pressure readings. Comparisons were made using the paired t test method for evaluation of statistical significance.[8] A value of −15 mm or more is considered significant.

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Structure of Warfarin in Solution[1]

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Warfarin in solution is shown to consist of three interconverting tautomeric structures, two of which are cyclic diastereomeric hemiketals, while the third and minor component is the open-chain intermediate form. The configurations of all the tautomers as well as the major conformations of the cyclic tautomers are assigned. The assignments are supported by comparison with the chemical shift and coupling constant parameters of structurally fixed model compounds.

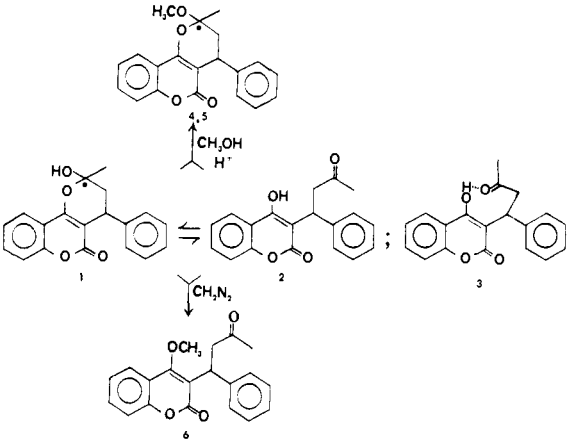
Warfarin [3-(1-phenyl-3-oxobutyl)-4-hydroxycoumarin, **2** (Scheme I)] is usually depicted in textbooks and review articles as the open tautomer, although Chmielewska and Cieslak postulated[2a] that its antivitamin K activity was due to the hemiketal tautomer, **1**. Hutchinson and Tomlinson, on the basis of NMR and IR data, suggested[2b] that the active form of the drug was the hydrogen bonded eight-membered ring structure, **3**. They further suggested that steric differences between the R and S forms of **3** may further account for the differences in potency between them (sic). Although Wawzonek and McIntyre[3] did not speculate on the biologically active form of the molecule, they suggested from polarographic data obtained in acetonitrile or 50% aqueous ethanol that warfarin exists in the open form, **2**, and is not in equilibrium with the cyclic form, **1**.

The molecular form in the crystalline state, both of the (*S*)-(−) isomer[4] and the racemate,[5] is the cyclic tautomer. Determination of its structure in solution has been hampered by its low solubility in common spectral solvents. Recently, the cyclic structure has been assigned[6] to warfarin on the basis of its ^{13}C NMR spectrum and those for certain model compounds. Our data provide configurational assignments and evidence that warfarin in solution exists in a dynamic equilibrium between the open and diastereomeric cyclic forms.

Results and Discussion

In order to probe the possible tautomeric equilibrium displayed by warfarin, it was necessary to synthesize pure model compounds that would mimic the various tautomeric structures and obtain the spectroscopic parameters which are characteristic of these forms. Warfarin can be converted to three isomeric methyl ethers (Scheme I) depending on the method of methylation. The isomeric

Scheme I



cyclocumarols [(2*S*,4*S*)-, (2*R*,4*R*)-, (2*R*,4*S*)-, and (2*S*,4*R*)-2,3*H*-2-methyl-2-methoxy-4-phenyl-5-oxobenzopyrano[3,4-*e*]dihydropyran; (2*S*,4*S*)- and (2*R*,4*R*)-**4**; and (2*S*,4*R*)- and (2*R*,4*S*)-**5**], prepared by treatment of **1** with methanol and acid, can be separated by fractional crystallization and studied individually. Warfarin 4-methyl ether [3-(1-phenyl-3-oxobutyl)-4-methoxycoumarin, **6**] is the sole product of methylation of **1** with diazomethane in ether.[7]

The structure of **5**, the minor cyclic ketal, in the crystalline state has the *R*,*S* and *S*,*R* configurations at C-11 and C-13 (Figure 1). The preferred conformation in the solid state is the half-chair in which the phenyl and methoxyl groups are pseudoaxially and axially disposed, respectively.[8] There is, therefore, a close nonbonded contact between C-16 and O-3 of 2.924 (4) Å. The relative stability of this unusual arrangement reflects the dipole

