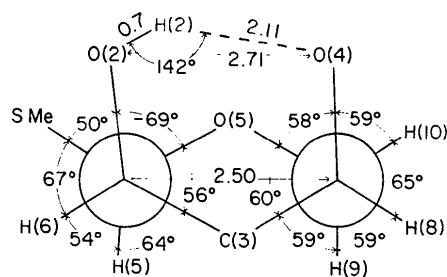


Fig. 3. The intramolecular hydrogen bonding in methyl 1-thio- $\alpha$ -D-ribofuranoside, viewed in the direction of the C(2)  $\rightarrow$  C(1), C(4)  $\rightarrow$  C(5) bonds. The standard deviations are given in Fig. 2.

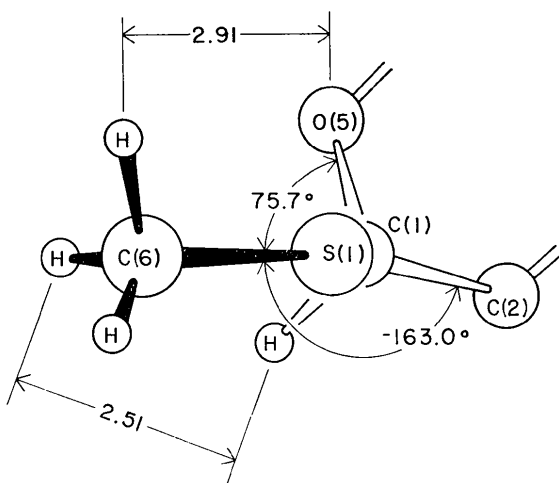


Fig. 4. Torsional angles and closest intramolecular contacts (Å) of the methyl group viewed down the S(1)-C(1) bond, in methyl 1-thio- $\alpha$ -D-ribofuranoside.

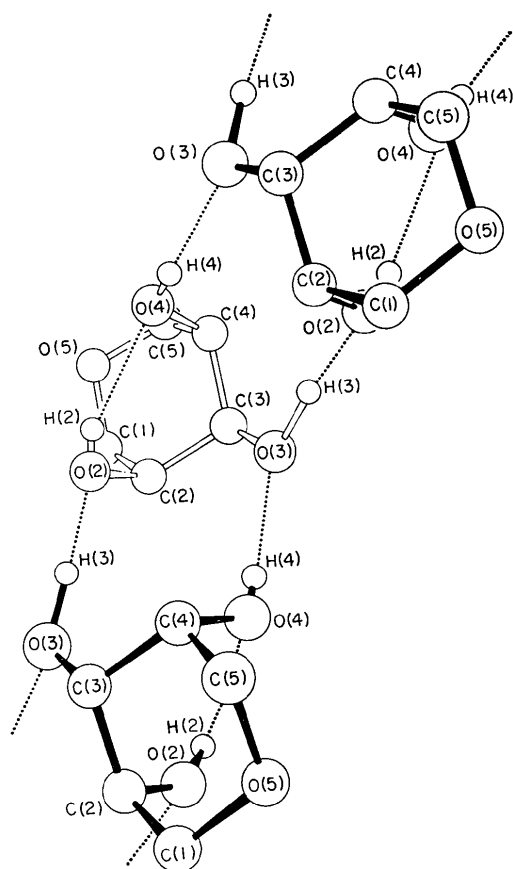


Fig. 5. Hydrogen bonding, represented by dotted lines, in the crystal structure of methyl 1-thio- $\alpha$ -D-ribofuranoside. View is the *ac* plane with *c* direction approximately parallel to the direction of the hydrogen bonding. The S-CH<sub>3</sub> and the methylene hydrogens have been omitted to simplify the diagram.

