4 °C. After 2 days, the crystals that formed were filtered off, washed with cold MeOH, and dried in vacuo at 80 °C. The yield of 4 was 1.7 g (60%).

Method B. 1-[[1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-2,4-dioxopyrimidin-5]oxy]acetamide (11). 5-Hydroxy-2′-deoxyuridine (1 g, 4.1 mmol) was dissolved in 1 N NaOH (4.1 mL, 4.1 mmol) and, to this solution, iodoacetamide (1.52 g, 8.2 mmol) was added. Within a few minutes, a colorless precipitate began to form. The mixture was stirred for a total of 48 h and then filtered. The crystalline precipitate was washed with cold water and then recrystallized twice from hot water. The yield after drying (80 °C, in vacuo; 24 h) was 0.91 g (72%).

Method C. 1-[[1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-2,4-dioxopyrimidin-5]oxy]acetic Acid (12). 5-Hydroxy-2′-deoxyuridine (282 mg, 1.15 mmol) was dissolved in 1.16 mL of 1 N KOH (1.16 mmol), and then iodoacetic acid (603 mg, 3.4 mmol) in H_2O (0.84 mL) was added. The solution was allowed to react for 48 h at ambient temperature after which time HCl (3 N, 1.06 mL) was added, and the resulting solution was concentrated to 0.5 mL in vacuo (40 °C). The addition of ethanol (6 mL) produced a precipitate which was filtered off and washed with cold ethanol (4 mL). The yield of product at this point was 150 mg (50%). The product was recrystallized twice from hot EtOH and then dissolved in a minimum of H_2O and applied to a Dowex 50 (H^+) column which was eluted with H_2O. The UV absorbing eluate was pooled and lyophilized. Chromatography on cellulose TLC with *i*-PrOH–1% $(NH_4)_2SO_4$ (2:1) gave but one spot with R_f 0.42.

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Conformations of Selected 3-Substituted 4-Hydroxycoumarins in Solution by Nuclear Magnetic Resonance. Warfarin and Phenprocoumon

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The chemical shift position of the benzylic proton, H_x, has been found to be diagnostic in indicating the preferred conformations of selected 3-substituted 4-hydroxycoumarins. In general, the nonrigid open-chain compounds, e.g., the open-chain tautomer of warfarin and phenprocoumon, are found to exist in equal populations of the two conformations in which the benzylic proton is in the plane of the coumarin ring and is either cis or trans to the 3,4 double bond. The cyclic compounds, e.g., cyclocumarol, are constrained to two limiting conformations defined as $axial_2$ or trans or intermediate conformations between these limits. Evidence is presented that suggests that the antivitamin K activity of warfarin is due to its open side-chain tautomeric form.

The oral anticoagulants are known to manifest their biologic activity by inhibiting the synthesis of the calcium binding sites in the vitamin K dependent clotting factors.[1-8] As a class of therapeutic agents they are highly susceptible to the phenomenon of drug interactions[9,10] and as such afford good model compounds to study such phenomena. When specific anticoagulants are chiral, e.g., warfarin, the normal metabolic patterns obtained from the two enantiomers are different[11,12] and the patterns are quantitatively and stereochemically sensitive to the presence of other drugs.[11,13] A knowledge of the structure and conformational preference of these agents in solution would provide a molecular basis for studying their interactions with the specific hemoproteins that lead to their biotransformation or as yet undefined receptors that lead to their inhibition of vitamin K.

The purpose of this report is to present evidence for the preferred conformations of open-chain warfarin, phenprocoumon, and a series of 3-substituted 4-hydroxycoumarins in solution and to demonstrate that the active form of warfarin at the vitamin K dependent site is probably the open-chain tautomer.

