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# Structures of Two Active Trimethoprim* Analogues: 2,4-Diamino-5-(4-isopropenyl-3,5-dimethoxybenzyl)pyrimidinium Ethanesulfonate, $C_{16}H_{21}N_4O_2^+.C_2H_5O_3S^-$ (I), and 2,4-Diamino-5-(3,5-dimethoxy-4-methoxycarbonylbenzyl)pyrimidine, $C_{15}H_{18}N_4O_4$ (II)†

BY VIVIAN CODY

*Medical Foundation of Buffalo Inc., 73 High Street, Buffalo, NY 14203, USA*

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**Abstract.** (I) $M_r = 410{\cdot}5$, $P\bar{1}$, $a = 9{\cdot}400$ (1), $b = 19{\cdot}563$ (2), $c = 5{\cdot}419$ (1) Å, $\alpha = 93{\cdot}29$ (1), $\beta = 94{\cdot}11$ (1), $\gamma = 93{\cdot}95$ (1)°, $V = 989{\cdot}8$ (3) Å$^3$, $Z = 2$, $D_x = 1{\cdot}38$ g cm$^{-3}$, Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å, $\mu = 17{\cdot}4$ cm$^{-1}$, $F(000) = 436$, $T = 257$ K, $R = 0{\cdot}048$ for 3596 unique significant reflections. (II) $M_r = 318{\cdot}3$, $P\bar{1}$, $a = 11{\cdot}738$ (2), $b = 18{\cdot}204$ (4), $c = 8{\cdot}001$ (2) Å, $\alpha = 90{\cdot}74$ (2), $\beta = 107{\cdot}32$ (2), $\gamma = 99{\cdot}94$ (2)°, $V = 1601{\cdot}2$ (10) Å$^3$, $Z = 4$, $D_x = 1{\cdot}32$ g cm$^{-3}$, Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å, $\mu = 8{\cdot}25$ cm$^{-1}$, $F(000) = 672$, $T = 293$ K, $R = 0{\cdot}056$ for 2975 unique significant reflections. The conformation of (I) is antiskewed and both molecules in (II) are twist. The 4′-isopropenyl group of (I) is perpendicular to the plane of the benzyl ring. The 4′-methoxycarbonyl group in molecule 2 (II) is rotationally (67/33%) disordered. In all three molecules the 3′,5′-dimethoxy groups are coplanar with the benzyl ring and have their respective methyl carbons pointing away from the 4′-position.

**Introduction.** The drug trimethoprim (TMP) inhibits the enzyme dihydrofolate reductase (DHFR), required in the biosynthetic pathways leading to DNA and RNA precursors and, as such, is one of the most widely used broad-spectrum antibiotics because of its high selectivity (>60 000 times) for bacterial rather than human DHFR. It has also been shown that the dihydrofolate reductase isolated from different sources has different sensitivities to these inhibitors (Hitchings & Burchall, 1965), and that enzyme inhibition can be modulated by small variations in the antifolate structure.

Of the structural modifications made to trimethoprim, only substitution at the 4′-position of the benzyl ring with functionalized carbon groups has produced more potent analogues (Kompis, Then, Boehni, Rey-Bellet, Zanetti & Montavon, 1980; Kompis, Then, Wick & Montavon, 1980). The two most active trimethoprim analogues in this series are the 4′-isopropenyl derivative which is three times more potent than TMP and has an eightfold increase in selectivity, and the 4′-methoxycarbonyl analogue which is equivalent to TMP and has a twofold increase in selectivity (Fig. 1).

Therefore, to investigate the conformational aspects of the 4′-functionalized TMP analogues and to compare them with the parent drug, the crystal structures of (I) and (II) were undertaken and their molecular structures compared with that of trimethoprim.

