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Comparison of the Structures of the Enantiomeric and Racemic Forms of an Imidazo[2,1-*b*]thiazole Anthelmintic Agent and their Hydrochlorides

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Abstract

Structure determinations were performed on 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole bases and their hydrochloride salts. The structures of the optically active base (LEVA), two polymorphic racemic bases (TETRA and TETRA2) and the racemic hydrochloride (TETRA.HCl) are compared both with each other and with the known structure of the optically active hydrochloride (LEVA.HCl) [Baker & Pauling (1973). *J. Chem. Soc. Perkin Trans.* 2, pp. 203–206]. LEVA, TETRA and TETRA2: $C_{11}H_{12}N_2S$, $M_r = 204.3$. LEVA: orthorhombic, $P2_12_12_1$, $a = 4.851$ (1), $b = 9.746$ (1), $c = 21.864$ (1) Å, $V = 1033.6$ Å^3, $D_x = 1.31$ g cm^{-3}, $Z = 4$, λ(Cu $K\alpha$) = 1.5418 Å, $\mu = 23.97$ cm^{-1}, $F(000) = 432$, $T = 296$ K, $R = 0.033$ for 1168 reflections [$I > 3.0\sigma(I)$]. TETRA: monoclinic, $P2_1/n$, $a = 9.557$ (1), $b = 9.773$ (1), $c = 11.286$ (1) Å, $\beta = 105.6$ (3)°, $V = 1015.3$ Å^3, $D_x = 1.336$ g cm^{-3}, $Z = 4$, λ(Cu $K\alpha$) = 1.5418 Å, $\mu = 24.40$ cm^{-1}, $F(000) = 432$, $T = 296$ K, $R = 0.053$ for 1962 reflections [$I > 3.0\sigma(I)$].

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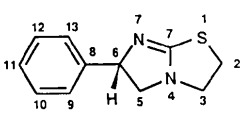
TETRA2: monoclinic, $P2_1/c$, $a = 19.622$ (1), $b = 8.830$ (1), $c = 12.017$ (1) Å, $\beta = 107.19$ (1)°, $V = 1989.1$ Å^3, D_x (296 K) = 1.330, D_x (110 K) = 1.364 g cm^{-3}, $Z = 8$, λ(Cu $K\alpha$) = 1.5418 Å, $\mu = 24.91$ cm^{-1}, $F(000) = 864$, $T = 110$ K, $R = 0.032$ for 3615 reflections [$I > 3.0\sigma(I)$]. TETRA.HCl: $C_{11}H_{13}N_2S^+.Cl^-$, $M_r = 240.76$, triclinic, $P\bar{1}$, $a = 5.940$ (3), $b = 8.805$ (2), $c = 12.030$ (2) Å, $\alpha = 74.53$ (1), $\beta = 75.27$ (3), $\gamma = 73.9$ (2)°, $V = 571.5$ Å^3, $D_x = 1.399$ g cm^{-3}, $Z = 2$, λ(Cu $K\alpha$) = 1.5418 Å, $\mu = 24.91$ cm^{-1}, $F(000) = 252$, $T = 296$ K, $R = 0.047$ for 1882 reflections [$I > 3.0\sigma(I)$]. The overall conformations of the optically active LEVA and the two polymorphic racemic bases TETRA and TETRA2 are very similar, as the differences between the corresponding endocyclic torsion angles and those describing the relative position of the phenyl group are less than 3 and 10°, respectively. Upon protonation, there is a significant flattening of the double ring system, as measured by the absolute values of all endocyclic torsion angles. In LEVA.HCl the phenyl group is rotated by 48° relative to its position in TETRA.HCl. Homo- and heterochiral interactions were studied by examining the intra- and intermolecular distances between the middle points of the double ring and the phenyl group.

Table 1. *Physico-chemical and crystallographic data*

	LEVA	TETRA	TETRA2	TETRA.HCl	LEVA.HCl
Formula	$C_{11}H_{12}N_2S$	$C_{11}H_{12}N_2S$	$C_{11}H_{12}N_2S$	$C_{11}H_{13}N_2S^+.Cl^-$	$C_{11}H_{13}N_2S^+.Cl$
M_r	204.30	204.30	204.30	240.76	240.76
Space group	$P2_12_12_1$	$P2_1/n$	$P2_1/c$	$P\bar{1}$	$P2_12_12_1$
M.p. (K)	333	363	364	513	488
Heat of fusion (kJ mol^{-1})	18.39	28.01	25.50	–	–
a (Å)	4.851 (1)	9.557 (1)	19.622 (1)	5.940 (3)	12.952 (4)
b (Å)	9.746 (1)	9.773 (1)	8.830 (1)	8.805 (2)	14.710 (5)
c (Å)	21.864 (1)	11.286 (1)	12.017 (1)	12.030 (2)	5.943 (3)
α (°)				74.53 (1)	
β (°)		105.6 (3)	107.19 (1)	75.27 (3)	
γ (°)				73.9 (2)	
V (Å^3)	1033.6	1015.3	1989.1	571.5	1132
Z	4	4	8	2	4

Introduction

Recognition of the importance of chirality in medicinal chemistry is well illustrated by the growing number of meetings held on different aspects of chirality and biological activity (*e.g.* Tubingen Symposium on Chirality and Biological Activity, Germany, 1988; Second Symposium on Chiral Drugs, Cologne, Germany, 1989; Drug Chirality, London, England, 1990). For an improved characterization of the different biological activities of optical isomers and racemates, a greater abundance of structural and physico-chemical data is required. Very few studies have been performed where the macroscopic properties of a racemic compound and its enantiomers have been correlated with the differences in their crystal structures (*e.g.* Faigl, Simon, Lopata, Kozsda, Hargitai, Czugler, Ács & Fogassy, 1990). The model compound 6-phenyl-2,3,5,6-tetrahydroimidazo-[2,1-*b*]thiazole (1) is known to be an extraordinarily efficient anthelmintic agent (Islip, 1979).