Results and Discussion

In the course of studying the ^1H NMR spectra of several anticoagulants and their derivatives, Table I, it became apparent that the range of values observed for the chemical shift of the benzylic proton, H_x, might be a useful probe

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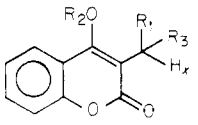
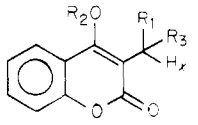
Table I. Chemical Shifts (in ppm) for Selected 3-Substituted 4-Hydroxycoumarins



Compd	R_1	R_2	R_3	δ
1	$-C_6H_5$	-H	$-CH_2COCH_3$	4.70
2	$-C_6H_5$	-H	$-CH_2CH_3$	4.60
3	$-C_6H_5$	-H	$-CH_2CH_2CH_3$	4.59
4	$-C_6H_5$	-H	$-CH_3$	4.70
5a (*SS* and *RR*)	$-C_6H_5$	-H	$-CHOHCH_3$	4.70
5b (*SR* and *RS*)	$-C_6H_5$	-H	$-CHOHCH_3$	4.60
6	$-C_6H_5$	-H	$-CH_2C(SCH_2CH_2S)CH_3$	4.75
7	$-C_6H_5$	$-CH_3$	$-CH_2COCH_3$	4.96
8	$-C_6H_5$	$-CH_3$	$-CH_2CH_3$	4.38
9		$-C_6H_4O-C(CH_3)-CH_2$		4.33
10a (*SS*)	$-C_6H_5$	$HO-C(CH_3)-CH_2$		4.13
10b (*SR*)	$-C_6H_5$	$HO-C(CH_3)-CH_2$		4.20
11a (*SS* and *RR*)	$-C_6H_5$	$CH_3O-C(CH_3)-CH_2$		4.16
11b (*SR* and *RS*)	$-C_6H_5$	$CH_3O-C(CH_3)-CH_2$		4.11
12a (*SS* and *RR*)	$-C_6H_5$	$CH_3-C(H)-CH_2$		4.11
12b (*SR* and *RS*)	$-C_6H_5$	$CH_3-C(H)-CH_2$		4.25

for determining the preferred conformations of these compounds in solution. For the series 1–12, R_3 is an open nonrigid aliphatic side chain or it is cyclized in a semirigid form through R_1 and R_2. R_1 is commonly a phenyl group.



In chloroform-*d*, three distinct benzylic proton resonances can be observed for warfarin (1), due to the existence of three interconverting tautomeric forms. (The percent of the three tautomers found in $CDCl_3$ is 45, major cyclic hemiketal; 40, minor cyclic hemiketal; and 15, open-chain warfarin. In Me_2SO-d_6 the percentage of the three forms is 70:30:0, respectively.) The signal at lowest field, 4.70 ppm, has been assigned to open warfarin while the signals at 4.13 and 4.20 ppm have been assigned to the two diastereomeric cyclic hemiketals formed by ring closure between the 4-hydroxy and side-chain carbonyl group.[14] The large chemical shift difference (about 0.5 ppm) cannot be attributed solely to the deshielding effect of a free carbonyl group in the open tautomer since the equivalent proton in the two diastereomeric alcohols, **5a** and **5b**, H_x occurs at 4.70 and 4.60 ppm, respectively. These substances do not have a side-chain carbonyl. Similarly, phenprocoumon (**2**) and warfarin dithioketal (**6**), substances which cannot form cyclic systems and which also do not have a side-chain carbonyl, display benzylic proton resonances at 4.60 and 4.75 ppm, respectively. The data suggest that what is being observed is a difference in the preferred conformation of the benzylic proton with respect to the coumarin ring in the cyclic vs. the open

