of orally administered digoxin may be due to variation in gastric pH, which would modify the composition of digoxin species available for absorption (12). The catalytic effect of montmorillonite will accentuate this problem. Therefore, the concomitant administration of drug products containing digoxin and montmorillonite should be avoided.

A similar catalytic effect may also occur with other neutral drugs that degrade by acid hydrolysis and should be considered in the formulation of clay-containing drug products or their coadministration with other drugs.

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NOTES

Crystal Structure of 1:1 Complex of Barbital with 1-Methylimidazole

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Abstract □ The prediction of a strong hydrogen-bonding interaction between barbital and 1-methylimidazole was confirmed. Two crystal complexes were obtained, 1:1 and 2:1, and the X-ray structure was determined for the 1:1 complex, which is monoclinic, space group $P2_1/c$, with a = 12.236(3) Å, b = 11.332(4) Å, c = 12.495(4) Å, and β = 120.67(1)°. The structure contains disk-shaped hydrogen-bonded tetramers with two molecules of each kind. There is a short NH···N hydrogen bond (2.82 Å) in which barbiturate provides the NH donor.

Keyphrases □ Barbital—complex with 1-methylimidazole, crystal structure determined □ 1-Methylimidazole—complex with barbital, crystal structure determined □ Complexes—barbital with 1-methylimidazole, crystal structure determined □ Crystal structure—determined for complex of barbital with 1-methylimidazole

Barbiturate drugs behave as strong hydrogen-bonding donors through their two NH groups but are weak acceptors through their three carbonyl oxygen atoms. These conclusions were derived from the hydrogen-bonding arrangements and interatomic distances observed in the crystal structures of a series of complexes of barbital with other small molecules representative of biological systems (1, 2). Thus, barbiturate drug receptor sites are likely to involve strongly electronegative hydrogen-bonding acceptor groups, such as the nitrogen atoms of adenine (3, 4), the imidazole ring in histidine or histamine (2), or the phosphoryl oxygen atoms of phospholipids (5).

These studies indicated that a strong hydrogen-bonding interaction would occur between barbital (5,5-diethylbarbituric acid) and 1-methylimidazole (Fig. 1), which might lead to crystal complexation. Indeed, 1-methylimidazole was a powerful solvent for barbital. The high viscosity of this solution made direct crystallization impractical. However, two crystal complexes were obtained from an ethanol solution; in one complex (1:1), crystal structure determination confirmed a short hydrogen bond NH···N (2.82 Å) in which barbital is the donor and 1-methylimidazole is the acceptor.

EXPERIMENTAL

Crystals of the 1:1 and 2:1 complexes were obtained from the same ethanolic solution, which was saturated at 60° with respect to both barbital and 1-methylimidazole, and slowly cooled in a sealed vial. Space groups and approximate cell data for these complexes were determined from X-ray precession photographs[1].

Crystals of the 1:1 complex, which dissociate at 96°, are monoclinic, space group $P2_1/c$, with a = 12.236(3) Å, b = 11.332(4) Å, c = 12.495(4) Å, and β = 120.67(1)°. The crystal density (1.190 g/cm^3) determined by

[1] No further work is planned on the 2:1 complex of barbital and 1-methylimidazole. These crystals are monoclinic, space group $P2_1/c$, with a = 16.7 Å, b = 12.1 Å, c = 12.4 Å, and β = 102°. There are eight barbital and four 1-methylimidazole molecules per unit cell.

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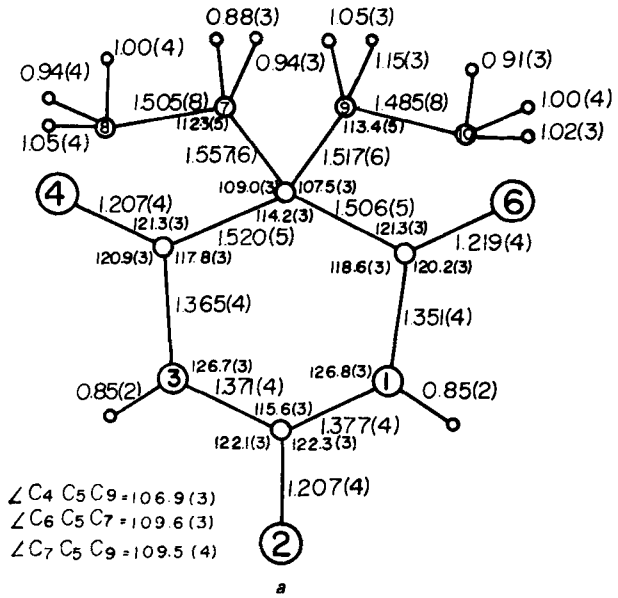

Figure 1 —*Bond lengths (angstroms) and angles (degrees) for barbital* (a) *and 1-methylimidazole* (b). *Estimated standard deviations are given in brackets. Circles of decreasing size represent oxygen, nitrogen, carbon, and hydrogen atoms, in that order.*

flotation in carbon tetrachloride–benzene agrees with the calculated density (1.187 g/cm^3), assuming that the unit cell contains four molecules of each kind.