(1)

Both the racemic (tetramisol hydrochloride) and the optically active *S* isomer (levamisol hydrochloride) are used as drugs (Newger, 1978). The biological activity resides in the levorotatory *S* isomer, which is several times more potent, but no more toxic than the dextrorotatory *R* isomer. The *S* form further exhibits a striking immunostimulant effect (Hess & Freter, 1979). The enantiomer separation is performed only if the drug is destined for human administration, and the racemate is marketed for veterinary purposes. Even the use of an otherwise efficient optical resolution method results in only an optically impure mixture (*e.g.* Fogassy, Ács, Felméri & Aracs, 1976). Easy and efficient separation of the racemic fraction and the enantiomeric excess involves a knowledge of the physico-chemical parameters of the racemates and enantiomers whose structural bases are the chirality specific (homo- and heterochiral) interactions (Fogassy, Faigl & Ács, 1985).

We observed a lower chemical stability for the optically active base than for the racemic one, and this phenomenon also called our attention to the lack of systematic investigations on chiral compounds. The thermal stability measurements revealed the existence of a second polymorphic modification of the racemic base (Brienne, Jacques, Marso & Ács, 1985). Powder diagrams and crystal data on the two polymorphic forms (TETRA and TETRA2) and on the *S* isomer (LEVA) have been reported previously (Ács, Fogassy, Faigl, Tomor, Simon, Marso, Fülöp, Brienne & Jacques, 1988).

The present paper reports the crystal structures of the optically active base (LEVA), two polymorphic racemic bases (TETRA and TETRA2) and the racemic hydrochloride (TETRA.HCl), and compares them with that of the optically active (*S*) hydrochloride (LEVA.HCl) [reported by Baker & Pauling (1973)]. An analysis of these structures should give an insight into the extent to which the homochiral (*S–S*) interactions observed in the crystal structures of LEVA and LEVA.HCl are similar to or different from the heterochiral (*S–R*) interactions found in the structures of TETRA, TETRA2 and TETRA.HCl. A mutual comparison of the five structures permits a study of enantiomers, racemates, polymorphs, and the effect of salt formation on the same model.

Table 2. *Data-collection and structure-refinement details*

	LEVA	TETRA	TETRA2	TETRA.HCl
Data collection				
Scan rate (° min $^{-1}$)	1–20	1–20	1–20	1–20
Scan type	ω–2θ	ω–2θ	ω–2θ	ω–2θ
Scan width (°)	0.45 + 0.14tanθ	0.4 + 0.3tanθ	1.5 + 0.14tanθ	0.5 + 0.3tanθ
Temperature (K)	296 (1)	296 (1)	110 (2)	296 (1)
Decay correction	None	None	None	None
Check reflections	0,0,14	312, 162	834, 713, 444	313, 051, 315
2θ max. (°)	150	150	152	150
No. of reflections measured	1343	2185	7757	2475
Unique reflections	1236	2032	4653	2136
Range of h	0→6	−12→12	−8→0	−7→0
k	0→12	0→13	−11→0	−11→11
l	0→27	0→15	−15→0	−15→15
Transmission-factor range	0.648–1.983	0.774–1.48	0.451–0.758	0.703–1.711
Crystal size (mm)	0.15 × 0.35 × 0.4	0.3 × 0.4 × 0.5	0.12 × 0.35 × 0.36	0.08 × 0.15 × 0.4
Structure refinement				
Reflections used	1168	1962	3615	1882
Unobserved reflections	68	70	1038	254
No. of variables	127	128	325	137
R, wR	0.030, 0.038	0.053, 0.082	0.032, 0.046	0.047, 0.05
R_{all}	0.033	0.054	0.045	0.054
Goodness of fit	3.9	1.99	1.29	4.79
Max. $\lvert\Delta/\sigma\rvert$	0.004	0.4	0.05	0.25
Max. peak (e Å $^{-3}$)	0.13	0.34	0.63	0.41
p	0.01	0.08	0.06	0.01

Experimental

Preparation of the starting materials

The racemic hydrochloride (TETRA.HCl) (Aldrich) was recrystallized and the enantiomers were separated by known methods (Fogassy, Ács, Felméri & Aracs, 1976; Ács, Faigl & Fogassy, 1985), using 0.25 equivalents of dibenzoyl-(*R*,*R*)-tartaric acid monohydrate, in a two-solvent phase system. $(LEVA)_2$-dibenzoyl-(*R*,*R*)-tartrate precipitates in a yield of 90% (calculated for the *S*-isomer content of the starting racemate). Decomposition of the salt was accomplished by alkalization with aqueous NaOH; the precipitating base (sensitive to heat and light) was powder-like; $[\alpha]_D^{RT} = 98°$, optical purity > 98% (Buyuktimkin & Schunack, 1983), melting point 373 K [in accordance with the published data (Brienne, Jacques, Marso & Ács, 1985)].

The racemic base was prepared by alkalization to pH 9 of a 15% aqueous solution of the commercially available hydrochloride. The precipitated base is stable up to its melting point (361–363 K). Its recrystallization from diethyl ether provides one of the polymorphic modifications, depending on the conditions employed. A higher temperature (> 313 K) favours TETRA2, whereas at or below room temperature TETRA precipitates. Upon standing in a refrigerator for *ca* 6 months TETRA2 underwent a partial solid-state polymorphic transformation. The powder diagram of the initially pure TETRA2 sample showed the presence of *ca* 50% of TETRA.

Single-crystal preparation

For the free bases (LEVA, TETRA and TETRA2), crystals were obtained by multiple crystallization from diethyl ether. Cubic crystals of the polymorphic modification more stable at room temperature (TETRA) were precipitated from a supersaturated solution at room temperature, while needles of TETRA2 were obtained at 313 K. The hydrochloride of the racemate (TETRA.HCl) was recrystallized from a refluxing toluene–isopropanol mixture (95:5) upon slow cooling to room temperature.