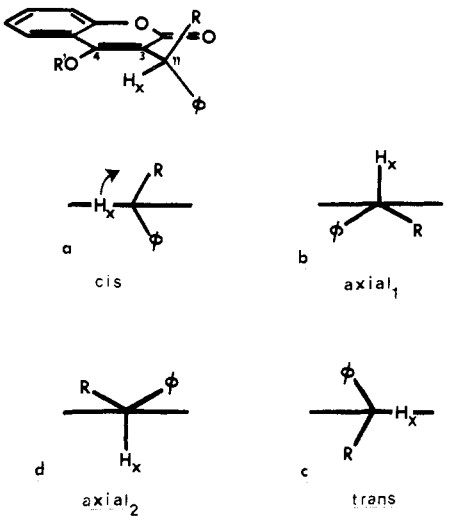


Figure 1. Minimum energy rotational conformers of 3-substituted 4-hydroxycoumarins.

compounds. The conformations, a–d, in Figure 1 are the minimum energy extremes possible and also the ones that would be expected to induce the largest chemical shift differences in H_x with respect to each other. These conformations are obtained by fixing the orientation of the coumarin ring and consecutively rotating the C(3)–C(11) bond through 90°. For the sake of clarity, the C(3)–C(4) double bond will be taken as a frame of reference and the orientation of the benzylic proton with respect to it will be used to describe a given conformation, Figure 1. Conformation a, in which H_x is adjacent to the C(3)–C(4) double bond and coplanar with it will be called cis; conformation b, in which H_x is normal to the plane of the coumarin ring and the phenyl group is 30° below the plane, will be called $axial_1$; conformation c, in which H_x is on the opposite side of the C(3)–C(4) double bond, will be called the trans conformation; and conformation d, in which H_x is again normal to the plane of the coumarin ring, will be called $axial_2$.

Compound **9**, Table I, has been shown to adopt an orientation that approximates the trans conformation (H_x actually out of the coumarin plane by 30°) as defined above.[15] The chemical shift for H_x in **9** is 4.33 ppm and this value will be taken as a rough measure of the trans conformation. Support for this assignment can be found in the analysis of compounds **10**–**12**. The *RR* and *SS* isomers of the cyclic dehydrated warfarin alcohols, **12a**, contain H_x in an $axial_2$ conformation. In this orientation, H_x has a chemical shift of 4.11 ppm. The trans *RS* and *SR* isomers, **12b**, are in equilibrium between two half-chairs in which the phenyl group is either pseudoaxial or pseudoequatorial.[16] When the phenyl is pseudoaxial, H_x corresponds most nearly to the trans conformation, c. When the phenyl is pseudoequatorial, H_x corresponds most nearly to conformation $axial_2$, d. Thus the chemical shift position of H_x would be expected to lie somewhere between the extreme values of 4.33 and 4.11 ppm, and, in fact, it is found at 4.25 for **12b**. Cyclic warfarin, **10**, and cyclocumarol, 11, also have H_x constrained to the $axial_2$ conformation or a mixture of conformations between the $axial_2$ and trans. The range of chemical shifts observed for H_x is 4.11–4.20 ppm in those compounds.

In the open compounds, 1–8, H_x is found downfield in every case with respect to its position in the cyclic compounds **9**–**12**. An examination of Dreiding models reveals that for the open-chain compounds, the cis and trans conformations would be expected to be the thermody-

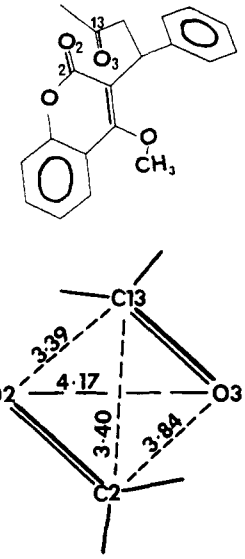


Figure 2. Carbonyl group interactions at the van der Waals contact distance in warfarin 4-methyl ether.

