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CRYSTAL STRUCTURES OF A PAIR OF BENZOTHIAZEPINES†

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N-Formyl-2,3,4,5-tetrahydro-2,4-diphenyl-1,5-benzothiazepine(FDPBT), $C_{22}H_{19}$ N O S, F.W = 345.44, monoclinic, $P2_1/c$, $a = 11.2268(1)$ Å, $b = 9.0297(1)$ Å, $c = 18.3813(1)$ Å, $\beta = 104.77(1)^\circ$, $V = 1801.8(3)$ Å^3, $Z = 4$, $D_{calc} = 1.273$ Mg/m^3, $\mu = 1.651$ mm^{-1}, $F_{000} = 728$, CuK$\alpha = 1.5418$ Å, final R1 and wR2 are 0.0757 and 0.1752, respectively. N-Chloroacetyl-2,3,4,5-tetrahydro-2,2,4-trimethyl-1,5-benzothiazepine(CTMBT), $C_{14}H_{17}Cl$ N O S, F.W = 282.80, monoclinic, P21/c, $a = 12.9740(1)$ Å, $b = 13.3530(1)$ Å, $c = 17.0790(1)$ Å, $\beta = 91.12(1)^\circ$, $V = 2958.2(4)$ Å^3, $Z = 8$, $D_{calc} = 1.270$ Mg/m^3, $\mu = 3.504$ mm^{-1}, $F_{000} = 1192$, CuK$\alpha = 1.5418$ Å, final R1 and wR2 are 0.0610 and 0.1609, respectively. The septilateral ring of the benzothiazepine in the two structures adheres to an identical boat conformation. The prow and stern angles are nearly the same for both the medium-sized rings.

Keywords: crystal structure; conformation; hydrogen bonding; FDPBT; CTMBT

INTRODUCTION

Geometrical ramifications of azepine compounds are embarked upon for a few decades. Among these, the benzoderivatives of azepines, like benzothiazepines, constitute a class of compounds with specific applications. The crucial role of L-type Ca^{2+} channels in the initiation of cardiac and smooth muscle contraction has made them major therapeutic targets for the treatment of cardiovascular diseases. These L-type channels share a

†The CDB Reference Numbers: FDPBT-CCDC 197372; CTMBT-CCDC 197373.

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common pharmacological profile, including high affinity voltage and frequency-dependent block by the phenylalkylamines, the benzothiazepines, and dihydropyridines. These drugs are thought to bind to three separate receptor sites on L-type Ca^{2+} channels that are allosterically linked. Though limited in applications, the benzothiazepines are important among the list of Ca^{2+} antagonists [1–3].

The analysis of seven-membered rings show close resemblance to the six-membered rings in view of flexibility in conformation [4]. The cycloheptanes are distinct, as they have two pairs of conformers, each comprising two interconvertible forms. The chair and the twist-chair forms, as well as the boat and the twist-boat forms, constitute the flexible forms of the heptagonal ring. The interconversion is accomplished by means of pseudorotation [5,6]. The energies of the conformations are not fixed values but rather functions of the pseudorotational coordinates. The chair form was predicted to be more stable than the boat, and the particular arrangement of chair, the twist-chair, was considerably preferred over the alternatives [4].

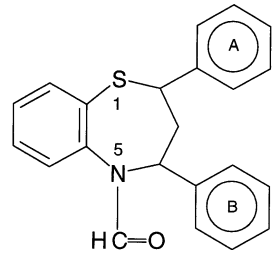
The structural studies of benzothiazepines are limited owing to the difficulty encountered in the cyclization of these seven-membered heterocycles. In general, cyclization of linear precursors is in principle an excellent route to heterocycles. However, for cycloheptane rings, this reaction is disfavored by entropic and enthalpic factors besides transannular interactions [7,8]. Hence, these heterocycles are usually obtained in good yield only when configurational and/or conformational constraints facilitate intramolecular cyclization.

