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SOLID-STATE CONFORMATIONS OF FOUR TRUXILLIC AND TRUXINIC DIAMIDES

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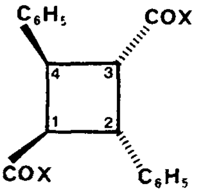
Abstract- Solid-state conformations were determined by crystal structural analyses in α- and ε-truxilloyldiamides and β- and δ-truxinoyldiamides (compounds 1-4) where each cyclobutyl carbon brings an independent substituent. While the cyclobutane ring of the virtual centrosymmetric 1 is slightly non-planar, with unusual bonds and angles values, that of all other three compounds is folded, with puckering angles up to 31°.

INTRODUCTION

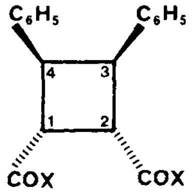
Bifunctional cyclobutane ring is experiencing a renewed interest in the photopolymerization of diolefin crystals, where affords rigid rod-shaped polymers with 1,3-*trans* disubstituted rings in the main chain,[1] as a rigid bivalent ligand in a selective antagonist of μ opioid receptor[2] and as a product of the topochemical photodimerization of aromatic retinoids.[3]

The solid-state structure of cyclobutane derivatives has been widely reviewed[4,5] but very few data are reported about compounds in which no bonds of the four-membered ring are inserted in a fused structure or in which each carbon of the ring bears one substituent. In particular, two reports only concern the X-ray structure of truxillic and truxinic compounds.[6,7] We determined the X-ray structure of the four diastereomeric truxillic and truxinic compounds 1-4 where the geometry of the four-membered ring is not restricted by rings fused to it.

$X=N(CH_3)_2$



1



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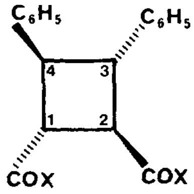

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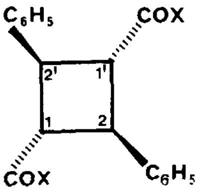

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The amides 1-4 were prepared by interfacial condensation of the corresponding acid chloride with dimethylamine hydrochloride. The corresponding acid precursors (X=OH, compds. 1 and 2) were obtained by solid-state photodimerization of the appropriate crystals of *trans*-cinnamic acid and by alkaline epimerization (X=OH, compds. 3 and 4) of these acid photodimers.

The structure 1 is slightly non planar, although the ring is centrosymmetrically substituted. The puckering of the ring is instead relevant in the structures 2-4 and different strategies were present to obtain minimum energy conformation in 1,2-*cis* disubstituted rings 1 and 2.

RESULTS AND DISCUSSION

Crystallographic data of the compounds 1-4 are shown in Table 1. Somewhat high R value for 1 is due to the poor quality of the crystal. The computer-generated views of 1-4 with atoms labeling are shown in Figs. 1-4.

The geometry of the cyclobutane ring in the four diastereomers should reflect a sensitive balance between ring strain forces and repulsive interactions between the bulky vicinal substituents. In the centrosymmetric head-to-tail compound 1 this equilibrium is reached with the cyclobutane skeleton slightly deviated from planarity, with a marked lenghtening of the C1-C4 and C3-C4 bonds, 1.59 and 1.60 A respectively. This lengthening of the bonds which originate from the C1-C4-C3 angle is compensated by the widening of the facing angle C1-C2-C3 (92°). Table 2 shows, in fact, selected bond distances, angles, and torsion angles for compound 1. The inner torsion angles are 3.2° and the puckering angle φ , defined as the complement of the dihedral angle between the planes C1-C2-C4 and C3-C2-C4[5], is only 4°. Other cyclobutane derivatives possessing a center of inversion and not involved in fused rings were found to have a planar ring[5,8], but in this case the steric hindrance between bulky 1,2-*cis* groups prevents this conformation and their corresponding bonds $C_{cyclobutyl}-C_{substituent}$ are slightly not eclipsed (torsion angle 2.3°). Moreover, to release the interference between the amide group at C1 and the phenyl at C2, and similarly at C3 and C4, the torsion angles formed by these substituents with the cyclobutane atoms average 105° and 63° respectively, as shown in Table 2 and Fig. 1. As a consequence, the amide groups are in a bisected conformation staying in the plane which includes the diagonal C1-C3. The average calculated distal D_{24}(2.2126 Å) is shorter than the D_{13} (2.2266 Å), as observed by Allen for bisected conformations[5]. However, the D_{13}-D_{24} difference is not significant probably because phenyl rings also lie in a bisected conformation. We believe that for compounds **1-4**, due to the leading role played by the bulky substituents, no particular importance in terms of conjugative ability of the carbonyl group should be given to the diagonal values, as suggested by Allen for cyclobutane bringing only one carbonyl substituent[5].

