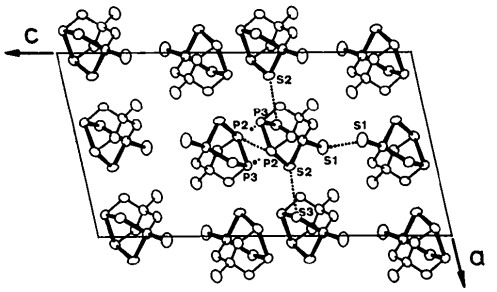

Fig. 2. Projection of the crystal structure along the *b* axis. H atoms have been removed for clarity.

P(2)–P(3) bond. The shortest intermolecular P···P distance in $C_5H_9P_3$ [4·013 (1) Å] is almost 1 Å longer.

The 'dimers' are held together by P(2)···P(3) [3·525 (1) Å] and P(2)···S(3) [3·895 (1) Å] interactions forming columns along **b**. Across the inversion centres ($0\frac{11}{44}$, $\frac{111}{244}$, $0\frac{33}{44}$, $\frac{133}{244}$) these columns are linked by S(1)···S(1) contacts [3·540 (1) Å] along **c**. Short contacts along **a** are exhibited by S(2)···S(3) 3·550 (1) and P(3)···P(3) 3·734 (1) Å. A projection of the unit cell along **b** is illustrated in Fig. 2.

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Trimethoprim Acetate

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Abstract. 2,4-Diamino-5-(3,4,5-trimethoxybenzyl)-1H^+-pyrimidinium acetate, $C_{14}H_{19}N_4O_3^+.C_2H_3O_2^-$, M_r = 350·38, monoclinic, $P2_1/c$, a = 11·085 (4), b = 19·137 (6), c = 9·641 (3) Å, β = 122·73 (3)°, U = 1720·5 (10) Å^3, Z = 4, D_x = 1·353 (1), D_m = 1·36 (1) g cm^{-3} (flotation in aqueous KI), $F(000)$ = 744, μ(Cu $K\alpha$) = 6·4 cm^{-1}, λ = 1·5418 Å, T = 293 K. The structure was solved by the symbolic addition method. Refinement by least squares gave R = 0·0399 for 1997 independent significant reflections, 0·0438 for all 2337 independent reflections measured. The molecular conformation is close to that in neutral trimethoprim, with the pyrimidine and phenyl rings inclined to the plane C(5)–C(7)–C(1′) at −77·5 and 157·2°, respectively. The pyrimidine ring is protonated at N(1), and molecules are linked in centrosymmetric pairs by hydrogen bonds between N(3) and N(4), and to the acetate groups by hydrogen bonds involving N(1) and N(2). Weaker hydrogen bonds are also present between the amino N atoms and the methoxy O atoms of two neighboring molecules.

Introduction. Trimethoprim (I) is a potent inhibitor of bacterial dihydrofolic acid reductase, but is less effective against mammalian, avian and viral forms of

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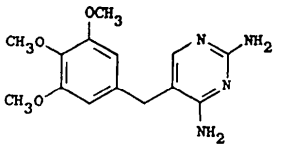
the enzyme (Hitchings & Burchall, 1965; Baker, 1967, 1969). Differences in potency are believed to be related to conformational differences in complexing in the hydrophobic region around the active site of the enzyme. Binding to the enzyme is also enhanced by protonation of the inhibitor at N(1), and hydrogen bonds involving N(1), N(2) and N(4) have been found in crystal structures of complexes between the enzyme and various inhibitors (Filman, Bolin, Matthews & Kraut, 1982; Bolin, Filman, Matthews, Hamlin & Kraut, 1982; Volz, Matthews, Alden, Freer, Hansch, Kaufman & Kraut, 1982). In this context, conformational differences and hydrogen-bonding patterns among different trimethoprim derivatives are of interest. We report here the crystal structure of the acetate salt of trimethoprim. This is a redetermination of the structure reported earlier by Haltiwanger (1971).



(I)

Experimental. Crystals suitable for X-ray study were provided by Dr Barbara Roth of the Burroughs Wellcome Co. The space group was uniquely determined by observation of systematic absences ($h0l$) with l odd and ($0k0$) with k odd on 25° precession photographs taken with Mo $K\alpha$ radiation.

