however, that the factors determining solution conformation are completely overridden by binding constraints placed on the nicotines as they approach the active site resulting in different conformations for **2**, **3**, and **4** at the active site. Future studies such as this on more complex model systems or directly on nicotines interacting with nicotinic receptors will undoubtedly shed more light on the fascinating picture of the mechanisms of cholinergic activity.

Acknowledgments. The authors wish to thank Dr. R. Wasylishen for helpful discussions of the conformational dependence of long-range coupling in aromatic systems. We are grateful to Mr. R. L. Bassfield for preparing the three-dimensional figure of the nicotines.

References and Notes

(1) The prefix number in 2-nicotine (**2**), 3-nicotine (**3**), and 4-nicotine (**4**) designates the pyridine ring position at which the pyrrolidine ring is attached. The boldface numbering system is chosen to correspond with the position of substitution for convenience in reading.
(2) We thank Professor Avram Goldstein and C. Romano for making available to us these unpublished results.
(3) T. P. Pitner, W. B. Edwards III, R. L. Bassfield, and J. F. Whidby, *J. Am. Chem. Soc.*, **100**, 246 (1978).
(4) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(5) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1965).
(6) The resonance of $CDCl_3$ must be used with caution as a secondary ^2H chemical shift standard. Its position can be influenced strongly by the solute, as is well known for $CHCl_3$. Since concentration was carefully controlled in the present study, the chemical shift of $CHCl_3$ and hence $CDCl_3$ was constant for all samples.
(7) P. R. Srinivasan and R. L. Lichter, *J. Magn. Reson.*, **28**, 227 (1977).
(8) D. F. Glenn and W. B. Edwards III, *J. Org. Chem.*, **43**, 2860 (1978).
(9) W. O. Crain, Jr., W. C. Wildman, and J. D. Roberts, *J. Am. Chem. Soc.*, **93**, 990 (1971).
(10) T. P. Pitner, J. I. Seeman, and J. F. Whidby, *J. Heterocycl. Chem.*, **15**, 585 (1978).
(11) P. C. Lauterbur, *J. Chem. Phys.*, **43**, 360 (1965).
(12) Y. Takeushi, *Org. Magn. Reson.*, **7**, 181 (1975).
(13) Measured previously by R. L. Lichter and J. D. Roberts, *J. Am. Chem. Soc.*, **94**, 2495 (1972).
(14) (a) M. Witznowski, T. Saluvere, L. Stefaniak, and H. Januszewski, *Mol. Phys.*, **23**, 1071 (1972); (b) A. J. DiGiola, G. T. Furst, L. Psota, and R. L. Lichter, *J. Phys. Chem.*, **82**, 1644 (1978).
(15) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy", Pergamon Press, New York, 1966, p 797.
(16) J. M. Briggs, L. F. Farnell, and E. W. Randall, *Chem. Commun.*, 70 (1973).
(17) P. Diehl in "Nuclear Magnetic Resonance of Nuclei Other than Protons", T. Axenrod and G. A. Webb, Ed., Wiley, New York, 1974, p 275.
(18) H. H. Mantsch, H. Saito, and I. C. P. Smith, *Prog. Nucl. Magn. Reson. Spectrosc.*, **11**, 211 (1977).
(19) J. F. Whidby and J. I. Seeman, *J. Org. Chem.*, **41**, 1585 (1976).
(20) M. Uskokovic, H. Bruderer, C. von Plantz, T. Williams, and A. Bressi, *J. Am. Chem. Soc.*, **86**, 3364 (1964).
(21) H. Booth and J. H. Little, *Tetrahedron*, **23**, 291 (1967).
(22) E. Breuer and D. Melumad, *J. Org. Chem.*, **38**, 1681 (1973).
(23) H. Nakanishi and O. Yamamoto, *Tetrahedron*, **30**, 2115 (1974).
(24) R. Wasylishen and T. Schaefer, *Can. J. Chem.*, **50**, 1852 (1972).
(25) J. B. Rowbotham and T. Schaefer, *Can. J. Chem.*, **50**, 2344 (1972).
(26) We thank Dr. R. Wasylishen for making available to us these calculations.
(27) J. B. Rowbotham, R. Wasylishen, and T. Schaefer, *Can. J. Chem.*, **49**, 1799 (1971).

Conformation of Dihydropyran Rings. Structures of Two 3,4-Dihydro-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-5-ones

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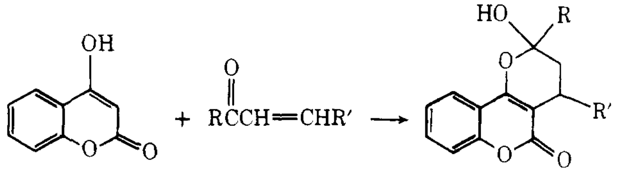
Received October 6, 1978

The crystal structures of *cis*-2-hydroxy- and *trans*-2-methoxy-2,4-dimethyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]-[1]benzopyran-5-one have been determined. The half-chairs of the dihydropyran rings are distorted toward the e,f and d,e diplanar (sofa) forms, respectively. The long endocyclic C–O bonds (cis, 1.475, 1.473 Å; trans, 1.459 Å) result from conjugation of the dihydropyran ring unsaturation with the coumarin carbonyl group. In each compound, the axial anomer is found. In solution, the hydroxy compound exists as a mixture of diastereomeric hemiketal and the open-chain keto forms. The *cis*-methyl ketal interconverts between alternate half-chair conformations, while the *trans*-methyl ketal has a preferred conformation similar to that found in the crystal.