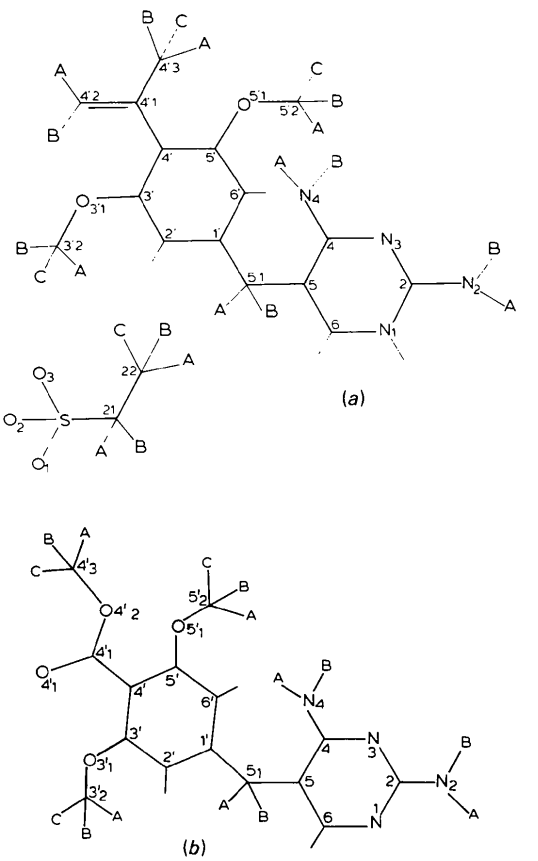


Fig. 1. (*a*) Schematic drawing of 4′-isopropenyl-TMP ethanesulfonate (ES) salt with numbering scheme. (*b*) Schematic drawing of 4′-methoxycarbonyl-TMP with numbering scheme.

* Trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl)-pyrimidine.

† IUPAC name: methyl 4-(2,4-diamino-5-pyrimidinylmethyl)-2,6-dimethoxybenzoate.

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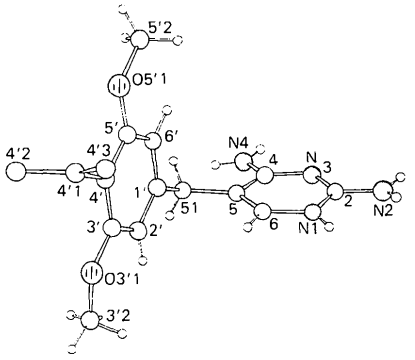
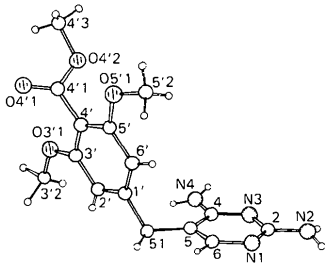
Table 1. *Atomic coordinates* ($\times 10^4$) *and* $B_{eq}$ ($Å^2 \times 10^2$) *with e.s.d.'s in parentheses for the 4′-isopropenyl-TMP structure*

$B_{iso} = \frac{4}{3}\sum_i\sum_j \beta_{ij}(\mathbf{a}_i.\mathbf{a}_j)$ (Hamilton, 1959).