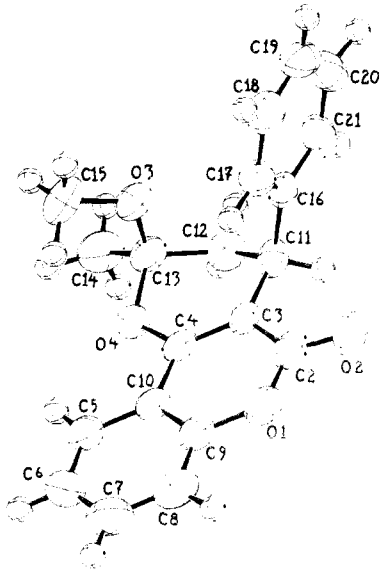
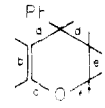


Figure 1. A thermal ellipsoid plot of the minor cyclic ketal, 5.

Table I. Torsional Angles[a] in Dihydropyran Rings



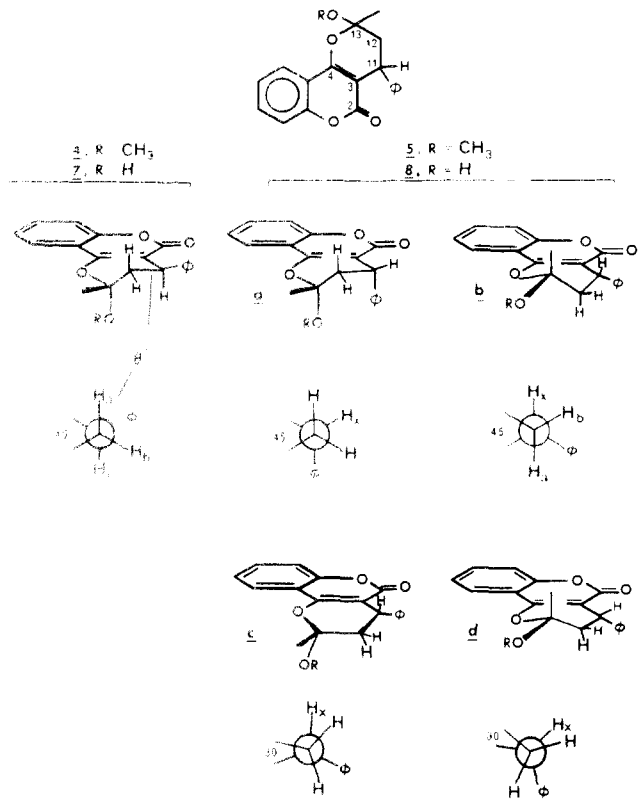
a	b	c	d	e	f	
15	0	15	−45	62	−45	Half-chair cyclohexene
11	3	14	−45	60	−42	5 (this work)
13	2	15	−46	62	−42	(±)-Warfarin·MeOH[b]
14	5	10	−43	62	−46	(−)-Warfarin[c]

[a] In degrees. [b] See ref 5. [c] See ref 4.

interactions of the oxygens bonded to the ketal carbon, C-13, and is analogous to the anomeric effect found in carbohydrate chemistry.[9,10] The dihedral angles within the ketal ring for **5** are compared to those calculated for the half-chair conformation of cyclohexene and those found for crystalline (*S*)-(−)- and *rac*-warfarin in Table I.

The major cyclic ketal, **4**, must have the *R,R* and *S,S* configuration because it is diastereomerically related to **5**. The NMR spectrum, Table II, shows a four-peak

Chart I



multiplet for the benzylic proton with apparent coupling constants of 12 and 7.0 Hz. An ABX analysis of the spectrum yields true coupling of J_{AX} = 11.6 Hz and J_{BX} = 6.8 Hz. Of the two possible half-chair conformations, only structure **4** (Chart I) in which the phenyl and methyl groups are pseudoequatorial and equatorial, respectively, is consistent with the magnitude of the calculated coupling constants. Since **4** has the all-staggered conformation in which no obvious nonbonded interactions occur, it is the most reasonable conformation based on steric and dipole effects. Additional support for this conformational assignment can be gained by analogy to the known preferred conformation of cis-cyclic dehydrated warfarin alcohol[11]