For dihydropyran rings, a natural point of reference is cyclohexene, with a half-chair (symmetry C_2) ground state conformation[1] and a rather flat pseudorotation potential amounting to only 1–2 kcal/mol to reach the 1,2-diplanar (sofa) form,[2] in consequence in part of a remarkably slight initial dependence of the 1,3-diaxial contact distances on distortion of the half-chair.[2–4] Dihydropyrans lack the cyclohexene symmetry and one of the diaxial contacts, but still retain conformations close to the half-chair.[5–7] The 1,2-diplanar form is found in other ring systems most commonly in which the unsaturation conjugates with an adjacent endocyclic atom.[8–10] Such a conformation could be approached in nonrigid dihydropyrans to which steric and anomeric effects simultaneously contribute. These features are evident in the Michael addition products of certain α,β-unsaturated ketones with 4-hydroxycoumarin, which may exist as hemiketals.[11] Warfarin (*trans* -4- phenyl -3,4- dihydro -2- hydroxy -2-



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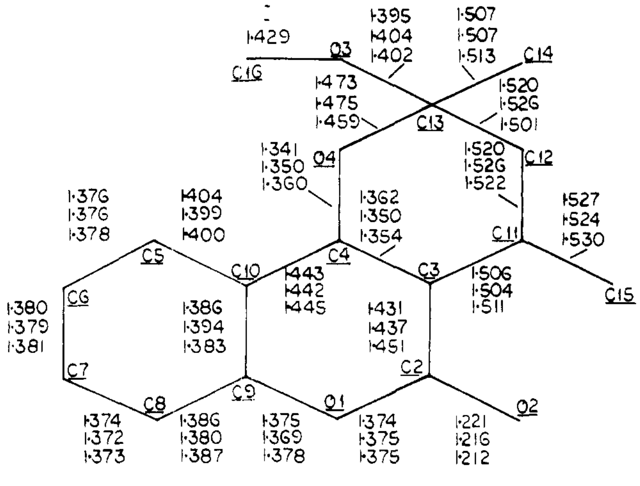


Figure 1. Bond lengths (in Å): upper entries for **1a**; lower entry for **1b**. Esd's ~0.003 Å.

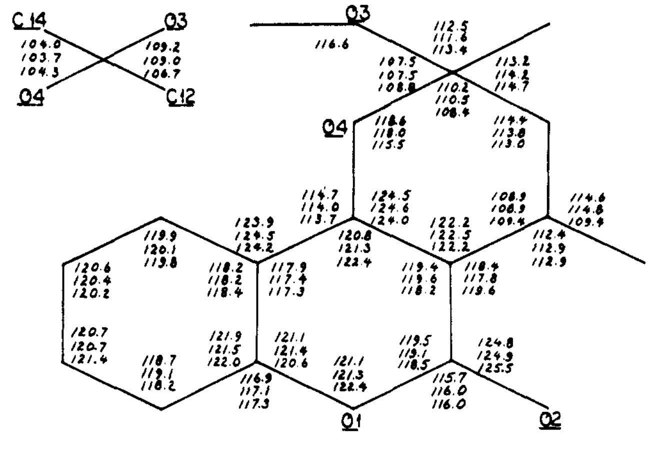
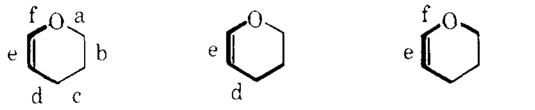


Figure 2. Interatomic angles (in degrees): upper entries for **1a**; lower entry for **1b**. Esd's ~0.3°.

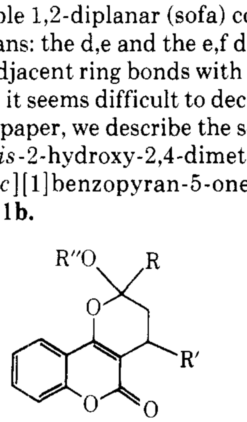
methyl-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-5-one; R = CH_3, R′ = C_6H_5), derived from benzalacetone and 4-hydroxycoumarin, is an important anticoagulant drug.[12] In the crystal, racemic,[13] and enantiomeric[14] warfarin are hemiketals with hydroxy trans to phenyl, while in solution mixtures of the diastereomeric hemiketals and the open side-chain forms are found.[15,16] The dihydropyran rings of warfarin and its *cis*-methyl ketal in the solid state are half-chairs, and the hydroxyl or alkoxyl group is axial, a preference suggesting an anomeric effect similar to that found in carbohydrate chemistry.