Data collection and structure solution

Crystallographic data and details of data collection and structure refinement for all structures are summarized in Tables 1 and 2. Data were collected on an Enraf–Nonius CAD-4 diffractometer, using graphite-monochromated Cu $K\alpha$ radiation (λ = 1.5418 cm^{-1}), with the ω–2θ scan technique. Non-H atoms were refined with anisotropic thermal parameters. All structures were solved by direct methods: LEVA, TETRA and TETRA.HCl by *MULTAN*80 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978) and TETRA2 by *SHELXS*86 (Sheldrick, 1986). Refinements were by least squares, minimizing $\sum w|F_o| - |F_c|)^2$, where $w = 4(F_o)^2/[\sigma(F_o^2)]^2$ and $\sigma(F_o^2) = \{[S^2(C + R^2B) + (pF_o^2)^2]/\mathrm{Lp}\}^2$, S being the scan rate, C the total integrated peak count, R the ratio of scan time to background counting time, B the total background count, Lp the Lorentz–polarization factor and the parameter p a factor introduced to downweight intense reflections (the actual value of p is given in Table 2).

After the isotropic refinement, an empirical spherical absorption correction was applied with the *DIFABS* program (Walker & Stuart, 1983). The H-atom positions were located in a difference Fourier map and refined isotropically in all cases except for the structure of LEVA. Scattering factors were

Table 3. *Fractional coordinates and equivalent isotropic thermal parameters* (Å^2) *for the non-*H *atoms of LEVA*

$U_{eq} = U_{11} + U_{22} + U_{33} + U_{23}b^*c^*bc\cos\alpha + U_{13}a^*c^*ac\cos\beta + U_{12}a^*b^*ab\cos\gamma)/3$.

	x	y	z	U_{eq}
S(1)	0.1006 (1)	0.4506 (5)	0.2944 (2)	0.0528 (2)
C(2)	0.2425 (6)	0.2869 (2)	0.3205 (9)	0.0572 (11)
C(3)	0.3902 (4)	0.2256 (2)	0.2657 (10)	0.0528 (10)
N(4)	0.2261 (3)	0.2658 (1)	0.2133 (6)	0.0405 (7)
C(5)	0.3240 (4)	0.2575 (2)	0.1503 (9)	0.0472 (10)
C(6)	0.1434 (4)	0.3672 (2)	0.1192 (8)	0.0442 (8)
N(7)	0.0704 (3)	0.4643 (1)	0.1692 (7)	0.0479 (7)
C(7)	0.1250 (4)	0.3984 (2)	0.2181 (8)	0.0405 (8)
C(8)	0.2808 (4)	0.4369 (1)	0.0656 (8)	0.0412 (8)
C(9)	0.2072 (5)	0.4046 (2)	0.0063 (8)	0.0518 (10)
C(10)	0.3363 (5)	0.4673 (2)	−0.0426 (9)	0.0608 (12)
C(11)	0.5366 (5)	0.5625 (2)	−0.0334 (9)	0.0583 (11)
C(12)	0.6131 (5)	0.5949 (2)	0.0254 (10)	0.0659 (12)
C(13)	0.4870 (5)	0.5334 (2)	0.0744 (9)	0.0566 (11)

Table 4. *Fractional coordinates and equivalent isotropic thermal parameters* (Å^2) *for the non-*H *atoms of TETRA*

$U_{eq} = U_{11} + U_{22} + U_{33} + U_{23}b^*c^*bc\cos\alpha + U_{13}a^*c^*ac\cos\beta + U_{12}a^*b^*ab\cos\gamma)/3$.

	x	y	z	U_{eq}
S(1)	0.6535 (1)	0.2948 (1)	0.3428 (1)	0.0322 (1)
C(2)	0.5885 (1)	0.1257 (1)	0.4028 (1)	0.0363 (3)
C(3)	0.5491 (1)	0.0508 (1)	−0.2986 (1)	0.0337 (3)
N(4)	0.6549 (1)	0.0974 (1)	−0.1874 (1)	0.0263 (2)
C(5)	0.6348 (1)	0.0793 (1)	−0.0649 (1)	0.0313 (3)
C(6)	0.7306 (1)	0.1958 (1)	0.0061 (1)	0.0296 (3)
N(7)	0.7313 (1)	0.3007 (1)	−0.0903 (1)	0.0300 (3)
C(7)	0.6873 (1)	0.2354 (1)	−0.1919 (1)	0.0238 (2)
C(8)	0.6789 (1)	0.2512 (1)	0.1114 (1)	0.0285 (3)
C(9)	0.7440 (1)	0.2113 (1)	0.2310 (1)	0.0390 (5)
C(10)	0.6946 (2)	0.2595 (2)	0.3283 (1)	0.0465 (6)
C(11)	0.5788 (1)	0.3478 (1)	0.3071 (1)	0.0418 (5)
C(12)	0.5123 (1)	0.3903 (1)	0.1879 (1)	0.0429 (5)
C(13)	0.5624 (1)	0.3417 (1)	0.0907 (1)	0.0372 (3)

Table 5. *Fractional coordinates and equivalent isotropic thermal parameters* (Å^2) *for the non-*H *atoms of TETRA2*

$U_{eq} = (U_{11} + U_{22} + U_{33} + U_{23}b^*c^*bc\cos\alpha + U_{13}a^*c^*ac\cos\beta + U_{12}a^*b^*ab\cos\gamma)/3$.