The crystal-structure determination was originally carried out using intensity data collected on a Picker four-circle diffractometer with Mo $K\alpha$ radiation. For the analysis reported here, intensity measurements were made on a single-crystal prism 0·33 mm on a side. A Nicolet $P3m$ diffractometer was used with Cu $K\alpha$ radiation (graphite monochromator) in the $\theta/2\theta$ scan mode with a scan range 1·2° on either side of the $K\alpha_1 - K\alpha_2$ window. Reflections were measured for a single quadrant of reciprocal space ($2\theta \leq 116°$) by scintillation counting, with pulse-height analysis, and intensity significantly above background was measured at 1997 of 2337 accessible reciprocal-lattice points [85·5%, $I > 3\sigma(I)$]. Reflections were measured for $0 \leq h \leq 12$, $0 \leq k \leq 21$, $-10 \leq l \leq 8$. No absorption corrections were made. Reflections $32\bar{2}$ and $3\bar{2}\bar{2}$ were chosen as standards. The mean intensities of these symmetrically equivalent reflections differed by 1·5% and each showed a random variation of <1% about its mean value during the course of the experiment. Unit-cell dimensions were obtained by a least-squares fit to the values of 2θ for 15 strong general reflections with 2θ in the range 53 to 95° (Cu $K\alpha$ radiation, $\lambda = 1{\cdot}5418$ Å).

The structure was solved from the original Mo data by hand application of the symbolic addition method (Karle & Karle, 1966). Phases for 200 $E(hkl)$ yielded positions for 16 of the 25 non-hydrogen atoms, and the remaining nine were located by Fourier methods. H-atom positions were found from general-plane electron-density syntheses. Refinement of the structure was carried out using the Cu data. Anisotropic thermal parameters were assumed for the non-hydrogen atoms. The scattering functions used were those of Cromer & Waber (1974) for O, N and C, and of Stewart, Davidson & Simpson (1965) for H. Block-diagonal least-squares refinement of all parameters, minimizing the function $\sum w(|F_o| - |F_c|)^2$, gave at convergence $R = 0{\cdot}0399$ and $wR = 0{\cdot}0372$ for the 1997 significant reflections.* For the complete set of observed structure amplitudes $R = 0{\cdot}0438$. The maximum shift-to-e.s.d. ratio in the final cycle of refinement was 0·08, and the average ratio 0·03. The standard deviation of an observation of unit weight was 0·72. The weighting factors used were $1/[\sigma^2(F) + gF^2]$, with $g = 0{\cdot}0001$. A final difference electron-density map showed the only significant density to be concentrated around the midpoints of the various bonds, and not to exceed 0·17 e Å^{-3}. All computations were carried out using programs in this laboratory for the Tandy TRS-80 model 2000 personal computer, with the exception of *ORTEP* (Johnson, 1965), for which a Cyber 855 computer was used.

Discussion. A stereoscopic view of the ion pair as found in the crystal is shown in Fig. 1. Final atomic parameters and equivalent isotropic B values are given in Table 1, and bond lengths and angles (not involving H) are given in Fig. 2.

The molecular dimensions in the pyrimidine ring compare well with the results of the neutron diffraction study of neutral trimethoprim carried out by Koetzle & Williams (1976) (KW). The protonation of the ring at N(1) leads to an increase in the length of the C(5)—C(6) bond from 1·352 to 1·379 Å, and a decrease in the lengths of C(2)—N(2) and C(4)—N(4) from 1·349 and 1·351 to 1·334 and 1·342 Å, respectively. In the anion there is a significant difference in the lengths of the two C—O bonds, attributable to the difference in hydrogen bonding of the two oxygen atoms. H(1) is 1·55 (3) Å from O(1) compared to H($2a$) which is 1·84 (3) Å from O(2), thus inducing a higher degree of sp^3 character in the C(1)—O(1) bond. There is, however, excellent agreement between the lengths of chemically equivalent bonds in the cation, with the same pattern of geometrical fine detail as observed by KW in the neutral molecule, both with respect to the orientations

* Lists of structure factors, H-atom coordinates and anisotropic thermal parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44310 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

and distortions of the three methoxy groups, and the displacement of C(7) from the two ring planes. The mean deviation of ring atoms from the phenyl plane is 0·003 Å, the maximum 0·007 Å. C(7) is displaced from that plane by 0·144 Å and away from the pyrimidine ring plane, and O(4′) by 0·092 Å in the opposite sense. The mean displacement of ring atoms from the pyrimidine plane is 0·006 Å, with N(3) and C(4) being displaced to opposite sides of the plane by 0·011 and 0·012 Å, respectively. C(7) is displaced from the plane by 0·075 Å, in a direction away from the phenyl plane.