In the hemiketals, increasing the bulk of R′ enhances its interaction with the coumarin carbonyl group and eventually this may favor pseudoaxial rather than pseudoequatorial dispositions for R′.[17] In warfarin analogues with R′ = CH_3, a more bulky substituent in effect than R′ = C_6H_5, R′ may go axial. If it does, the dihydropyran ring conformation could be further modified because of the consequent diaxial repulsions.



half-chair d,e diplanar e,f diplanar

There are two possible 1,2-diplanar (sofa) conformations for 3,4-dihydro-2*H*-pyrans: the d,e and the e,f diplanar forms, so named for the two adjacent ring bonds with small endocyclic torsional angles, and it seems difficult to decide which should be preferred. In this paper, we describe the solution and solid state structures of *cis*-2-hydroxy-2,4-dimethyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-5-one, **1a**, and its *trans*-methyl ketal, **1b**.



1a, R″ = H; R = R′ = CH_3

b, R″ = CH_3; R = R′ = CH_3

Experimental Section

2-Hydroxy-2,4-dimethyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]-[1]benzopyran-5-one (1a). The Michael addition of 3-penten-2-one to 4-hydroxycoumarin was done in boiling water with a trace of triethylamine. Clusters of colorless crystals of the title compound, mp 141 °C,[11] were grown from acetone–water mixtures. An individual of dimensions 0.4 × 0.3 × 0.2 mm so produced was separated and mounted along the long crystal axis. Photographic examination suggested no symmetry greater than $\bar{1}$, but two molecules in the asymmetric unit. Lacking evidence for spontaneous resolution, we assigned the conventional triclinic cell in space group $P\bar{1}$. Cell constants were obtained by careful observation of 29 reflections on a GE Datex XRD-5 diffractometer with Cu Kα radiation: a = 11.026 (1) Å, b = 13.181 (1) Å, c = 9.212 (1) Å, α = 104.10 (1)°, β = 99.53 (1)°, γ = 106.29 (1)°. Data were collected in ten concentric shells extending to 2θ = 155°, over a scan (2θ) range corrected at high angle for the α_1–α_2 separation. Three standards were observed periodically; initial instability required the recollection of portions of several of the inner shells. No deterioration was observed, and reflections observed more than once were averaged, with those suspected of error due to the instability being given lower weight. The 5115 unique observations were corrected for coincidence losses, but not for absorption. The distribution of intensities supported the choice of the centric space group, and MULTAN[18] was used to discover the structure. The strong $22\bar{2}$, second highest E, corresponds to the expected 3.4-Å inter-coumarin ring distance, and it was assigned phase π (suggested by Dr. R. E. Marsh) to allow the coumarin rings to pack around the centers of symmetry. The program then developed a starting set of phases that revealed 34 of the 36 carbon and oxygen atoms among the highest 43 features of an E map. The remaining atoms were placed at calculated positions. Four cycles of full-matrix least-squares minimizing the F^2 differences by varying the positions and isotropic Gaussian amplitudes of the C and O atoms led to R = 0.15 with 3750 reflections of lowest θ.[41] The H atoms were placed at calculated positions, and the C and O atoms were refined with anisotropic U's in two full-matrix cycles with all of the data. The H atoms and their isotropic amplitudes were then included with the other atoms in two final cycles of refinement, concluding at R = 0.047, GOF = 4.6.[42] A difference map calculated at this point revealed bonding electron density but no unusual features. The bond lengths and interatomic angles are presented in Figures 1 and 2. Beginning with the final atom parameters, the 2000 data of highest θ were used in a separate refinement of the C and O atoms, with the H atoms making a fixed contribution. Three full-matrix least-squares cycles on these data gave R (on F) = 0.057, GOF = 1.5. The average and maximum differences in bond lengths and bond angles between the two models are 0.007 and 0.017 Å and 0.43 and 0.7°. The values for the restricted data set are better, in our view, because the differences, both average and maximal, between the two independent molecules are smaller (0.006, 0.012 Å and 0.54, 1.05° vs. 0.004, 0.008 Å and 0.45, 0.9°) and because the case can be made or implied that the lower order data and their interpretation are more seriously subject to systematic error (extinction, absorption, deviations from the assumed spherical atom model, failure to treat the H atoms correctly, etc.). The bond lengths and angles for the two independent **1a** molecules following the restricted data set refinement are presented in Figures 3 and 4. In the Discussion, the results of the complete data set refinement will be used. The associated (least-squares) error estimates are surely too small.

The ^1H and ^{13}C magnetic resonance spectra of **1a** (Varian CFT-20, T-60, and HA-100 spectrometers) in $CDCl_3$ are similar to those for warfarin[16] in that a mixture of two diastereomeric cyclic forms and the open side-chain form is present: ^1H NMR δ (reference $(CH_3)_4Si$) 7.4–8.1 (m, 4 H, aromatic H), 2.1–3.8 (multiplets for open and cyclic

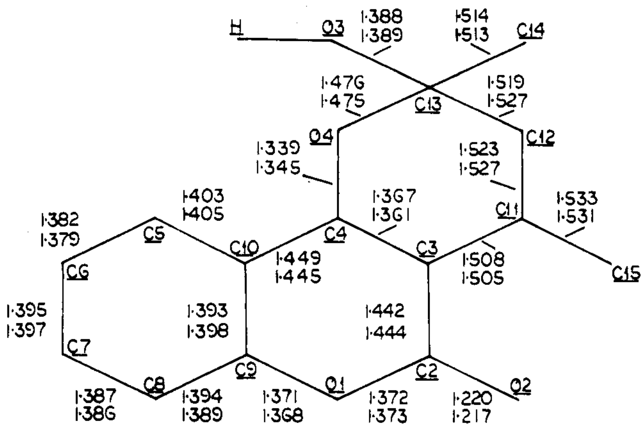


Figure 3. Bond lengths (in Å) for 1a molecules following the restricted refinement (see Experimental Section).