All these facts kindle interest in the study of the structural and conformational features of a set of benzothiazepines, namely N-Formyl-2, 3,4,5-tetrahydro-2,4-diphenyl-1,5-benzothiazepine(FDPBT) and N-Chloroacetyl-2,3,4,5-tetrahydro-2,2,4-trimethyl-1,5-benzothiazepine(CTMBT). The chemical diagrams of FDPBT and CTMBT are shown in Figure 1.

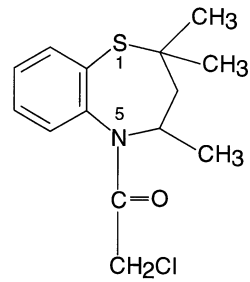
X-RAY DATA COLLECTION, STRUCTURE SOLUTION, AND REFINEMENT

Data Collection

Colorless crystals of FDPBT and CTMBT were chosen for the single crystal X-ray data collection. The Enraf-Nonius CAD4 diffractometer [9] with graphite monochromated CuKα radiation employing $\omega - 2\theta$ scan mode was used for data collection. Initially, the accurate unit cell parameters were determined from the least-squares refinement of 25 reflections in the range $14 < 2\theta < 25°$. In order to check the intensity deterioration due to radiation damage or crystal degradation, three



FDPBT



CTMBT

FIGURE 1 Structura formulae of FDPBT and CTMBT.

standard reflections were monitored every 1 h or every hundred reflections, whichever is earlier. The intensity data were corrected for Lorentz, polarization, and absorption effects [10].

Structure Solution and Refinement

Both the structures were solved by direct methods using SHELXS97 [11] program. Successive least-squares full-matrix refinement of the structures were done using SHELXL97 [12]. Extinction correction was necessitated for the crystal structure FDPBT during the course of refinement. All the hydrogen atoms of the thiazepine pair FDPBT and CTMBT were appropriately affixed by the riding model at the final stages of refinement. The final parameters which determine convergence implying the best fit—including $R1 = 0.0757$ and 0.0610, $wR2 = 0.1752$ and 0.1609—with goodness-of-fit 1.072 and 1.053, respectively for the sturctures FDPBT and CTMBT. The geometrical parameters were computed using the program PARST [13].

RESULTS AND DISCUSSION

The crystal and refinement data are given in Table 1. The perspective view of the molecules using ORTEPIII [14] are shown in Figures 2 (FDPBT), 3 (Molecule A of CTMBT), and 4 (Molecule B of CTMBT). The interatomic distances spanned by bonds in the two benzothiazepines are in good agreement with each other. The two structural entities in CTMBT duplicate

TABLE 1 Crystal Data for FDPBT and CTMBT

Parameters	FDPBT	CTMBT
Empirical formula	$C_{22}H_{19}N$ O S	$C_{14}H_{17}$ Cl N O S
Formula weight	345.44	282.80
Temperature (K)	293(2)	293(2)
Wavelength (Å)	1.54178	1.54178
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
Unit cell dimensions		
a (Å)	11.2268(1)	12.9740(1)
b (Å)	9.0297(1)	13.3530(1)
C (Å)	18.3813(1)	17.0790(1)
β (°)	104.77(1)	91.12(1)
Volume (Å^3)	1801.8(3)	2958.2(4)
Z	4	8
Calculated density (Mg/m^3)	1.273	1.270
Absorption coefficient (mm^{-1})	1.651	3.504
F (000)	728	1192
Crystal size (mm)	$0.40 \times 0.32 \times 0.18$	$0.35 \times 0.30 \times 0.22$
Theta range (°)	4.07 to 71.92	3.41 to 71.97
Index ranges	$0 \leq h \leq 13$	$0 \leq h \leq 15$
	$0 \geq k \geq 10$	$0 \leq k \leq 16$
	$-22 \leq 1 \leq 21$	$-21 \leq 1 \leq 21$
Reflections collected/unique	3716/3377	6041/5786
	[R(int)=0.0154]	[R(int)=0.0162]
Completeness	89.5%	95.4%
Refinement method	Full matrix least squares on F^2	Full matrix least squares on F^2
Data/restraints/parametes	3377/0/227	5786/0/325
Observed reflections [$I > 2\sigma(I)$]	2837	3978
Goodness-of-fit on F^2	1.072	1.053
Final R indices [$I > 2\ \sigma(1)$]	R1=0.0757,	R1=0.0610,
	wR2=0.1752,	wR2=0.1609
R indices (all data)	R1=0.0855,	R1=0.0960
	wR2=0.1926	wR2=0.1819
Extinction coefficient	0.077(5)	–
Largest diff. peak and hole (e Å^{-3})	0.459 and −0.482	0.818 and −0.450