the O-H...O intramolecular hydrogen bond compared with the alternative *syn-axial* O-H...S bond which would be possible with (III). The intramolecular hydrogen bond, shown in Fig. 4, has also been observed in methyl 1,5-dithio- $\alpha$ -D-ribofuranoside (Girling & Jeffrey, 1971), which also has the <sup>1</sup>C<sub>4</sub> ring conformation. It is transannular to the pyranose ring, forming the fused ring system shown in Fig. 3, which would limit conformational change should it persist in the solution. Evidence that it can persist is cited by Lemieux & Levine (1964), Lemieux & Pavia (1969), Lemieux (1971) and others (Kabayama & Patterson, 1958; Foster, Harrison, Lehmann & Webber, 1963) to show that *syn-axial* intramolecular hydrogen bonds are important factors in determining the population of conformers in non-hydrolytic solvents, where competitive intermolecular hydrogen-bonding with the solvent species cannot occur. In 2-*C*-methyl  $\beta$ -L-ribofuranoside in CCl<sub>4</sub> solution, for example, the band at 3512 cm<sup>-1</sup> in the IR spectrum has been assigned to this 2,4(OH)<sub>2</sub> hydrogen-bonding interaction (Ferrier, Overend, Rafferty, Wall & Williams, 1963).

The effect of this intramolecular bond formation on the pyranose ring geometry can be obtained by comparison with a model ring based on substituting an oxygen for methylene in the cyclohexane molecular structure (Stoddart, 1971; Davies & Hassel, 1963) or with the 'best' pyranoid ring suggested by Arnott & Scott (1972), or with the mean observed ring-torsional angles in aldopyranoses (Jeffrey, 1972). All three results give *syn-axial* O(2)...O(4) separations of 2.65–2.70 Å with C(2)...C(4) distances in the pyranose ring of 2.50–2.55 Å. The observed distances for O(2)...O(4) and C(2)...C(4) of 2.71(1) and 2.50(1) Å in this structure indicate that the formation of the intramolecular hydrogen bond brings about no significant deformation of the pyranose ring (see Fig. 3 and Table 3). This is an contrast to epi-inositol (Jeffrey & Kim, 1971) and methyl 5-thio- $\alpha$ -D-ribofuranoside (Jeffrey & Girling, 1972), where the *syn-axial* O-O interactions without intramolecular H-bonding result in an O...O separation of nearly 3.0 Å with an accompanying distortion of the pyranose ring.

Table 3. Torsional angles for methyl 1-thio- $\alpha$ -D-ribofuranoside

(Ring angles are given in Fig. 3.)

O(4)-C(4)-C(5)-O(5)	-58.5 (0.5)°
O(4)-C(4)-C(3)-O(3)	-61.3
O(4)-C(4)-C(3)-C(2)	+62.0
O(3)-C(3)-C(4)-C(5)	-179.9
O(3)-C(3)-C(2)-O(2)	+56.2
O(3)-C(3)-C(2)-C(1)	-179.5
O(2)-C(2)-C(3)-C(4)	-69.9
O(2)-C(2)-C(1)-O(5)	+69.0
O(2)-C(2)-C(1)-S(1)	-50.5
S(1)-C(1)-C(2)-C(3)	-174.5
S(1)-C(1)-O(5)-C(5)	-179.6
C(6)-S(1)-C(1)-O(5)	+75.2
C(6)-S(1)-C(1)-C(2)	-163.3

Since the formation of the *syn-axial* intramolecular hydrogen bond is so consistent with unstrained pyranose ring geometry, one might ask why it is not more commonly observed in the crystal structures of pyranose sugars. In solution, these bonds are believed to be formed only where there is a lack of competition from other suitable hydrogen-bonding groups, as in non-hydrolytic solvents (Stoddart, 1971). Similarly, in the solid state, the hydrogen bonding function of the hydroxyl groups is generally fully utilized in intermolecular cohesion and intramolecular hydrogen bonding appears to be secondary. The reason may be that the bond energy for an intramolecular bond is less than for a comparable intermolecular bond because of less favorable H $\cdots$ O distances and O-H $\cdots$ O bond angles which are constrained in pyranose sugars to be about 2.0 Å and 140°, as compared with the commonly observed intermolecular hydrogen bond distances of 1.7–1.8 Å and 170–180°.

