Acta Cryst. (1983). B39, 438–444

Structural Studies of Intermediates in Antibiotic Synthesis. II. The Structures of Methoxyiminomalonic Acid and its Methyl and Benzhydryl Monoesters

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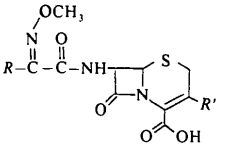
(*Received* 10 *June* 1982; *accepted* 20 *December* 1982)

Abstract

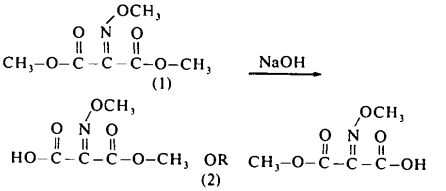
The crystal and molecular structures of methoxyiminomalonic acid monohydrate (I), methyl methoxyiminomalonate (II) and the sodium salt of benzhydryl methoxyiminomalonate trihydrate (III), were determined by direct methods from diffractometer data and refined to R values of 0·03, 0·07 and 0·04 for 1305, 1229 and 2484 observed reflections, respectively. The crystal data are: $C_4H_5NO_5.H_2O$, $M_r = 165$, $P\bar{1}$, $a = 6{\cdot}735\ (1)$, $b = 8{\cdot}035\ (2)$, $c = 7{\cdot}609\ (5)$ Å, $\alpha = 72{\cdot}20\ (4)$, $\beta = 69{\cdot}58\ (3)$, $\gamma = 70{\cdot}84\ (3)°$, $Z = 2$, $V = 355{\cdot}8$ Å^3, $D_m = 1{\cdot}54$, $D_x = 1{\cdot}538$ g cm^{-3}, Mo $K\alpha$, $\mu = 0{\cdot}89$ cm^{-1}, $T = 293$ K for (I); $C_5H_7NO_5$, $M_r = 161$, $P2_1/n$, $a = 7{\cdot}874\ (2)$, $b = 8{\cdot}179\ (2)$, $c = 11{\cdot}722\ (3)$ Å, $\beta = 96{\cdot}97\ (2)°$, $Z = 4$, $V = 749{\cdot}3$ Å^3, $D_m = 1{\cdot}42$, $D_x = 1{\cdot}425$ g cm^{-3}, Cu $K\alpha$, $\mu = 8{\cdot}88$ cm^{-1}, $T = 293$ K for (II); $C_{17}H_{14}NO_5^-.Na^+.3H_2O$, $M_r = 389$, $C2/c$, $a = 15{\cdot}940\ (8)$, $b = 5{\cdot}795\ (1)$, $c = 40{\cdot}392\ (13)$ Å, $\beta = 98{\cdot}11\ (3)°$, $Z = 8$, $V = 3693{\cdot}6$ Å^3, $D_m = 1{\cdot}4$, $D_x = 1{\cdot}397$ g cm^{-3}, Mo $K\alpha$, $\mu = 0{\cdot}88$ cm^{-1}, $T = 83$ K for (III). In all three molecules the methoxime group is antiplanar to a free carboxyl group, while the *syn*-oriented carboxyl group is perpendicular to that plane. These findings show that basic half-hydrolysis of the diester of methoxyiminomalonic acid takes place exclusively on the *anti* carboxyl group and is attributed to steric effects, whereas half-esterification of the corresponding diacid with diphenyldiazomethane, in a non-polar medium, yields preferentially the *syn* ester probably because of the different relative acidities of the two carboxylic acid groups.

Introduction

In a series of experiments, an attempt has been made to synthesize new cephalosporin antibiotics having the following structure:



The stereochemistry of the methoxyimino group is crucial for the antibiotic activity. It has been shown in related compounds (Bucourt, Heymes, Lutz, Penasse & Perronet, 1978; O'Callagham, Sykes, Ryan, Foord & Muggleton, 1976) that the *syn* configuration is essential for high activity. The idea was to synthesize a derivative of methoxyiminomalonic acid where the *anti* carboxyl group was blocked and the *syn* carboxyl group was free for subsequent attachment to the cephalosporanic amine. In the first experiment, the diester of methoxyiminomalonate was treated with one mole of NaOH. Subsequent acidification yielded only one of the possible isomers (2). It has also been established that no epimerization about the C=N double bond takes place under the reaction conditions.



In the second experiment, when methoxyiminomalonic acid was treated with diphenyldiazomethane, only one of the two possible isomers (4) was obtained.