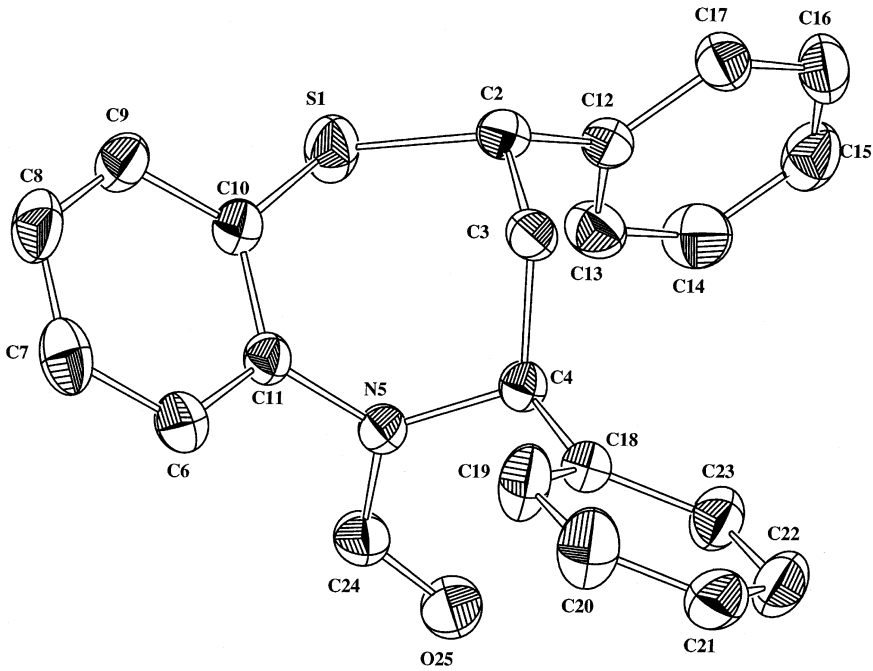


FIGURE 2 ZORTEP diagram of FDPBT.

each other in relation to atomic intimacies, as seen from the bond distances and bond angles.

Replacement of a carbon with a sulphur atom has influence upon the geometry of the ring atoms adjacent to the hetero atom. Non-negligible cyclic distortions are eventually expected in comparison with their carbocyclic analogues [5]. The presence of sulphur atom in benzothiazepine also brings into effect the delocalization of π-electrons over the C-S-C composite, upon fusion with the benzene ring [15] (Fig. 5). Here, the bond lengths (S1-C2), (S1-C10)—being respectively 1.836(2) Å, 1.762(2) Å in FDPBT, and 1.875(4) Å, 1.757(3) Å and 1.840(3) Å, 1.762(3) Å in molecules A and B of CTMBT—exemplify such alterations in their septagonal ring geometries.

The delocalization of hetero π-electrons over N-C=O moiety is a common feature in both the structures. This is clearly seen from the nearly tantamount bond distances (N5-C24 =) 1.353(3) Å in FDPBT, and (N5-C15 =) 1.352(4) Å, 1.350(5) Å in molecules A and B of CTMBT. The sum of bond angles around the hetero nitrogen in the two structures, nearly equal to 359.98° (FDPBT), 360°, and 360.1° (in molecules A and B of CTMBT), signify the flattening of their respective thiazepine moieties.