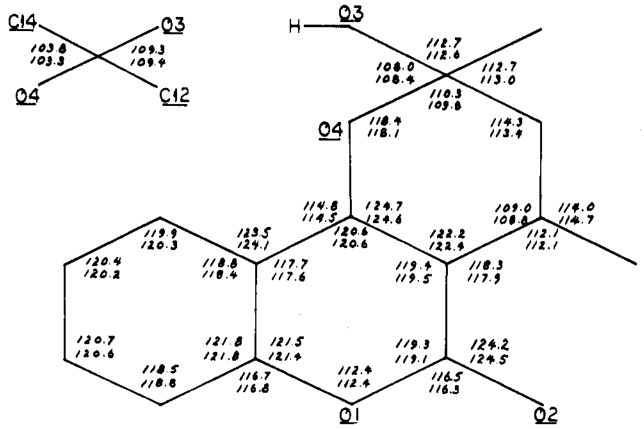


Figure 4. Interatomic angles (in degrees) for 1a molecules following restricted refinement (see Experimental Section).

forms, 3 H, H–CH_2), 2.30 (s, open CH_3, 30%), 1.87, 1.81 (singlets, cyclic CH_3, 35% each), 1.57 (d, open CH_3CH), 1.51 (d, cyclic CH_3CH). ^{13}C NMR (reference $(CH_3)_4Si$) (upfield portion): C15, 19.0, 18.5, 17.7; C11, 25.0, 24.8, 23.5; C14, 29.6, 28.3, 28.2; C12, 49.0, 41.4, 38.7; C13, 99.1, 100.2 (open C=O, 206.0); C3, 105.9, 106.2, 109.9.

2-Methoxy-2,4-dimethyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]-[1]benzopyran-5-one (1b). Treating 1a with methanol, boiling in the presence of protonated ion-exchange resin, and refluxing through 3Å molecular sieves gave a mixture of diastereomeric methyl ketals. On crystallization from 95% ethanol, thin colorless blocks of the trans diastereomer **1b**, mp 121.1–121.4 °C,[11] were obtained, leaving the other as a slowly solidifying oil. A crystal of **1b** measuring 0.06 × 0.4 × 0.15 mm was mounted along the long crystal axis. Photographs revealed monoclinic symmetry, space group $P2_1/c$ (systematically absent reflections for $h0l$, l odd; $0k0$, k odd), and $Z = 4$. Cell constants were obtained by averaging those calculated from 30 carefully centered reflections on the diffractometer (Co Kα) and 20 reflections from an $h0l$ precision Weissenberg photograph (Cu Kα): a = 14.697 (1) Å, b = 5.8682 (4) Å, c = 16.585 (1) Å, β = 112.345 (3)°. Intensity data were collected as described above. Standard reflections indicated a 2% intensity decrease during data collection, and the 1788 reflections were scaled appropriately; no corrections were made for coincidence or absorption losses. Program MULTAN[18] solved the structure, locating all 19 C and O atoms in the top 23 E map peaks. Refinement was carried out essentially as above, except on F, and the H atoms were added to the model after two cycles of refinement on the C and O positions and anisotropic amplitudes were completed. When R reached 0.040, and GOF = 2.0, several further cycles of refinement on the F^2 differences led to a model not significantly different; the final R was 0.044, GOF = 1.6, for 1719 reflections greater than $1\sigma(F)$. The final bond lengths and angles are given in Figures 1 and 2. Programs used in the above calculations were parts of the XRAY-76,[19] CRYRM, and ORTEP.[20]

The 60-MHz ^{1}HMR spectrum of **1b** in $CDCl_3$ showed an overlapped but partially simplified ABX pattern for which $\Delta\delta(H_aH_B)$ was 41 Hz and J_{gem} was 13 Hz. The unanalyzed spectrum: δ (reference $(CH_3)_4Si$)

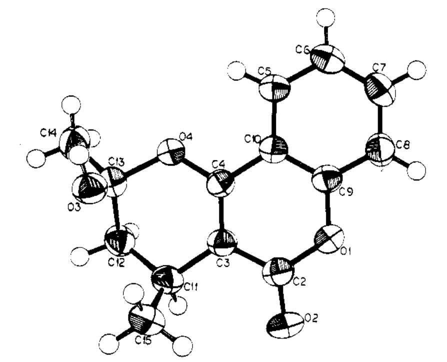


Figure 6. Ellipsoid plot and numbering scheme for one of the **1a** molecules.