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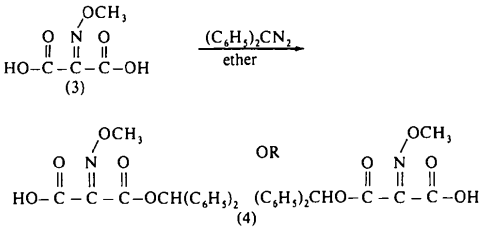


We have undertaken the X-ray structure analysis of the reaction products as all other chemical and spectral methods failed to reveal their configuration. Compounds (2), (3) and (4) were crystallized. From the cell parameters of these crystals we realized that the benzhydryl ester (4) decomposed during the crystallization, probably yielding crystals of methoxyiminomalonic acid. This assumption was later confirmed by the X-ray analysis. When benzhydryl methoxyiminomalonate (4) was converted to its sodium salt, it could be crystallized without any degradation. In the following sections we describe the crystal and molecular structures of the three compounds: methoxyiminomalonic acid monohydrate (I), methyl methoxyiminomalonate (II) and the sodium salt of benzhydryl methoxyiminomalonate trihydrate (III).

Experimental

The three compounds (I), (II) and (III) were crystallized from ether/benzene, benzene/cyclohexane and methanol/ether solutions respectively. Three-dimensional intensity data were collected on an automatic Enraf–Nonius CAD-4 diffractometer with either Mo $K\alpha$ or Cu $K\alpha$ graphite-monochromated radiation at low or room temperature, depending on the diffractometer setting at the time of the data collection. Crystal data are summarized in the *Abstract*. Three or four reflections were monitored every two hours. The scale factor derived from the monitor reflections and applied to the intensity data did not change significantly during data collection. The intensities were corrected for Lorentz and polarization effects. No absorption corrections were made in view of the low values of the absorption coefficients. The details of the data collection and processing for (I), (II) and (III), respectively, are as follows: $\sin\theta_{max}/\lambda$: 0·70, 0·63, 0·64 Å^{-1}; number of independent reflections: 1553, 1425, 3222; number of observed reflections [$F_o > 3\sigma(F_o)$]: 1305, 1229, 2484; temperature: 293, 293, 83 K.

Intensity statistics indicated that the diacid structure (I) was centrosymmetric ($P\bar{1}$). Several attempts to solve this structure with the computer program *MULTAN* (Main, Lessinger, Woolfson, Germain & Declercq, 1977) in space group $P\bar{1}$ or $P1$ failed, although some of the E maps yielded a nearly complete molecular fragment. The structure was eventually solved by the program *QDM* [a direct-method procedure which incorporates negative quartets (Sheldrick, 1980)] using the noncentrosymmetric space group $P1$. The non-hydrogen atoms of two molecules related by a center of symmetry, as well as two water molecules, were located from the best E map. The structure was refined in space group $P\bar{1}$ by a full-matrix least-squares program. All H atoms were located from a difference Fourier synthesis. We used the *SHELX* 76 (Sheldrick, 1976) set of programs for refinement and Fourier synthesis for all structures. After several cycles of refinement, with anisotropic thermal parameters for non-hydrogen atoms and isotropic parameters for H atoms, the final R value ($R = \sum |kF_o - |F_c|| \sum kF_o$) was 0·034.

The structures of the esters (II) and (III) were solved by *MULTAN*. After several cycles of refinement, the positions of all the H atoms were located from difference electron density maps. After a further refinement for each structure, with anisotropic thermal parameters for non-hydrogen atoms and isotropic ones for H atoms, the final R values were 0·070 and 0·039 for (II) and (III) respectively. Unit weights were used for all three structures.

Results

The results for the three compounds are presented in Tables 1–5.* Fig. 1 shows perspective views and the numbering schemes of (I), (II) and (III). Figs. 2–4 show the packing arrangements of the three structures. The Na coordination sphere of (III) is shown in Fig. 5.

* Lists of structure factors, anisotropic thermal parameters for non-hydrogen atoms, coordinates and isotropic thermal parameters for hydrogen atoms for (I), (II) and (III) and hydrogen-bond distances for (I) and (III) have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38288 (37 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Methoxyiminomalonic acid monohydrate: atom coordinates* ($\times 10^4$) *and* U_{eq} (Å^2 $\times 10^3$)

$U_{eq} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j$.