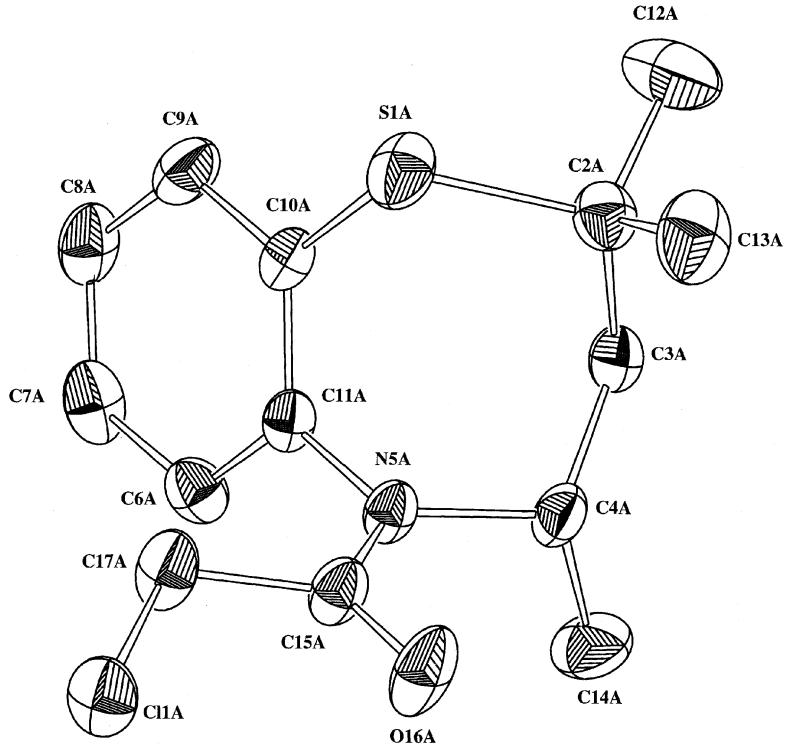


FIGURE 3 ZORTEP diagram of molecule A of CTMBT.

The widening of the angles N5A-C15A-C17A (115.1(2)°) in molecule A and N5B-C15B-C17B (117.7(3)°) in molecule B of CTMBT entails steric repulsion between their chloroacetyl components and benzene rings.

The benzene rings are planar (maximum deviation ±0.010(3) Å for C9 atom in FDPBT—and ±0.018(3) Å for C6A and ±0.009(4) Å for C6B in CTMBT). The dihedral angles between the benzene and thiazepine rings are 53.27(8)° for FDPBT, and 58.84(10)° and 55.58(11)° for molecules A and B in CTMBT, respectively.

The phenyl rings, substituted at 2nd and 4th positions of the seven-membered ring in FDPBT, are planar. The angular separation between these phenyl rings A and B is estimated to be 73.06(8)°. The phenyl ring at C2 is equatorial (C10-S1-C2-C12 = 149.53(1)°), while at C4 it is axial (C11-N5-C4-C18 = 98.1(2)°). Sulphur heterocycles are akin to oxygen heterocycles in producing strong dipolar effects with respect to polar substituents, particularly on the adjacent carbon atoms. It enforces the substituents into an axial conformation (anomeric effect), thereby affecting the conformation of the entire molecule [16]. This does not come into