The cell data and the X-ray intensities were measured at room temperature using a four-circle computer-controlled diffractometer[2] with graphite-monochromated MoKα-radiation (λ = 0.7093 Å). The crystal (0.32 × 0.22 × 0.20 mm) was mounted with the *c*-axis almost along the diffractometer Φ-axis. Integrated intensities for 2625 nonsymmetry related reflections were measured by *θ*/2*θ* scans. The variance in an integrated intensity was assumed to be $\sigma^2(I) = \sigma^2 + (0.02I)^2$, where σ^2 is the variance due to counting statistics. There were 1887 reflections with an intensity greater than $2\sigma(I)$. No corrections were made for X-ray absorption or extinction.

The phase problem was solved by direct methods, using symbolic addition and tangent refinement procedures (6). The nonhydrogen atomic parameters obtained from an E-map were refined initially by block-diagonal least-squares methods. Nine of the 18 hydrogen atoms were readily found in a difference Fourier map. The remainder, which consisted mostly of terminal methyl hydrogen atoms, were found near the end of a full matrix least-squares refinement.

The function minimized by least squares was $\Sigma w_H \Delta_H^2$, where $\Delta_H = |F_{obs}| - |F_{calc}|$ and $w_H = 1/\sigma^2(F_{obs})$. Atomic scattering factors were those of Cromer and Waber (7) for nonhydrogen and of Stewart *et al.* (8) for hydrogen. The data were suspected to be subject to X-ray extinction since reflections with strong intensities and large d-spacings gave calculated structure amplitudes systematically larger than the observed values. In the final refinement, seven such reflections were omitted. The final *R*-

[2] Enraf-Nonius CAD-4.

Table I—Atomic Positional Parameters for the 1-Methylimidazole–Barbital Complex [a]

	x	y	z
	Nonhydrogen Atoms[b]—Barbital		
N(1)	5936 (2)	4106 (2)	6423 (2)
C(2)	4719 (3)	4016 (2)	6211 (3)
O(2)	3818 (2)	4452 (2)	5313 (2)
N(3)	4602 (2)	3424 (2)	7104 (2)
C(4)	5557 (3)	2909 (3)	8153 (3)
O(4)	5346 (2)	2439 (2)	8896 (2)
C(5)	6881 (3)	2908 (3)	8328 (3)
C(6)	6995 (3)	3611 (3)	7367 (3)
O(6)	8013 (2)	3727 (2)	7421 (2)
C(7)	7843 (4)	3384 (6)	9651 (4)
C(8)	7617 (5)	4663 (6)	9802 (4)
C(9)	7199 (4)	1635 (5)	8222 (5)
C(10)	6312 (5)	1093 (4)	6997 (5)
	Nonhydrogen Atoms[b]—1-Methylimidazole		
NI(1)	1138 (2)	2571 (2)	7773 (2)
CI(1)	807 (4)	1866 (4)	8538 (4)
CI(2)	2204 (3)	2479 (3)	7728 (3)
NI(3)	2230 (2)	3217 (2)	6957 (2)
CI(4)	1116 (3)	3825 (3)	6476 (3)
CI(5)	443 (3)	3436 (3)	6974 (3)
	Hydrogen Atoms[c]—Barbital		
H(1)	595 (2)	453 (2)	587 (2)
H(3)	386 (2)	340 (2)	700 (2)
H(71)	870 (3)	335 (3)	984 (2)
H(72)	773 (3)	301 (2)	1020 (3)
H(81)	786 (3)	519 (3)	931 (3)
H(82)	827 (4)	491 (3)	1059 (4)
H(83)	675 (3)	481 (3)	977 (3)
H(91)	715 (3)	118 (3)	893 (3)
H(92)	819 (3)	158 (3)	834 (3)
H(101)	659 (3)	34 (3)	701 (3)
H(102)	609 (3)	145 (3)	618 (3)
H(103)	535 (3)	100 (3)	653 (3)
	Hydrogen Atoms[c]—1-Methylimidazole		
HI(11)	0 (3)	165 (3)	814 (3)
HI(12)	84 (3)	242 (3)	913 (3)
HI(13)	140 (3)	127 (3)	903 (3)
HI(2)	283 (2)	192 (2)	821 (2)
HI(4)	92 (2)	446 (2)	583 (2)
HI(5)	966 (2)	363 (2)	684 (2)

[a] Positional parameters are given as fractions of the lattice translations. Estimated standard deviations given in parentheses refer to the least-significant figures in parameter values. [b] Positional parameters × 10^4. [c] Positional parameters × 10^3.