	x	y	z	U_{eq}
S(11)	0.2347 (1)	0.1395 (1)	0.7575 (1)	0.0179 (1)
C(21)	0.2499 (1)	0.3139 (2)	0.8436 (1)	0.0220 (2)
C(31)	0.1888 (1)	0.4198 (2)	0.7816 (1)	0.0205 (2)
N(41)	0.1775 (1)	0.3914 (1)	0.6574 (8)	0.0172 (2)
C(51)	0.1123 (1)	0.4384 (1)	0.5669 (1)	0.0193 (2)
C(61)	0.1112 (1)	0.3219 (1)	0.4702 (1)	0.0165 (2)
N(71)	0.1502 (1)	0.1871 (1)	0.5340 (8)	0.0170 (2)
C(71)	0.1833 (1)	0.2385 (1)	0.6349 (9)	0.0153 (2)
C(81)	0.0369 (1)	0.2809 (1)	0.3955 (1)	0.0160 (2)
C(91)	0.0098 (1)	0.3377 (2)	0.2832 (1)	0.0218 (2)
C(101)	−0.0593 (1)	0.3009 (2)	0.2156 (1)	0.0251 (2)
C(111)	−0.1013 (1)	0.2058 (2)	0.2600 (1)	0.0223 (2)
C(121)	−0.0744 (1)	0.1481 (1)	0.3721 (1)	0.0196 (2)
C(131)	−0.0057 (1)	0.1860 (1)	0.4397 (1)	0.0172 (2)
S(12)	0.2673 (1)	−0.1469 (3)	0.0064 (3)	0.0201 (1)
C(22)	0.2572 (1)	−0.3192 (2)	0.0852 (1)	0.0239 (2)
C(32)	0.3229 (1)	0.4147 (2)	0.0917 (1)	0.0222 (2)
N(42)	0.3367 (1)	−0.3902 (1)	−0.0198 (9)	0.0168 (2)
C(52)	0.4052 (1)	−0.4282 (1)	−0.0391 (1)	0.0181 (2)
C(62)	0.4038 (1)	−0.3203 (1)	−0.1409 (1)	0.0162 (2)
N(72)	0.3594 (1)	−0.1886 (1)	−0.1241 (8)	0.0177 (2)
C(72)	0.3255 (1)	−0.2405 (1)	−0.0565 (9)	0.0156 (2)
C(82)	0.4771 (1)	−0.2720 (1)	−0.1439 (1)	0.0158 (2)
C(92)	0.5053 (1)	−0.3239 (2)	−0.2306 (1)	0.0208 (2)
C(102)	0.5738 (1)	−0.2821 (2)	−0.2306 (1)	0.0239 (2)
C(112)	0.6147 (1)	−0.1874 (2)	−0.1440 (1)	0.0208 (2)
C(122)	0.5870 (1)	−0.1348 (1)	−0.0571 (1)	0.0184 (2)
C(132)	0.5185 (1)	−0.1773 (1)	−0.0573 (1)	0.0161 (2)

Table 6. *Fractional coordinates and equivalent isotropic thermal parameters* (Å^2) *for the non-*H *atoms of TETRA*.HCl

$U_{eq} = U_{11} + U_{22} + U_{33} + U_{23}b^*c^*bc\cos\alpha + U_{13}a^*c^*ac\cos\beta + U_{12}a^*b^*ab\cos\gamma)/3$.

	x	y	z	U_{eq}
S(1)	0.8384 (1)	−0.1128 (1)	0.9441 (1)	0.042 (1)
C(2)	0.7263 (6)	−0.2940 (3)	0.9655 (2)	0.052 (2)
C(3)	0.5536 (5)	−0.2628 (3)	0.8861 (2)	0.046 (2)
N(4)	0.5486 (4)	−0.1028 (2)	0.8138 (1)	0.038 (1)
C(5)	0.4193 (5)	−0.0103 (3)	0.7200 (2)	0.042 (2)
C(6)	0.4794 (5)	0.1586 (3)	0.6958 (2)	0.038 (2)
N(7)	0.6637 (4)	0.1261 (2)	0.7659 (1)	0.042 (1)
C(7)	0.6784 (5)	−0.0180 (3)	0.8342 (2)	0.036 (2)
C(8)	0.5580 (4)	0.2293 (2)	0.5671 (2)	0.034 (1)
C(9)	0.3861 (5)	0.3260 (3)	0.5040 (2)	0.042 (2)
C(10)	0.4502 (6)	0.3950 (3)	0.3867 (2)	0.051 (2)
C(11)	0.6832 (6)	0.3702 (3)	0.3327 (2)	0.056 (2)
C(12)	0.8550 (6)	0.2749 (4)	0.3930 (2)	0.058 (3)
C(13)	0.7935 (5)	0.2020 (3)	0.5114 (2)	0.047 (2)
Cl	0.8976 (1)	0.3402 (1)	0.8417 (1)	0.0403 (6)

Table 7. *Bond lengths* (Å) *with e.s.d.'s in parentheses*

	LEVA	TETRA	TETRA2 (*A*)	TETRA2 (*B*)	TETRA.-HCl	LEVA.-HCl
S(1)—C(2)	1.829 (2)	1.831 (1)	1.830 (2)	1.834 (2)	1.828 (5)	1.838 (8)
S(1)—C(7)	1.748 (2)	1.745 (1)	1.753 (1)	1.752 (1)	1.720 (4)	1.722 (8)
C(2)—C(3)	1.519 (3)	1.516 (2)	1.529 (2)	1.524 (2)	1.497 (6)	1.502 (11)
C(3)—N(4)	1.449 (3)	1.457 (2)	1.464 (1)	1.460 (1)	1.442 (4)	1.448 (8)
N(4)—C(5)	1.460 (3)	1.456 (2)	1.472 (1)	1.467 (1)	1.459 (5)	1.461 (9)
N(4)—C(7)	1.386 (3)	1.388 (2)	1.388 (1)	1.390 (1)	1.314 (5)	1.303 (9)
C(5)—C(6)	1.541 (3)	1.544 (2)	1.547 (1)	1.545 (1)	1.559 (5)	1.552 (9)
C(6)—N(7)	1.490 (3)	1.496 (2)	1.498 (1)	1.502 (1)	1.470 (5)	1.486 (8)
C(6)—C(8)	1.509 (3)	1.505 (2)	1.512 (1)	1.510 (1)	1.511 (4)	1.521 (7)
C(7)—N(7)	1.275 (3)	1.281 (2)	1.278 (1)	1.277 (1)	1.308 (4)	1.327 (9)
C(8)—C(9)	1.381 (3)	1.381 (2)	1.390 (2)	1.394 (1)	1.382 (5)	1.398 (9)
C(8)—C(13)	1.386 (3)	1.391 (2)	1.396 (1)	1.394 (1)	1.374 (6)	1.384 (10)
C(9)—C(10)	1.382 (3)	1.389 (2)	1.398 (1)	1.394 (1)	1.380 (4)	1.405 (9)
C(10)—C(11)	1.358 (4)	1.373 (2)	1.388 (2)	1.390 (2)	1.355 (7)	1.361 (11)
C(11)—C(12)	1.373 (3)	1.388 (2)	1.390 (2)	1.393 (2)	1.360 (7)	1.364 (12)
C(12)—C(13)	1.372 (3)	1.393 (2)	1.393 (1)	1.394 (1)	1.397 (5)	1.391 (11)