	x	y	z	U_{eq}
C(1)	2559 (4)	8399 (4)	3320 (3)	54 (2)
O(2)	2618 (2)	8636 (2)	5094 (2)	45 (1)
N(3)	4604 (2)	7683 (2)	5453 (2)	34 (1)
C(4)	4594 (3)	7730 (2)	7114 (2)	30 (1)
C(5)	6588 (3)	6820 (2)	7800 (2)	35 (1)
O(6)	8243 (2)	6081 (2)	6528 (2)	51 (1)
O(7)	6550 (2)	6824 (2)	9390 (2)	56 (1)
C(8)	2611 (3)	8704 (2)	8455 (2)	31 (1)
O(9)	2398 (2)	10266 (2)	8471 (2)	48 (1)
O(10)	1262 (2)	7737 (2)	9501 (2)	52 (1)
O*W*(11)	8159 (2)	5499 (2)	2675 (2)	46 (1)

Table 2. *Methyl methoxyiminomalonate: atom coordinates* ($\times 10^4$) *and* U_{eq} ($Å^2 \times 10^3$)

$U_{eq} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j$.

	x	y	z	U_{eq}
C(1)	215 (9)	2515 (1)	5224 (6)	61 (4)
O(2)	1327 (4)	3343 (5)	4526 (3)	47 (2)
N(3)	483 (4)	3556 (5)	3429 (3)	40 (2)
C(4)	1490 (5)	4188 (6)	2778 (4)	37 (2)
C(5)	810 (5)	4529 (6)	1560 (4)	39 (2)
O(6)	−804 (4)	4335 (5)	1290 (3)	57 (2)
O(7)	1831 (4)	4962 (5)	895 (3)	50 (2)
C(8)	3300 (6)	4719 (7)	3188 (4)	47 (3)
O(9)	3615 (5)	5994 (5)	3672 (3)	66 (3)
O(10)	4395 (4)	3581 (6)	2951 (3)	62 (2)
C(11)	6182 (7)	4030 (1)	3319 (6)	99 (6)

Table 3. *Sodium salt of benzhydryl methoxyiminomalonate trihydrate: atom coordinates* ($\times 10^4$) *and* U_{eq} ($Å^2 \times 10^3$)

z coordinates are multiplied by 10^5 and U_{eq} of Na(27) is multiplied by 10^4. $U_{eq} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j$.

	x	y	z	U_{eq}
C(1)	4219 (2)	−3062 (5)	59841 (7)	20 (1)
O(2)	3528 (1)	−1505 (3)	60121 (4)	19 (1)
N(3)	3497 (1)	162 (4)	57624 (5)	15 (1)
C(4)	2880 (2)	1554 (5)	57712 (6)	14 (1)
C(5)	2742 (2)	3505 (5)	55192 (6)	15 (1)
O(7)	2123 (1)	4797 (3)	55511 (4)	18 (1)
O(6)	3243 (1)	3656 (3)	53100 (4)	17 (1)
C(8)	2274 (2)	1309 (5)	60228 (6)	15 (1)
O(9)	1608 (1)	319 (3)	59728 (4)	19 (1)
O(10)	2590 (1)	2301 (3)	63148 (4)	15 (1)
C(11)	2109 (2)	1881 (5)	65921 (6)	15 (1)
C(12)	1354 (2)	3477 (5)	65762 (6)	16 (1)
C(13)	1270 (2)	5479 (5)	63869 (7)	18 (1)
C(14)	565 (2)	6896 (5)	63884 (7)	20 (1)
C(15)	−61 (2)	6316 (5)	65780 (7)	20 (1)
C(16)	18 (2)	4311 (5)	67690 (7)	21 (1)
C(17)	719 (2)	2897 (5)	67674 (6)	17 (1)
C(18)	2736 (2)	2181 (5)	69078 (6)	15 (1)
C(19)	2815 (2)	435 (5)	71445 (7)	19 (1)
C(20)	3378 (2)	681 (6)	74398 (7)	23 (2)
C(21)	3867 (2)	2648 (6)	74947 (7)	24 (1)
C(22)	3791 (2)	4384 (6)	72585 (7)	23 (1)
C(23)	3224 (2)	4177 (5)	69656 (7)	19 (1)
O*W*(24)	3549 (1)	7667 (4)	49992 (5)	19 (1)
O*W*(25)	4540 (1)	11632 (4)	46994 (5)	18 (1)
O*W*(26)	4621 (1)	6347 (4)	45681 (5)	18 (1)
Na(27)	4289 (1)	878 (2)	52663 (2)	160 (5)

In all three molecules a free carboxyl or carboxylate group is coplanar and oriented *anti* with respect to the methoxyimino group whereas the other carboxyl group is perpendicular to that plane. In other words, both reactions (half-hydrolysis of the diester and half-esterification of the diacid) do not yield the desired *syn* isomer. The crystal and molecular structures of these molecules as well as the factors that control the reaction path in each case are discussed below.