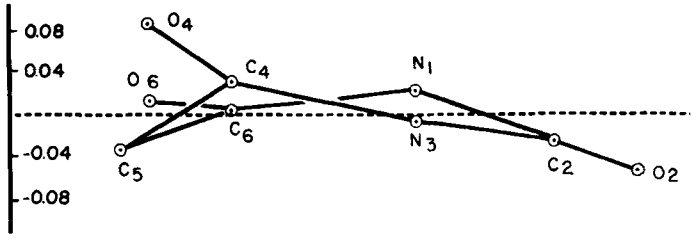

Figure 2—*Barbital ring. The dashed line is the trace of the best least-squares plane through the ring atoms. Atomic displacements from this plane (angstroms) are shown on a vertical scale eight times greater than the horizontal scale.*

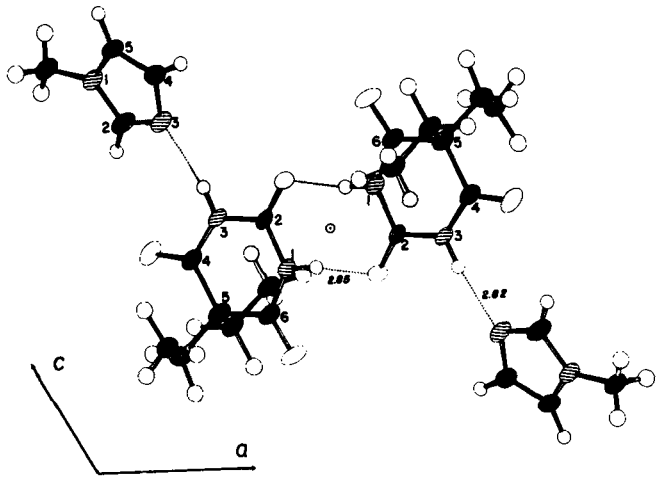

Figure 3—*Hydrogen-bonded tetramer. Thermal ellipsoids are shown that have 50% probability of enclosing each vibrating atom. Nitrogen atom ellipsoids are hatched, and carbon atom ellipsoids are cross-hatched. Hydrogen-bonded N···O and N···N distances (angstroms) are shown.*

factors were $R = \Sigma_H|\Delta_H|/\Sigma_H F_{obs} = 0.077$ and $R_w = [\Sigma_H(w\Delta_H)^2/\Sigma_H(wF_{obs})^2]^{1/2} = 0.034$. A list of observed and calculated structure factors and a table of anisotropic temperature factors for nonhydrogen atoms were compiled[3]. Final atomic positional parameters are given in Table I.

DISCUSSION

Bond lengths and angles (Fig. 1) agree with those in the barbital–imidazole complex (2) within the limits of experimental error. The barbital ring atoms are in an almost coplanar conformation (Fig. 2) similar to that observed in a number of other barbiturate crystal structures (Fig. 3 in Ref. 9). The ethyl group carbon atoms and the ring atom C(5) in barbital are almost coplanar, with atom C(2) having the largest displacement (0.065 Å) from the least-squares plane. This coplanar group and the ring plane make a dihedral angle of 91.7°. In 1-methylimidazole, the imidazole ring atoms and the 1-methyl carbon atom are coplanar.

The most interesting feature in the structure is the formation of hydrogen-bonded tetramers consisting of two molecules of each kind (Fig. 3). Two barbital molecules related by a crystallographic center of symmetry form N(1)H···O(2) hydrogen bonds with N···O distance (2.85 Å). This distance is within the range (2.8–3.0 Å) observed for other hydrogen bonds between barbiturates (1). The other barbital N(3)H donor group forms a very short hydrogen bond (N···N, 2.82 Å) with the nitrogen acceptor atom of 1-methylimidazole (2). The NH···N angle is 172°. The barbiturate and imidazole rings of molecules that form a tetramer are at dihedral angles of 19.1°. The tetramers are thus disk shaped, with nonpolar groups forming most of the outer surface. There is an unusual CH···O interaction between tetramers (C···O distance, 3.31 Å; CH···O angle 154.1°) involving the 1-methylimidazole C(5)–H(5) group and barbiturate atom O(6). This interaction is not considered to be a hydrogen bond because the C···O distance is too long.

The hydrogen-bonding arrangement is quite different from that of the imidazole complex with barbital. In that complex, barbitals dimerize through NH···O hydrogen bonds involving O(6) rather than O(2). These dimers are cross-linked by hydrogen bonds formed at opposite sides of imidazole molecules to make infinite ribbons through the crystal structure. The important feature common to both crystal complexes is the short NH···N hydrogen bond (N···N distance, 2.78 Å in the imidazole complex) in which barbiturate is the donor.

Thus, the present crystal structure fits a pattern of behavior in which barbiturate NH groups form strong hydrogen bonds with acceptor groups in other molecules.

[3] Available on request from authors.

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