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The Mechanism and Crystal Structure of 2-Methoxy-2-methyl-4-phenyl-3,4,4a,10b-tetrahydro-2H,5H-pyrano[3,2-c]chromen-5-one. Acetal of Warfarin Acid

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Acetal of warfarin acid has been synthesized via a hemi acetal intermediate and structurally characterized by X-ray diffraction. The crystal structure shows that the title compound was formed by the hydrolysis of warfarin acid in methanol at pH 3, with space group $P2_1/n$ and unit cell parameters a = 5.859 (17), b =16.745 (5), c = 16.402 (5) Å, $\alpha = 90.00$; $\beta = 94.853$ (4), and $\gamma = 90.00^\circ$.

Key Words: Warfarin acid, synthesis, acetal, crystal structure.

Introduction

Acetals are useful as protecting groups for both carbonyl compounds and alchohols.[1] Acetals contribute valuable functionality to organic synthesis.[2] O,O-Acetals are particularly useful as protected aldehydes and ketones, which are deprotected by mild acid hydrolysis.[3] S,S-Acetals are important acyl anion equivalents (reversal of polarity), and are hydrolyzed to carbonyl compounds under oxidative conditions.[4] Acid hydrolysis of other types of acetals (e.g., O,S-, N,S-, N,N-, and N,O-acetals) has also been described in the literature.[5−8] Acetyals are intermediates used for the synthesis of natural products and related compounds[9−11] due to the useful biological activities associated with some of their derivatives.[12,13] To the best of our knowledge, there is currently only one crystal structure reported in the literature on this kind of structure.[14]

We describe the crystal structure of the title compound in this paper. The crystal structure reveals that the hydrolysis of warfarin acid in methanol at pH 3, through the proposed multi-step mechanism, gives 2-methoxy-2-methyl-4-phenyl-3,4,4a,10b-tetrahydro-2H,5H-pyrano[3,2-c]chromen-5-one.

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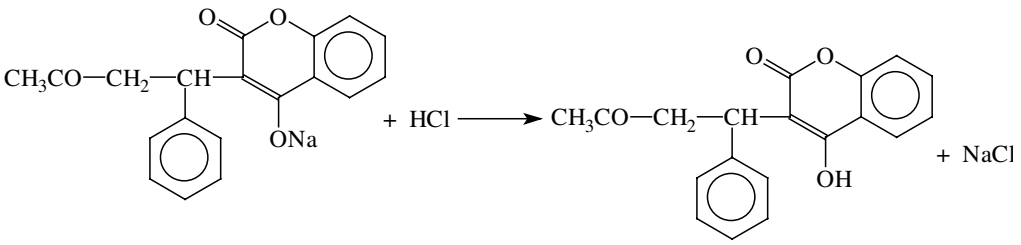
Experimental

Conversion of warfarin sodium into warfarin acid

The sodium salt (1 mmol) was dissolved in distilled water (30 mL). To this solution, conc. HCl was added dropwise until a white precipitate was obtained. This was filtered, washed with distilled water, and air dried.

Yield: 93%, m.p. 152-154 °C. Analysis Calc. for $C_{19}H_{16}O_4$: C, 74.02; H, 5.19. Found C, 74.09; H, 5.22 (%). IR (KBr, cm^{-1}), 1707, 1682 ν(C=O), 3415 ν(OH). ^{1}H NMR: ($CDCl_3$, ppm, 300 MHz), 9.83 (m, 3H, CH_3CO-), 2.52 (s, 1H, CH-), 11.3 (s, 1H, OH). ^{13}C NMR: ($CDCl_3$, ppm, 300 MHz), 185.6 (-CH_3CO), 20.5 (-CH), 22.1 (CH_2), 173.1 (-OCO).

