

The Structure of Stiripentol: 4,4-Dimethyl-1-(3,4-methylenedioxyphenyl)-1-penten-3-ol – a Novel Antiepileptic Drug

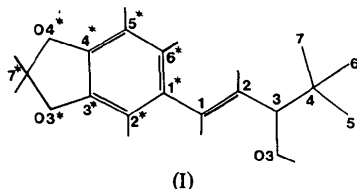
BY JOHN N. LISGARTEN AND REX A. PALMER†

Department of Crystallography, Birkbeck College, University of London, Malet Street, London WC1E 7HX, England

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Abstract. $C_{14}H_{18}O_3$, $M_r = 234.29$, monoclinic, $P2_1/a$, $a = 14.550$ (8), $b = 6.133$ (4), $c = 15.703$ (7) Å, $\beta = 116.1$ (4)°, $V = 1254.4$ (5) Å³, $Z = 4$, $D_m = 1.24$ (4), $D_x = 1.239$ g cm⁻³, $\lambda(\text{Cu } K\alpha) = 1.54184$ Å, $\mu = 6.15$ cm⁻¹, $F(000) = 504$, room temperature, $R = 0.065$ for 2426 observed reflections. The five-membered ring *A* has an envelope conformation, the apical atom C(7)* being out of the plane. The conformation of the side chain attached to C(1)* is almost fully extended. The molecules are packed in a head-to-tail fashion as hydrogen-bonded dimers: O(3)···O(4)* [$1-x, y, 1-z$] = 3.124 (8), HO(3)···O(4)* = 2.19 (9) Å, O(3)···HO(8)···O(4)* = 160.2 (6)°.

Introduction. Stiripentol (I) is a new antiepileptic drug structurally unrelated to existing drugs (Lin, Levy, Blehaut & Tor, 1984). It was selected from a range of α -ethylene alcohols which were found to exhibit central nervous system activity. In contrast to most other anticonvulsant drug molecules, it does not possess a nitrogenous heterocycle or carbonyl group – both of which are normally considered to contribute significantly to the activity of anticonvulsants. The structure analysis reported here was undertaken as part of a programme of study of convulsant and anticonvulsant compounds being carried out in this department.



(I)

Experimental. Sample provided by Laboratories Biocedex, France. Colourless crystal 0.11 × 0.40 × 0.45 mm used for data collection; preliminary Weissenberg photographs yielded approximate cell dimensions and showed monoclinic ($2/m$) Laue symmetry. Space group $P2_1/a$ from systematic absences ($0k0$, $k = 2n + 1$; $h0l$, $h = 2n + 1$); D_m by flotation (n -heptane/carbon

tetrachloride); Enraf–Nonius CAD-4 automated diffractometer, graphite monochromator, Cu $K\alpha$ radiation, 25 high-angle reflections ($25 < \theta < 28^\circ$) used to obtain accurate cell dimensions by least-squares fit. Data collection by ω - 2θ scan, scan width ($0.85 + 0.15 \tan \theta$)°, vertical aperture = 4 mm; 2667 unique reflections measured ($0 \leq h \leq 17$, $0 \leq k \leq 7$, $-19 \leq l \leq 19$), 2426 with $I > 3\sigma(I)$, $3 < \theta < 69^\circ$; three intensity standards (600, 401 and 814) monitored at intervals of 100 reflections showed no significant variations during data collection; intensity data corrected for Lorentz–polarization factors; empirical absorption correction based on ϕ scans for each of three reflections (North, Phillips & Mathews, 1968) near $\chi = 90^\circ$ measured at 10° intervals from $\phi = 0$ to $\phi = 360^\circ$, normalized transmission factors 0.99 to 0.73. Structure solution by direct methods with SHELX76 (Sheldrick, 1976). Atomic scattering factors from SHELX76; E map gave positions of the non-hydrogen atoms. Refinement by full-matrix least squares with anisotropic thermal factors for all the

