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ALKOXIDE-INDUCED RING-OPENING OF METHOXYMETHYLIDENE-SUBSTITUTED HOMOPHTHALIC ANHYDRIDE PART 2 STRUCTURE AND CONFORMATIONAL ANALYSIS OF THE DIHYDROISOCOUMARIN PRODUCTS

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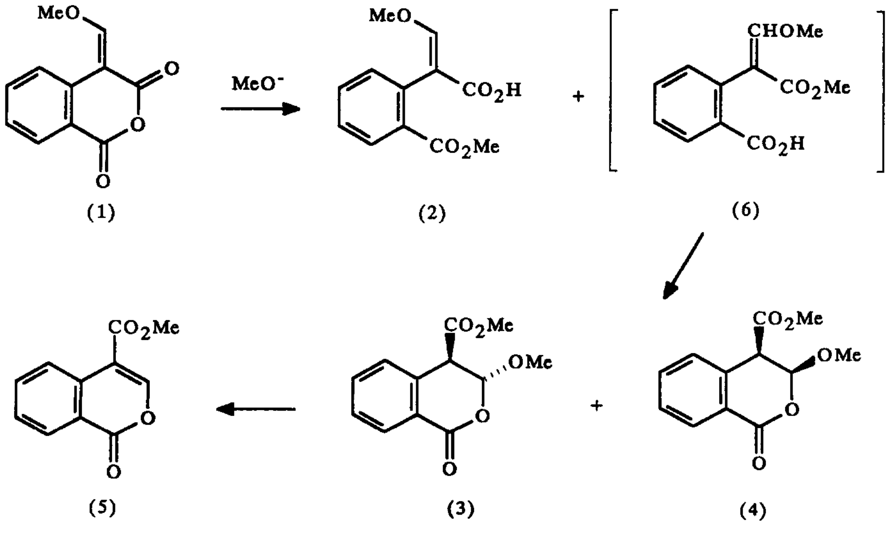
Abstract - The title reaction leads to a stable acid-ester, an isocoumarin and the two isomeric 3-methoxy-4-methoxycarbonyldihydroisocoumarins. X-ray structure determination of one of these isomers reveals a *trans*-diaxial conformation N m r data indicate this geometry also pertains in solution. ^1H-^{13}C vicinal coupling constants for the alternative *cis*-isomer correspond to equatorial-3-methoxy, axial-4-methoxycarbonyl. The trends of two ^{13}C n.m.r. chemical shifts are opposite to those suggested by literature precedents Empirical force field calculations are consistent with the experimentally determined conformations

In an earlier paper, it was shown that reaction between the homophthalic anhydride derivative (1) and methoxide in methanol led to four identifiable products, (2), (3), (4) and (5)[1] The important result was that the acid-ester product has structure (2), in contrast to an earlier report which incorrectly assigned the isomeric structure (6)[2] However, it was also concluded that the acid-ester (6) is an unstable primary product of the reaction which cyclises rapidly to the two isomeric dihydroisocoumarins (3) and (4) These in turn are precursors to the isocoumarin (5) Isomers (3) and (4) could be separated into a crystalline material and an impure oil, whose gross structures were deduced from spectroscopic data[1] The crystalline isomer was believed to have the *trans*-stereochemistry shown for (3), with the impure component being mainly the *cis*-isomer (4)



(1) (2) (6)

(5) (3) (4)

However, it was stated[1] that there remained a degree of ambiguity over these stereochemistry assignments In this paper we now report an unequivocal X-ray structure determination which shows that the crystalline component does indeed have *trans*-stereochemistry (3) In the light of this, the n m r spectroscopic data for both (3) and (4) are discussed in more detail Additionally, results of empirical force field (molecular mechanics) calculations are reported for dihydroisocoumarins (3) and (4), and also some simple derivatives, the results of which aid in understanding the conformations deduced

RESULTS AND DISCUSSION

X-ray Structure Determination of Dihydroisocoumarin (3) - Crystals of the pure dihydroisocoumarin isomer (3) suitable for X-ray structure determination were readily grown from methanol as colourless tablets A view of the structure of (3) is given in the Figure Bond lengths and angles are unexceptional Important bond lengths are recorded in the caption to the Figure The lactone ring has a half-chair conformation, with the result that substituents at carbon atoms C3 and C4 may be positioned in well-defined axial or equatorial orientations Dihedral angles around the C3-C4 bond are close to multiples of 60° (see Table 1) It is immediately apparent from the Figure that dihydroisocoumarin (3) adopts the *trans*-diaxial conformation in the crystal