Table II. Partial ^{1}H and ^{13}C Magnetic Resonance Chemical Shifts[a] and Coupling Constants[b] for Warfarin and Some Derivatives

	^{1}H NMR[c]								
Compd	CH_3	OCH_3	H_X	H_A	H_B	J_{AX}	J_{BX}	J_{gem}	Solvent
1 {7	1.66		[4.0]	[1.75-2.41]		d	d	d	Me_2SO-d_6
1 {8	1.60								
1 {2	2.24		4.70	3.25	3.85	4.0	8.8	18	
1 {7	1.65		4.13	2.04 [1.95]	2.34 [2.45]	11.6 [11.6]	7.6 [6.8]	14	$CDCl_3$
1 {8	1.64		4.20	2.37 [2.30]	2.43 [2.50]	9.4 [6.4]	7.0 [4.0]	14	
4	1.70	3.37	4.16	2.02 [2.00]	2.51 [2.52]	11.6 [12.0]	6.8 [7.0]	14	$CDCl_3$
5	1.60	3.23	4.11	2.30 [2.26]	2.44 [2.48]	10.0 [7.0]	7.3 [4.3]	14	$CDCl_3$
6	2.14	4.00	4.96	3.27	3.87	5.7	9.2	18	$CDCl_3$

	^{13}C NMR						
Compd	C-3	C-11	C-12	C-13	C-14	OCH_3	Solvent
1 {7	101.3	35.2	42.9	99.6	27.3		Me_2SO-d_6
1 {8	102.0	36.1	41.5	103.4	25.9		
1 {2	116.8	35.2	45.4	212.0	30.0		$CDCl_3$
1 {7	100.7	35.5	42.8	99.2	27.6		
1 {8	101.5	34.6	40.4	104.3	28.1		
4	105.8	35.7	43.5	101.6	22.3	49.8	$CDCl_3$
5	103.5	35.7	40.0	102.7	22.5	49.3	$CDCl_3$
6	119.8	36.4	45.7	207.1	30.1	61.9	$CDCl_3$

[a] In parts per million downfield from Me_4Si. [b] In hertz. [c] Brackets indicate approximate or unanalyzed values. [d] The methylene proton at the higher field is called H_A.

(*cis*-2,3*H*-2-methyl-4-phenyl-4*H*-pyrano[3,2-*c*]benzopyran-5-one).

The upfield portion of the ^{13}C NMR spectrum of pure **4** in $CDCl_3$ is reported in Table II and is based on the assignments made by Giannini et al.[6] for the major isomeric species present in the spectrum of the unseparated cyclocumarols.

In solution, the minor cyclic methyl ketal, **5**, shows a four-peak multiplet with apparent coupling constants of 7.0 and 4.3 Hz. An ABX analysis of the system yields true coupling constants of J_{AX} = 10.0 Hz and J_{BX} = 7.3 Hz. If **5** largely preserves its solid-state structure, **5a** (Chart I), in solution, the coupling constants would be expected to be small, 2–4 Hz,[12] since the orientation of H_X nearly bisects the dihedral angle between the methylene protons. The observed values are much larger than can be accounted for by this hypothesis and imply that whatever the preferred conformation of **5** in solution may be, it is not **5a**.

The possibility that the other half-chair conformation, **5b** (Chart I), is the preferred conformation in solution is consistent with the magnitude of the analyzed coupling constants. However, serious nonbonded interactions between the axial methyl and pseudoaxial benzylic hydrogen as well as the dipolar repulsion between the equatorial methoxyl and the pyran oxygen apparent in this conformation make this assignment doubtful.

If a dynamic equilibrium existed between half-chair conformations **5a** and **5b**, the population-averaged coupling constant for J_{BX} should lie between 3 and 7 Hz. Since the actual coupling constant is found to be 7.3 Hz, such an equilibrium can be discounted. Thus, other potentially energetically feasible conformations such as the envelope–sofa, 1,3-diplanar, and boat forms[13,14] must be considered.