Table 1. Atomic positional parameters and equivalent isotropic temperature factors for non-hydrogen atoms with e.s.d.'s in parentheses

$$U_{eq} = (U_{11}U_{22}U_{33})^{1/3}$$

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{eq}(\text{\AA}^2)$
C(1)*	0.3502 (3)	0.0411 (7)	0.4374 (3)	0.047 (26)
C(2)*	0.4077 (3)	0.2209 (7)	0.4883 (3)	0.049 (26)
C(3)*	0.4452 (4)	0.2150 (7)	0.5850 (3)	0.048 (26)
C(4)*	0.4278 (3)	0.0433 (8)	0.6319 (3)	0.049 (28)
C(5)*	0.3726 (4)	-0.1348 (8)	0.5851 (3)	0.060 (30)
C(6)*	0.3331 (4)	-0.1328 (8)	0.4854 (3)	0.053 (29)
C(7)*	0.5148 (5)	0.2984 (9)	0.7395 (4)	0.075 (40)
C(1)	0.3086 (3)	0.0287 (8)	0.3326 (3)	0.050 (27)
C(2)	0.3077 (4)	0.1892 (7)	0.2752 (3)	0.054 (29)
C(3)	0.2706 (4)	0.1658 (7)	0.1697 (3)	0.051 (27)
C(4)	0.1719 (4)	0.2878 (7)	0.1076 (3)	0.049 (26)
C(5)	0.0842 (4)	0.1905 (8)	0.1260 (3)	0.064 (33)
C(6)	0.1808 (4)	0.5317 (8)	0.1291 (3)	0.062 (34)
C(7)	0.1452 (4)	0.2530 (9)	0.0023 (3)	0.061 (31)
O(3)*	0.5069 (4)	0.3675 (6)	0.6504 (2)	0.067 (23)
O(4)*	0.4781 (3)	0.0801 (6)	0.7293 (2)	0.064 (23)
O(3)	0.3488 (3)	0.2448 (8)	0.1458 (2)	0.067 (23)
HO(3)	0.414 (5)	0.172 (9)	0.185 (4)	0.09 (2)†

* Refer to atoms in methylenedioxyphenyl group.

† U_{iso} .

† To whom all correspondence should be addressed.

Table 2. Bond lengths (Å) and bond angles (°) with *e.s.d.'s in parentheses*

C(7)*-O(4)*	1.424 (6)	C(1)*-C(2)*	1.400 (6)
C(7)*-O(3)*	1.417 (5)	C(1)*-C(1)	1.481 (6)
C(3)*-O(3)*	1.384 (5)	C(1)-C(2)	1.332 (5)
C(3)*-C(4)*	1.372 (6)	C(2)-C(3)	1.503 (6)
C(3)*-C(2)*	1.366 (5)	C(3)-O(3)	1.433 (5)
C(4)*-O(4)*	1.389 (5)	C(3)-C(4)	1.524 (6)
C(4)*-C(5)*	1.361 (6)	C(4)-C(5)	1.549 (6)
C(5)*-C(6)*	1.407 (6)	C(4)-C(7)	1.537 (6)
C(6)*-C(1)*	1.391 (6)	C(4)-C(6)	1.526 (6)
O(4)*-C(7)*-O(3)*	108.0 (4)	C(1)*-C(1)-C(2)	126.2 (4)
O(3)*-C(3)*-C(4)*	109.5 (4)	C(1)-C(2)-C(3)	124.5 (4)
O(3)*-C(3)*-C(2)*	127.8 (4)	C(2)-C(3)-O(3)	108.6 (4)
C(4)*-C(3)*-C(2)*	122.6 (4)	C(2)-C(3)-C(4)	115.6 (4)
O(4)*-C(4)*-C(3)*	109.5 (4)	C(4)-C(3)-O(3)	107.4 (3)
C(3)*-C(4)*-C(5)*	122.2 (4)	C(3)-C(4)-C(5)	108.1 (4)
O(4)*-C(4)*-C(5)*	128.2 (4)	C(3)-C(4)-C(7)	109.6 (4)
C(4)*-C(5)*-C(6)*	116.3 (4)	C(3)-C(4)-C(6)	112.2 (4)
C(5)*-C(6)*-C(1)*	121.8 (4)	C(5)-C(4)-C(6)	109.4 (4)
C(6)*-C(1)*-C(2)*	120.1 (4)	C(7)-C(4)-C(6)	109.3 (4)
C(6)*-C(1)*-C(1)	118.7 (4)	C(5)-C(4)-C(7)	108.2 (4)
C(2)*-C(1)*-C(1)	121.3 (4)	C(7)*-O(4)*-C(4)*	105.3 (3)
C(3)*-C(2)*-C(1)*	117.0 (4)	C(7)*-O(3)*-C(3)*	105.8 (4)