The conformation of the methoxy group at C3 is such that lone pair participation in anomeric conjugation with the C3-O2 bond is maximised Empirical force field calculations, discussed below, probe this point further These calculations also address the question of nonbonded interaction between the methoxycarbonyl group on C4 and the adjacent aromatic CH group

Although the structure of dihydroisocoumarin (3) is *trans*-diaxial in the crystalline phase, it does not necessarily follow that this conformation is preferred over diequatorial in solution N m r data resolve this point, as discussed in the next section

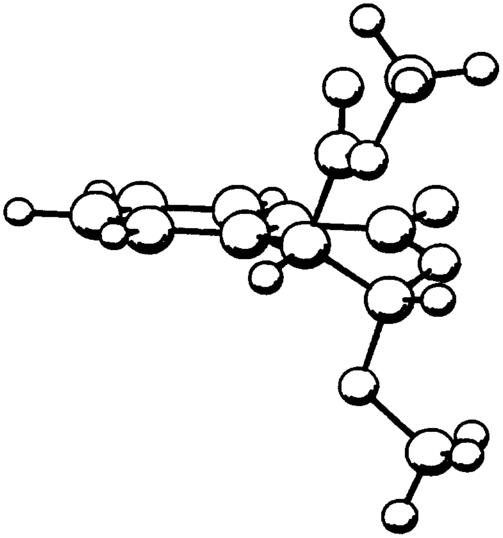
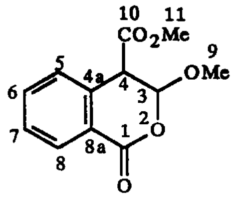
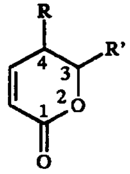
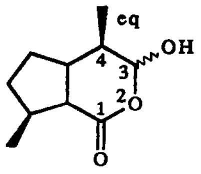


Figure The solid state structure of dihydroisocoumarin (3) Principle bond lengths (Å) (atom numbering as in Table 1) C1=O 1 198(11), C1-O2 1 382(11), C1-C8a 1 485(12), O2-C3 1 440(10), C3-C4 1 507, C3-OMe 1 405(10), C4-C4a 1 495(12), C4-C10 1 523 (12), C4a-C5 1 375(12), C4a-C8a 1 374(11), C5-C6 1 397(14), C6-C7 1 378(16), C7-C8 1 379(14), C8-C8a 1 408(12), C10-=O 1 179(13), C10-OMe 1 317(11), OMe-C9 1 434(12), OMe-C11 1 457(10)

Table 1 N.m r and Conformation Data for Dihydroisocoumarins (3) and (4) and Analogues







		(3) *trans*	(4) *cis*	(7)	(8) *ax*-OH	*eq*-OH
^3J (Hz)	H3-H4	2.5	3.7	2.6-6.0(*gauche*) 10.0-13.6(*anti*)		
	H3-C10	1.9	4.6			
	H3-C4a	6	<3			
	H4-C8a	4	4			
δ (ppm)	H3	5.67	5.52		5.79	5.35
	C1	162.63	163.27		177.46	175.82
	C3	102.05	101.39		98.97	101.36
Dihedral angles (°)	O2-C3-C4-C4a	54.3		43.6-55.5		
	C10-C4-C3-OMe	173.1		163.0-177.9		
	OMe-C3-C4-H4	53.4		31.9-58.9		
	H3-C3-C4-H4	67.8		69.3-103.2		
Literature		—— this work ——		refs 3,4	——ref 6——	

Solution Stereochemistry of Dihydroisocoumarins (3) and (4) - Data pertinent to the discussion of the stereochemistry of the two isomers (3) and (4) are recorded in Table 1 Included are selected ^1H and ^{13}C n m r shifts and coupling constants, and dihedral angle values In order to aid interpretation of these data, literature n.m r. values were collected for analogues of the dihydroisocoumarin system Apart from the isomers of nepetalic acid (8), these all included the substructure (7) (Table 1), for which n.m r data are available alongside definitive X-ray structures Thus, coupling constants $^3J_{H3-H4}$ for *gauche* arrangements of H3 and H4 (axial-equatorial or equatorial-equatorial) for several natural products listed in the footnote,[3] range from 2.6 to 6 Hz Values for the corresponding *anti* geometry (axial-axial) are distinctively higher, as expected, at 10.0 to 13.6 Hz [3a,4]

Comparison of the $^3J_{H3-H4}$ data for (3) and (4) (Table 1) shows that both are typical of *gauche* relationships for these protons Thus, it is immediately established that the *trans*-isomer (3) must exist in solution with its 3- and 4-substituents diaxial, just as in the solid state.