If one starts with half-chair conformation **5a** and rotates C-11 such that C-12 is brought into the coumarin plane, one of the two possible envelope–sofas is obtained. The dihedral angles between the methylene and benzylic protons change from approximately 60° in **5a** to about 30 and 90° in the envelope–sofa. The magnitude of the coupling constants expected for this conformation is inconsistent[15] with the experimental results. If one continues the rotation an additional 30°, the 1,3-diplanar conformation is obtained (dihedrals of about 0 and 120°) and it can be discounted by a similar argument. A further 30° rotation leads to the boat form **5c** and dihedrals of about 30 and 150°. The expected coupling constants are now consistent with those obtained experimentally. The major destabilizing influence in this conformation is the eclipsed arrangement of the groups on C-13 and the methylene protons of C-12. Thus **5c** must be considered as a reasonable possibility, particularly if the interactions discussed above can be relieved by a minor rotation.

If one again begins with **5a** and rotates C-11 such that C-13 is brought into the coumarin plane, the other possible envelope–sofa is obtained. Further rotation yields the 1,3-diplanar and the alternate boat conformations. Generation of these three conformations by the described rotation causes little change in the dihedral angles between the methylene and benzylic protons and, therefore, all three can be eliminated. A similar analysis beginning with **5b** yields envelope–sofa **5d** as the energetically most reasonable conformation consistent with the coupling constant data and steric interactions. Thus **5c** and **5d** would appear to be the most likely conformations adopted by **5** but a definitive assignment based on the present evidence is not possible.

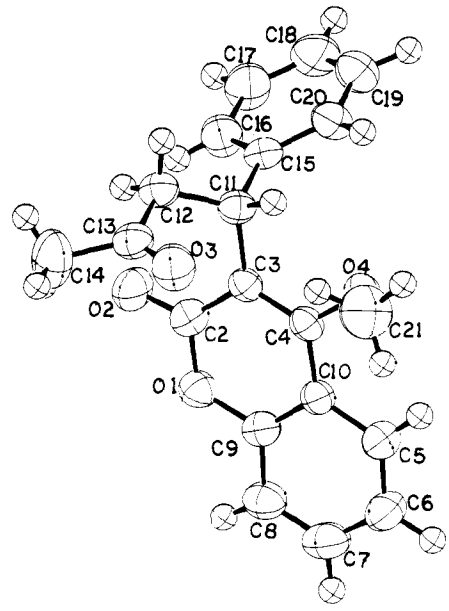


Figure 2. A thermal ellipsoid plot of warfarin 4-methyl ether, **6**.

Warfarin 4-methyl ether (**6**) is an example of an open side-chain derivative of warfarin. An ORTEP drawing of the crystal structure is shown in Figure 2. No unusual bond lengths or angles are observed; the most interesting structural feature is the arrangement of the substituents on C-11 such that the hydrogen on this carbon is cis and nearly coplanar to the double bond in the unsaturated lactone ring, C-3–C-4. An ABX system is observed in the proton NMR spectrum in $CDCl_3$. The chemical shift of H_X is about 1 ppm further downfield than that in either **4** or **5**. This shift cannot be explained solely by the anisotropic deshielding effect of the carbonyl group, since other similar compounds which lack a side-chain carbonyl group show similar downfield shifts.[16] This suggests that the cause of the increased deshielding of H_X in **6**, compared to **4** and **5**, is a change in the orientation of the coumarin and phenyl groups with respect to H_X. Indeed recent work suggests[16] that in solution **6** adopts a preferred conformation in which the orientation of H_X and the side chain is similar to that found in the solid state.

Warfarin. A 100-MHz proton NMR spectrum of warfarin in Me_2SO-d_6 can be interpreted in terms of two interconverting cyclic hemiketals as follows: two distinct methyl proton resonances (in a relative ratio of 70:30 by integration) are observed while the methylene resonances are spread over the 1.75–2.4-ppm range; the methine resonance occurs at 4 ppm. The lack of a methylene resonance at 3.3–3.9 ppm and a methine resonance at 5 ppm excludes a significant contribution by the open side-chain form, **2**, in this solvent. An 80-MHz proton NMR spectrum of (–)-**1** in $CDCl_3$ [the (–) isomer of **1** has greater solubility than the racemate in this solvent] shows that both the open and closed side-chain forms (**2** and **1**) exist simultaneously in solution. The methyl group resonances and the regions associated with the open and closed chain aliphatic resonances are apparent. Comparison of these regions with the positions of the aliphatic proton resonances as well as the coupling constants for the model compounds **4**, **5**, and **6** suggests that the isomers of warfarin in solution correspond with structures **2**, **7**, and **8**. The methyl proton resonance for the major hemiketal tautomer of warfarin occurs downfield from that for the minor hemiketal tautomer in both $CDCl_3$ and Me_2SO-d_6 and in mixtures of these solvents of varied composition.