| | x | y | z | $B_{eq}$ |
|---|---|---|---|---|
| N(1) | −3830 (1) | 1070 (1) | 9615 (3) | 237 (3) |
| C(2) | −3095 (2) | 570 (1) | 10643 (3) | 221 (3) |
| N(3) | −1811 (1) | 424 (1) | 9958 (3) | 237 (3) |
| C(4) | −1244 (2) | 782 (1) | 8169 (3) | 215 (3) |
| C(5) | −1919 (1) | 1355 (1) | 7153 (3) | 206 (3) |
| C(6) | −3217 (2) | 1467 (1) | 7936 (3) | 232 (3) |
| C(51) | −1191 (2) | 1795 (1) | 5341 (4) | 264 (4) |
| C(1′) | −1644 (2) | 2525 (1) | 5377 (3) | 225 (3) |
| C(2′) | −2688 (2) | 2714 (1) | 3653 (3) | 243 (4) |
| C(3′) | −3094 (2) | 3390 (1) | 3753 (3) | 244 (4) |
| C(4′) | −2441 (2) | 3883 (1) | 5511 (3) | 236 (4) |
| C(5′) | −1382 (2) | 3681 (1) | 7217 (3) | 238 (4) |
| C(6′) | −994 (2) | 3004 (1) | 7160 (3) | 243 (4) |
| N(2) | −3710 (2) | 228 (1) | 12376 (3) | 298 (4) |
| N(4) | −15 (2) | 593 (1) | 7393 (3) | 293 (4) |
| O(3′1) | −4146 (1) | 3612 (1) | 2179 (3) | 336 (3) |
| C(3′2) | −4679 (2) | 3166 (1) | 103 (4) | 325 (4) |
| O(5′1) | −768 (1) | 4189 (1) | 8859 (3) | 312 (3) |
| C(5′2) | 331 (2) | 4015 (1) | 10615 (4) | 360 (5) |
| C(4′1) | −2853 (2) | 4615 (1) | 5611 (3) | 266 (4) |
| C(4′2) | −2080 (6) | 5073 (2) | 3972 (10) | 303 (10) |
| C(4′3) | −3649 (5) | 4860 (2) | 7437 (10) | 267 (10) |
| C(4′2*) | −2437 (5) | 5051 (2) | 3880 (9) | 276 (9) |
| C(4′3*) | −3918 (6) | 4773 (3) | 7307 (11) | 335 (12) |
| S | 2993 (1) | 1335 (1) | 3142 (1) | 259 (1) |
| O(1) | 3444 (1) | 1449 (1) | 663 (3) | 341 (3) |
| O(2) | 3948 (2) | 898 (1) | 4465 (3) | 385 (4) |
| O(3) | 1492 (1) | 1111 (1) | 3165 (3) | 368 (3) |
| C(21) | 3218 (2) | 2146 (1) | 4804 (5) | 371 (5) |
| C(22) | 2316 (3) | 2679 (1) | 3703 (7) | 493 (8) |




(*a*)




(*b*)

Fig. 2. (*a*) Molecular conformation of 4′-isopropenyl-TMP. (*b*) Molecular conformation of 4′-methoxycarbonyl-TMP, molecule 2.

Table 2. *Atomic coordinates* ($\times 10^4$) *and* $B_{eq}$ ($Å^2 \times 10$) *with e.s.d.'s in parentheses for 4′-methoxycarbonyl-TMP structure*