Table 4. *Bond lengths* (Å), *bond angles* (°) *and torsion angles* (°)

	(I)	(II)	(III)
C(1)–O(2)	1·435 (2)	1·438 (6)	1·440 (3)
O(2)–N(3)	1·380 (2)	1·384 (4)	1·392 (3)
N(3)–C(4)	1·274 (2)	1·274 (5)	1·277 (3)
C(4)–C(5)	1·491 (2)	1·489 (5)	1·517 (4)
C(4)–C(8)	1·512 (2)	1·511 (6)	1·504 (4)
C(5)–O(6)	1·302 (2)	1·281 (5)	1·245 (4)
C(5)–O(7)	1·203 (2)	1·237 (5)	1·259 (3)
C(8)–O(9)	1·219 (2)	1·198 (6)	1·200 (3)
C(8)–O(10)	1·282 (2)	1·321 (6)	1·344 (3)
O(10)–C(11)	–	1·466 (6)	1·465 (3)
N(3)–O(2)–C(1)	110·2 (1)	109·3 (4)	109·1 (2)
C(4)–N(3)–O(2)	110·8 (1)	110·1 (3)	111·5 (2)
C(5)–C(4)–N(3)	120·3 (1)	118·2 (4)	119·5 (2)
C(8)–C(4)–N(3)	122·4 (1)	123·9 (4)	122·0 (2)
C(8)–C(4)–C(5)	117·4 (1)	117·8 (3)	118·5 (2)
O(6)–C(5)–C(4)	113·3 (1)	116·3 (4)	114·6 (2)
O(7)–C(5)–C(4)	120·0 (1)	118·2 (4)	117·5 (2)
O(7)–C(5)–O(6)	126·7 (2)	125·5 (4)	128·0 (2)
O(9)–C(8)–C(4)	120·5 (2)	122·3 (5)	124·7 (2)
O(10)–C(8)–C(4)	113·6 (2)	110·2 (4)	110·8 (2)
O(10)–C(8)–O(9)	125·8 (2)	127·6 (4)	124·5 (2)
C(11)–O(10)–C(8)	–	112·9 (5)	115·3 (2)
C(1)–O(2)–N(3)–C(4)	−173·3 (2)	−175·4 (6)	178·3 (2)
O(2)–N(3)–C(4)–C(5)	−178·8 (1)	−179·3 (5)	179·7 (2)
O(2)–N(3)–C(4)–C(8)	0·7 (2)	−4·0 (9)	−0·9 (3)
N(3)–C(4)–C(5)–O(6)	2·3 (2)	8·2 (9)	0·4 (2)
N(3)–C(4)–C(5)–O(7)	−177·9 (2)	−171·8 (6)	179·2 (4)
C(8)–C(4)–C(5)–O(6)	−177·3 (2)	−167·4 (6)	−179·0 (3)
C(8)–C(4)–C(5)–O(7)	2·6 (3)	12·7 (9)	1·4 (2)
N(3)–C(4)–C(8)–O(9)	−93·0 (2)	−79·9 (10)	−94·9 (3)
N(3)–C(4)–C(8)–O(10)	86·7 (2)	98·8 (8)	83·5 (3)
C(5)–C(4)–C(8)–O(9)	86·5 (2)	95·4 (8)	84·5 (3)
C(5)–C(4)–C(8)–O(10)	−93·8 (2)	−85·9 (7)	−97·1 (3)
C(4)–C(8)–O(10)–C(11)	–	179·3 (7)	−171·7 (2)
O(9)–C(8)–O(10)–C(11)	–	−2·1 (12)	6·8 (4)

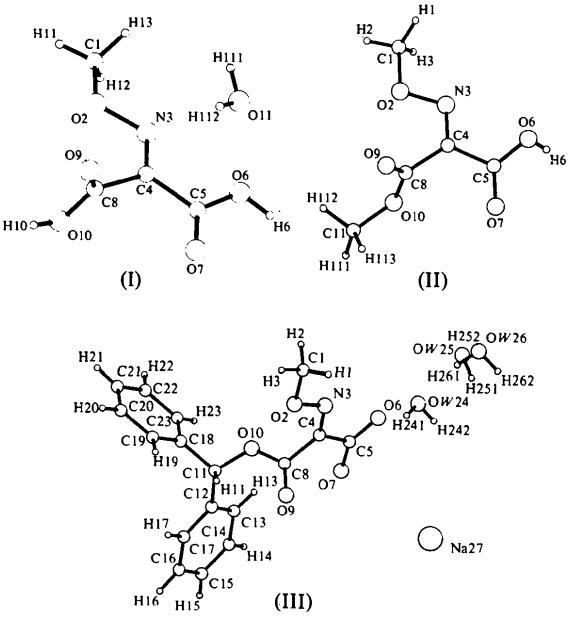


Fig. 1. Perspective views of molecules (I), (II) and (III) showing the atom-numbering scheme.