The chemical reaction is given below:



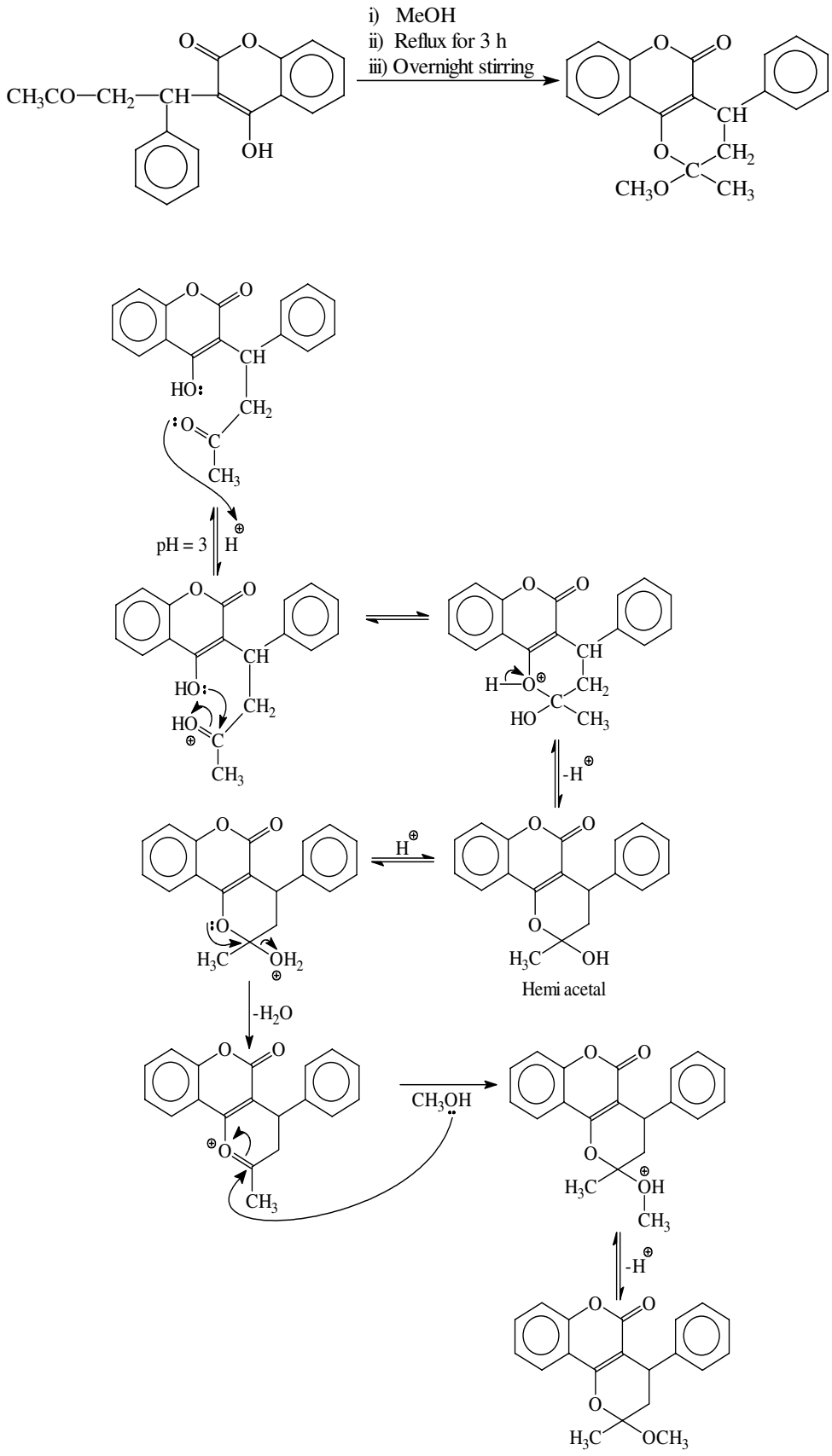
Synthesis

Warfarin acid (2 g, 1 mmol) was dissolved in dry methanol (30 mL) in a 100-mL round bottom flask equipped with a water condenser at constant pH 3, accompanied by stirring and heating. The mixture was refluxed for 3 h and left for overnight stirring at room temperature. After the solvent was removed by evaporation, the crude product formed was crystallized in 1:1 methanol/n-hexane to yield good quality needle-like white crystals. The general chemical reaction is given below:

The proposed mechanism is given in the Scheme. It has been suggested from the above mechanism that hydrolysis of warfarin acid is thermodynamically and kinetically favorable in an acidic medium. It is a multi-step mechanism. Formation of a five- or six-membered ring is easy. After hemi acetal formation, it will get protonated. In the next step, removal of H_2O, followed by a CH_3OH attack on the carbon and subsequent removal of H^+, gives the acetal.