However, the conformation of the *cis*-isomer (4) cannot be determined on the basis of proton-proton coupling constants Three-bond ^1H-^{13}C coupling constants are more revealing. A Karplus-type relationship is known to exist for vicinal ^1H-^{13}C coupling constants.[5] Since $^3J_{H4\text{-}C8a}$ is the same for each of the isomers (3) and (4), it is inferred that the orientation of the methoxycarbonyl substituent is the same in each, that is, axial The 3-methoxy group of (4) must therefore be equatorial.

Most of the remaining data summarised in Table 1 can be interpreted in terms of the *trans*-diaxial and *cis*-*ax*-ester-*eq*-methoxy conformations, as follows.

(a) $^3J_{H3\text{-}C4a}$ is significantly greater in (3) (6 Hz) than in (4) (3 Hz), implying an *anti* relationship in the former (H3 equatorial), and *gauche* in the latter (H3 axial). The X-ray structure of (3) gives the H3-C3-C4-C4a dihedral angle as 172.6° (*anti*) The corresponding *gauche* dihedral angle for O3-C3-C4-C4a in (3) is -66.2° The Karplus relationship suggests coupling constants of about 7 and 3 Hz for these dihedral angles, respectively, consistent with experiment.[5]

(b) Conversely, $^3J_{H3\text{-}C(ester)}$ is smaller in (3) than (4) The same conclusion as in (a) applies. In both cases, the lesser values are in the range expected for a *gauche* relationship, while the higher values are typical of *anti* relationships.[5]

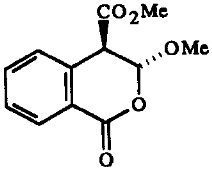
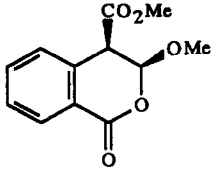
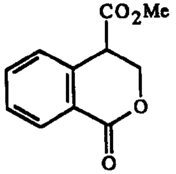
We have been unable to accommodate the above ^1H-^{13}C coupling constant data in any alternative interpretation based on an *eq*-ester group in the *cis*-isomer (4). Other observations based on the n m r data are as follows

(c) The dihedral angle between two equatorial hydrogen atoms in dihydro-2-pyrone-type structures is consistently greater than 60°, as typified for various withanolides, where it ranges from 69 3° to 103 2° (Table 1),[3] and for (3), where this angle is 67 8° In contrast, the dihedral angle between an axial and an equatorial substituent (also *gauche*) in such systems is invariable less than 60° (Table 1) For such molecules, the Karplus relationship therefore suggests that $^3J_{Heq\text{-}Heq}$ should be less than $^3J_{Heq\text{-}Hax}$, and this is indeed observed for (3) and (4) (Table 1: for (3) $^3J_{HH}$ = 2.5 Hz, for (4) $^3J_{HH}$ = 3 7 Hz) While distinguishing the *cis* and *trans* isomers, this observation in itself sheds no light on the conformation of the *cis*-isomer (4).

(d) Finally, the relative order of chemical shifts of the H3 protons in (3) and (4) are δ 5.67 and 5.52 p p m, respectively This is the same relative order as for the isomers of nepetalic acid (8)[6] (δ_{H3} *ax*-OH 5 79, *eq*-OH 5.35 p.p m), which is the best model compound found for (3) and (4) where both anomers of a hydroxy-substituted lactone ring are known.

Despite the consistency and satisfactory interpretation of all these data, there were two other observations which were *not* consistent, and which gave rise to the earlier belief that a degree of ambiguity still existed in the structure assignments of (3) and (4) [1] Firstly, it is normally the case that the ^{13}C-shift of the anomeric carbon in 2-hydroxy-tetrahydropyran isomers and δ-lactone analogues is higher when the hydroxy substituent is axial.[6,7] Secondly, and conversely, the lactone carbonyl carbon shifts in isomers of structures such as nepetalic acid, (8), are lower when the hydroxy substituent is axial (Table 1) [6,7] These relative orderings are *opposite* to those exhibited by (3) and (4) (Table 1), given the structure and conformation assignments deduced on the irrefutable basis of the X-ray structure of isomer (3) Therefore the above generalisations concerning ^{13}C n m r chemical shifts in anomers of hydroxy-substituted δ-lactones do not apply to benzo-fused systems (dihydroisocoumarins) In the latter, the order of chemical shifts is reversed

Table 2 Relative Total Strain Enthalpies from EFF Calculations (kcal/mole)

 (3)		 (4)		 (9)	
ax,ax	0 0	3-*eq*,4-*ax*	1 50	*ax*	0 0
eq,eq	1 34	3-*ax*,4-*eq*	2 77	*eq*	0 7
		(relative to *ax,ax*-(3))			

Empirical Force Field Calculations - EFF calculations with full geometry optimisation have been performed on both of the limiting conformations for each of (3) and (4), as well as a simple derivative, (9) (Table 2)