Table 8. *Bond angles* (°) *with e.s.d.'s in parentheses*

	LEVA	TETRA	TETRA2 (*A*)	TETRA2 (*B*)	TETRA.-HCl	LEVA.-HCl
C(2)—S(1)—C(7)	91.1 (2)	90.9 (1)	90.7 (1)	90.9 (1)	89.8 (3)	89.5 (6)
S(1)—C(2)—C(3)	105.9 (3)	106.2 (2)	105.4 (1)	105.4 (2)	109.7 (5)	109.4 (9)
C(2)—C(3)—N(4)	104.9 (3)	105.0 (2)	104.6 (2)	104.8 (2)	107.7 (6)	107.7 (10)
C(3)—N(4)—C(5)	123.5 (3)	122.8 (2)	122.8 (1)	122.5 (2)	132.1 (5)	131.0 (9)
C(3)—N(4)—C(7)	112.8 (3)	112.5 (2)	111.6 (1)	112.1 (1)	116.9 (5)	116.6 (10)
C(5)—N(4)—C(7)	103.8 (3)	103.9 (2)	103.5 (1)	103.5 (1)	111.0 (5)	110.6 (10)
N(4)—C(5)—C(6)	101.2 (3)	101.1 (2)	100.6 (1)	100.5 (1)	102.0 (5)	101.6 (9)
C(5)—C(6)—N(7)	104.6 (3)	104.2 (2)	104.6 (1)	104.2 (1)	102.5 (5)	102.1 (8)
C(5)—C(6)—C(8)	113.8 (3)	113.6 (2)	113.8 (1)	113.5 (1)	114.1 (5)	113.9 (9)
N(7)—C(6)—C(8)	112.9 (3)	113.2 (2)	111.7 (1)	112.2 (1)	113.7 (5)	113.8 (8)
C(6)—N(7)—C(7)	104.2 (3)	104.2 (2)	104.1 (1)	103.9 (1)	110.0 (5)	108.2 (9)
S(1)—C(7)—N(4)	111.5 (2)	112.0 (1)	112.4 (1)	112.0 (1)	115.7 (5)	116.3 (10)
S(1)—C(7)—N(7)	129.7 (3)	129.7 (2)	128.7 (1)	129.3 (1)	130.8 (5)	129.8 (10)
N(4)—C(7)—N(7)	118.7 (3)	118.3 (2)	118.8 (1)	118.6 (1)	113.5 (5)	113.9 (11)
C(6)—C(8)—C(9)	120.8 (3)	120.8 (2)	121.0 (2)	121.1 (2)	118.5 (5)	120.4 (9)
C(6)—C(8)—C(13)	121.1 (3)	120.9 (2)	119.9 (1)	120.0 (1)	122.3 (6)	120.0 (10)
C(9)—C(8)—C(13)	118.1 (3)	118.3 (2)	119.0 (2)	118.9 (2)	119.2 (6)	119.3 (10)
C(8)—C(9)—C(10)	120.6 (4)	121.1 (2)	120.5 (2)	120.6 (2)	120.5 (6)	119.0 (11)
C(9)—C(10)—C(11)	120.7 (4)	120.3 (3)	120.1 (2)	120.2 (2)	120.1 (7)	120.8 (12)
C(10)—C(11)—C(12)	119.3 (4)	119.6 (3)	119.7 (2)	119.6 (2)	120.3 (7)	120.2 (12)
C(11)—C(12)—C(13)	120.6 (4)	119.8 (2)	120.1 (2)	120.0 (2)	120.4 (7)	120.5 (13)
C(8)—C(13)—C(12)	120.7 (4)	120.9 (2)	120.5 (2)	120.8 (2)	119.5 (6)	120.2 (12)

taken from Cromer & Waber (1974), anomalous-dispersion effects were included in F_c (Ibers & Hamilton, 1964), and the values of $\Delta f'$ and $\Delta f''$ were those of Cromer (1974). All calculations were performed on a PDP 11/34 minicomputer, using *SDP* (Frenz, 1978) and local programs.

Table 9. *Torsion angles* (°) *with e.s.d.'s in parentheses*

	LEVA	TETRA	TETRA2 (*A*)	TETRA2 (*B*)	TETRA.HCl	LEVA.HCl
C(3)—N(4)—C(7)—S(1)	−24.5 (2)	−23.9 (1)	−23.5 (1)	−23.3 (1)	0.7 (4)	−6.9 (7)
N(4)—C(3)—C(2)—S(1)	−35.0 (2)	−34.9 (1)	−37.7 (1)	−37.2 (1)	4.0 (3)	−3.4 (6)
N(4)—C(7)—S(1)—C(2)	1.5 (2)	1.3 (1)	0.5 (1)	−0.5 (1)	1.5 (5)	3.8 (9)
C(6)—N(7)—C(7)—N(4)	−0.5 (2)	−0.7 (1)	−1.8 (1)	−0.3 (1)	7.4 (5)	7.6 (9)
N(7)—C(6)—C(5)—N(4)	25.8 (2)	27.0 (1)	26.8 (1)	28.6 (1)	8.9 (4)	18.2 (7)
N(7)—C(7)—N(4)—C(5)	18.0 (3)	19.0 (2)	20.0 (1)	19.7 (1)	−0.8 (5)	5.6 (9)
C(7)—S(1)—C(2)—C(3)	19.8 (2)	19.9 (1)	22.4 (1)	22.1 (1)	−3.2 (4)	0.1 (8)
C(7)—N(4)—C(3)—C(2)	38.9 (3)	38.3 (2)	39.8 (2)	39.5 (2)	−3.2 (6)	6.5 (11)
C(7)—N(4)—C(5)—C(6)	−25.4 (3)	−26.7 (2)	−26.9 (1)	−28.0 (1)	−5.5 (5)	−15.4 (9)
C(7)—N(7)—C(6)—C(5)	−16.3 (3)	−16.9 (2)	−16.3 (1)	−18.3 (1)	−10.1 (5)	−16.3 (9)
C(8)—C(6)—C(5)—N(4)	149.5 (3)	150.7 (2)	149.0 (2)	151.0 (2)	132.3 (6)	141.3 (10)
C(8)—C(6)—N(7)—C(7)	−140.6 (3)	−140.9 (2)	−139.9 (2)	−141.6 (2)	−133.7 (6)	−139.5 (11)
C(9)—C(8)—C(6)—N(7)	−136.5 (4)	−141.0 (2)	−137.2 (2)	−132.3 (2)	−152.8 (6)	158.3 (12)
C(13)—C(8)—C(6)—N(7)	44.5 (3)	40.4 (2)	43.6 (2)	49.4 (2)	26.7 (6)	−29.2 (10)