namically most stable of the four described since in these two conformations the phenyl group and the side chain groups lie maximally out of the coumarin plane thereby minimizing nonbonded interactions. Of these two conformations, H_x in the trans conformation would be expected to occur at roughly 4.3 ppm based on the model compounds, while the chemical shift of H_x in the cis conformation is undetermined. Since all of the open compounds have H_x at positions downfield of that which can be accounted for by the trans conformation or either axial conformation, the cis conformation must contribute significantly to the overall conformational equilibrium. In fact, the solid-state structure of (−)-phenprocoumon (2) contains both cis and trans conformations.[17] If one examines Dreiding models of these two conformations for phenprocoumon, they appear energetically equivalent, suggesting that in solution one might expect about a 50:50 mixture of the two. Support for this conclusion can be gained by examination of the chemical shift values for H_x in compounds 1–8. The range of values observed for H_x in these compounds is only 0.16 ppm. Although they all have an α-methylene group in common, the remainder of the side chain varies considerably in bulk, length, and electronic properties. Thus they must all have nearly the same conformational composition. The average chemical shift position within this group is 4.68 ppm and if one assumes this value represents an equal mixture of the cis and trans conformations, then the pure cis conformation must have a value of approximately 5.0 ppm.

Deviations from the general trend established above can be found in the chemical shift positions in the open methyl ethers 7 and 8, derived from warfarin and phenprocoumon, respectively. The resonance of H_x in 7 is found at 4.96 ppm and is therefore significantly deshielded with respect to its position in 1. The solid-state structure of 7 reveals that H_x lies nearly in the cis conformation while the carbonyl groups are aligned antiparallel at a van der Waals contact distance (3.4 Å),[14] Figure 2. A similar dipole interaction could also be significant in solution and thus affect the conformational preference of 7 relative to 1. Examination of models of 7 demonstrates that the side-chain carbonyl group can interact more effectively with the coumarin carbonyl when H_x in cis rather than trans. The cis conformation would be expected to be favored and the observed chemical shift value of 4.96 ppm is thus in good agreement with the value expected for this conformation

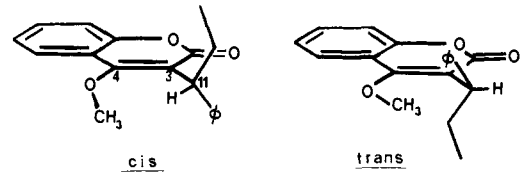


Figure 3. Cis and trans conformations of phenprocoumon 4-methyl ether.

as derived above. In 8, H_x is found significantly upfield relative to its position in 2. The reason for this is apparent upon examination of Dreiding models. Introduction of a 4-methoxyl group leads to a nonbonded interaction between H_x and the methoxyl-methyl group in those conformations which approach the cis structure, Figure 3. Conversely, the trans conformation is free of such an interaction and would therefore be expected to be thermodynamically more stable. The observed chemical shift value for H_x at 4.38 ppm in 8 is consistent with this argument.

These results suggest that the chemical shift position of H_x can be diagnostic in determining the major contributing conformations to the solution structures of the 3-substituted 4-hydroxycoumarins presented in this study. In the nonrigid open compounds (except 7 and 8) nearly equal populations of the cis and trans conformers (H_x at 5.0 and 4.3 ppm, respectively) lead to an observed averaged chemical shift of 4.68 ppm. The cyclic compounds which give chemical shift values for H_x of less than 4.3 ppm are constrained to axial$_2$, trans, and conformations intermediate to these two limiting cases.