The enthalpy of the *trans*-isomer, (3), is calculated to be less for the diaxial conformation compared with diequatorial by 1 3 kcal/mole This is in line with the X-ray structure, and with the conformation taken up in solution as deduced by n m r measurements A calculated enthalpy preference of 1 2 kcal/mole for the *eq*-OMe, *ax*-COOMe conformer of *cis*-isomer (4) is also consistent with the conclusion based on n m r measurements for this isomer The axial preference of the 4-COOMe group is probably at least partly due to its unfavourable nonbonded interaction with the adjacent aromatic 5-CH unit when in the alternative equatorial position This is borne out by calculations on the simplified model compound (9) In the absence of the 3-OMe substituent an axial preference (by 0 7 kcal/mole) is still observed However, it is important to note that entropy effects have been ignored in the above discussion (see below)

Under basic, equilibrating conditions in methanol, the experimental isomer ratio (3) (4) was observed by both n m r spectroscopy and h p l c to be about 5 at room temperature[1] This equilibrium ratio corresponds to a free energy difference between the two isomers of about 0 9 kcal/mole On the basis of only the lowest enthalpy conformers calculated for each of the two isomers, the *trans*-isomer (3) is about 1 5 kcal/mole more stable than the *cis*-(4) Again, this value does not take into account entropy differences between the two isomers

In fact, recent results have shown that conformational preferences can be dominated by entropy, rather than enthalpy, effects[8] Both (3) and (4) contain an anomeric methoxy group in a lactone ring It is therefore particularly relevant that the "anomeric effect" observed in 2-methoxytetrahydropyran - preferred axial orientation of the methoxy group - is determined by the higher entropy of the axial isomer compared with the equatorial, rather than by enthalpy differences[8] Caution is therefore advised in the interpretation of EFF-derived strain energies (enthalpies) such as those discussed above[9]

Notwithstanding this caveat, it is gratifying that the EFF-calculated dipole moments of (3) and (4) (4 57 and 5 10D, respectively) are consistent with the polarities of these molecules as reflected by their chromatographic behaviour H p l c under reversed phase conditions (aqueous elluent) eluted the more polar (4) faster than less polar (3)[1]

EXPERIMENTAL

Synthesis and X-ray structure determination of dihydroisocoumarin (3) - The preparation and separation of dihydroisocoumarins (3) and (4) was described previously.[1] A crystal of (3) grown from methanol of dimensions ca 0 28x0 26x0 16 mm was selected Formula. $C_{12}H_{12}O_5$, formula weight 236 23 Intensity measurements were collected on a Philips PW 1100 four-circle diffractometer with MoKα radiation (λ = 0 71069 Å) from a graphite monochromator in the θ-2θ scan mode The unit cell parameters were determined from 25 medium angle reflections space group $P2_1/n$, a = 8 174(2), b = 18 720(4), c = 7 559(2) Å, ß = 94 4(2)°, Z = 4. Number of reflections scanned 1796. The structure was solved by direct methods [10] Most hydrogen atoms were located in difference Fourier syntheses but for consistency were included in idealised positions (C-H 1 08Å) riding on the relevant C-atom; the orientations of the methyl groups were determined by using the best located H-atom for each. The non-hydrogen atoms were assigned anisotropic thermal parameters in the final stages of full-matrix refinement, which converged at R = 0 099 for 1070 data with $I/\sigma(I) > 2$ 0 Lists of atom parameters have been deposited at the Cambridge Crystallographic Data Centre

N.m.r. spectra were recorded in deuterochloroform at 250 MHz (^{1}H) or 62 9 MHz (^{13}C) on a Bruker WM250 instrument [1] Specific features are discussed above

Empirical force field calculations were carried out on a VAX 11/750 computer using graphical input via an Evans and Sutherland PS340 colour graphics terminal Energy minimisation used version 2 1 of the AESOP package of Dr B Masek (ICI Pharmaceuticals) available throughout ICI.[11] This is based on the MM2 force field of Allinger [12] No attempts were made to locate local energy minima other than those discussed above Input structures were based on the X-ray determined skeleton of dihydroisocoumarin (3), using the strucure building facilities present in the ICI molecular modelling software VIKING to introduce substituents in idealised equatorial and axial positions

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9 The force field used calculates a preferred axial conformation for 2-methoxytetrahydropyran by 1 2 kcal/mole (gas phase enthalpy) In $CFCl_3/CDCl_3$ solution, the experimentally determined enthalpy difference is only 0 03 kcal/mole [8a] The corresponding free energy difference is 0 79 kcal/mole at 300 K [8a] We thank a referee for drawing our attention to these results

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