| | x | y | z | $B_{eq}$ |
|---|---|---|---|---|
| Molecule I | | | | |
| N(1) | 14378 (3) | 7559 (2) | 10160 (5) | 43 (1) |
| C(2) | 15053 (4) | 8196 (3) | 9932 (6) | 37 (2) |
| N(3) | 14864 (3) | 8895 (2) | 10151 (5) | 36 (1) |
| C(4) | 13885 (4) | 8954 (2) | 10670 (6) | 35 (1) |
| C(5) | 13099 (4) | 8317 (2) | 10933 (6) | 36 (1) |
| C(6) | 13401 (4) | 7642 (3) | 10662 (6) | 40 (2) |
| C(51) | 12013 (4) | 8372 (3) | 11553 (7) | 39 (2) |
| C(1′) | 10935 (4) | 8589 (2) | 10221 (6) | 34 (1) |
| C(2′) | 10131 (4) | 8939 (2) | 10814 (7) | 34 (2) |
| C(3′) | 9125 (4) | 9121 (2) | 9629 (6) | 32 (1) |
| C(4′) | 8872 (4) | 8973 (2) | 7877 (6) | 34 (1) |
| C(5′) | 9867 (4) | 8617 (2) | 7275 (6) | 36 (2) |
| C(6′) | 10668 (4) | 8427 (3) | 8439 (7) | 39 (2) |
| N(2) | 16051 (4) | 8130 (3) | 9449 (7) | 52 (2) |
| N(4) | 13720 (4) | 9656 (2) | 10955 (6) | 49 (2) |
| O(3′1) | 8292 (2) | 9456 (2) | 10128 (4) | 39 (1) |
| C(3′1) | 8418 (6) | 9533 (4) | 11958 (7) | 45 (2) |
| O(5′1) | 9328 (3) | 8494 (2) | 5490 (4) | 51 (1) |
| C(5′2) | 9957 (8) | 8010 (5) | 4837 (8) | 75 (3) |
| C(4′1) | 7821 (5) | 9201 (3) | 6579 (7) | 52 (2) |
| O(4′1) | 7942 | 9845 | 5824 | 60 (1) |
| O(4′2) | 6788 | 8791 | 6297 | 77 (2) |
| C(4′3) | 5894 (8) | 8958 (7) | 4691 (13) | 90 (4) |
| O(4′1*) | 7680 | 9797 | 6333 | 34 (2) |
| O(4′2*) | 6902 | 8617 | 5820 | 23 (1) |
| C(4′3*) | 6544 (17) | 9869 (11) | 4650 (21) | 68 (7) |
| Molecule II | | | | |
| N(1) | 14129 (3) | 4758 (2) | 1549 (5) | 41 (1) |
| C(2) | 14279 (4) | 4052 (2) | 1336 (6) | 38 (2) |
| N(3) | 13973 (3) | 3476 (2) | 2249 (5) | 41 (1) |
| C(4) | 13538 (4) | 3641 (3) | 3553 (7) | 42 (2) |
| C(5) | 13410 (4) | 4367 (3) | 3959 (6) | 39 (2) |
| C(6) | 13716 (4) | 4888 (3) | 2894 (6) | 39 (2) |
| C(51) | 13046 (5) | 4570 (3) | 5546 (7) | 48 (2) |
| C(1′) | 11734 (4) | 4248 (2) | 5489 (6) | 38 (2) |
| C(2′) | 11559 (5) | 3926 (3) | 6969 (7) | 41 (2) |
| C(3′) | 10371 (4) | 3659 (3) | 6998 (6) | 40 (2) |
| C(4′) | 9399 (4) | 3715 (2) | 5542 (6) | 38 (2) |
| C(5′) | 9591 (4) | 4024 (3) | 4068 (6) | 41 (2) |
| C(6′) | 10787 (5) | 4290 (3) | 4040 (7) | 42 (2) |
| N(2) | 14748 (4) | 3907 (3) | 30 (6) | 50 (2) |
| O(3′1) | 10087 (3) | 3321 (2) | 8372 (4) | 51 (1) |
| C(3′2) | 11050 (6) | 3246 (4) | 9897 (8) | 57 (2) |
| O(5′1) | 8576 (3) | 4056 (2) | 2721 (5) | 55 (1) |
| C(5′2) | 8688 (7) | 4337 (4) | 1118 (9) | 58 (2) |
| C(4′1) | 8132 (4) | 3428 (3) | 5596 (7) | 46 (2) |
| O(4′1) | 7641 (4) | 3722 (2) | 6464 (6) | 74 (2) |
| O(4′2) | 7640 (4) | 2804 (2) | 4592 (5) | 53 (1) |
| C(4′3) | 6378 (6) | 2499 (6) | 4449 (12) | 74 (3) |