Table 5. Na *coordination bonds*

	Symmetry element*	Translation along a	b	c	
Na(27)···N(3)	(1)	0	0	0	2·548 Å
Na(27)···O(6)	(1)	0	0	0	2·342
Na(27)···O*W*(24)	(1)	0	−1	0	2·378
Na(27)···O*W*(25)	(2)	1	0	1	2·355
Na(27)···O*W*(25)	(1)	0	0	0	2·419
Na(27)···O*W*(26)	(2)	1	1	1	2·392
Na(27)···Na(27)	(2)	1	0	1	3·490

* (1) x,y,z. (2) $-x,-y,-z$.

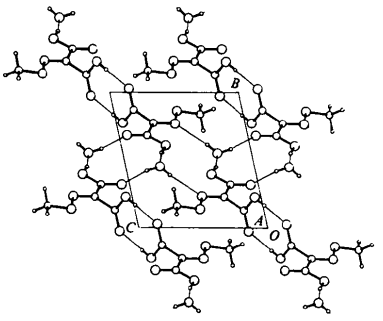


Fig. 2. Molecular packing of (I) viewed down the *a* axis.

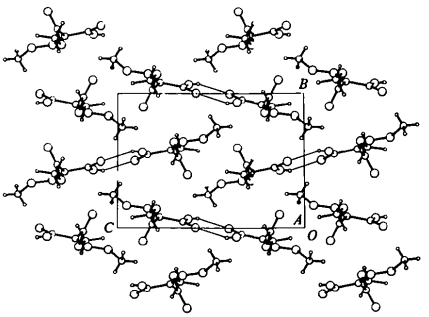


Fig. 3. Molecular packing of (II) viewed down the *a* axis.

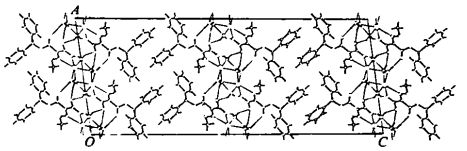


Fig. 4. Molecular packing of (III) viewed down the *b* axis.

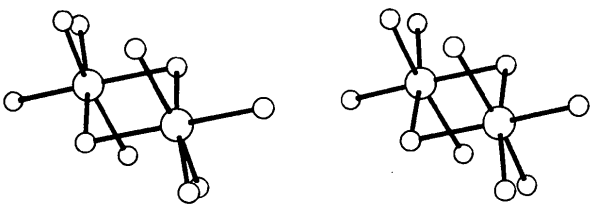


Fig. 5. A stereoview of the Na coordination sphere of molecule (III).

Discussion

Molecular packing

In all three structures the molecules are held together by intermolecular hydrogen bonds and van der Waals interactions.

In the structure of the diacid (I) the molecules form hydrogen bonds involving the four O atoms of the two carboxyl groups, the N atom and the water of hydration. The hydrogen-bonding network consists of three types of hydrogen-bonded planar rings. The first is a six-membered ring (counting only non-hydrogen atoms) formed by two O(9)–C(8)–O(10)–H(10) groups around a center of inversion at (0,0,0). The second is an eight-membered ring of hydrogen-bonded atoms which include the two O(7)–C(5)–C(6)–H(6)···O(11)–H(111) groups from two molecules related by a center of inversion at $(0,\frac{1}{2},0)$ and the third is a ten-membered ring, formed by the N(3)–C(4)–C(5)–O(6)–H(6)···O(11)–H(112) atoms from two molecules related by a center of inversion at $(0,\frac{1}{2},\frac{1}{2})$. The last two hydrogen-bonded systems are nearly coplanar and perpendicular to the first.

In the structure of the methyl ester (II), the molecules pack in centrosymmetric dimers stacked along the *a* axis. The dimer is formed by two hydrogen bonds between the hydroxyl and carbonyl groups of the free acid moieties related by the center of inversion. The packing is of the 'herring-bone' type arrangement, which is similar to that observed for propionic acid (Leiserowitz, 1976).