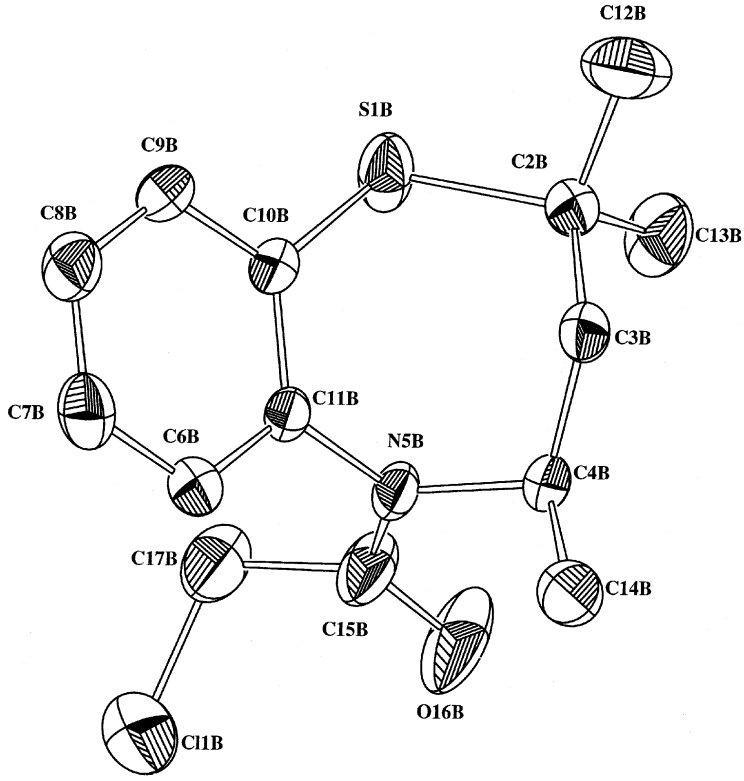
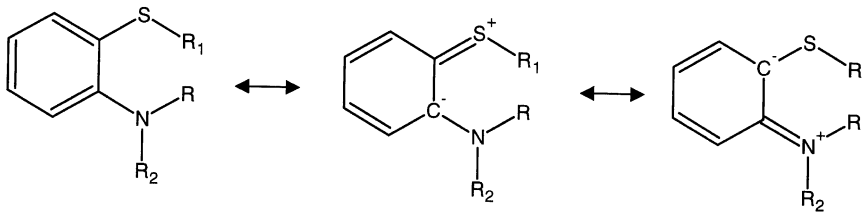


FIGURE 4 ZORTEP diagram of Molecule B of CTMBT.

effect in FDPBT as has the nonpolar aromatic (phenyl) subtituent adjoining the carbon atom C2, next to S1.

In CTMBT, it is seen that one of the methyl groups at C2A in molecule A, namely C12A (C10A-S1A-C2A-C12A = 97.1(3)°), and C2B in molecule B, namely C12B (C10B-S1B-C2B-C12B = −105.5(3)°), are each axial. The torsion angles of other methyl substituents C13A (C10A-S1A-C2A-C13A = −146.0(3)°) at C2A in molecule A and C13B (C10B-S1B-C2B-C13B = 138.1(3)°) at C2B in molecule B prove their equatorial orientations in the respective molecules of CTMBT. The methyl group C14A at C4A in molecule A is in axial orientation (C11A-N5A-C4A-C14A = 94.9(4)°). Similar axial orientation of the methyl substitutent C14B at the corresponding position C4B in molecule B is evidenced from the torsion angle value of (C11B-N5B-C4B-C14B =)82.8(4)°.

The formyl group at N5 in FDPBT is *synclinal* with respect to the thiazepine moiety as witnessed from the angular separation (58.08(9)°)



$R = R_1 = C$

R_2 = formyl; chloroacetyl

FIGURE 5 Resonance effect over the C-S-C composite on fusion with the benzene ring.

between their normals. A dihedral angle of 1.75(2)° indicates approximately a coplanar setting of the formyl unit in relation to the C11-N5-C4 fragments. The formyl composite is *syn* to C4[C4-N5-C24-O25 = 2.0(4)°] and *anti* to C11 [C11-N5-C24-O25 = −179.3(2)°] in FDPBT.