Results

The coordinates and U_{eq} values for the non-H atoms of LEVA, TETRA, TETRA2 and TETRA.HCl are listed in Tables 3–6. Bond lengths, bond angles and selected torsion angles for these four structures and for LEVA.HCl (Baker & Pauling, 1973) are given in Tables 7, 8 and 9, respectively. The crystal packings for the five structures are shown in Figs. 1–5.

The corresponding bond lengths of the bases [LEVA, TETRA, and TETRA2 molecules (*A*) and (*B*)] are the same within 0.02 Å (Table 7). Upon protonation the N(4)—C(7) bond length decreases by *ca* 0.08 Å, while the C(7)—N(7) bond length increases. Accordingly, the positive charge seems to be delocalized over the atoms N(7), C(7) and N(4) (Table 7).

Both for the bases and for the protonated forms, the S(1)—C(7) bond is significantly shorter than the S(1)—C(2) bond, in accordance with the sp^2 and sp^3 character of atoms C(7) and C(2), respectively.

Protonation causes an increase in the values of all bond angles, except those of C(7)—S(1)—C(2), C(5)—C(6)—N(7) and N(4)—C(7)—N(7) (Table 8). The oveall increase in the bond angles at N(4) reveals that in the protonated form N(4) has sp^2 character

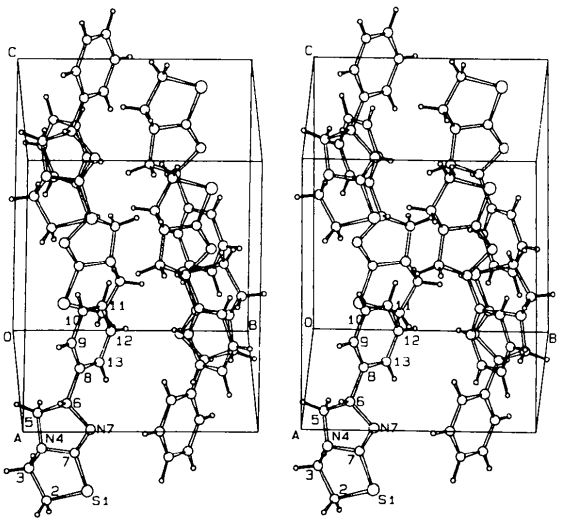


Fig. 2. Stereoscopic view of the molecular packing of TETRA, projected down the *a* axis.

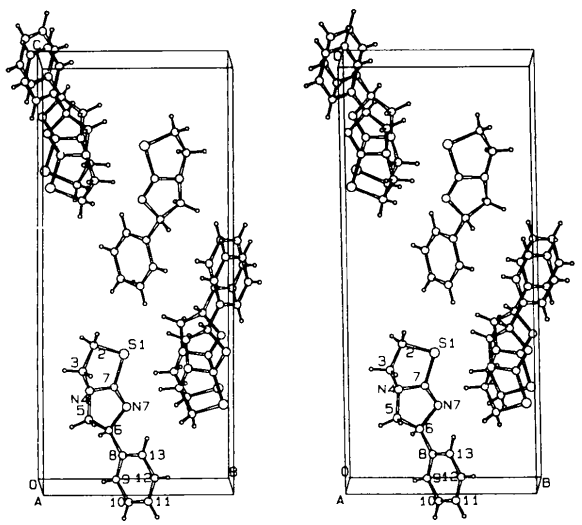


Fig. 1. Stereoscopic view of the molecular packing of LEVA, projected down the *a* axis.

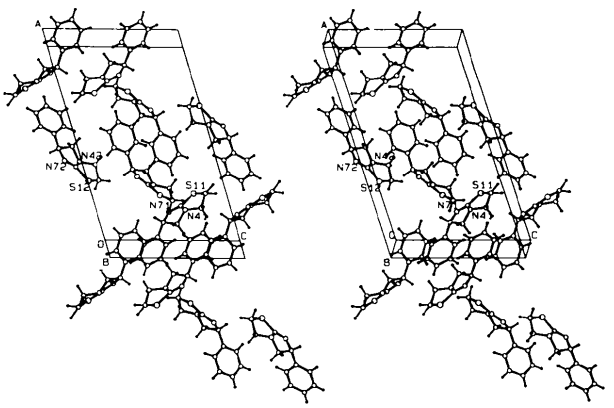


Fig. 3. Stereoscopic view of the molecular packing of TETRA2, projected down the *b* axis.

and the lone pair of N(4) is delocalized, causing a shortening of the N(4)—C(7) and S(1)—C(7) bonds and a lengthening of the C(7)—N(7) bond.

Upon protonation, there is an overall flattening of the double ring system. Accordingly, the absolute values of all endocyclic torsion angles, except those whose absolute values are already below 10° [at N(7)—C(7) and C(7)—S(1)] decrease (Table 9).* Protonation causes downfield shifts in the NMR signals of the protons attached to the atoms bearing partially positive charge (a table of relevant NMR data has been deposited).†

Stacking analysis

The intra- and intermolecular distances between the middle points of the N(4)—C(7) bond and the phenyl ring [C(8)···C(11)] were calculated. The N(4)C(7)···C(8)C(11) intermolecular distance is about 4.8 Å in all cases. In LEVA, the N(4)C(7)···N(4)C(7)(1 + x, y, z) and C(8)C(11)···C(8)C(11)(1 + x, y, z) distances are both 4.85 Å, corresponding to the length of the a axis. A common feature of TETRA and TETRA2 is that heterochiral N(4)C(7)···C(8)C(11) intermolecular distances are found within the 5 Å limit. In both TETRA.HCl and LEVA.HCl, the same type of N(4)C(7)···C(8)C(11) contact is present (heterochiral in the former and homochiral in the latter case), in addition to the fact that planarization of the double ring allows shorter contacts: in LEVA.HCl an N(4)C(7)···C(8)C(11) type (3.928 Å), and in TETRA.HCl an N(4)C(7)···N(4)C(7) type (4.425 Å). A short N(4)C(7)···N(4)C(7) distance is found for TETRA.HCl, while in LEVA.HCl N(4)C(7)···C(8)C(11) is 3.928 Å. (Distances less than 5 Å are given in Table 10.)