The structure of the benzhydryl ester (III) consists of alternating polar and hydrophobic layers parallel to the *ab* plane. The hydrophobic layer is formed by the aromatic benzhydryl groups with partial stacking between phenyl rings related by the twofold screw axes. The polar layer is formed by the free-carboxyl-group termini of the molecules, the methoxime group and the Na^+ ions with their waters of hydration. This layer is held by an extensive network of hydrogen bonds and Na coordination bonds (Table 5).

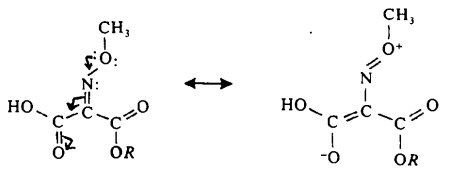
The Na^+ ions in the crystal structure form two distorted octahedra related by a center of inversion (Fig. 5). The coordination sphere is filled by the three water molecules, the carboxyl-group O atom, O(6), and the N atom, N(3). The two O(25) water O atoms are shared between the two octahedra. This type of Na coordination has been observed in other Na complexes (Wei & Ward, 1977; Cody, Langs & Hazel, 1979). The coordination distances and angles around the Na^+ ions are given in Table 5. The Na–ligand distances are similar to those observed in the other Na structures.

Bond lengths and angles

The individual values of bond lengths, bond angles and torsion angles for the three compounds are listed in Table 4.

The methoxyimino-group geometry does not change significantly in this series of compounds. A similar geometry was observed in other methoxyimino molecules (Laurent & Durant, 1981*a*,*b*; Laurent, Durant & Evrard, 1981; Laurent, Parmentier, Durant & Evrard, 1981; Laurent, Parmentier, Evrard & Durant, 1981). Larger differences between the three structures are observed for the other bond lengths as acids, esters and carboxylate groups are compared.

A significant difference between the two single C—C bonds is observed in all three molecules. In both the diacid (I) and the monoacid (II) the C(4)—C(5) bond [1·491 (2), 1·489 (5) Å] is shorter than the C(4)—C(8) bond [1·512 (2), 1·511 (6) Å] by 0·02 Å. This phenomenon was also observed in other similar systems (Hall, Raston & White, 1977; Raston, Sarma, Skelton & White, 1978; Craven & Mascarenhas, 1964; Laurent & Durant, 1981*a*,*b*; Laurent, Durant & Evrard, 1981; Laurent, Parmentier, Durant & Evrard, 1981; Laurent, Parmentier, Evrard & Durant, 1981). The difference between the C—C single bonds in (I) and (II) may be attributed to resonance effects which are more pronounced in the planar conjugated system of the molecule, thus leading to the shortening of the C(4)—C(5) bond relative to the C(4)—C(8) bond (scheme 1).



Scheme (1)

In the benzhydryl ester molecule (III) the situation is reversed. The C(4)—C(5) bond [1·517 (4) Å] is longer than the C(4)—C(8) bond [1·504 (4) Å]. It is likely that the resonance formula of scheme (1) is less important for the carboxylate ion than for the free acid.

As the free carboxyl group in the benzhydryl ester (III) is ionized, it is reasonable to compare the geometry (*cf.* Table 4) of this group between the diacid (I) and the methyl ester (II) only. In the diacid molecule (I) the C(5)—O(7) double bond [1·203 (2) Å] and the C(5)—O(6) single bond [1·302 (2) Å] are similar in length to the bonds found in free carboxyl groups of related compounds. Examples are: aminomalonic acid (Kanters, Kroon, Beurskens & Vliegenthart, 1966), 1·309 (3) and 1·213 (3) Å; benzylmalonic acid (Lepore, Castronuovo Lepore & Ganis, 1975), 1·307 (5) and 1·194 (4) Å; tartronic acid (Roelofsen, Kanters, Kroon, Doesburg & Koops, 1978), 1·300 (3) and 1·215 (3) Å for one carboxyl group, and 1·309 (3), 1·219 (3) Å for the other. However, the corresponding bond lengths of the other carboxyl group in (I) and the free hydroxyl group in the methyl ester (II) are significantly different from the quoted values. The single C—O bonds are shorter [1·282 (2) and 1·281 (5) Å for (I) and (II) respectively] and the C=O double bonds are longer [1·219 (2) and 1·237 (5) Å for (I) and (II) respectively]. Since each of these free carboxyl groups forms a centrosymmetric hydrogen-bonded dimer in the crystal, the above observation may be attributed to a partial disorder resulting from a 180° rotation around the C(4)—C(8) bond in (I) and the C(4)—C(5) bond in (II). In such cases, the observed C=O and C—O bond lengths represent average weighted values of the two forms shown in scheme (2) as discussed by Leiserowitz (1976). In the carboxylate group of the benzhydryl ester molecule (III), the C(5)—O(7) and C(5)—O(6) bond lengths [1·259 (3), 1·245 (4) Å] are similar to those reported for the carboxylate group of aminomalonic acid (Kanters *et al.*, 1966).

