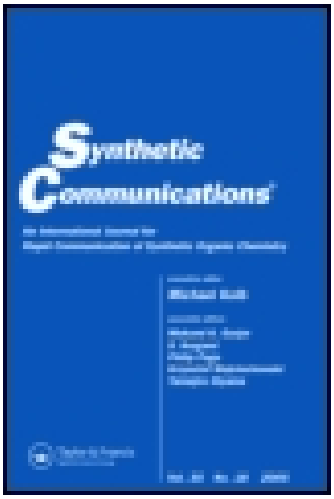

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SYNTHESIS OF ACYLATED STEROIDAL OLEFINS AND THEIR DERIVATIVES

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Acylation of cholest-5-ene and cholest-5-ene 3-one with anhydrides in the presence of zinc chloride and characterization of products thus obtained on the basis of elemental analysis, spectral data, and chemical transformations are reported.

Keywords: Acetic anhydride; anhydrous sodium sulfate; Baeyer–Villiger oxidation; carbon tetrachloride; sodium bicarbonate solution (5%); zinc chloride

Acylation has shown interesting results,[1–3] and in the Friedel–Crafts method, the β,γ-unsaturated ketone is the main product.[4–6] No attempt has been reported of similar studies on steroidal olefins, and our continued interest in oxygen-containing steroids[7–9] prompted us to investigate similar reactions with steroidal olefins.

Cholest-5-ene(1),[10] on treatment with acetic anhydride and zinc chloride, afforded two products with melting points of 92 °C (**3**) and 125 °C (**4**) (Figure 1), which were almost identical in terms of composition and infrared (IR) spectral values (Table 1). Distinguishing the isomeric products was made possible with the help of ^{1}H NMR spectra. Compound **3** showed a distorted doublet at δ2.94 with $J = 5.5$ Hz for one proton ascribable to C6-αH (equatorial),[11] making the acetyl group β (axial) oriented. For compound **4**, the peak for the C6-proton was observed at δ 3.25 with $J = 11.9$ Hz (β, axial-H), making the acetyl group α-oriented.

The chemical shift for the C4-vinylic proton is influenced by the orientation of the C6-acetyl group. In compound **3**, the proton appears at δ5.67 (C6β-acetyl), whereas in its isomer (**4**), the same proton appeared at relatively upfield δ4.99 because of the carbonyl cone effect possible when the acetyl group is equatorially oriented.[11]

This stereochemical assignment of the acetyl group in compounds **3** and **4** is strongly supported by the observation that under electron-impart mass spectrometry (EI-MS), the loss of the β-oriented acetyl group in compound **3** is much faster than the same loss in compound **4**.

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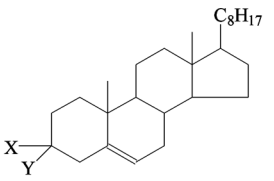
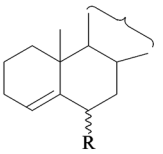
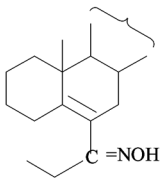


(1) X=Y=H
(1a) X=Cl,Y=H
(1b) X=OAc,Y=H
(2) X,Y=O



(3) R = β-$COCH_3$
(4) R = α-$COCH_3$
(5) R = β-$COCH_2CH_3$
(6) R = β-$C(CH_3)$=NOH
(7) R = α-$C(CH_3)$=NOH



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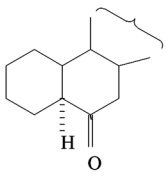

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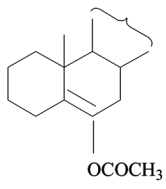

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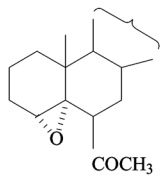

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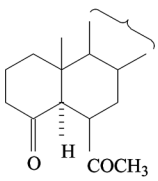

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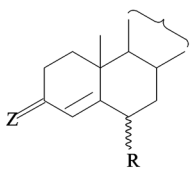
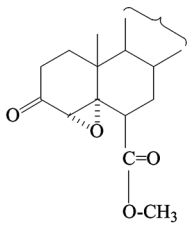


(13) R = H, Z=O
(14) R = α-$COCH_3$, Z=O
(15) R = α-CCH_3=NOH, Z=NOH
(18) R = β-$OCOC_2H_5$, Z=O



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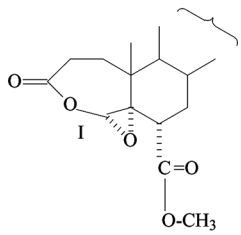


(17)

Figure 1.