The molecular structure of compound **2** (Fig. 2 and Table 2) is characterized by a folded cyclobutane ring formed by two head-to-head cinnamoyl groups. The inner torsion angles average 18.5° and the resulting puckering angle is 26.4°. To release the steric hindrance between the 3,4-*cis* phenyl groups, the C3-C4 distance is longer with respect to the other cyclobutyl distances and the phenyl rings lie on planes having an inner dihedral angle of 48.2°. The molecule adopts instead a different strategy to balance the interaction between the 1,2-*cis* amide groups. In fact, one group is almost eclipsed at C1-C2 bond (torsion angle 1.3°) and the dihedral angle between the amide planes is 120°. This is probably due to a more convenient electro-

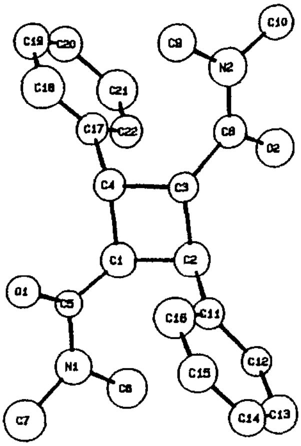

Fig. 1. Perspective view of 1.

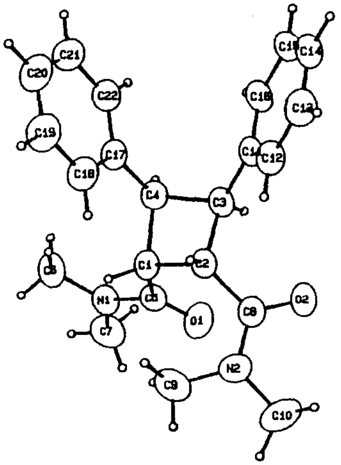

Fig. 2. Perspective view of 2.

Table 1. Crystallographic data of Compounds 1-4.

	1	2	3	4
formula	$C_{22}H_{26}N_2O_2$	$C_{22}H_{26}N_2O_2$	$C_{22}H_{26}N_2O_2$	$C_{22}H_{26}N_2O_2$
mol. weight	350.5	350.5	350.5	350.5
Crystal System	Orthorhombic	Orthorhombic	Monoclinic	Monoclinic
Space Group	$P_{na}2_1$	Fdd 2	C_c	C2/c
a (Å)	15.972(5)	23.535(4)	12.404(2)	18.397(9)
b (Å)	6.084(6)	36.621(7)	15.324(2)	5.977(1)
c (Å)	19.498(5)	8.917(2)	10.415(5)	17.438(2)
α (°)	90	90	90	90
β (°)	90	90	101.61(3)	90.57(3)
γ (°)	90	90	90	90
V (Å^3)	1891(3)	7685(4)	1939(2)	1918(2)
Z	4	16	4	4
T (°K)	295	297	299	297
D_{calc}, gcm^{-3}	1.231	1.212	1.200	1.214
Crystal dimension, mm	0.20x0.28x0.36	0.12x0.16x0.48	0.20x0.36x0.40	0.12x0.27x0.30
Radiation	MoKα	CuKα	CuKα	CuKα
μ, cm^{-1}	0.74	5.80	5.75	5.81
ϑ limits (°)	1-25	2-75	2-75	2-60
Unique reflections	1716	2111	2084	1428
obsd. reflections	1230 [I>0]	1804 [I>3σ(I)]	1993 [I>3σ(I)]	911 [I>3σ(I)]
Variables	234	251	290	127
Extinction		2.9(2)x10^{-6}	6.5(8)x10^{-6}	5.2(5)x10^{-6}
R	0.11	0.039	0.034	0.074
Rw	0.14	0.048	0.056	0.091
Residual d., eÅ^{-3}	0.51	0.16	0.19	
H atoms	CH_3 H ignored, others calcd	cyclobutane H refined,others fixed	CH_3 H fixed others refined	cyclobutane H refined,others others fixed