The bond distances and bond angles, which differ from 109.5  $\pm$  0.5°, for methyl 1-thio- $\alpha$ -D-ribofuranoside are given in Table 4. They do not differ significantly from those expected from other carbohydrate structure determinations and from the results of Mathieson & Poppleton (1966) for methyl 1-thio- $\beta$ -D-xylopyranoside. Although S(1)–C(1) is 0.013 Å shorter than S(1)–C(6), this observation is of marginal significance in relation to the anomeric bond shortening effect (Berman, Chu & Jeffrey, 1967). The estimated standard deviation of the S(6) parameters is relatively large because of the greater thermal motion of the aglycone group.

Table 4. Bond distances and angles (other than 109.5°) for methyl 1-thio- $\alpha$ -D-ribofuranoside

S(1)–C(1)	1.796 (3) Å	C(1)–S(1)–C(6)	99°
S(1)–C(6)	1.809 (6)	O(5)–C(1)–S(1)	108
C(1)–C(2)	1.534 (5)	C(3)–C(4)–C(5)	108
C(2)–C(3)	1.525 (5)	C(4)–C(5)–O(5)	111
C(3)–C(4)	1.527 (5)	C(5)–O(5)–C(1)	111
C(4)–C(5)	1.512 (5)	O(5)–C(1)–C(2)	111
C(2)–O(2)	1.425 (4)	C(1)–C(2)–O(2)	112
C(3)–O(3)	1.416 (4)	C(3)–C(2)–O(2)	112
C(4)–O(4)	1.421 (4)	C(4)–C(3)–O(3)	114
C(5)–O(5)	1.426 (4)		
C(1)–O(5)	1.435 (4)		

Intramolecular H-bond

O(2) $\cdots$ O(4)	2.709 (7) Å	O(2)–H(2) $\cdots$ O(4)	142°
H(2) $\cdots$ O(4)	2.1 (1)		
O(2)–H(2)	0.7 (1)		

The methyl group torsion angle C(6)–S(1)–C(1)–O(5) is 15° greater than the ideal 60° for normal +*synclinal* orientation of an aglycone bond. This additional twist is in the direction such as to increase the H $\cdots$ O(5) non-bonding distance at the expense of the H $\cdots$ H distance, as shown in Fig. 4.

The hydrogen bonding, shown in Fig. 5, is compara-

tively simple. It consists of infinite chains with a sequence of one intra- and two intermolecular bonds,  $\rightarrow$ O(2)H  $\rightarrow$  O(4)H  $\rightarrow$  O(3)H  $\rightarrow$  O(2)H  $\rightarrow$ , forming a two stranded ribbon which extends in the *c* direction. This ribbon of hydrogen bonds links successive molecules related by the screw axes parallel to *c* in a buckled column one molecule wide along *a* and two molecules in the *b* direction, as shown in Fig. 6. The nonpolar groups are on the exterior of these columns and their intermolecular contacts correspond to van der Waals forces as shown by the intermolecular non-bonded distances given in Table 5; none are significantly less than the sum of the van der Waals radii. The thermal motion of the non-hydrogen atoms reflects the unidirectional character of the hydrogen bonding by having larger r.m.s. components in the *a* and *b* directions than in the *c* direction.