The same substrate (**1**) under similar conditions, using propanoic anhydride and zinc chloride, furnished only one compound (mp 99 °C) characterized as 6β-propionyl cholest-4-ene (**5**). The stereochemical assignment of the propionyl group (axial) is based on the observation of a multiplet at δ2.88 ($W1/2 = 3$ Hz) for one proton at C6 (equatorial). The elemental analysis and IR spectral values (Table 1) for the compound are in full agreement with the structure (**5**).

The formulations **3**, **4**, and **5** find further support on the basis of preparation of simple derivatives. The compounds **3–5** afforded the corresponding oximes **6**, **7**, and **8**, respectively.

Table 1. Analytical and spectral data of the compounds

Compound	Composition	Analysis (%), found (calculated) C	H	N	IR (KBr/NuJol) (υ max cm^{-1})	^1H NMR (100 Hz)	Mass EI (m/z)
3	$C_{29}H_{48}O$	84.40 (84.46)	11.54 (11.65)	—	1710 (C=O), 1650 (C=C)	5.67 (1H, m, C4H), 2.94 (1H, dis.d, $J = 5.5$ Hz C6αH), 2.14 (3H, s, CH_3CO), 0.90, 0.87, 0.84, 0.67 (other methyl protons)	412 (M^+), 397 (M-CH_3), 384 (M-CO/C_2H_4), (M-CH_2-=C=O), 369 (397-CO)
4	$C_{29}H_{48}O$	84.41 (84.46)	11.55 (11.65)	—	1710 (C=O), 1655 (C=C)	4.99 (1H, m, C4H), 3.25 (1H, dis.d, $J = 11.9$ Hz C6βH), 2.17 (3H, s, CH_3CO), 1.09, 0.88, 0.85, 0.67 (other methyl protons)	412 (M^+), 397 (M-CH_3), 384 (M-CO/C_2H_4), 370 (M-CH_2-=C=O), 369 (397-CO)
5	$C_{30}H_{50}O$	84.41 (84.43)	11.78 (11.81)	—	1710, 1650	5.65 (1H, m, C4H), 2.8 (1H, m, W1/2 = 3 Hz, C6αH), 2.4 (2H, q, $COCH_2CH_3$), 1.8, 1.63, 1.2, 1.08, 0.85, 0.7 (other methyl protons)	426 (M^+)
6	$C_{29}H_{49}NO$	81.36 (81.49)	11.50 (11.47)	3.11 (3.27)	3250 (OH), 1655–1615 (C=C, C=N)	8.67 (1H, s, C=NOH), 5.54 (1H, m, C4H), 2.85 (1H, dis.α, $J = 4.7$ Hz, C6 α-H), 1.80 (3H, s, CH_3-C=NOH), 1.02, 0.90, 0.87, 0.81, 0.65 (other methyl protons)	427 (M^+), 412 (M-CH_3), 409 (M-H_2O), 384 (M-CH_2=C=O) 369 M- CH_2=C=O (M-CH_3-C=N-O-H)
7	$C_{29}H_{49}NO$	81.38 (81.49)	11.41 (11.47)	3.18 (3.27)	3280 (OH), 1640–1620 (C=C, C=N)	5.0 (1H, m, C4-H), 3.0 (1H, m, W1/2 = 8 Hz, C6 β-H), 1.8 (3H, s, CH_3-C=N-OH), 1.43, 1.33, 1.26, .0.95, 0.83 (other methyl protons)	427 (M^+), 412, 409, 384, 369
8	$C_{30}H_{51}NO$	81.58 (81.56)	11.59 (11.63)	3.11 (3.17)	3280, 1660	3.25 (2H, m, ClH_2), 1.23, 1.2, 0.93, 0.85, 0.77 (methyl protons).	—
9	$C_{29}H_{48}O_2$	81.36 (81.30)	11.28 (11.21)	—	1720 (CH_3CO), 1660 (C=C)	2.17 (3H, s, CH_3COO), 1.06, 0.9, 0.87, 0.84, 0.62 (other methyl protons)	428 (M^+), 413 (M-CH_3), 386 (M-CH_2CO), 385 (M-CH_3CO), 369 (M-CH_3COO)
11	$C_{29}H_{48}O_2$	81.34 (81.30)	11.26 (11.21)	—	1710, 860 (epoxy ring)	3.29 (1H, d, $J = 12.5$ Hz, C4 β-H), 2.86 (1H, d, $J = 4.1$ Hz, C6 α-H),	428 (M^+), 399 (M-CHO), 386, 385, 368