Therefore, the relative positions of the methyl resonances for **4** and **5** correspond to the major and minor hemiketal resonances found for **7** and **8**, respectively. In addition, the chemical shift positions for H_X, H_A, H_B and the coupling constants of **7** correspond to the values found for **4**. A similar comparison of chemical shift and coupling constant data for **8** and **5** suggests that the configurations of these two compounds correspond. In $CDCl_3$, the relative ratios by integration of the isomers **7**, **8**, and **2** are 45:40:15 while in Me_2SO-d_6 they are 70:30:~0. This difference in the isomeric populations may be attributed to the ability of the solvent to stabilize one epimer over another.

The ^{13}C NMR spectrum of warfarin (Table II) has been compared to similar spectra for **4** and **5**.[6] The Me_2SO-d_6 spectrum supports the hemiketal structure for warfarin in solution. The ^{13}C NMR spectrum of (-)-**1** in $CDCl_3$ shows the resonances due to all three interconverting isomers. The ^{13}C resonances due to **2**[17] are associated with the weaker absorptions and account for 15–20% of the mixture. The resonances for C-11, C-12, and C-14 consist of three peaks each in the 20–50-ppm region arising from the isomers **2**, **7**, and **8**. The 100-ppm region shows the four resonances for C-3 and C-13 of the ring isomers. The comparable ^{13}C resonances for **2** are downfield at 116.8 and 212.0 ppm, respectively.

These studies show that although warfarin can exist in the open side-chain form in some solvents, the major forms in solution are the two diastereomeric hemiketals. Some solvents permit observable amounts of the open side-chain isomer to exist. Variability in hydrogen-bonding ability and perhaps solvent polarity alter the tautomeric composition of warfarin. Although a relationship between these tautomeric forms and the biologically active site has not been established, it is clear that all three must be considered in any theoretical speculation. Moreover, the difficulties in approximating the complexities of the biological microenvironment with pure solvent systems underscore the necessity of making such extrapolations with great caution.

Experimental Section

NMR spectra were recorded on Varian T-60, CFT-20, and HA-100 spectrometers at 37 °C. Analyses were performed by Huffman Laboratories, Wheatridge, Colo. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. X-Ray data were collected on a Picker card-controlled four-circle diffractometer, routines used to refine the structures were part of the X-RAY 72 system of computer programs,[18] and ORTEP[19] drawings were prepared to illustrate the structures.

Warfarin (3-α-Acetonylbenzyl-4-hydroxycoumarin, 2). Panwarfarin (Abbott), a brand of sodium warfarin, was dissolved in water and treated with aqueous HCl to liberate warfarin. This was recrystallized from acetone and water and used in subsequent synthesis: mp 159.5–160.5 °C. (-)-Warfarin was resolved by a literature method:[20] mp 172.5 °C (lit. 172–173 °C); $[\alpha]^{25}_D$ -130.6 ± 0.4° (*c* 1.2, 0.5 N NaOH). NMR are reported partially in Table I.