* The conformational similarities are well represented in Fig. 3 of our preliminary communication (Ács, Fogassy, Faigl, Tomor, Simon, Marso, Fülöp, Brienne & Jacques, 1988) where the individual asymmetric units are projected onto the plane of the imidazothiazole ring system.

† Lists of structure factors, anisotropic thermal parameters, NMR data and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54446 (64 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Discussion

Stacking differences between the corresponding pairs

Stacking analysis of corresponding pairs (LEVA and TETRA; LEVA.HCl and TETRA.HCl; TETRA and TETRA.HCl; TETRA and TETRA2) revealed that stacking is established between the phenyl and imidazothiazole rings, except for the optically active

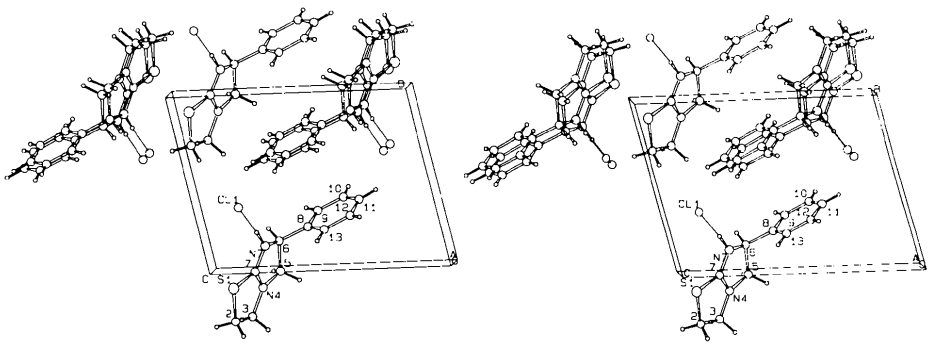


Fig. 4. Stereoscopic view of the molecular packing of TETRA.HCl, projected down the a axis.

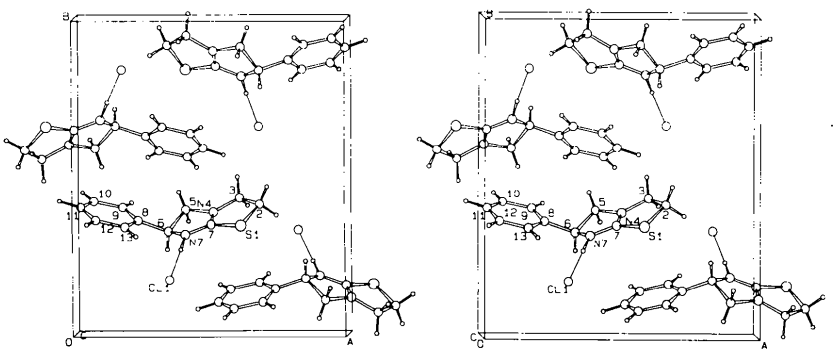


Fig. 5. Stereoscopic view of the molecular packing of LEVA.HCl, projected down the a axis.

Table 10. *Intra- and intermolecular distances* (Å) *less than* 5 Å *between the middle points of the* N(4)—C(7) *bonds and the* C(8)–C(11) *phenyl groups*

LEVA		
N(4)C(7)···C(8)C(11)	(x, y, z)	4.795
N(4)C(7)···N(4)C(7)	$(1+x, y, z)$	4.851
C(8)C(11)···C(8)C(11)	$(1+x, y, z)$	4.851
TETRA		
N(4)C(7)···C(8)C(11)	(x, y, z)	4.806
N(4)C(7)···C(8)C(11)	$(\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z)$	4.821
TETRA2		
N(41)C(71)···C(81)C(111)	(x, y, z)	4.808
N(42)C(72)···C(82)C(112)	(x, y, z)	4.808
N(41)C(71)···C(81)C(111)	$(-x, 1-y, 1-z)$	4.930
N(42)C(72)···C(82)C(112)	$(1-x, 1-y, -z)$	4.862
TETRA.HCl		
N(4)C(7)···C(8)C(11)	(x, y, z)	4.762
N(4)C(7)···C(8)C(11)	$(1-x, 1-y, 1-z)$	4.990
N(4)C(7)···N(4)C(7)	$(1-x, -y, 2-z)$	4.425
LEVA.HCl		
N(4)C(7)···C(8)C(11)	(x, y, z)	4.869
N(4)C(7)···C(8)C(11)	$(\frac{1}{2}-x, 1-y, \frac{1}{2}+z)$	4.958
N(4)C(7)···C(8)C(11)	$(\frac{1}{2}+x, \frac{1}{2}-y, 1-z)$	3.928

Table 11. *Hydrogen bonds and close contacts* (Å) *shorter than the sum of van der Waals radii* (C 1.8, H 1.2, Cl 1.8, N 1.55, O 1.5, S 1.8 Å)