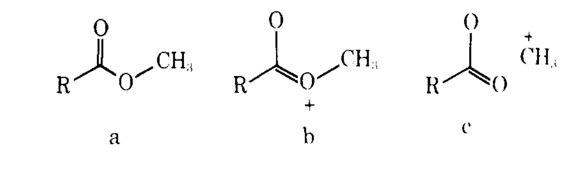
7.1–7.8 (m, 4 H, aromatic H), 3.19 (s, 3 H, OCH_3), 3.05 (m, 1 H, W = 42 Hz, methine), 2.26 (dd, J_{BX} = 6.5 Hz, 1 H, CH_AH_B), 1.64 (s, 3 H, CH_3), 1.58 (dd, J_{AX} = 12.0 Hz, 1 H, CH_AH_B), 1.39 (d, J = 6.5 Hz, 3 H, CH_3CH). The *cis*-methyl ketal of **1a** gave a spectrum similar to that for the minor cyclocumarol isomer,[16] a complex ABX pattern which, on analysis, gave the following: δ (reference $(CH_3)_4Si$) 7.1–7.8 (m, 4 H, aromatic H), 3.40 (s, 3 H, OCH_3), 2.97 (m, 1 H, W = 30 Hz, methine), 2.08 (eight-peak multiplet, 2 H, CH_AH_B, $\Delta\delta(H_AH_B)$ = 7 Hz, J_{gem} = 13.8 Hz, J_{AX} = 8.3 Hz, J_{BX} = 6.5 Hz), 1.70 (s, 3 H, CH_3), 1.48 (d, J = 5 Hz, CH_3CH).

Results and Discussion

The hemiketal **1a** crystallized as the cis isomer, in contrast to warfarin, with two independent molecules in the asymmetric unit. The coumarin planes of both molecules are nearly parallel to the $22\bar{2}$ crystal planes while the gross orientations of the inequivalent molecules are related by a roughly 90° rotation of one molecule about the normal to the coumarin plane. Molecules with similar orientation are arranged in pairs across symmetry centers with the usual interaromatic spacing of 3.4 Å. The hydrogen bonding scheme links the hydroxyl group of each molecule with the carbonyl group of an inequivalent molecule (Figure 5, see Supplementary Material). The two H bonds both have O3...O2′ distances of 2.830 (3) Å. The inequivalent molecules are nearly identical (a drawing of one is given in Figure 6), but they do differ slightly in the amount of bending of the dihydropyran ring away from the benzo plane, which is about equal but opposite in direction for the two, for reasons that are not clear. The conformations of the dihydropyran rings of the two molecules are modified half-chairs distorted toward the e,f diplanar (sofa) arrangement. These descriptions are best appreciated in terms of the torsional angles for the rings, which are given in Table I. The hydroxyl and C15 methyl are axial and pseudoaxial, respectively, separated by 3.10 Å, achieved by rotating O3 away from C15, which moves C13 more nearly into the coumarin plane.

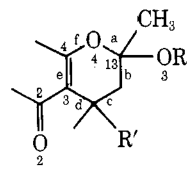
The methyl ketal **1b** has the trans configuration with the C15 methyl pseudoequatorial and methoxy group axial (Figure 7). The dihydropyran ring is a modified half-chair but distorted toward the d,e diplanar conformation. The C15 methyl is rotated slightly away from the coumarin carbonyl group, bringing C12 more nearly into the coumarin plane, as seen by the decreases in the torsional angles c and d (Table I).

In both **1a** and **1b**, the C13–O4 bond is long compared to that found in saturated heterocycles (1.42 Å). Bonds between



a b c

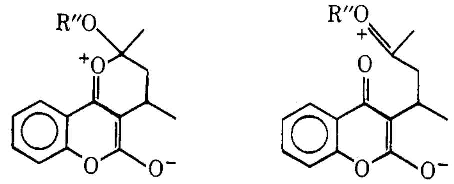
Table I. Selected Results for Dihydropyran Derivatives[a,b]



compd	R	R′	O2–C2	C2–C3	C3–C4	C4–O4	O4–C13	C13–O3	a	b	c	d	e	f	C4–O4–C13	O4–C13–O3	ref
			bond distances, Å						torsional angles, deg						bond angles, deg		
(*SS*)-warfarin	H	C_6H_5	1.217_3	1.439_3	1.351_3	1.351_2	1.483_2	1.385_3	43	−62	46	−14	−5	−10	115.6_2	108.0_2	*c*
(±)-warfarin·CH_3OH	H	C_6H_5	1.212_3	1.439_3	1.362_3	1.347_3	1.474_3	1.383_4	46	−62	42	−13	−2	−15	116.8_3	108.5_3	*d*
	H	C_6H_5	1.208_5	1.450_5	1.361_5	1.345_5	1.460_5	1.388_4	46	−61	44	−15	−2	−13	117.3_4	109.3_4	*d*
(*RS, SR*)-cyclocumarol	CH_3	C_6H_5	1.213_4	1.432_6	1.351_4	1.350_5	1.449_5	1.404_5	45	−60	42	−11	−3	−14	116.4_3	108.0_3	*e*
1a	H	CH_3	1.221_3	1.431_2	1.362_2	1.341_2	1.473_2	1.395_2	35	−54	43	−17	0	−10	118.4_1	107.5_2	*f*
			1.216_2	1.437_3	1.350_2	1.350_2	1.475_2	1.404_3	36	−54	44	−16	−1	−9	118.0_1	107.5_2	
1b	CH_3	CH_3	1.212_3	1.451_3	1.354_2	1.360_3	1.459_2	1.402_2	48	−60	39	−7	−5	−17	115.2_2	108.5_3	*f*

[a] Estimated standard deviations are subscripted. [b] Torsional angles refer to a common configuration. [c] See text ref 14. [d] See text ref 13. [e] See text ref 16. [f] This work.