Cyclocumarol (2,3*H*-2-Methyl-2-methoxy-4-phenyl-5-oxobenzopyrano[3,4-*e*]dihydropyran, 4 and 5). The diastereomeric cyclocumarols were synthesized by the literature method[7] with the modification that Dowex 50 resin in the protonated form was used as the acid catalyst and water was removed from the reaction mixture by refluxing the solution in a Soxhlet charged with 3-Å molecular sieves. Recrystallization of the product from 95% ethanol gave rods of the major isomer, **4** (yield 75%), followed by blocks of the minor isomer, **5**. A second recrystallization of the isomers from ethanol gave samples found to be pure by NMR. **4** gave mp 167.2–168.4 °C; **5** gave mp 183.8–186.0 °C. Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.5; H, 5.6; O, 19.9. Found (for **4**): C, 74.57; H, 5.63; O, 19.95. Found (for **5**): C, 74.21; H, 5.72; O, 20.13. See Table I for spectra. Crystals of **4** were found in space group $P2_1/n$ with cell constants (Mo Kα) a = 16.22 (1), b = 5.86 (1), and c = 16.63 (1) Å, β = 95.0 (5)°, and d_{calcd} = 1.35 g cm^{-3} for Z = 4. The structure of **4** was not attempted because the minor isomer, **5**, seemed more interesting. Crystals of **5** occurred in space group $I2_1/a$ and a crystal suitable for diffraction study of dimensions 0.4 × 0.4 × 0.5 mm was mounted on a four-circle diffractometer. Cell constants were determined by carefully locating 15 reflections with $2\theta > 25°$. They are (Mo Kα) a = 19.943 (3), b = 8.516 (1), and c = 20.027 (5) Å, β = 106.92 (2)°, for which d_{calcd} = 1.314 g cm^{-3}, Z = 8. A total of 2133 reflections to $\sin\theta/\lambda$ = 0.54 Å^{-1} was measured by the θ–2θ scan technique over a scan range of 1.8° in 2θ corrected for the α_1 – α_2 separation. Background counts were measured at each limit of the scan range. No decomposition was detected from analysis of standard reflections which were periodically observed during the course of data collection. After coincidence, Lorentz, and polarization corrections (no absorption correction was made), the 200 highest E's were computed and input to program MULTAN.[21] A favorable set of phases for which R_{Karle} = 24.8 and ABSFOM = 0.94 was used to compute an E map that revealed 23 of the 24 nonhydrogen atoms in the molecule. A Fourier synthesis revealed the remaining atom at which time R stood at 0.32. Three cycles of full-matrix least-squares refinement of the nonhydrogen atoms and their isotropic thermal parameters reduced R to 0.147. One further cycle refining the nonhydrogen atoms and their anisotropic thermal parameters lowered R to 0.117 at which point the hydrogen atoms were located. Four least-squares cycles on the whole model, involving positional and anisotropic thermal parameters for the carbons and oxygens and the positional and isotropic thermal parameters for the hydrogen atoms, the last two cycles of which employed a weighting scheme corresponding to $1/\sigma(F)^2$ and a $2\sigma(F)$ cutoff, reduced R to 0.058, R_w = 0.034 (excluding three very strong reflections considered to be affected by secondary extinction). The final goodness of fit was 1.5.

Warfarin 4-Methyl Ether (3-α-Acetonylbenzyl-4-methoxycoumarin, 6). A method similar to the literature preparation[7] was used in which an ethereal solution of diazomethane was prepared by the dropwise addition of 21.5 g (0.5 mol) of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald, Aldrich) in 200 mL of anhydrous ether to a solution of 5 g of potassium hydroxide in 8 mL of water and 25 mL of 95% ethanol, heated to 65 °C. The distillate was collected in a receiver cooled to 0 °C and divided into two equal parts and each part was allowed to react with 500 mg of warfarin in 40 mL of diethyl ether, cooled to 0 °C. After standing for 1 h, the excess CH_2N_2 and the ether were allowed to evaporate in a well-ventilated hood at ambient temperature. The resulting solid was recrystallized from acetone and then benzene to yield 0.5 g [48%; mp 126 °C (lit. mp 127 °C)]. An alternate method utilizing 33 g (0.1 mol) of sodium warfarin, U.S.P., in 300 mL of acetone to which 20 g (0.14 mol) of iodomethane is added was also used. The mixture was refluxed 36 h and after vacuum distillation of the acetone the product was partitioned between 300 mL of ether and 30 mL of 1 N sodium hydroxide. Concentration of the ether solution gave a white crystalline solid: 15.5 g (48%); mp 124–126 °C; mmp (with diazomethane preparation) 124–126 °C. TLC of the products of these reactions in a variety of solvent systems showed that **6** was the sole product. A partial magnetic resonance spectrum is given in Table I. A crystal of **6** of dimensions 0.6 × 0.6 × 0.5 mm was chosen for diffraction work. Preliminary precession photographs revealed that the crystals were monoclinic, space group $P2_1/c$ (absences $h0l$, l odd; $0k0$, k odd). The crystal was mounted on a four-circle diffractometer and cell constants were obtained from the settings of 13 reflections for which $2\theta > 20°$. The cell constants are (Mo Kα) a = 9.358 (1), b = 13.664 (4), and c = 14.358 (2) Å, β = 114.19 (2)°, d_{calcd} = 1.277 g cm^{-3}, Z = 4. A total of 3006 reflections to $\sin\theta/\lambda$ = 0.60 Å^{-1} was measured by the θ–2θ scan technique over a range in 2θ of 1.4° corrected for the α_1 – α_2 separation. Background counts were measured at each limit of the scan range. Standard reflections were measured at frequent intervals and a correction for deterioration (maximum 2.4%) was applied to the data, as well as coincidence, Lorentz, and polarization corrections. The 200 highest E's were supplied to program MULTAN[21] and the phase determination routine gave a set with favorable figures of merit (R_{Karle} = 29.60, ABSFOM = 1.17). An E map calculated from this set revealed all the nonhydrogen atoms in 24 of the 27 highest peaks. Initially using only