Scheme (2)

The angles around the sp^2 C atoms should be ideally 120°. However, it has been shown in many crystal structures determined so far that the angles may range from 110 to 130° depending on the substituent atoms and the corresponding 1···3 and 1···4 non-bonded interactions. An angle 'widening' effect is always accompanied by an angle 'shrinking' effect so as to retain the coplanarity of the four-atom system. In the present molecules the largest values are observed at the O—C=O bond angles of the carboxyl group and the smallest at the adjacent C—C—O angles.

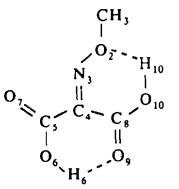
Molecular conformation and chemical reactivity

In all three molecules one carboxyl group is coplanar with the methoxyimino group whereas the second carboxyl is nearly perpendicular to the plane through the other two groups. The methoxyimino bond O(2)—N(3) is antiplanar to C(4)—C(5) and synplanar to C(4)—C(8). The twist of nearly 90° about C(4)—C(8) brings the two O atoms of the *syn* carboxyl [O(9), C(10)] to nearly equal distances (av. 3·3 Å) from both O(2) and O(7) atoms. This type of conformation seems to be favorable in the crystalline state, as it also allows the formation of intermolecular hydrogen bonds to neighboring molecules. It is noteworthy that in malonic acid (Goedkoop & MacGillavry, 1957) and its derivatives (Kanters *et al.*, 1966; Lepore *et al.*, 1975; Roelofson *et al.*, 1978) the two carboxyl groups are also nearly mutually perpendicular (the dihedral angles range between 67 and 114°).

In the methyl ester (II) the methoxyimino side chain is *anti* with respect to the free carboxyl group, whereas the desired compound for the antibiotic synthesis is the one with the *syn* conformation as discussed earlier. This

analysis demonstrates that the first hydrolysis of the dimethyl ester is directed exclusively at the *anti* carboxyl group and may be rationalized on the basis of steric-hindrance effects. A referee has pointed out that the non-planar arrangement observed in the crystal may be favorable in solution as well. If this is the case, C(8) is shielded from attacks by nucleophiles from either side by the presence of O(2) and O(7). C(5), on the other hand, can be freely attacked from both sides. It seems reasonable that even in cases where the conformation is different from the observed one, the accessibility of the *syn* carboxyl group to nucleophiles is less than that of the *anti* group as any rotation of the methoxime methyl around O(2)—N(3) in solution would interfere with the reaction at the *syn* site only.

In the structure of the benzhydryl ester (III) the methoxyimino group is antiplanar to the free hydroxyl group, whereas the *syn*-oriented ester is perpendicular to that plane. Here again, the undesired *anti* isomer was obtained. This observation indicates that half-esterification of the diacid in solution has taken place on the sterically hindered carboxyl group. However, since the reactivity of the diazo reagent increases with acidity (March, 1977), the esterification is expected to proceed preferentially at the more acidic carboxyl group. Assuming that the crystal conformation is also important in solution then the conjugation between the methoxyimino group and the coplanar carboxyl group (scheme 1) decreases its acidity relative to the perpendicular carboxyl group. Another conformation which may be favorable in solution is shown in scheme (3). It incorporates two intramolecular hydrogen bonds where the two carboxyl groups display the *anti* conformation (the hydroxyl group is oriented *anti* to the carbonyl group). One hydrogen, H(6), is bonded to the carbonyl oxygen, O(9), and the other, H(10), to the methoxyimino oxygen, O(2). A similar intramolecular hydrogen bond involving a methoxy O and a carboxylic acid group with the *anti* conformation was observed in *o*-methoxybenzoic acid (Leiserowitz, 1976). The *anti* conformation of carboxylic acids was also found in crystals of maleic acid, 3,4-furandicarboxylic acid and 1,1-cyclopropanedicarboxylic acid (Leiserowitz, 1976). Intramolecular hydrogen bonds involving a methoxyimino O were observed in ethyl 2-amino-α-(*E*-methoxyimino)-4-thiazoleacetate (Laurent & Durant, 1981*a*) and its hydrobromide salt (Laurent & Durant, 1981*b*). Since a carbonyl O is expected to be a better acceptor for a hydrogen bond than a methoxime O, it is reasonable to assume that the first hydrogen bond is stronger than the second, and hence H(10) is more acidic than H(6), which is in accordance with the preferred esterification at the *syn* carboxyl group.