**Experimental.** Crystals of both compounds obtained from methanol solutions containing ethanesulfonic acid; cell dimensions from least-squares refinement of 40 reflections, $2\theta$ range 52·62 to 69·94° for (I); 50 reflections, $2\theta$ range 40·08 to 58·08° for (II); Enraf–Nonius CAD-4 diffractometer, Ni-filtered Cu $K\alpha$ radiation, $\theta$–$2\theta$ scan, $\theta_{max} = 75°$ ($-12 \le h \le 12$, $-25 \le k \le 25$, $0 \le l \le 7$) for (I), and $\theta_{max} = 60°$ ($0 \le h \le 14$, $-21 \le k \le 21$, $-9 \le l \le 9$) for (II); (I) 0·12 × 0·12 × 0·86 mm, (II) 0·8 × 0·16 × 1·2 mm, 4 standard reflections monitored at intervals of 7200 s, no crystal decomposition, no correction for extinction or absorption; 4054 unique reflections (I), 3610 with $I > 2\sigma(I)$ (Stout & Jensen, 1968), 4744 unique reflections (II), 2992 with $I > 2\sigma(I)$; direct methods (*MULTAN*: Germain, Main & Woolfson, 1971; *NQEST*: DeTitta, Edmonds, Langs & Hauptman, 1975), refinement on $F$ by full-matrix least squares,

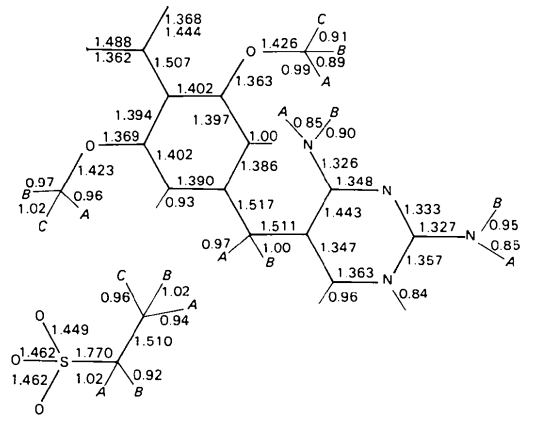
anisotropic thermal parameters, H positions located in difference Fourier syntheses, refined isotropically; final difference Fourier maps for (I) and (II) showed no peaks $>0.15$ e Å$^{-3}$, $\sum w(|F_o| - |F_c|)^2$ minimized, $w = 1/[\sigma(I)^2 + (0.02I)^2]$, final $R = 0.048$, $R_w = 0.064$, max. $\Delta/\sigma$ 0.01 for (I); final $R = 0.056$, $R_w = 0.083$, max. $\Delta/\sigma$ 0.02 for (II); atomic scattering factors from *International Tables for X-ray Crystallography* (1974); all calculations performed on a VAX 11/780 computer using the Enraf–Nonius crystallographic package.

Since the carbon positions of the 4′-propenyl group refined to equivalent bond lengths, a 50% rotationally disordered model was indicated. The two rotomers of this disordered model were refined at half-occupancy in the final cycles of the refinement. A similar situation was observed in molecule 1 of the methoxycarbonyl structure in which an extra peak, about $\frac{1}{3}$ the height of a carbon, was located near the non-methylated oxygen, indicative of a rotational disorder. A model with a 67/33% occupancy for the two methoxycarbonyl positions was refined in the final cycles of the structure refinement.

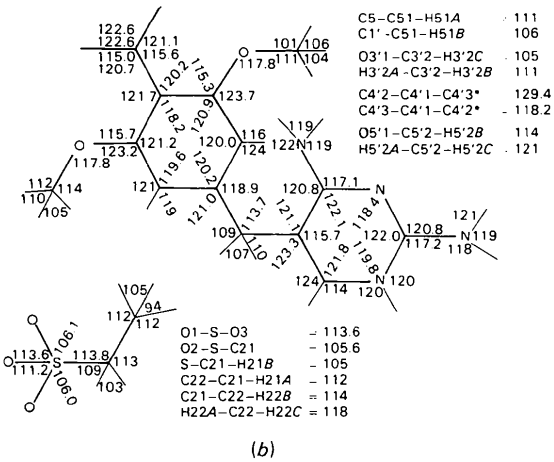
**Discussion.** Final fractional coordinates and equivalent $B$ values for the two structures are listed in Tables 1 and 2.* The molecular conformations and geometry for these structures are illustrated in Figs. 2–4, respectively.