O and C longer than about 1.42 Å were first identified by O'Gormann et al.[21] for several methyl esters like a in the gas phase. The terminal methyl to oxygen bond was found to be about 1.46 Å, although there is some uncertainty about this in subsequent studies.[22,23] The lengthening can be explained in essence as follows. The participation of resonance structure b implies a displacement of positive charge on to the ester oxygen, which is extended in the extreme case, c, to a nonbonded methyl and lengthens the CH_3–O bond. This bond lengthening has been found in the solid state structures of esters and lactones, as tabulated and discussed by Merlino,[24] and also in carbamate esters,[25] acceptor complexes of esters[26] and carbamate esters,[27] ester oximes,[28] chromans,[29–32] and conjugated dihydropyrans related to the compounds discussed here.[13,14,16] Resonance similar to that for the carboxylic acid



d e

esters can be envisioned for each of these compound types. In the present case, the resonance forms d and e tend to lengthen the C13–O4 bond in **1a** and **1b**. The resonance effects can clearly be seen in the shortening of C4–O4 and C2–C3 and the lengthening of C3–C4 as well (Table I). In general, as the double bond character increases at C4–O4, the bond angle C4–O4–C13 widens and the sum of the torsional angles around C3–C4 and C4–O4 diminishes, leading toward the e,f diplanar form. In the methyl ketals (R = CH_3), the C13–O4 bond is slightly shorter than in the hemiketals, representing probably an understandably decreased importance of the resonance forms.

The combination of a long C–O bond and attendant bond length changes reinforced by resonance forms can also be seen in the chroman structures of bruceol and several similar compounds.[29,30] Of particular interest is the exceptional C–O length (1.49–1.51 Å) in those dihydropyran rings constrained to near twist-boat conformations. Perhaps a combination of steric and resonant effects further lengthens these C–O bonds. In the substituted chromans lacking the distant terminal oxygen conjugated with the dihydropyran, the C–O bonds are

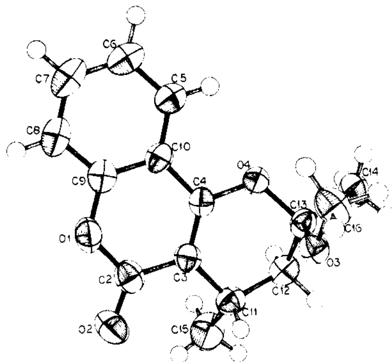


Figure 7. Ellipsoid plot and numbering scheme for **1b**.

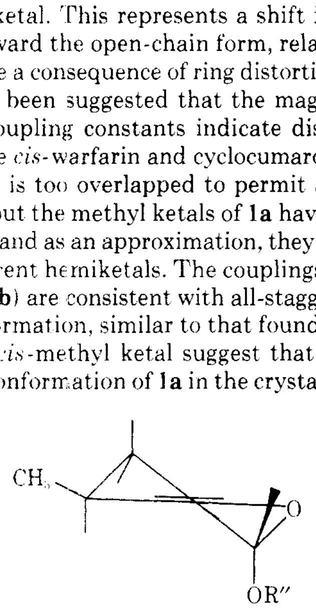
slightly shorter and the intervening bond lengths are normal.[31,32]

Another interesting aspect of the structures of **1a** and **1b** is the preference for an axial oxygen substituent on C13, related to the anomeric effect in carbohydrate chemistry. The structural resemblance between pyranoses/pyranosides and conjugated 2-hydroxy-/2-methoxy-3,4-dihydro-2*H*-pyrans involves the sequence C_B–O_B–C_A–O_A–R (R = H, CH_3), where C_A is the anomeric carbon, common to both compounds types. In the sugars, the endocyclic C–O bonds are nearly equal in length (1.42–1.44 Å).[33] The exocyclic C_A–O_A bond is shorter as a consequence of back-donation of oxygen's nonbonded electrons into the σ^* orbitals on the adjacent bonds, based on the MO treatment of several small model compounds.[34,35] The corresponding exocyclic bond, C13–O3, in the dihydropyrans (Table I) is shortened analogously, as represented here in terms of resonance form e.