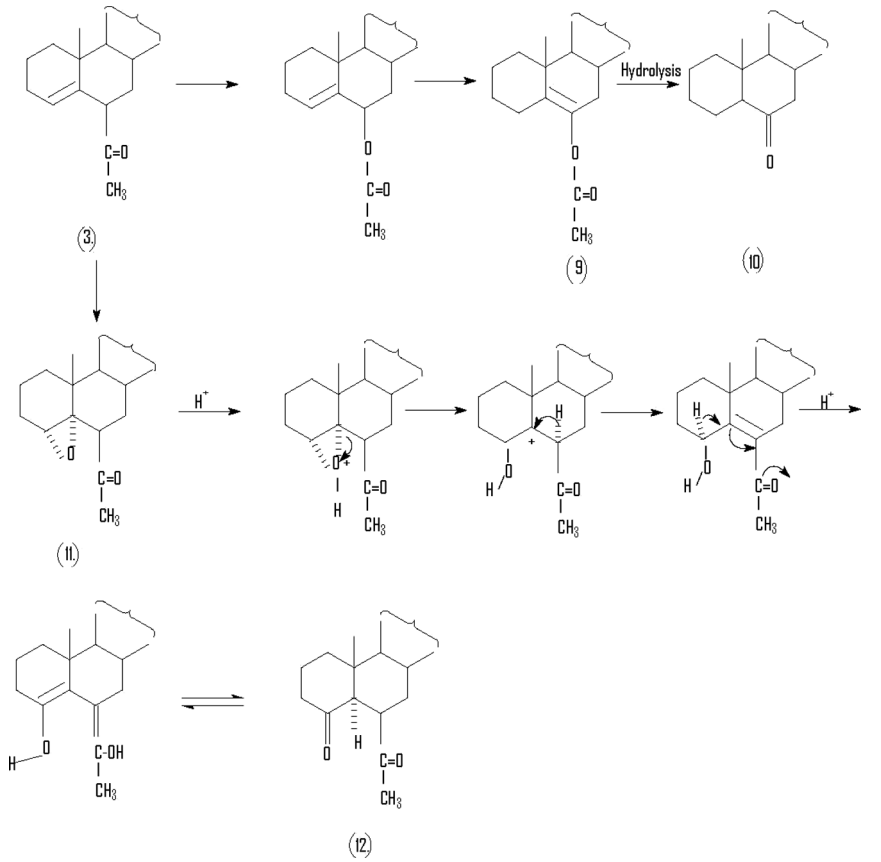
						2.17 (3H, s, CH_3CO), 1.11, 0.99, 0.87, 0.84, 0.62 (other methyl protons)	
12	$C_{29}H_{48}O_2$	81.34 (81.30)	11.24 (11.21)	—	1720–1680 (more than one CO)	2.92 (1H, m, C6 α –H) 2.81 (1H, d, $J = 3.8$ Hz, C5 α-H), 2.2 (2H, m, $C3H_2$), 2.05 (3H, s, CH_3CO), 1.12, 0.92, 0.88, 0.84, 0.68 (other methyl protons)	428 (M^+), 413, 400, 386, 315 ($M\text{-}C_8H_{17}$)
14	$C_{29}H_{46}O_2$	81.61 (81.63)	10.78 (10.86)	—	1710 (C=O), 1680 (C=C-CO), 1615 (C=C)	5.96 (1H, s, C4-H), 3.2, (1H, m, W1/2 = 9 Hz, C6 β-H), 2.13 (3H, s, CH_3CO), 1.25, 1.0, 0.9, 0.8, 0.7 (other methyl protons)	426 (M^+)
15	$C_{29}H_{48}N_2O_2$	76.22 (76.26)	10.51 (10.59)	6.08 (6.13)	3240, 1650, 1630	7.0 (2H, bs, two NOH), 5.57 (1H, s, C4-H), 2.81 (1H, m, C6β-H), 2.1 (3H, bs, CH_3-C=NOH), 1.2, 0.91, 0.8, 0.6 (other methyl protons)	—
16	$C_{29}H_{46}O_4$	75.92 (75.93)	10.09 (10.11)	—	1740, 1705, 910 (epoxy)	3.8 (1H, s, C4β-H), 3.6 (3H, s, CH_3-O-CO), 3.3 (1H, m, W1/2 = 9 Hz, C6 β-H), 2.03 (2H, bm, C_2- H_2), 1.2, 1.16, 0.95, 0.85, 0.71 (other methyl protons).	—
17	$C_{29}H_{46}O_5$	73.35 (73.37)	9.72 (9.76)	—	1750 br, 910	4.0 (1H, s, C4aβ-H), 3.5 (3H, s, $COOCH_3$), 3.1 CO), 3.1 (1H, bm, W1/2 = 10 Hz, C6 β-H), 2.56 (2H, bm, C_2-H_2), 1.28, 1.12, 1.01, 0.8, 0.7 (other methyl protons)	—
18	$C_{30}H_{48}O_3$	78.81 (78.89)	10.49 (10.59)	—	1740, 1680	5.7 (1H, s, C4-H), 5.45 (1H, m, W1/2 = 8 Hz, C6 α-H), 2.36 (4H, bm, C_2-H_2 and CH_3-CH_2-CO), 1.18, 1.1, 0.9, 0.8, 0.7 (other methyl protons)	