The general conformation of trimethoprim is defined by the torsion angles $\tau_1$ [C(4)–C(5)–C(51)–C(1′)] and $\tau_2$ [C(5)–C(51)–C(1′)–C(6′)]. The relative orientation of the pyrimidine and benzyl rings can be described as skewed ($\tau_1/\tau_2 \simeq \pm 90/0°$), antiskewed ($\tau_1/\tau_2 \simeq 0/\pm 90°$), twist ($\tau_1/\tau_2 \simeq \pm 70/\pm 40°$), butterfly ($\tau_1/\tau_2 \simeq \pm 37/$

* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39210 (46 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

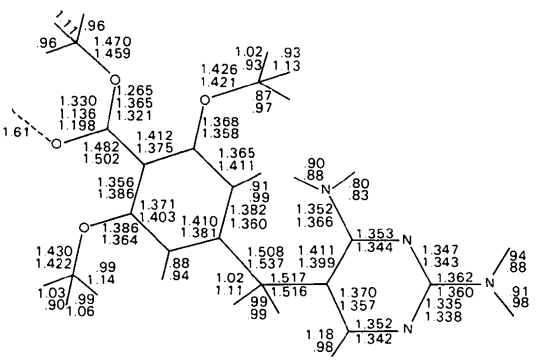


(*a*)




(*b*)

Fig. 3. (*a*) Bond lengths (Å) in 4′-isopropenyl-TMP–ES. The e.s.d.'s are 0.002 Å. The second set of values on the 4′-substituent refer to the geometry of the disordered model. (*b*) Bond angles (°) in 4′-isopropenyl-TMP–ES. The e.s.d.'s are 0.1°. The second set of values on the 4′-substitutents refer to the disordered model.



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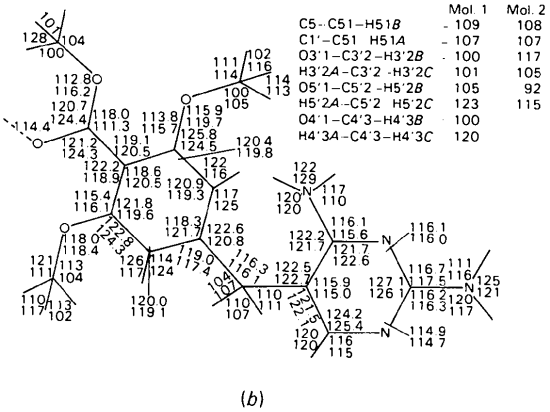


(*b*)

Fig. 4. (*a*) Bond lengths (Å) in 4′-methoxycarbonyl-TMP, for molecules 1 (top) and 2 (bottom). The first two sets of values at the 4′-methoxycarbonyl group are for the disordered model in molecule 1, the third set are for molecule 2. The e.s.d.'s are 0.006 Å. (*b*) Bond angles (°) in 4′-methoxycarbonyl-TMP, for molecules 1 and 2. The e.s.d.'s are 0.4°.

$\pm 37°$) or perpendicular ($\tau_1/\tau_2 \simeq \pm 90/\pm 90°$) (Cody, 1978; van der Heijden, Griffith, Chandler & Robertson, 1975). Since these structures are observed in centrosymmetric space groups, both conformational enantiomorphs, as defined by the signs of the torsion angles, exist in the crystal lattice. Therefore, the enantiomorph for which $\tau$ is positive (0–180°) was chosen. As illustrated (Fig. 2), the conformation of 4′-isopropenyl-TMP is antiskewed ($\tau_1/\tau_2 = 153{\cdot}1/97{\cdot}7$), while that of each molecule of 4′-methoxycarbonyl-TMP is twist ($\tau_1/\tau_2 = 73{\cdot}5/29{\cdot}2°$ and $70{\cdot}2/46{\cdot}4°$, for molecule 1 and 2, respectively).

The conformations reported for other trimethoprim structures are either twist (Koetzle & Williams, 1976, 1978; Haltiwanger, 1971; Shimizu & Nishigaki, 1982; Oberhänsli, 1970) or antiskewed (Giuseppetti, Tadini, Bettinetti, Giordano & La Manna, 1980; Phillips & Bryan, 1969), with the twist conformation being the most frequently observed.