It has been demonstrated that warfarin exists in a solvent-dependent dynamic equilibrium comprised of three tautomeric structures.[14] The major contributors to the equilibrium are the two diastereomeric hemiketals while a minor contribution is made by the open form.[14] Since pharmacokinetic parameters such as differences in half-life do not entirely account for the differences in biologic potency displayed by the two enantiomers of warfarin,[18,19] it appears that the exact topology of the molecule may be important at the receptor level for vitamin K inhibition. Phenprocoumon on a molar basis in vivo is more potent[20,21] than warfarin as an anticoagulant while warfarin is more potent than cyclocoumarol.[22] Moreover, (*S*)-(−)-phenprocoumon, which corresponds to (*S*)-(−)-warfarin configurationally,[21] is considerably more potent than (*R*)-(+)-phenprocoumon.[20] The fact that phenprocoumon is a potent anticoagulant which cannot exist in a cyclic structure suggests that the active form of warfarin is the open tautomer. Insofar as the biological activity of warfarin might be expected to be reduced to the extent that it exists in the cyclic form, an equimolar concentration of phenprocoumon might be expected to be more active than warfarin. This assumes that the intrinsic activities of the open forms of the two drugs are comparable. Consistent with this deduction Bell et al.[23] found that in vitro phenprocoumon is approximately ten times as potent as warfarin in inhibiting prothrombin synthesis while 3-phenyl-4-hydroxycoumarin, a compound not only unable to cyclize but also one which lacks a side chain altogether, is a weak inhibitor in vivo but is more than 100 times as potent as warfarin in vitro.

Experimental Section

Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on Varian T-60, CFT-20, and HA-100 spectrometers at about 37 °C, using tetramethylsilane as an internal standard, except for the CFT-20 which uses $CDCl_3$ as an internal standard and

tetramethylsilane as a reference. Chemical shifts (accurate to ±0.02 ppm) and coupling constants (accurate to 0.2 Hz), read directly from the spectra, are reported in brackets adjacent to the analyzed (ABX) values.

Warfarin [3-(1-Phenyl-3-oxobutyl)-4-hydroxycoumarin (1)] and 2,3*H*-2-Methyl-4-phenyl-5-oxobenzopyrano[3,4-*e*]dihydropyran-2-ol (10a,b). Sodium warfarin U.S.P. is converted into warfarin by acidification with HCl and is obtained as white crystals from acetone and water. The product is a mixture of 1, **10a**, and **10b** in solution: NMR ($CDCl_3$ + D_2O) δ (for 1) 2.23 (s, 3 H), 3.25 (dd, 1 H, J = 4 Hz, J_{gem} = 18 Hz), 3.85 (dd, 1 H, J = 8.8 Hz), 4.70 (dd, 1 H), 7.2–7.9 (m, 9 H); NMR (for **10a**) δ 1.65 (s, 3 H), 2.04 [1.95] (dd, 1 H, J = 11.6 [11.6] Hz, J_{gem} = 14.0 Hz), 2.34 [2.43] (dd, 1 H, J = 7.6 [6.8] Hz), 4.13 (dd, 1 H), 7.18 (s, 5 H), 7.2–7.8 (m, 4 H); NMR (for **10b**) δ 1.64 (s, 3 H), 2.37 [2.30] (dd, 1 H, J = 9.4 [6.4] Hz, J_{gem} = 14.0 Hz), 2.43 [2.50] (dd, 1 H, J = 7.0 [4.0] Hz), 4.20 (dd, 1 H), 7.21 (s, 5 H), 7.2–7.8 (m, 4 H); relative integrated ratios of 1:**10a**:**10b** are 15:45:40.

Phenprocoumon [3-(1-Phenylpropyl)-4-hydroxycoumarin (2)]. Phenprocoumon U.S.P. was used: mp 178.8–180.8 °C; NMR ($CDCl_3$ + D_2O) δ 1.06 (s, 3 H), 2.23 (quintet, 2 H, J = 7, 2 Hz), 4.60 (t, 1 H), 7.2–7.8 (m, 9 H).

3-(1-Phenylbutyl)-4-hydroxycoumarin (3). This material was synthesized by reduction of **6** with Raney nickel in absolute EtOH[24] and occurs as white crystals: mp 132.5–133.35 °C; NMR ($CDCl_3$ + D_2O) δ 0.95 (t, 3 H, J = 7.0 Hz), 13.8 (m, 2 H, J = 7–8 Hz), 2.17 (quintet, 2 H, J = 7–8 Hz), 4.59 (t, 1 H), 7.2–7.7 (m, 9 H).