Compound **3** under Baeyer–Villiger oxidation conditions using m-chloroperbenzoic acid gave four products identified as 6β-acetoxycholestan-5-ene (**9**), 5α-cholestan-6-one (**10**),[12] [normal Baeyer–Villiger (B.V.) product], 6β-acetyl-4α,5-epoxy-5α-cholestane (**11**), and 6β-acetyl-5α cholestan-4-one (**12**). Scheme 1 explains the formation of these products starting from compound **3**.

Cholest-5-ene-3-one (**2**)[13] on treatment with acetic anhydride in the presence of zinc chloride afforded two products: cholest-4-en-3-one (**13**)[13] and 6α-acetyl cholest-4-en-3-one (**14**). Compound **13** is a simple isomerized product that refuses the Friedel–Crafts reaction because the double bond is in conjugation with the carbonyl group, whereas the compound **14** is obtained by the Friedel–Crafts reaction before the isomerization can take place.

The characterization of **14** is based on the ^{1}H NMR spectrum, which gave two signals of interest at δ3.2 ($W1/2 = 9$ Hz) and δ5.96 for one proton each. These can be ascribed to C6β-H and C4-vinylic H, and hence the acetyl group at C6 is α-oriented (equatorial).

Compound **14**, on oximation, gave a compound with a melting point of 145 °C, which was analyzed to show two nitrogen atoms. In its IR spectrum, the carbonyl



Scheme 1.