In order to evaluate the conformational flexibility about the methylene bridge in trimethoprim, the conformational potential energy as a function of the rotations $\tau_1$ and $\tau_2$ was calculated (Koetzle & Williams, 1976). These data suggested that TMP can assume a variety of equal-energy conformations. These data indicate that the relative energy difference between the twist and antiskewed conformation is small (~4 kJ); therefore, either the twist or antiskewed conformations should be readily accessible in solution.

The structure of trimethoprim bound to bacterial and avian dihydrofolate reductase has been observed in crystal-structure complexes (Baker, Beddell, Champness, Goodford, Norrington, Smith & Stammers, 1981; Matthews & Volz, 1982). These studies show that, in the bacterial reductase binding site, TMP has an antiskewed conformation similar to that observed in the 4′-isopropenyl-TMP structure, while that in chicken liver DHFR is twist, similar to the conformation of the 4′-methoxycarbonyl-TMP structure.

Binding to DHFR is enhanced by the protonation of the antifolate at N(1) (Hitchings & Burchall, 1965). Hydrogen bonds involving N(1), N(2) and N(4), observed in the crystallographic studies of DHFR–antifolate complexes (Filman, Bolin, Matthews & Kraut, 1982; Bolin, Filman, Matthews, Hamlin & Kraut, 1982; Volz, Matthews, Alden, Freer, Hansch, Kaufman & Kraut, 1982), appear vital to the high-affinity binding. The hydrogen-bonding patterns of these two structures (Fig. 5) show that all the amino hydrogens of 4′-isopropenyl-TMP, and all but one of the 4′-methoxycarbonyl-TMP, participate in the hydrogen bonding, as observed in other diaminopyrimidine structures (Cody & Zakrzewski, 1982).

Since the conformations of these active analogues are similar to that of the parent drug trimethoprim, their enhanced binding affinity to the bacterial DHFR most probably results from the placement of lipophilic bulk on the 4′-position perpendicular to the benzyl plane. Thus, when bound to the enzyme, this group can interact favorably with the hydrophobic residues in the bacterial reductase.

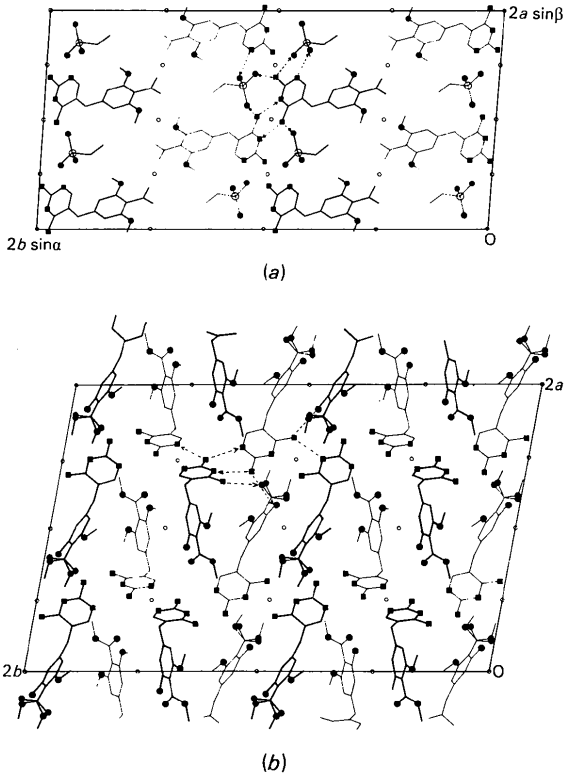


Fig. 5. (*a*) Packing diagram for 4′-isopropenyl-TMP–ES projected down **c**. The large open circles are S, squares N, filled circles O. The hydrogen-bonding scheme about one molecule is shown with dashed lines. (*b*) Packing diagram for 4′-methoxycarbonyl-TMP. The squares are N, filled circles, O. The hydrogen-bonding scheme is shown with dashed lines.