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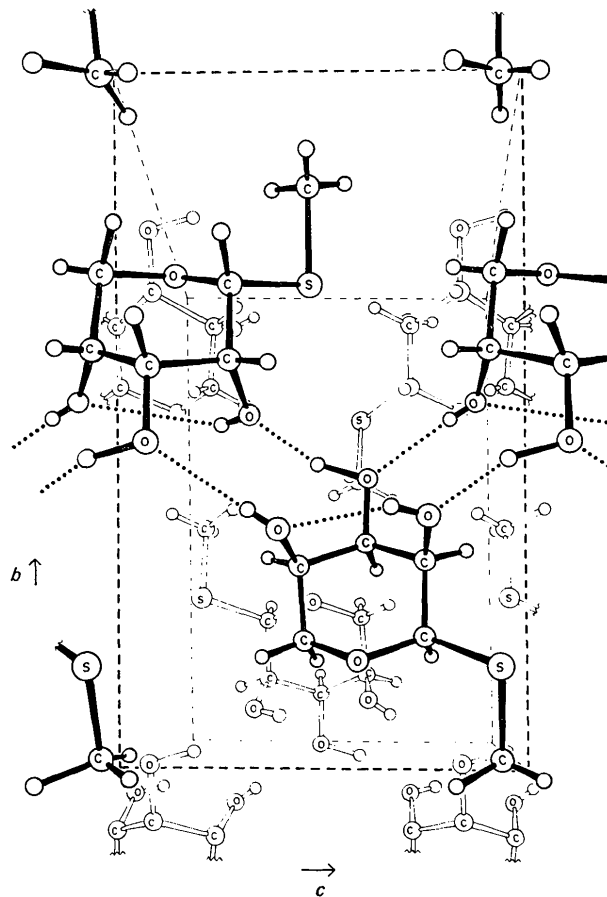


Fig. 6. A perspective view of the molecular packing in the crystal structure of methyl 1-thio- $\alpha$ -D-ribofuranoside. The dotted lines indicate the ribbons of the hydrogen bonds which link the molecules into columns extending in the *c* direction.

Table 5. *Intermolecular approaches in methyl 1-thio- $\alpha$ -D-ribose less than 3.5 Å for non-hydrogen atoms and less than 3.0 Å involving hydrogen atoms*

## Intermolecular H-bonds

O(2)···O(3)	2.748 (8) Å
O(3)···O(4)	2.703 (8)
H(4)···O(3)	2.1 (1)
H(3)···O(2)	2.0 (1)
O(2)···H(3)	1.7 (1)
O(4)–H(4)···O(3)	178°
O(3)–H(3)···O(2)	174

## Van der Waals distances

O(2)···C(4)	3.46 (1) Å	H(2)···H(3)	2.2 (2) Å
O(2)···O(4)	3.41 (1)	H(2)···H(13)	2.3 (2)
O(3)···C(2)	3.49 (1)	H(2)···H(9)	2.6 (2)
O(5)···C(3)	3.39 (1)	H(3)···H(4)	2.9 (2)
O(5)···C(4)	3.50 (1)	H(3)···H(6)	2.5 (2)
		H(3)···H(12)	2.8 (2)
C(2)···H(3)	2.6 (1)	H(3)···H(13)	2.9 (2)
C(5)···H(7)	2.9 (1)	H(4)···H(5)	2.9 (2)
O(2)···H(13)	2.7 (1)	H(4)···H(6)	2.8 (2)
O(3)···H(12)	2.8 (1)	H(4)···H(9)	2.9 (2)
O(4)···H(9)	2.6 (1)	H(7)···H(10)	2.4 (2)
O(5)···H(7)	2.6 (1)	H(8)···H(13)	2.8 (2)

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Structure du *m*-Crésol

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Crystals of *m*-cresol are monoclinic, with 24 molecules in a unit cell of dimensions  $a=25.90$ ,  $b=6.20$ ,  $c=33.06$  Å,  $\beta=133.9^\circ$ , space group  $P2_1/c$ . The structure, determined from three-dimensional single-crystal X-ray data registered at  $-100^\circ\text{C}$ , has been automatically solved by direct methods. The structure was refined to a final  $R$  of 7.6% for 3835 reflexions. The molecules are linked by hydrogen bonds to form eight chains parallel to the  $b$  direction.

Ce travail qui vient terminer l'étude structurale des crésols (Bois, 1970, 1972) s'intègre dans une étude plus générale des xylénols et des crésols, entreprise au laboratoire.

## Etude expérimentale

La température de solidification du *m*-crésol est de  $11^\circ\text{C}$ , mais il présente une importante surfusion. Nous