X-Ray Crystallography

X-ray data were collected on a Bruker SMART diffractometer with graphite monochromated M_oK_α radiation (λ = 0.71073 Å). The structure was solved by direct methods[15] and refined by full matrix least-squares.[15] All non-hydrogen atoms were refined anisotropically in F^2 mode. H atoms were included in calculated positions using the riding method. The experimental absorption correction type is multi-scan. Experimental absorption correction (Tmin) is 0.9683, while experimental absorption correction (Tmax) is 0.9817.


i) MeOH
ii) Reflux for 3 h
iii) Overnight stirring
pH = 3
Hemi acetal
-H2O
CH3OH

Results and Discussion

Crystal data and refinement parameters are listed in Table 1, and the interatomic bond distances (Å) and bond angles (^{o}) are listed in Table 2. The molecular structure of the title complex is given in Figure 1.

Table 1. Crystal data of the reported complex.

Empirical formula	$C_{20}H_{18}O_4$
Formula weight	322.34
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	
a(Å)	5.859(17)
b(Å)	16.745(5)
c(Å)	16.402(5)
$\alpha(^o)$	90.00
$\beta(^o)$	94.853(4)
$\gamma(^o)$	90.00
V(Å^3)	1603.4(8)
Z	2
θ range for data collection (^{o})	2.733-25.401
Crystal size (mm)	0.35 × 0.32 × 0.20
Dc (g cm^{-3})	1.335
F(000)	680
Total reflections	2806
Independent reflections	2023
R indices (all data)	$R_1 = 0.0545$, $wR_2 = 0.990$
Final R indices [I > 2σ(I)]	$R_1 = 0.372$, $wR_2 = 0.918$
Goodness-of-fit	0.974
Data/restraints/parameters	2806/0/284

The crystal structure contains one molecule in the asymmetric unit. The C(14), C(19), C(15), and C(18) atoms are coplanar. In this plane, the atom distances range from 1.35(2) to 1.44(2) Å, with an average of 1.38(2) Å. The C(19)-O(3)-C(11) bond angle (122.04(12)°) is slightly different from O(2)-C(13)-C(12) (124.00(15)°). C(1), C(2), C(13), C(14), and C(19) are coplanar, and, in this plane, the C-C bond distances range from 1.35(2) to 1.50(2) Å, with an average of 1.31(2) Å. The C-C bond angles are in the range of 107.11(14) ∼ 125.78(17)°. The aromatic ring in the molecule does not show any unusual features, and the bond lengths and the bond angles are within the normal range. The C-C distances found in the title compound are quite similar to those of 6-bromo-piperonal-dimethyl acetal.[14] A view of the unit cell contents is shown in Figure 2.

Table 2. Selected bond lengths (Å) and bond angles (°) of the reported complex.

Bond Lengths		Bond Angles	
C(1)-C(2)	1.50(2)	O(1)-C(2)-C(3)	107.11(14)
C(2)-O(1)	1.40(18)	O(1)-C(2)-C(1)	113.81(14)
C(2)-C(3)	1.50(2)	C(3)-C(2)-C(1)	114.04(15)
C(3)-C(4)	1.53(2)	C(12)-C(4)-C(3)	109.73(14)
C(4)-C(5)	1.52(2)	C(6)-C(5)-C(4)	121.11(15)
C(4)-C(12)	1.51(2)	O(4)-C(11)-O(3)	115.81(15)
C(5)-C(6)	1.37(2)	O(4)-C(11)-C(12)	125.78(17)
C(5)-C(10)	1.38(2)	O(3)-C(11)-C(12)	118.40(14)
C(6)-C(7)	1.38(2)	O(2)-C(13)-C(12)	124.00(15)
C(11)-O(4)	1.20(18)	O(2)-C(13)-C(14)	114.23(13)
C(11)-O(3)	1.38(2)	C(19)-C(14)-C(13)	117.75(14)
C(11)-C(12)	1.44(2)	C(16)-C(15)-C(14)	120.29(18)
C(12)-C(13)	1.35(2)	C(17)-C(18)-C(19)	118.47(18)
C(13)-O(2)	1.35(18)	O(3)-C(19)-C(14)	120.77(15)
C(13)-C(14)	1.44(2)	O(3)-C(19)-C(18)	117.32(15)
C(14)-C(19)	1.38(2)	C(14)-C(19)-C(18)	121.91(16)
C(19)-O(3)	1.37(18)	C(2)-O(1)-C(29)	116.30(14)
C(29)-O(1)	1.42(2)	C(19)-O(3)-C(11)	122.04(12)