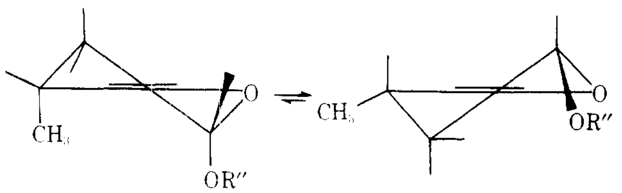
The influence of the anomeric effect on the conformational preferences of the dihydropyrans is determined by electrostatic, steric, and dipole–dipole effects.[7,36] The more stable conformation is the gauche–gauche arrangement which maximizes the attractions O_A. . .C_B and R. . .O_B, while minimizing nonbonded repulsions. The axial anomer is distinguished by fewer steric interactions (because of ring flattening near the double bond) and the O3. . .C4 (O_A. . .C_B) attraction. In sugars, increasingly more electrophilic substituents on C_B enhance the anomeric effect.[37] The longer C13–O4 bond in the conjugated dihydropyrans, compared to sugars, allows the

O4-C13-O3 angle to drop below the tetrahedral value, in response to the O3. . .C4 attraction and for steric reasons. The comparable value in the axial anomers of pyranoses/pyranosides is usually greater than 111° because of the shorter endocyclic C–O bond and attendant O. . .O repulsions, as well as 1,3-diaxial interactions. The equatorial disposition of the bulky C14 methyl in the axial anomers of the conjugated dihydropyrans lends additional stabilization over the alternate half-chair. The hydrogen (in **1a**) and the methyl (in **1b**) on O3 are each trans to C12, the conformation which minimizes nonbonded interactions and admits a weak electrostatic attraction to O4.

In solution ($CDCl_3$), the spectrum of **1a** shows nearly equal amounts of the open-chain keto form and each cyclic diastereomeric hemiketal. This represents a shift in the solution equilibrium toward the open-chain form, relative to warfarin,[16] and may be a consequence of ring distortion in the cyclic isomers. It has been suggested that the magnitudes of the ABX vicinal coupling constants indicate distortion of the half-chair in the *cis*-warfarin and cyclocumarol isomers. The spectrum of **1a** is too overlapped to permit analysis of the ABX portion, but the methyl ketals of **1a** have almost unobscured spectra, and as an approximation, they may exemplify those of the parent hemiketals. The couplings for the *trans*-methyl ketal (**1b**) are consistent with all-staggered half-chair preferred conformation, similar to that found in the crystal. Those for the *cis*-methyl ketal suggest that the half-chair similar to the conformation of **1a** in the crystal cannot be the



trans



cis

preferred form in solution. If an average between alternating half-chairs is considered, the $J_{a,a'}$ and $J_{e,e'}$ couplings can be taken as a measure of the equilibrium position using the extreme values 12.5 and 1.15 Hz, respectively, for $J_{a,a'}$ and $J_{e,e'}$.[38] The average coupling in the cis series decreases in proportion to the preference for the pseudoequatorial R′ group: cyclocumarol (10 Hz, 78%), warfarin hemiketal (9.4 Hz, 73%), and **1a** methyl ketal (8.2 Hz, 62%). This represents larger R′. . .C=O repulsion, which accompanies substitution of R′ = CH_3 for C_6H_5, and the preference for diaxial CH_3. . .H over CH_3. . .OCH_3 interactions. The smaller couplings, $J_{e,a'}$ and $J_{a,e'}$, also decrease in the cis series [cyclocumarol (7.3 Hz), warfarin hemiketal (7.0 Hz), and **1a** methyl ketal (6.5 Hz)], implying $J_{e,a'} > J_{a,e'}$ and, in the major conformer, $J_{e,a'} > 7.3$ Hz. Generally smaller but similarly inequivalent couplings have been observed in dihydropyran derivatives,[7,39,40] and though larger $J_{e,a'}$ values may follow from substituent effects, ring distortion toward the d,e diplanar conformation cannot be disregarded. The Karplus relationship itself, however, may not be sensitive enough to establish it. Though a case can be made for distortions in a given structure, there remains too great an uncertainty in distinguishing the modest conformational differences between half-chair and sofa forms in solution.

Acknowledgments. We would like to thank Dr. Richard E. Marsh and Dr. Edward C. Lingafelter for their interest, valuable discussions, and generous financial support for our computations (R.E.M., NIH GM16966).

Registry No.—**1a**, 68844-37-1; **1b**, 68844-38-2; 3-penten-2-one, 625-33-2; 4-hydroxycoumarin, 1076-38-6.