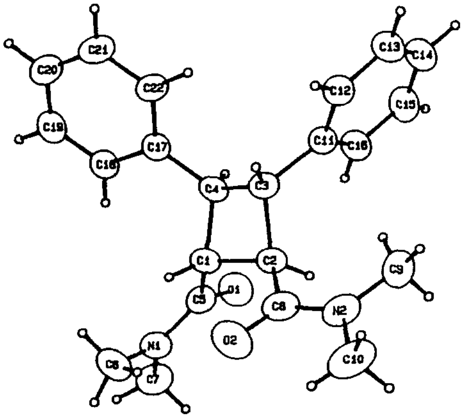

Fig. 3. Perspective view of 3.

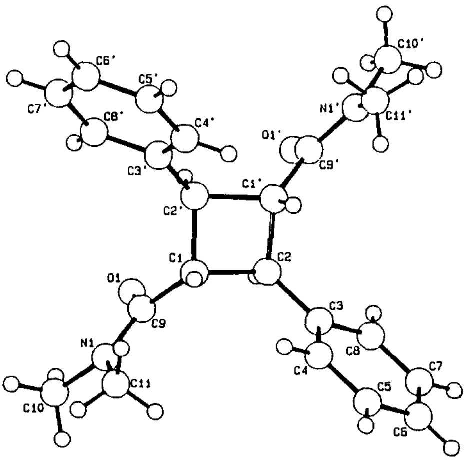

Fig. 4. Perspective view of 4.

static interaction between the opposite charges of the amide dipoles.

The molecular structure of compound 3 (Fig. 3 and Table 2) has also a folded cyclobutane ring. However, the two head-to-head cinnamoyl groups are not related by any symmetry element. The ring valence angles C2-C1-C4 and C2-C3-C4 are markedly decreased from 90° and this causes a significant value (almost 30°) and an inner torsion angle of 20.4°.In this case, the vicinal substituents are always *trans* each other in a preferred pseudo-diequatorial conformation. Here, the amide group attached at C2 is almost eclipsed at the C1-C2 bond and the phenyl planes form a dihedral angle of 116° and a lipophylic region protuding outside the rest of the molecule.

The molecular structure of compound **4** (Fig. 4 and Table 2) is characterized by a folded cyclobutane ring. The molecule reveals a C_2 axis passing through the cyclobutane ring centre, perpendicular to the ring plane. The corresponding atoms, when related by such C_2 rotation, superimpose each other. All the ring valence angles are significantly smaller than 90° and the ring interatomic distances have normal values[4,5]. The resulting ring strain is relieved by large torsion and puckering angles (22.4° and 31.7°, respectively). To gain stability, all the substituents are pseudo-equatorial as for the compound 3. The phenyl ring planes are slightly skew with respect to the C3'-C2'-C2-C3 plane and this preferred conformation forms a non-polar region in the molecule while the bulky amide groups both point in an average plane perpendicular to the aromatic rings. The similarity between the overall conformation in compounds 3 and **4** is retained in solution and it explains their interaction with lipophylic stationary phases in HPLC.[9]

Therefore, it is evident that the stereochemical relationship between the substituents influences strongly the balance between the ring strain forces and the steric repulsion of the four independent groups attached to the four cyclobutyl carbons and this leads to distinct solid-state conformations of the four diastereomers. The puckering angles of compounds 3 and **4** are larger than the reported mean values[4,5,10] for cyclobutanes having a variety of not fused substituents only.