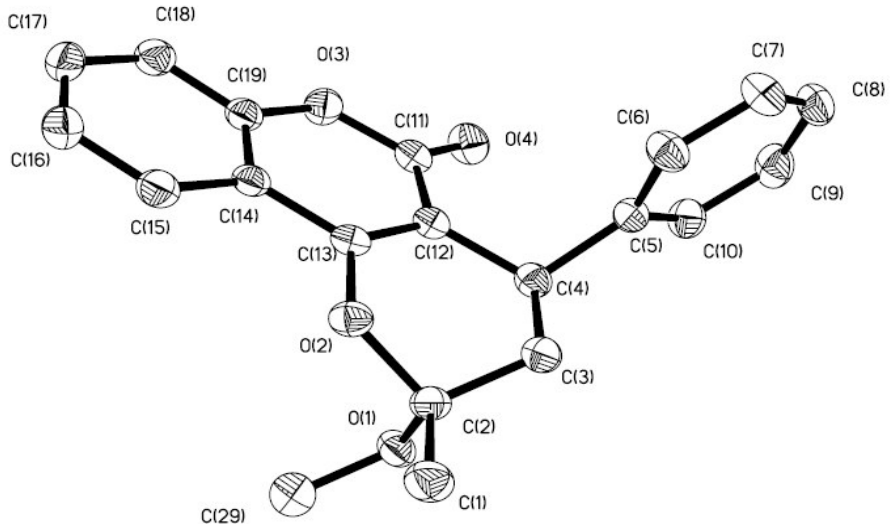


Figure 1. ORTEP drawing of the complex with atomic numbering scheme.

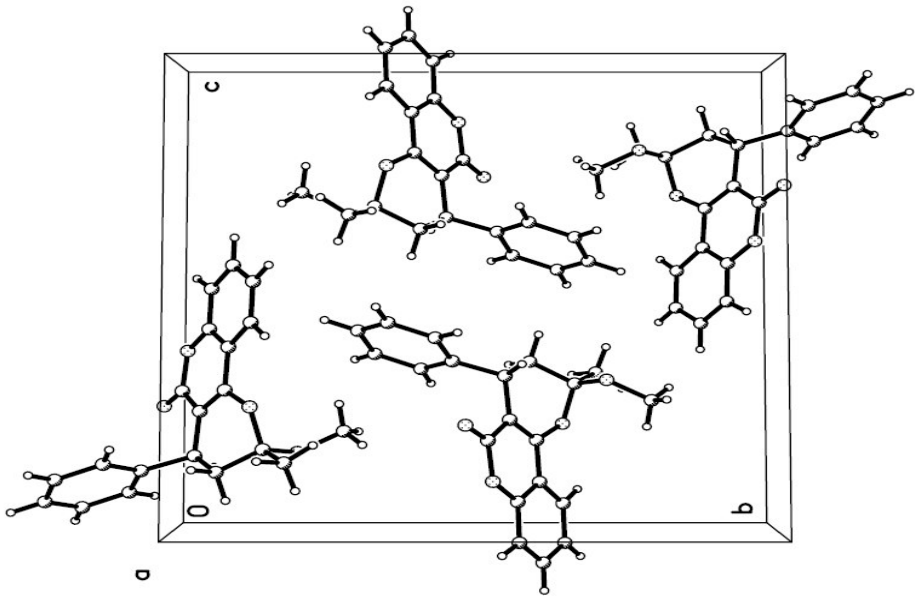


Figure 2. The molecular packing of the title complex viewed down the a-axis.

Supplementary Material

Crystallographic data for structure analysis for the title complex have been deposited with the Cambridge Crystallographic Data Center, CCDC No. 280088. Copies of the information may be obtained from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336033; Email: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

Acknowledgments

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