The chloroacetyl functional group, operating as a barrier to the atomic inversion of introgen in CTMBT, is anchored to the seven-membered heterocycle at equivalent *synclinal* orientations (because the dihedral angles between them amount to 64.30(9)° in molecule A and 64.43(10)° in molecule B). The dihedral angles 2.38(26)° and 1.72(24)° (in molecules A and B) between the acetyl group and the C4-N5-C11 atomic set connote their confinement in the same plane. In molecule A, the acetyl substituent is *syn* to C4A (C4A-N5A-C15A-O16A = −3.2(5)°) and *anti* to C11A (C11A-N5A-C15A-O16A = 179.4(3)°). Likewise, the acetyl component in molecule B is *syn* with respect to C4B (C4B-N5B-C15B-O16B = 5.8(8)°) and *anti* in relation to C11B (C11B-N5B-C15B-O16B = −175.8(5)°).

The sulphur-containing thiazepine rings in FDPBT and CTMBT tend to have boat conformations. The ring asymmetry parameters from out-of-plane atomic displacements show the mirror symmetries ΔCs = (0.051(1), through C3 in FDPBT; 0.035(1), through C3A in molecule A of CTMBT; and 0.043(1), through C3B in molecule B of CTMBT), which all characterize the boat conformations as expected from endocyclic torsion angles [17].

The prow and stern angles are nearly the same for the different septagonal rings in 1,5-benzothiazepine structures. The relative prow and stern angles for the boat conformer in all the structures are listed below:

1. The prow angle (the angle between the planes through (S1, C2, C4, N5) and (C4, C3, C2)) 56.49(15)° and the stern angle (the angle between

the planes through (S1, C2, C5, N5) and (S1, N5, C10, C11)) 57.89(8)° describe the boat conformer in FDPBT.

2. The prow angles (the angle between the planes through (S1, C2, C4, N5) and (C4, C3, C2)) 54.45(26)° and 55.98(23)° and the stern angles (the angle between the planes through (S1, C2, C4, N5) and (S1, N5, C10, C11)) 61.25(12)° and 57.80(12)° for the molecules A and B, respectively describe the boat form of the thiazepine rings in CTMBT.

The similarity in crystallization of the benzothiazepines FDPBT and CTMBT in close-packing space groups $P2_1/c$ [18] does not lead to identical packing motifs (Figs. 6 and 7). The packing of molecules in FDPBT consists of evently spaced steps of bimolecular strips. Weak C-H···O