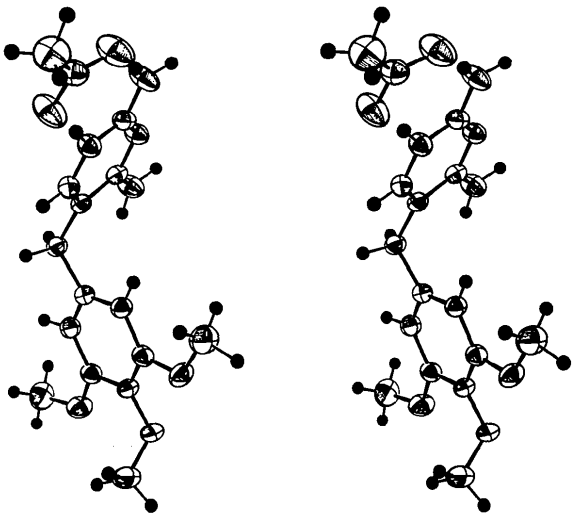


Fig. 1. Stereoscopic view (*ORTEP*; Johnson, 1965) of the ion pair in the conformation found in the crystal. Thermal ellipsoids are drawn at the 50% probability level.

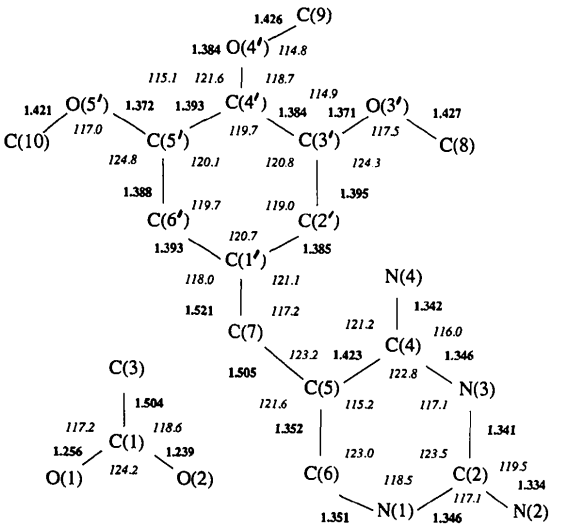


Fig. 2. Bond lengths (Å, bold face) and angles (°, italics) for trimethoprim acetate. E.s.d.'s are in the range 0·002–0·003 Å and 0·15–0·19°.

Table 1. *Fractional coordinates* ($\times 10^4$) *and equivalent isotropic B values* (Å^2)

$B_{eq} = \frac{4}{3}\sum_i \sum_j \beta_{ij} \mathbf{a}_i . \mathbf{a}_j$.

	x	y	z	B_{eq}
O(1)	2507 (2)	5737 (1)	9807 (2)	4·9
O(2)	4694 (2)	6177 (1)	11154 (2)	5·4
O(3′)	3165 (2)	1837 (1)	7001 (2)	3·4
O(4′)	1611 (2)	1085 (1)	4318 (2)	3·4
O(5′)	−465 (2)	1668 (1)	1447 (2)	3·7
N(1)	2937 (2)	5185 (1)	7639 (2)	2·7
N(2)	5010 (2)	5800 (1)	8589 (2)	3·9
N(3)	4140 (2)	5139 (1)	6228 (2)	2·8
N(4)	3282 (2)	4464 (1)	3931 (2)	3·5
C(1)	3521 (3)	6069 (1)	10989 (3)	3·4
C(2)	4023 (2)	5365 (1)	7467 (3)	2·7
C(3)	3300 (3)	6321 (2)	12314 (3)	4·8
C(4)	3130 (2)	4691 (1)	5145 (3)	2·6
C(5)	1941 (2)	4482 (1)	5232 (3)	2·4
C(6)	1921 (2)	4745 (1)	6521 (3)	2·6
C(7)	753 (2)	4021 (1)	3961 (3)	2·7
C(1′)	1057 (2)	3241 (1)	4059 (3)	2·4
C(2′)	2082 (2)	2930 (1)	5534 (3)	2·5
C(3′)	2216 (2)	2204 (1)	5605 (3)	2·6
C(4′)	1365 (2)	1798 (1)	4217 (3)	2·6
C(5′)	341 (2)	2117 (1)	2740 (3)	2·7
C(6′)	187 (2)	2838 (1)	2656 (3)	2·7
C(8)	4176 (3)	2229 (1)	8424 (3)	4·6
C(9)	570 (3)	670 (1)	4372 (3)	4·3
C(10)	−1622 (3)	1963 (1)	−33 (3)	4·6

Conformationally, the molecule is defined by the angles τ_1 and τ_2 made by the pyrimidine and phenyl ring planes with the plane formed by the three central atoms C(5)–C(7)–C(1′) and possible combinations of these angles have been defined by Cody (1984). In this compound these angles are −77·5 (8) and 157·2 (10)°, compared with −89·4 and 153·3° reported by KW for the neutral molecule, and correspond to a twist conformation in Cody's terms. Based on the conformational energy contour map presented by KW, the energy of the cation in this conformation is about 1·5 kcal mol^{-1} lower than that of trimethoprim in the crystal and is closer to one of the local minima. Other quite different conformations of comparable energy are possible and known (Phillips & Bryan, 1969; Giuseppetti, Tadini, Bettinetti, Giordano & La Manna, 1980; Cody, 1984).