Table 2. Substrate, reagent, and the products

Substrate (wt/mol)	Reagent	Product	Solvent system for elutions	Crystallized form	Yield (g/mol)	Mp (°C)
1, 2.5 g, 0.0067 mol	$(CH_3CO)_2O \cdot ZnCl_2$	3	Petrol/ether 100:2	MeOH	1.15 g, 0.003 mol	92
		4	Petrol/ether 100:5	MeOH	0.63 g, 0.0015 mol	125
2 g, 0.005 mol	$(C_2H_5CO)_2O \cdot ZnCl_2$	5	—	MeOH	0.75 g, 0.0017 mol	99
2.3 g, 0.0078 mol	$(CH_3CO)_2O \cdot ZnCl_2$	13	Petrol/ether 25:1	MeOH	0.5 g, 0.001 mol	80 (81)
0.0078		14	Petrol/ether 16:1	MeOH	0.62 g, 0.001 mol	100
1 g	$(C_2H_5CO)_2O \cdot ZnCl_2$	13	Petrol/ether 25:1	MeOH	0.06 g, 0.00015 mol	80
		18	Petrol/ether 18:1	MeOH	0.7 g, 0.0015 mol	119
3, 2 g, 0.005 mol	$NH_2OH \cdot HCl$	6	—	MeOH and CH_3COCH_3	2 g, 0.003 mol	184
4, 2 g, 0.005 mol	$NH_2OH \cdot HCl$	7	—	—	0.7 g, 0.0017 mol	Oil
5, 1 g, 0.002 mol	$NH_2OH \cdot HCl$	8	—	MeOH	1 g, 0.0017 mol	187
3, 2.5 g, 0.006 mol	Meta-chloroperbenzoic acid	9	Separated	MeOH	0.28 g, 0.0007 mol	98
		10	Prep. TLC	MeOH	0.52 g, 0.001 mol	68–70
		11		—	0.62 g, 0.001 mol	Oil
		12		—	0.8 g, 0.0018 mol	Oil
14, 2 g	$NH_2OH \cdot HCl$	15	Petrol	MeOH and CH_3COCH_3	0.5 g, 0.001 mol	145
	Meta-chloroperbenzoic acid	16	Petrol/ether 15:1	—	0.5 g, 0.001 mol	Oil
		17	Petrol/ether 10:1	—	0.8 g, 0.0017 mol	Oil

band was absent; therefore, it can be formulated as 6α-acetylcholest-4-en-3-one-1′,3-dioxime (**15**).

Baeyer–Villiger oxidation of 6α-acetylcholest-4-en-3-one (**14**) afforded methyl 4 α-5-epoxy-5α-cholestan-3-oxo-6α-carboxylate (**16**) and methyl 3-oxo-4aα,5-epoxy-A-homo-5-α-cholestan-4-oxo-6-α-carboxylate (**17**). A similar attempt using propionic anhydride–zinc chloride with cholest-5-ene-3one (**2**) gave the propionoxy derivative (**18**). The data (Table 1) are in full agreement with the structure being 6β-propionoxy-cholest-4-ene-3-one (**18**).

Similar treatment to 3β-chlorocholest-5-ene (**1a**)[14] resulted in simple replacement of chlorine by the acetoxy group, whereas the 3β-acetoxy cholest-5-ene (**1b**)[15] completely refused to react under the conditions.

EXPERIMENTAL

General Procedure for Acylation

A solution of cholest-5-ene (**1**) (2.5 g, 0.007 mol) in carbon tetrachloride (40 ml) was added in small portions to a well-stirred mixture of acetic anhydride (20 ml) and dry zinc chloride (1 g, 0.007 mol) over a period of 40–45 min. The temperature of the reaction mixture was maintained between 0 and 5 °C by external cooling. After the addition was complete, stirring was continued for 8 h at room temperature under anhydrous conditions. The reaction mixture was then poured into ice-cooled water. The organic matter was extracted with carbon tetrachloride; washed successively with water, sodium bicarbonate solution (5%), and water; and then dried over anhydrous sodium sulfate. Evaporation of solvent under reduced pressure afforded an oil, which was chromatographed over silica gel (50 g). The column was eluted with light petroleum ether to provide different fractions with increasing proportions of ether as shown in Table 2.

Baeyer–Villiger oxidation was carried out according to the literature procedure,[16] and the products are given in Table 2.

Oximation of the ketones as reported was carried out following the procedure reported in the literature,[17] and the products are listed in Table 2.

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