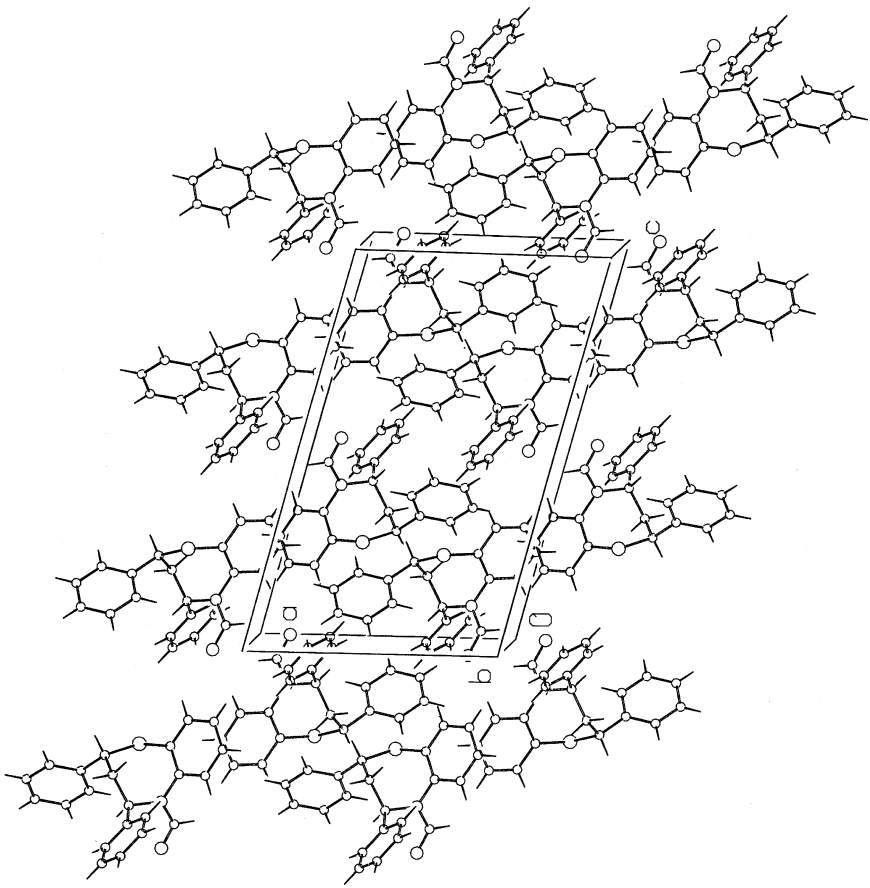


FIGURE 6 Packing diagram of molecules in FDPBT.

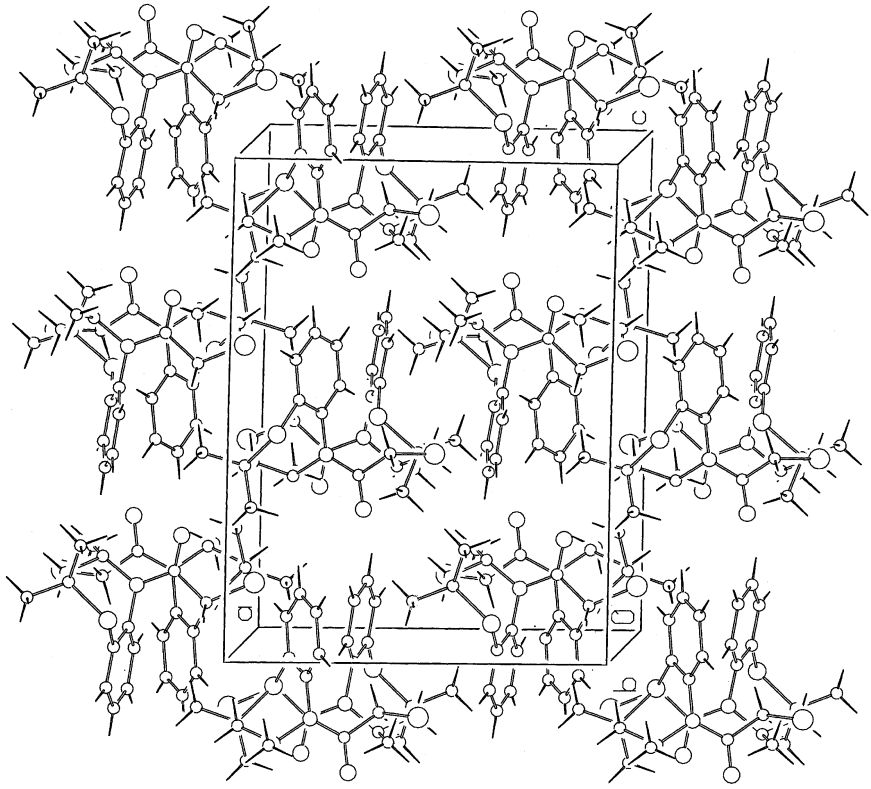


FIGURE 7 Packing diagram of molecules in CTMBT.

intermolecular interactions (C15 $\cdots$ O25($-$x + 1,$-$y + 2, $-$z) = 3.392(4) Å C15-H15 $\cdots$ O25 = 157.49(19)°) participate in stabilization of FDPBT structure. In CTMBT, the structure consists of molecules packed with no contacts shorter than the sum of the van der Waals radii.

Preparation of FDPBT and CTMBT

The acylation of respective N-free analogues of benzothiazepines with

1. Chloroacetyl chloride in dry benzene solvent in the presence of the catalyst triethylamine yielded FDPBT.
2. Acetic-formic anhydride in dry benzene medium at room temperature offered CTMBT.

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