Table 2. Selected bond distances[a], bond angles[b], torsion and dihedral angles[c], with esd's in parentheses, for compounds 1-4.

1

a(Å)		b(°)		c(°)	
C4-C17	1.59(2)	C3-C4-C17	120.5(9)	C3-C4-C17-C22	64.3
C2-C11	1.55(2)	C4-C3-C8	116(1)	C4-C3-C8-O2	-107.3
C3-C8	1.50(2)	C1-C2-C11	115(1)	C2-C1-C5-O1	102.5
C1-C5	1.43(2)	C2-C1-C5	123(1)	C1-C2-C11-C16	-61.1
C1-C2	1.55(2)	C1-C3-C4	88.7(8)	C5-C1-C2-C11	2.4
C2-C3	1.55(2)	C2-C3-C4	89.4(9)	C8-C3-C4-C17	2.3
C3-C4	1.60(2)	C1-C2-C3	92(1)	C4-C1-C2-C3	3.3
C1-C4	1.59(2)	C2-C1-C4	90(1)	C2-C3-C4-C1	3.2
				C1,C2,C4/C3,C2,C4	176.1
				C2,C1,C3/C4,C1,C3	176.1

2

a(Å)		b(°)		c(°)	
C4-C17	1.517(2)	C3-C4-C17	116.0(1)	C3-C4-C17-C18	-83.2
C3-C11	1.502(2)	C4-C3-C11	119.4(1)	C4-C3-C11-C16	-66.0
C1-C5	1.508(2)	C1-C2-C8	123.8(1)	C2-C1-C5-O1	-1.3
C2-C8	1.514(2)	C2-C1-C5	115.8(1)	C1-C2-C8-O2	121.4
C1-C2	1.554(2)	C1-C4-C3	87.4(1)	C5-C1-C2-C8	-27.5
C2-C3	1.533(2)	C2-C3-C4	88.4(1)	C2-C1-C4-C3	18.3
C3-C4	1.585(2)	C1-C2-C3	89.7(1)	C1-C2-C3-C4	18.7
C1-C4	1.566(2)	C2-C1-C4	88.3(1)	C11-C3-C4-C17	-27.0
				C1,C2,C4/C3,C2,C4	153.6
				C3,C2,C4/C1,C2,C4	153.6

3

a(Å)		b(°)		c(°)	
C4-C17	1.503(2)	C3-C4-C17	121.3(1)	C3-C4-C17-C18	-159.0
C3-C11	1.506(2)	C4-C3-C11	117.3(1)	C4-C3-C11-C12	125.0
C2-C8	1.522(2)	C2-C1-C5	115.5(1)	C1-C2-C8-O2	-1.2
C1-C5	1.519(2)	C1-C2-C8	114.5(1)	C2-C1-C5-O1	-56.5
C1-C2	1.544(2)	C1-C2-C3	88.8(1)	C2-C3-C4-C1	20.4
C2-C3	1.572(2)	C2-C3-C4	86.67(9)	C4-C1-C2-C3	20.5
C3-C4	1.552(2)	C1-C4-C3	89.3(1)	C5-C1-C2-C8	-98.7
C1-C4	1.551(2)	C2-C1-C4	87.70(9)	C11-C3-C4-C17	-93.2
				C1,C2,C4/C3,C2,C4	151.0
				C2,C3,C1/C4,C3,C1	150.5

4[d]

a(Å)		b(°)		c(°)	
C2-C3	1.484(4)	C1-C2-C3	121.6(2)	C9-C1-C2-C3	-95.0
C1-C2	1.566(3)	C2-C1-C9	115.9(2)	C2-C1-C9-O1	-55.5
C1-C9	1.521(4)	C1-C2-C1'	87.7(2)	C1-C2'-C1'-C2	22.4
C1-C2'	1.546(4)	C2-C1-C2'	87.9(2)	C1-C2-C3-C4	-24.9
				C1,C2,C2'/C1¦C2,C2'	148.3

[d] the asymmetric unit is half molecule: corresponding distances and bond values unreported are the same shown here.