Scheme (3)

It is therefore suggested that in a polar aprotic solvent, the acidity of the two H atoms is determined by their association with solvent molecules and, therefore, both isomers can be obtained. A recent experiment has indeed shown that in a polar solvent (*e.g. N,N*-dimethylformamide) both half-ester products are obtained (Nudelman, 1982).

In view of the observed arrangement of the diacid molecules in the crystal another way of performing the reaction may be envisaged. The molecular packing of methoxyiminomalonic acid shows that the *syn* carboxyl group is hydrogen-bonded directly to another *syn* carboxyl whereas the *anti* carboxyl group is associated with another *anti* group through water molecules. Therefore, half-esterification in the solid state by a gaseous reagent, under conditions which will eliminate the water of hydration in the first step, may proceed preferentially at the *anti* carboxyl group. This may eventually yield the half-ester intermediate needed for the synthesis of the potentially active antibiotic compound.

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Structural Study of Two Isomeric (2-Phenyl-3-chromanyl)methanols

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(*Received* 1 *March* 1982; *accepted* 14 *January* 1983)

Abstract

The crystal structures of *trans* and *cis*-diphenyl(2-phenyl-3-chromanyl)methanol, $C_{28}H_{24}O_2$, M_r = 392·49, have been determined from three-dimensional X-ray diffraction data. The crystals are respectively orthorhombic, *Pbca*, with a = 9·970 (17), b = 18·787 (21), c = 22·445 (23) Å, V = 4204·1 Å^3, Z = 8, D_m = 1·24 (2), D_x = 1·28 Mg m^{-3}, Cu $K\alpha$, λ = 1·5418 Å, μ = 6·07 cm^{-1}, $F(000)$ = 1664, T = 294 (2) K, and monoclinic, $P2_1/c$ with a = 10·768 (17), b = 16·197 (19), c = 12·038 (18) Å, β = 91·26 (11)°, V = 2099·02 Å^3, Z = 4, D_m = 1·24 (2), D_x = 1·27 Mg m^{-3}, Mo $K\alpha$, λ = 0·7107 Å, μ = 0·82 cm^{-1}, $F(000)$ = 832, T = 294 (2) K. Both structures were solved by direct methods and refined by full-matrix least squares with anisotropic thermal parameters for the heavy atoms and isotropic thermal coefficients for the hydrogen atoms. The residual R factors are respectively 6 and 4·8% for the observed structure factors having intensities higher than $3\sigma(I)$. A least-squares analysis of the rigid-body motion of the molecules shows that the *cis*-diphenyl(2-phenyl-3-chromanyl)methanol molecule is more rigid than the *trans* one. In the *trans* compound the dihydropyran ring adopts a slightly distorted half-chair conformation bearing its substituents in axial position, whereas in the *cis* one a sofa conformation is preferred in which all its atoms except C(3) are in the same plane. Furthermore the structure reveals the presence of a weak hydrogen bond between the hydroxyl group and the heterocyclic oxygen atom [O···H 2·09 (6), O···O 2·86 (7) Å] in the *trans* substance; on the other hand, a strong OH···π bond is observed in the *cis* molecule, which involves the alcohol hydroxyl and the 2-phenyl group, and contributes to the rigidity of the whole molecule.

Introduction

In a monosubstituted six-membered ring, usually a substituent prefers the equatorial position of a chair conformation (Eliel, Allinger, Angyal & Morrison, 1966). In heterocyclic compounds, the axial position may be favoured when an anomeric effect operates as in 2-halo, 2-alkoxy or 2-acyloxytetrahydropyrans (Lemieux, Kullnig, Bernstein & Schneider, 1958; Booth & Ouellette, 1966; Anderson & Sepp, 1967, 1968).

In the absence of polar effects, the preferred conformation for a vicinally *trans* disubstituted ring is the diequatorially substituted chair (*e-e* conformation). For instance, *trans*-1,2-dimethylcyclohexane exists 99% in the diequatorial conformation (Eliel, 1962).

But, if steric hindrance between the two substituents becomes too high, one can expect that the diaxially substituted chair (*a-a* conformation) would be favoured over the diequatorial conformation. Such a diaxially substituted chair has been reported in the case of *trans*-dimethyl 2,2′-(1,2-cyclohexylene)bis(2-methylpropanoate) (compound I). X-ray structure determination has shown that this derivative presents a chair conformation bearing the substituents in axial positions

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0108-7681/83/040444-07$01.50