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# Structures of the Antileprosy Phenazine Derivatives B673 and B741: 3-(*p*-Chloroanilino)-10-(*p*-chlorophenyl)-2-cyclohexylimino-2,10-dihydrophenazine, $C_{30}H_{26}Cl_2N_4$, and 3-(*p*-Chloroanilino)-10-(*p*-chlorophenyl)-2,10-dihydro-2-(4-methylcyclohexylimino)phenazine, $C_{31}H_{28}Cl_2N_4$

BY URSZULA RYCHLEWSKA,* M. BETH HUMPHREY BROOM AND DEREK J. HODGSON†

*Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina, 27514, USA*

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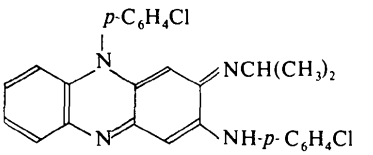
**Abstract.** B673: $M_r = 513{\cdot}47$, triclinic, $P\bar{1}$, $a = 10{\cdot}992\ (3)$, $b = 12{\cdot}191\ (7)$, $c = 10{\cdot}458\ (6)$ Å, $\alpha = 112{\cdot}13\ (5)$, $\beta = 91{\cdot}57\ (3)$, $\gamma = 88{\cdot}58\ (3)°$, $U = 1298\ (2)$ Å$^3$, $Z = 2$, $D_m = 1{\cdot}29\ (2)$, $D_x = 1{\cdot}31$ Mg m$^{-3}$, Mo $K\alpha_1$, $\lambda = 0{\cdot}70926$ Å, $\mu = 0{\cdot}28$ mm$^{-1}$, $F(000) = 536$, $T = 295$ K, $R = 0{\cdot}068$ for 1861 reflections. B741: $M_r = 527{\cdot}49$, triclinic, $P\bar{1}$, $a = 12{\cdot}161\ (14)$, $b = 12{\cdot}692\ (4)$, $c = 10{\cdot}448\ (7)$ Å, $\alpha = 111{\cdot}60\ (4)$, $\beta = 113{\cdot}52\ (6)$, $\gamma = 91{\cdot}92\ (5)°$, $U = 1344\ (4)$ Å$^3$, $Z = 2$, $D_m = 1{\cdot}29\ (2)$, $D_x = 1{\cdot}30$ Mg m$^{-3}$, Mo $K\alpha_1$, $\lambda = 0{\cdot}70926$ Å, $\mu = 0{\cdot}27$ mm$^{-1}$, $F(000) = 552$, $T = 295$ K, $R = 0{\cdot}042$ for 1784 reflections. The two compounds have substantially similar structures, except that in B673 the imino nitrogen atom N(2) is equatorial to the cyclohexyl group while in B741 it is axial to the 4-methylcyclohexyl group. Consequently, approach to the presumed active sites at N(2) and N(3) is unhindered in B673 but hindered in B741.

**Introduction.** The substituted iminodihydrophenazine clofazimine (I) and its analogs are of considerable current significance because of their use and/or potential as antileprosy drugs. Indeed, clofazimine has been in use for more than twenty years (Browne & Hogerzeil, 1962) and is still regarded by many workers as the best drug available (Jacobson, 1981). Regrettably, as has been the case for the sulfone dapsone, 4,4′-diaminodiphenyl sulfone, for many years (Pearson, 1981; Guinto, Cellona, Fajardo & de la Cruz, 1981), bacterial resistance to clofazimine has recently emerged (Warndorff-van Diepin, 1982). Consequently, the need for the development of suitable clofazimine analogs is both great and immediate.

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* Permanent address: Faculty of Chemistry, A. Mickiewicz University, ul. Grunwaldzka 6, 60-780 Poznań, Poland.
† Author to whom correspondence should be addressed.

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