Contrary to the conclusions drawn by KW, the hydrogen-bonding pattern in the crystal of the acetate is not the same as that in crystalline trimethoprim. In trimethoprim, both N(1) and N(3) act as acceptors, and the bases are linked in infinite ribbons by hydrogen bonds between N(1) and N(2) [3·059 (2) Å] and N(3) and N(4) [3·036 (2) Å]. In this salt N(1) is protonated, and each acetate anion is hydrogen-bonded to a single cation, with N(1) and N(2) acting as donors [N(1)···O(1) 2·606 (2) Å; N(2)···O(2) 2·774 (2) Å]. The bases are, in turn, linked as centrosymmetric dimers with N(4) acting as a donor to N(3) [N(4)···N(3) 3·040 Å; H(4*a*)···N(3) 2·06 (3) Å]. As in trimethoprim, there is evidence that the ether O atoms are involved in hydrogen bonding. N(4) acts as a donor to O(3′) of a

neighboring molecule at x, $0{\cdot}5-y$, $1{\cdot}5-z$, through H(4*b*) [N(4)···O(3′) 3·070 (2) Å; H(4*b*)···O(3′) 2·42 (3) Å], and H(2*b*) participates in a bifurcated donation to both O(3′) and O(4′) of a neighboring molecule at $1-x$, $0{\cdot}5+y$, $1{\cdot}5-z$ [N(2)···O(3′) 3·098 (2) Å; N(2)···O(4′) 3·196 (2) Å; H(2*b*)···O(3′) 2·34 (3) Å; H(2*b*)···O(4′) 2·44 (3) Å].

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Structure of Ethyl 6-(*p*-Chlorophenyl)-3-phenylimidazo[2,1-*b*]thiazol-2-ylacetate

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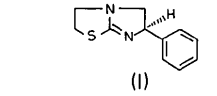
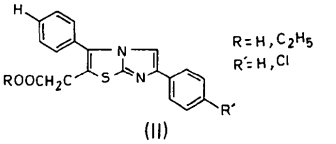
Abstract. $C_{21}H_{17}ClN_2O_2S$, $M_r = 396{\cdot}95$, monoclinic, $P2_1/a$, $a = 21{\cdot}022$ (7), $b = 8{\cdot}301$ (1), $c = 10{\cdot}823$ (3) Å, $\beta = 99{\cdot}14$ (2)°, $V = 1864{\cdot}7$ (9) Å^3, $Z = 4$, $D_x = 1{\cdot}414$, D_m(flotation) = 1·43 g cm^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 29{\cdot}80$ cm^{-1}, $F(000) = 824$, $R = 0{\cdot}037$ for 2020 unique observed reflections. The compound is of a class which on hydrolysis yields an acid that is anti-inflammatory. The molecule consists of two fused five-membered rings which form an approximately coplanar configuration with the *p*-chlorophenyl ring. The 3-phenyl is oriented at about 64° to this plane. The ethoxycarbonylmethyl group has an extended configuration. The S–C average distance (1·756 Å) is shorter than for a single bond.

Introduction. Following the discovery of levamisol (I), the *S*-(−) isomer of tetramisol, and its ability to potentiate the immune system in man, as a potent anthelmintic drug (Raeymakers, Roevens & Janssen, 1967; Wilkins & Olkowski, 1977) and as an anti-inflammatory and anti-arthitic agent (Lambardino, 1978), many compounds with imidazo[2,1-*b*]thiazole and imidazo[2,1-*b*]benzothiazole moieties have been synthesized by Abignente, Arena, de Capariis & Parente (1976). Degradation of (±)-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole was shown by a single-crystal X-ray diffraction study to give 1-(2′-*p*-bromobenzylthio)ethyl-4-phenylimidazole by Fibiger, Banks, Jones, Haltiwanger & Watt (1978). Sawhney, Kodali, Dhindsa & Singh (1982) prepared some arylimidazo-[2,1-*b*]thiazole compounds for the evaluation of their activities as potential anti-inflammatory agents. The parent compound (II, $R = H$, $R' = H$) showed the highest activity in the series but substitution on either of the aryl groups was not found favourable and further esterification resulted in the loss of activity (II, $R = C_2H_5$, $R' = Cl$).



(I)



(II)

So far crystal and molecular structure determinations of few such adversely affected compounds have

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