Supplementary Material Available: A packing diagram for **1a** (Figure 5) and a list of atom coordinates and Gaussian amplitudes for the two structures (Tables II–VIII) (9 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Chiang, J. F.; Bauer, S. H. *J. Am. Chem. Soc.* **1969,** *91,* 1898.
(2) Bucourt, R.; Hainaut, D. *Bull. Soc. Chim. Fr.* **1965,** 1366.
(3) Bernard, M.; St.-Jacques, M. *Tetrahedron* **1973,** *29,* 2539.
(4) Allinger, N. L.; Hirsch, J. A.; Miller, M. A.; Tyminski, I. J. *J. Am. Chem. Soc.* **1968,** *90,* 5773–80.
(5) Achmatowicz, O.; Banaszek, A.; Chmielewski, M.; Zamojski, A. *Carbohydr. Res.* **1974,** *36,* 13–22. Wells, J. A.; Mallory, T. B. *J. Chem. Phys.* **1974,** *60,* 3987–93.
(6) Ferrier, R. J.; Sankey, G. H. *J. Chem. Soc. C* **1966,** 2345. DeLerma, J.; Martinez-Carrera, S.; Garcia-Blanco, S. *Acta Crystallogr., Sect. B* **1973,** *29,* 537.
(7) Sepp, D. T.; Anderson, C. B, *Tetrahedron* **1968,** *24,* 6873–81. Cook, M. J.; Desimoni, G. *ibid.* **1971,** *27,* 257–63. Bolger, J.; Hirwe, A.; Marathe, G.; Philbin, E. M.; Vickars, M. A. *ibid.* **1966,** *22,* 621–8.
(8) Clark-Lewis, J. W. *Aust. J. Chem.* **1968,** *21,* 2059–75.
(9) Nagarejan, K.; Nair, M. D.; RangaRao, V.; Venkateswarla, A.; Kartha, G. *Tetrahedron* **1973,** *29,* 2571–3.
(10) Bock, K.; Pedersen, C. *Tetrahedron Lett.* **1969,** 2979; among many.
(11) Ikawa, M.; Stahmann, M.; Link, K. P. *J. Am. Chem. Soc.* **1944,** *66,* 902.
(12) O'Reilly, R. A. *Annu. Rev. Med.* **1976,** *27,* 245–61. Suttie, J. W. *Semin. Hematol.* **1977,** *14* (3), 365–74.
(13) Bravic, G.; Gaultier, J.; Hauw, C. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1973,** *277,* 1215–8. Csoregh, I.; Edstrom, S. *Chem. Commun., Univ. Stockholm* **1976** (4), 1–20.
(14) Valente, E.; Trager, W. F.; Jensen, L. H. *Acta Crystallogr., Sect. B* **1975,** *31,* 954–60.
(15) Giannini, D.; Chan, K. K.; Roberts, J. D. *Proc. Natl. Acad. Sci. U.S.A.* **1974,** *71,* 4221–3.
(16) Valente, E.; Lingafelter, E.; Porter, W.; Trager, W. F. *J. Med. Chem.* **1977,** *20,* 1489–93.
(17) Johnson, F.; Mulhotra, S. K. *J. Am. Chem. Soc.* **1965,** *87,* 5492–3. Johnson, F. *Chem. Rev.* **1968,** *68,* 375–413.
(18) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr. Sect. A* **1971,** *27,* 360.
(19) Stewart, J. F.; Kundell, F.; Simpson, N., University of Maryland, 1976.
(20) Johnson, C. 1965, Oak Ridge National Laboratory Report ORNL-3794.
(21) O'Gorman, J. M.; Shand, W.; Schomaker, V. *J. Am. Chem. Soc.* **1950,** *72,* 4222.
(22) Curl, J. J. *Chem. Phys.* **1959,** *30,* 1529.
(23) Shen, Q. *Acta Chem. Scand., Ser. A* **1977,** *31,* 795.
(24) Merlino, S. *Acta Crystallogr., Sect. B* **1971,** *27,* 2491–2.
(25) Bracher, B. H.; Small, R. W. H. *Acta Crystallogr.* **1967,** *23,* 410.
(26) Brun, L. *Acta Crystallogr.* **1966,** *20,* 739.
(27) Graziani, R. *J. Chem. Soc., Dalton Trans.* **1973,** 451.
(28) Larsen, I. K. *Acta Chem. Scand.* **1971,** *25,* 2409.
(29) Begley, M. J.; Crombie, L.; King, R. W.; Slack, D. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1977,** 2393–402.
(30) Begley, M. J.; Crombie, L.; Slack, D. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1977,** 2402–10.
(31) Cannon, J. R.; McDonald, I. A.; Sierakowski, A. F.; White, A. H.; Willis, A. C. *Aust. J. Chem.* **1975,** *28,* 57.
(32) Jones, P. G.; Kennard, O.; Sheldrick, G. M. *Acta Crystallogr., Sect. B* **1977,** *33,* 1982.
(33) Berman, H. M.; Chu, S. S. C.; Jeffrey, G. A. *Science* **1967,** *157,* 1576. Sundaralingam, M. *Biopolymers* **1968,** *6,* 189.
(34) Jeffrey, G. A.; Pople, J. A.; Radom, L. *Carbohydr. Res.* **1972,** *25,* 117–31, and **1974,** *38,* 81–95.
(35) Jeffrey, G. A.; Pople, J. A.; Binkley, J. S.; Vishvashwara, S. *J. Am. Chem. Soc.* **1978,** *100,* 373–9.
(36) Abe, A. *J. Am. Chem. Soc.* **1976,** *98,* 6477–80.
(37) Allinger, N. L.; Eliel, E. L. *Top. Stereochem.* **1967,** *2,* 161.
(38) Desimoni, G.; Invernizzi, A. G.; Righetti, P.; Tacconi, G.; Faucitano, A. *J. Chem. Soc., Perkin Trans. 2* **1977,** 1725–8.
(39) Desimoni, G.; Astolfi, L.; Cambieri, M.; Gamba, A.; Tacconi, G. *Tetrahedron* **1973,** *29,* 2627.
(40) Desimoni, G.; Gamba, A.; Monticelli, M.; Nicola, M.; Tacconi, G. *J. Am. Chem. Soc.* **1976,** *98,* 2947–52.
(41) $R = \sum \left| F_{obsd} - |F_{calcd}| \right| / |F_{obsd}|$.
(42) GOF (goodness of fit) = $(\sum w(F_{obsd}^2 - F_{calcd}^2)^2/(N_{refl} - N_{var}))^{1/2}$.