EXPERIMENTAL

Preparation of the compounds **1-4**. N,N-Dimethylamides **1-4** were prepared by interfacial condensation of their acid chloride dissolved in dry ether with dimethylamine hydrochloride dissolved in water in the presence of dilute sodium hydroxide under stirring in a Waring blender. Preparative details have been previously reported[11] and the compounds were identified by comparison of the m.p., mass and ^{1}H NMR spectra with those reported.[9,11,12,13]

The acid chlorides (X=Cl) were prepared from the corresponding acids by treatment with thionyl chloride and their m.p. were coincident with those reported in the literature.[14-17]

The α-truxillic acid[18] (X=OH in 1) was prepared by photodimerization of commercial *trans*-cinnamic acid (the α crystalline stable form[19]) suspended in water added of a few drops of Triton X-100 in the Pyrex flask of a rotovapor under stirring and irradiation by a Q 1200 Quarzlampengesellschafts (Hanau, West Germany) high-pressure mercury lamp, luminous flux 29000 lm, for 15 days. The β-truxinic acid[20] (X=OH in 2) was obtained by a Q 1200 irradiation of freshly precipitated *trans*-cinnamic acid (the crystalline metastable β-form[19]) as a fine powder in Pyrex flasks frequently stirred and held at room temperature for 20 days. The δ-truxinic acid[21] (X=OH in 3) and ε-truxinic acid[17] (X=OH in 4) were prepared by alkaline fusion of the compounds 2 and **4**, respectively. All acids were identified by comparison of the m.p. and ^{1}H NMR spectra[12] with those reported in the literature. Crystals suitable for X-ray analysis were obtained by slow evaporation of a hexane/2-propanol 20:1 solution of compounds 1-3. Multiple attempts to obtain good crystals of compound **4** were performed: crystals for X-ray analysis were only obtained by very slow evaporation of a heptane/dichloromethane 20:1 solution.

Crystal structural determination[22]. Intensity data for all four isomers were collected on four-circle automated Enraf-Nonius CAD 4 diffractometers equipped with either MoK$_\alpha$ (λ =0.71073 Å) or CuK$_\alpha$ (λ =1.54184 Å) radiations and graphite monochromators. Variable scans were employed in the ω-2ϑ scans in order to achieve nearly equal precision for all observable reflections. For the monoclinic crystals, one quadrant of data was collected; for the orthorhombic crystals, one octant. Data reduction included corrections for background, Lorentz, polarization and, for the CuKα datasets, absorption. Absorption corrections were based on psi scans, and minimum relative coefficients were 97.75 % (2) and 74.17 % (3). Crystals data and angular limits for each structure are given in Table 1.

All structures were solved by direct methods and refined by full matrix least squares based on F with weights $w=\sigma^{-2}(F_o)$. Non-hydrogen atoms were refined anisotropically, while hydrogen atoms were treated as specified in Table 1. Hydrogen positions were visible in difference maps for compounds 2, 3 and 4, but due to the poor quality of the crystals of the compound 1, these could not be directly observed. Secondary extinction coefficients were refined for compounds 2, 3 and 4. R factors as well as residual densities in final difference maps are given in Table 1.

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22. Supplementary material (atomic coordinates, bond distances, bond and torsion angles, anisotropic thermal parameters) are available on request from the Director of the *Cambridge Crystallographic Data Centre*, Univ. Chem. Lab., Lensfield Road, Cambridge CB2 1EW, U.K.. Any request should be accompanied by a full literature citation of this communication.