3-(1-Phenylethyl)-4-hydroxycoumarin (4). A sample of this compound was supplied by Pohl,[25] a white crystalline solid: mp 201.7–202.5 °C; NMR ($CDCl_3$ + D_2O) δ 1.73 (d, 3 H, J = 8 Hz), 4.78 (quartet, 1 H, J = 8 Hz), 7.3–7.8 (m, 9 H).

Warfarin Alcohols, 3-(1-Phenyl-3-hydroxybutyl)-4-hydroxycoumarin (5a,b). Samples of these compounds were supplied by Pohl[25] as white solids: NMR ($CDCl_3$) δ (for **5a**) 1.32 (d, 3 H, J = 6.3 Hz), 1.72 (m, br, 2 H), 2.32 (m, 1 H), 3.8 (s, br, 1 H), 4.70 (dd, 1 H, J = 6.3, 7.0 Hz), 7.22 (s, 5 H), 7.2–7.8 (m, 4 H); NMR (for **5b**) δ 1.34 (d, 3 H, J = 6.1 Hz), 1.76 (m, br, 2 H), 2.35 (m, 1 H), 3.9 (s, br, 1 H), 4.60 (dd, J = 4.6, 12.6 Hz, 1 H), 7.22 (s, 5 H), 7.2–7.8 (m, 4 H).

3-(1-Phenyl-3-ethylenedithiobutyl)-4-hydroxycourmarin (6). This compound was synthesized by the method of West et al.[24] as a white crystalline solid: mp [(–) isomer] 194.8–195.0 °C (lit. 193–195 °C); NMR ($CDCl_3$ + D_2O) δ 1.85 (s, 3 H), 3.12 (ddd, 2 H, J = 15, 4, 9 Hz), 3.33 (s, 4 H), 4.75 (dd, 1 H), 7.25–8.0 (m, 9 H).

3-(1-Phenyl-3-oxobutyl)-4-methoxycourmarin (7). This compound was synthesized as described previously[24] as colorless crystals: NMR ($CDCl_3$) δ 2.14 (s, 3 H), 3.27 (dd, 1 H, J = 18, 5.7 Hz), 3.87 (dd, 1 H, J = 9.2 Hz), 4.00 (s, 3 H), 4.96 (dd, 1 H), 7.2–7.8 (m, 9 H).

3-(1-Phenylpropyl)-4-methoxycoumarin (8). To a suspension of **2** (100 mg) in 50 mL of ether was added a sufficient amount of ethereal CH_2N_2 to cause the mixture to enter solution. After evaporation of excess ether and CH_2N_2, an oil was obtained. This was chromatographed on silica gel G (1.5 × 20 cm), eluted with 50:50 $CHCl_3$–benzene. The title compound eluted first, R_f 0.70, and was obtained as a colorless oil that crystallized on long standing: yield 65 mg (63%). The chromone ether, R_f 0.50, comprised the remainder of the product: NMR ($CDCl_3$) δ 0.97 (s, 3 H), 2.27 (quintet, 2 H, J = 7 Hz), 3.78 (s, 3 H), 4.38 (t, 1 H, J = 7 Hz), 7.2–7.7 (m, 9 H). Anal. C, H.

Cyclocumarols, 2,3*H*-2-Methyl-2-methoxy-4-phenyl-5-oxobenzopyrano[3,4-*e*]dihydropyran (11a,b). These compounds were prepared as described previously,[26] separated and studied individually. The NMR spectra were reported[14] except for the aromatic region ($CDCl_3$) δ 7.2–7.9 (m, 9 H).

Dehydrated Warfarin Alcohols, 4*H*-2-Methyl-4-phenyl-5-oxobenzopyrano[3,4-*e*]dihydropyran (12a,b). The synthesis and spectra of these compounds have been reported previously.[16]

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