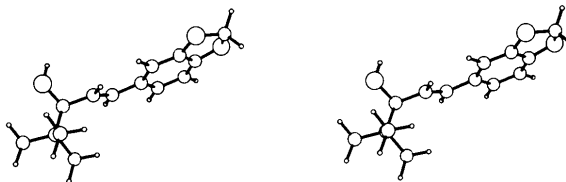
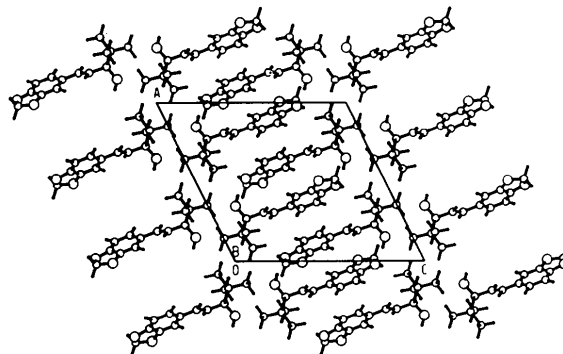
non-hydrogen atoms, isotropic for H atoms. The hydroxyl hydrogen, HO(3), was located from a difference synthesis and coordinates were refined; the remaining seventeen were obtained by calculation and tied at a C-H distance of 1.08 Å. Function minimized was $\sum w(|F_o| - |F_c|)^2$, $w^{-1} = 7.38^{-1}(\sigma^2 |F| + 0.00039 |F_o|^2)$, $R = 0.065$, $wR = 0.070$, R (all data) = 0.120, $(\Delta/\sigma)_{\max} = 0.02$. Final difference electron density -0.26 to $+0.23$ e Å⁻³. Calculations carried out on Amdahl 470 V/8 computer. Geometrical calculations performed with *XAMADU* (Roberts & Sheldrick, 1975) and illustrations were drawn with *PLUTO* (Motherwell & Clegg, 1978).

Discussion. The final atomic coordinates and equivalent isotropic thermal parameters for the non-H atoms are given in Table 1.† Bond distances and angles are listed in Table 2. Fig. 1 shows a stereoview of the molecule and Fig. 2 is a view of the structure along *b*.

The benzyl ring, *B*, of the 3,4-methylenedioxyphenyl moiety is planar. The equation of the least-squares plane defined by the atoms C(1)*, C(2)*, C(3)*, C(4)*, C(5)*, C(6)* is: $0.836x' - 0.440y' - 0.327z' - 2.205 = 0$, where x' , y' , z' are the coordinates in Å with respect to the orthogonal cell (Rollett, 1965). The root mean square displacement of the six atoms from the plane is 0.002 Å. The adjacent oxygen and carbon atoms O(4)*, O(3)* and C(1) are approximately coplanar with ring *B*, having deviations from the plane

of 0.06, 0.07 and 0.04 Å respectively, consistent with extensive electron delocalization in this part of the molecule. The average value of the bond lengths in the benzyl ring is 1.383 (6) Å and the average value for bond angles is 120.0 (4)°. Apart from C(6)*-C(1)*-C(2)* = 120.1°, all bond angles in this ring exhibit significant (5σ - 9σ) deviations from the average value. This effect may be associated with the presence of the unsaturated ring *A*.

There is also a slight buckling of the molecule about the C(3)*-C(4)* bond common to the two rings. Ring *A* shows a similar geometry to that in Berberine sulfate (Abadi, Moss & Palmer, 1984) having an envelope conformation exhibiting pseudosymmetry with $\Delta C_s^1 = 0.33^\circ$, C(7)* being 0.21 Å from the plane *A* defined by the atoms O(3)*, C(3)*, C(4)*, O(4)*. The equation of the least-squares plane through these four atoms is $-0.809x' + 0.465y' + 0.359z' + 1.812 = 0$. The root mean square displacement of the four atoms from the plane is 0.002 Å and the dihedral angle made with plane *B* is 2.80°. Bond lengths and angles in the side chain linked to C(1)* confirm its chemical assignment as pent-1-en-3-ol, C(2)-C(3) and C(3)-C(4) having values typical of C(sp^2)-C(sp^3) and C(sp^3)-C(sp^3) bonds respectively, and the double bond C(1)=C(2) = 1.332 (5) Å. The conformation of the side chain attached to C(1)* which may be defined by the torsion angles C(6)*-C(1)*-C(1)=C(2) = 170.1 (9), C(1)*-C(1)=C(2)-C(3) = 176.0 (8)° is almost fully extended. The molecules are packed in a head-to-tail fashion as hydrogen-bonded dimers through atoms O(3), H(3) and O(4)* related by (1-x, y, 1-z), the H-bond dimensions being: O(3)-HO(3)

Fig. 1. Stereoview of the molecule along *b*.Fig. 2. The crystal structure viewed along *b*.

† Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51171 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

$= 0.97$ (2), $O(3)\cdots O(4)^* = 3.124$ (8), $HO(3)\cdots O(4)^* = 2.19$ (3) Å, $O(3)-HO(3)\cdots O(4)^* = 160.2$ (6)°.

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Structure of 5,5-Dimethyl-4-(2-methylallyl)-2-tolyl-1,2,4-triazolidine-3-thione

BY KLAUS SCHULZE AND CHRISTIAN RICHTER

Sektion Chemie, Karl-Marx University, DDR 7010, Leipzig, German Democratic Republic

AND RENÉ FAURE

Laboratoire de Chimie Analytique II, Université Lyon I, 43 boulevard du 11 Novembre 1918, 69622 Villeurbanne CEDEX, France

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Abstract. $C_{15}H_{21}N_3S$, $M_r = 275.4$, monoclinic, $P2_1/c$, $a = 11.047$ (2), $b = 14.050$ (4), $c = 11.608$ (3) Å, $\beta = 119.27$ (2)°, $V = 1572$ (1) Å³, $Z = 4$, $D_x = 1.16$ Mg m⁻³, $\lambda(Mo K\alpha) = 0.7107$ Å, $\mu = 0.197$ mm⁻¹, $F(000) = 592$, $T = 295$ K, $R = 0.053$ for 2682 unique observed reflections. The 1,2,4-triazolidine ring is in a near envelope conformation, the flap of which is N(1). There are two kinds of C–N bond lengths: two single-bond lengths [1.484 (2) and 1.472 (2) Å] and two intermediate single–double-bond lengths [1.352 (2) and 1.364 (2) Å], indicating considerable conjugation with the thione. The C–S bond length [1.677 (2) Å] is similar to that found in other 1,2,4-triazoline-3-thiones.

Introduction. Triazolidine-3-thiones and thiazolidine-3-imines are isomeric compounds. They can be synthesized by cyclization reactions with thiosemicarbazides and thiosemicarbazones (Willems, 1965; Malbec, Milcent & Barbier, 1984). Depending on the reaction conditions, triazolidines or thiazolidines (Malbec *et al.*, 1984) or mixtures of both heterocycles (Valters & Flitsch, 1985; Jensen, 1969) are formed. Also, one of these heterocyclic compounds can be rearranged to the other by Dimroth rearrangement (L'Abbé, 1984). Sometimes, the determination of the structure is difficult (Jensen, 1969; Buccheri, Cusmano, Noto, Rainieri & Werber, 1987).

In connection with our investigations of 1,4- and 2,4-disubstituted thiosemicarbazides, we have found a

new cyclization reaction between 2,4-disubstituted thiosemicarbazides and ketones (Schulze & Richter, 1988), and we are interested in the structure determination of the cyclization product. We report here the molecular structure of the title compound. To the best of our knowledge, no structural investigations have been carried out for such substituted triazolidine-3-thiones. Only mercapto-1,2,4-triazoles (Senko & Templeton, 1958) and triazoline-3-thiones have been investigated (Gors, Devos, Baert, Henichart & Houssin, 1977; Isaacs & Kennard, 1970).

Experimental. The title compound was synthesized by condensation between 4-(2-methylallyl)-2-tolylthiosemicarbazide and acetone in ethanol with some drops of concentrated H₂SO₄. A white precipitate was formed on diluting with water and cooling. Transparent crystal from ethanol, 0.3 × 0.3 × 0.4 mm. Nonius CAD-4 diffractometer, graphite monochromator, Mo K α radiation, ω - $\frac{1}{2}\theta$ scan, $2 \leq 2\theta \leq 60^\circ$. Unit-cell parameters refined from setting angles of 25 selected reflections ($24.20 < 2\theta < 41.54$). 4532 independent reflections, only 2682 observed [$I > 1.4\sigma(I)$ and $I > 1.3 \times I_{\text{background}}$]. $-15 \leq h \leq 13$, $0 \leq k \leq 19$, $0 \leq l \leq 16$. Standard reflection, 656, showed 2.9% intensity variation. Lp corrections, no absorption correction. Direct methods: program *MULTAN78* (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). Full-matrix refinements based on F with $w = (a + b|F_o|)^{-2}$