LEVA		
C(9)···C(12)	$(-1+x, y, z)$	3.45
H(10)···S(1)	$(\frac{1}{2}-x, 1-y, -\frac{1}{2}+z)$	2.93
C(9)···H(9)	$(\frac{1}{2}+x, \frac{1}{2}-y, -z)$	2.95
H(2*B*)···N(7)	$(-x, -\frac{1}{2}+y, \frac{1}{2}-z)$	2.70
C(2)···H(13)	$(1-x, -\frac{1}{2}+y, \frac{1}{2}-z)$	2.85
TETRA.HCl		
Cl···N(7)	(x, y, z)	3.05
Cl···H(N7)	(x, y, z)	2.04
Cl···S(1)	$(2-x, 2-y, 2-z)$	3.26
Cl···C(2)	$(2-x, -y, 2-z)$	3.49
Cl···H(6)	$(1+x, y, z)$	2.69
C(8)···C(10)	$(1-x, 1-y, 1-z)$	3.48
LEVA.HCl		
Cl···N(7)	(x, y, z)	3.09
Cl···H(N7)	(x, y, z)	1.89
Cl···S(1)	$(-\frac{1}{2}+x, \frac{1}{2}-y, 2-z)$	3.30
Cl···C(2)	$(-\frac{1}{2}+x, \frac{1}{2}-y, 2-z)$	3.45
Cl···H(3*A*)	$(1-x, -\frac{1}{2}+y, \frac{3}{2}-z)$	2.69
Cl···H(6)	$(x, y, 1+z)$	2.72
Cl···H(9)	(x, y, z)	2.80
C(12)···H(5*B*)	$(\frac{1}{2}-x, 1-y, \frac{1}{2}+z)$	2.92
TETRA		
N(7)···H(2*A*)	$(x+\frac{1}{2}, \frac{1}{2}-y, z+\frac{1}{2})$	2.64
C(2)···C(2)	$(1-x, -y, 1-z)$	3.42
C(5)···H(5*A*)	$(1-x, -y, -z)$	2.94
TETRA2		
C(32)···H(21*A*)	$(x, y-1, z-1)$	2.81
N(42)···H(21*A*)	$(x, y-1, z-1)$	2.40
C(52)···H(21*A*)	$(x, y-1, z-1)$	2.79
H(32*B*)···H(21*A*)	$(x, y-1, z-1)$	2.33
H(52*B*)···H(21*A*)	$(x, y-1, z-1)$	2.35
H(111)···S(12)	$(-x, -y, -z)$	2.97
H(121)···N(71)	$(-x, -y, 1-z)$	2.70
H(32*B*)···C(102)	$(1-x, -1-y, -z)$	2.93
H(32*B*)···C(112)	$(1-x, -1-y, -z)$	2.95
H(122)···N(72)	$(1-x, -y, -z)$	2.65
H(132)···C(132)	$(1-x, -y, -z)$	2.90
N(72)···H(32*A*)	$(x, -\frac{1}{2}-y, -\frac{1}{2}+z)$	2.74
N(71)···H(21*B*)	$(x, \frac{1}{2}-y, -\frac{1}{2}+z)$	2.65
C(121)···H(91)	$(-x, -\frac{1}{2}+y, \frac{1}{2}-z)$	2.84
H(92)···C(122)	$(1-x, -\frac{1}{2}+y, -\frac{1}{2}-z)$	2.83
N(42)···C(21)	$(x, -1+y, -1+z)$	3.28
C(102)···C(32)	$(1-x, -1-y, -z)$	3.47

base (LEVA), in which chain-like structure is formed by the phenyl–phenyl and the imidazothiazole–imidazo–thiazole stacking, along the *a* axis.

Packing differences for the base structures

The *homochemical* (phenyl–phenyl and imidazothiazole–imidazo–thiazole) van der Waals interactions between the parallel molecular fragments of LEVA result in a less-stable structure than the *heterochemical* connections between the parallel phenyl and imidazothiazole rings in TETRA and TETRA2. The van der Waals interactions holding the molecule together do not differ significantly (Table 11). The great number of short contacts in TETRA2 is partly due to the low-temperature measurement conditions.

Packing of the salt structures

The salts are packed through Coulombic interactions and, although the relative interaction possibilities are preserved, the individual contacts differ significantly. The molecules of the racemic salt (TETRA.HCl) are linked through apparently charged interactions.

Comparison of corresponding structures

The interactions between unlike molecular fragments in the racemic bases lead to more stable crystal structures (higher densities, higher heats of fusion, higher melting points; Table 1). The mirror-image isomers in both cases form molecular compounds, with a higher stability than the corresponding optically active forms (Table 1) (Jacques, Collet & Wilen, 1981), although because of the higher conglomerate-forming frequency among the salts (Jacques, Leclercq & Brienne, 1981), it could be expected that TETRA.HCl would form a mechanical mixture of the optically active compounds. In fact, instead of conglomerate formation, a very stable racemate is produced. As experienced for other tertiary amines [*cf. N,N*-disubstituted β-phenylisopropylamine hydrochloride (Simon, Podányi, Ecsery & Tóth, 1986)] the only H atom attached to the quaternary N atom cannot establish an extended hydrogen-bonding network leading to the formation of a conglomerate.

The authors thank Professor E. Fogassy (Technical University of Budapest) for fruitful discussions.

Note added in proof: The Technical Editor revealed during a routine check for structure duplication that the crystal structure of TETRA had already been published (Spek, 1972). Our e.s.d.'s for the TETRA structure are, however, about three times smaller than those in the above publication.

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1-(2,3-Dideoxy-*erythro*-β-D-hexopyranosyl)cytosine: an Example of the Conformational and Stacking Properties of Pyranosyl Pyrimidine Nucleosides. A Crystallographic and Computational Approach*

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Abstract

$C_{10}H_{15}N_3O_4$, $M_r = 241.25$, orthorhombic, $P2_12_12_1$, $a = 7.4013$ (4), $b = 8.7563$ (5), $c = 17.392$ (1) Å, $V = 1127.1$ (1) Å^3, $Z = 4$, $D_m = 1.42$, $D_x = 1.422$ Mg m^{-3}, Ni-filtered Cu $K\alpha$ radiation, $\lambda = 1.54178$ Å, $\mu = 0.895$ mm^{-1}, $F(000) = 512$, $T = 293$ K, final $R = 0.044$ for 1024 unique observed [$F \geq 6\sigma(F)$] reflections. The conformational parameters are in accordance with the IUPAC–IUB Joint Commission on Biochemical Nomenclature [*Pure Appl. Chem.* (1983), **55**, 1273–1280] guidelines. In order to assess the possible use of pyranosyl-modified pyrimidine nucieosides in the design of new synthetic oligonucleotides, the conformational and packing proper-

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