the data to sin $\theta/\lambda = 0.54$ Å^{-1}, four cycles of least-squares refinement on the nonhydrogen atoms and their isotropic thermal parameters reduced R to 0.14. The anisotropic thermal parameters for these atoms were introduced as well as the hydrogen atoms in positions calculated 1 Å from the attached atom with isotropic thermal parameters. Two further cycles lowered R to 0.088. One further cycle followed by introduction of a weighting scheme corresponding to $1/\sigma(F)^2$, together with a $1\sigma(F)$ cutoff and the inclusion of the remainder of the data (to sin $\theta/\lambda = 0.60$ Å^{-1}) and ignoring 17 reflections with large F_o considered to be affected by secondary extinction, led to a suitable conclusion with $R = 0.069$, $R_w = 0.044$.

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Supplementary Material Available: A listing of structure-factor amplitudes and the thermal parameters for the coordinates listed in Tables III and IV (27 pages). Ordering information is given on any current masthead page.

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Notes

Azabicyclo Chemistry. 6. An Investigation of One of the Chemical Parameters for Analgetic Activity. Synthesis of 2-Methyl-2-azabicyclo[3.3.1]non-6-ene and -non-7-ene[1]

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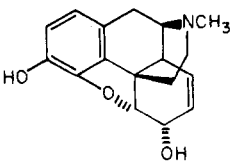
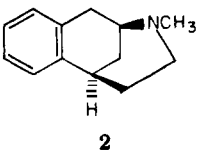
The olefins 2-methyl-2-azabicyclo[3.3.1]non-6-ene (**3**) and -non-7-ene (**6**) were prepared in order to evaluate their analgetic activity. The reduction of 2-methyl-2-azabicyclo[3.3.1]nonan-7-one (**4**) with $NaBH_4$ gave, stereospecifically, the axial alcohol **5**. Reaction of **5** with CH_3SO_2Cl–pyridine gave directly the olefins **3** and **6**, both of which upon hydrogenation gave the known 2-methyl-2-azabicyclo[3.3.1]nonane (**7**). The structural proof of **3**, **5**, and **6** was ascertained by spectral methods. Of the compounds prepared, **3**, **5**, and **6** were essentially inactive as analgetics when tested in mice by the hot-plate method, while **4** had marginal activity.

It has been recognized for some time that certain structural features of morphine (1) should be maintained in any modification of its structure in order to retain analgetic potency. They are (1) the phenyl nucleus, (2) the quaternary carbon attached to this nucleus, and (3) the tertiary nitrogen two carbon atoms removed from the quaternary carbon.[2] Several years ago, May and coworkers[3] described the synthesis and biological evaluation of 2-methyl-6,7-benzomorphan (**2**), the simplest member of a family of strong analgetics,[2] a class which has begun to yield compounds which are devoid of any physical dependence capacity.[4]

Inasmuch as the biologically active benzomorphan **2** represents an abbreviated morphine structure wherein the



1



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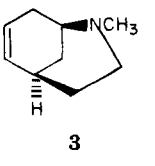

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