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REACTION OF CHOLEST-4-ENE-3,6-DIONE WITH PERBENZOIC ACID. FORMATION OF NOVEL OXETALACTONES

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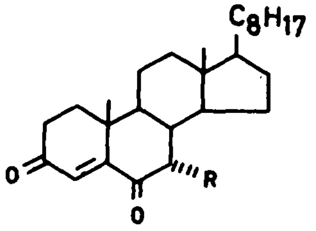
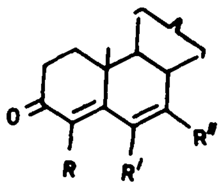
Abstract—Oxidation of **1** with perbenzoic acid (*p*-toluene-sulphonic acid monohydrate as catalyst) provided novel oxetalactones **4** and **5** along with compounds **2** and **3**. Treatment of **2** with perbenzoic acid yielded **4**. A probable pathway for the formation of **4** from **1** involving the intermediacy of **2** has been suggested.

Continuing earlier studies,[1-4] perbenzoic acid oxidation of cholest-4-ene-3,6-dione **1** was considered worthy of study (strong tendency for enolization of the functionalities present). With 1 mole equiv of perbenzoic acid (catalytic amount of *p*-toluene-sulphonic acid monohydrate) **1** afforded compounds **2**, **3** and oxetalactone **4**: and with an excess (2.5 mole equiv) oxetabislactone **5** was produced along with **4**.

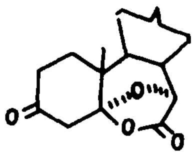
The compound **2** ($C_{27}H_{42}O_3$) indicated the incorporation of only one oxygen atom. The UV absorption maximum at 245 nm (ε 12216) evidenced the presence of an α,β-unsaturated chromophore. The IR spectrum supported structure **2** (broad band at 3330 cm^{-1} for hydroxyl function). A broadened singlet at δ 3.98 (1H) in NMR spectrum of **2** has been assigned to C7-βH[1]. An examination of the Dreiding model of **2** revealed that the dihedral angle between C7-βH and C8-βH is almost 90°, which may account for the absence of sharp splitting of this signal. To substantiate the presence of a hydroxyl group in **2**, it



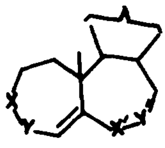
1: R = H
2: R = OH
8: R = AcO



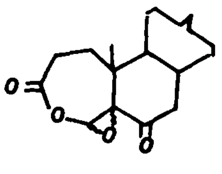
3: R = OH, R' = CH3O, R'' = H
6: R = H, R' = AcO, R'' = AcO
7: R = H, R' = AcO, R'' = H



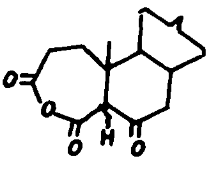
4



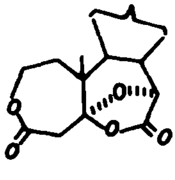
4a: X = X' = CO, Y = Y' = O
4b: X = X' = O, Y = Y' = CO
4c: X = Y' = CO, X' = Y = O
4d: X = Y' = O, X' = Y = CO



4e



4f



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was subjected to acetylation on a steam bath which provided the diacetate **6**. Attempts to prepare a monoacetate **8** from **2** by employing milder conditions (room temp) also resulted in the formation of **6**. The formation of **6** from **2** requires that the latter undergoes enolization during acetylation. For further support, ketone **1** was heated with acetylating reagent to afford the corresponding enol acetate **7**.

The elemental analysis of **3** showed the composition $C_{28}H_{44}O_3$. The UV absorption maximum at 335 nm (ε 22 700) suggested a dienone like chromophore with a hydroxyl group α to keto function. The presence of a methoxy function in the compound was revealed by its NMR spectrum which gave a singlet at δ 3.71 (3H) (methanol present in chloroform solution of PBA).

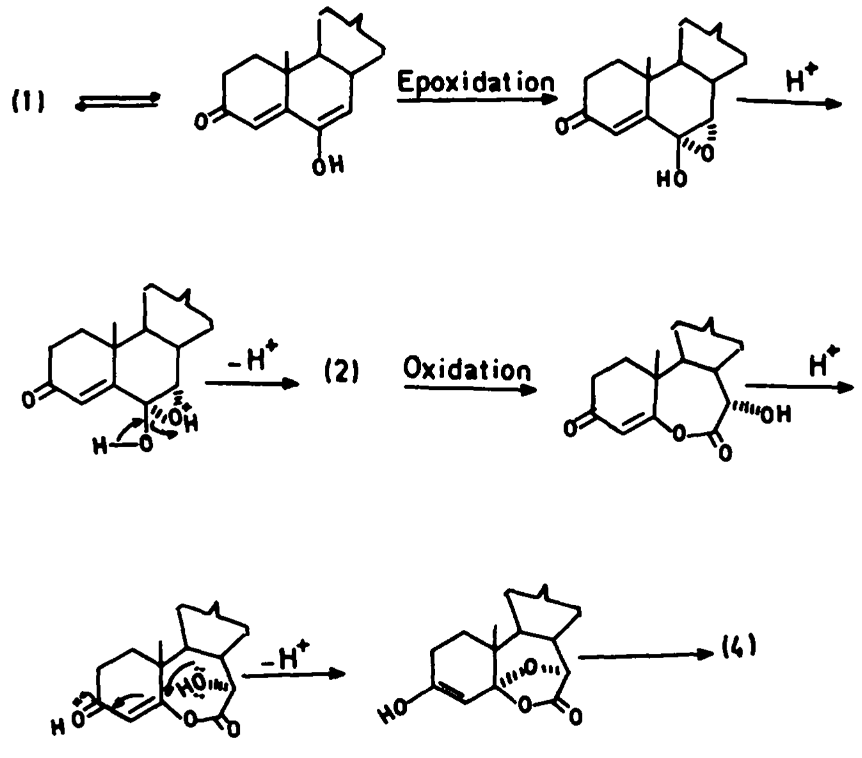
The compound **4** analysed for $C_{27}H_{42}O_4$. From the molecular composition it is evident that two oxygen atoms have been added to **1** during the course of reaction. The UV spectrum was found to be featureless in the region 200–360 nm. The NMR spectrum gave signals at δ 5.6 (1H), 2.9 (d, 1H, J = 15 Hz; gem coupling) and 2.3 (d, 1H, J = 15 Hz; gem coupling). The latter two signals are ascribable to two nonequivalent protons of an isolated methylene group[5] (AB system centred at δ 2.6) as present in **4** $\left(C_4\begin{matrix}\diagup H_A\\ \diagdown H_B\end{matrix}\right)$. Besides **4**, several other structures such as (**4a**–**4f**) can be formulated for this product, which are logically derivable from **1** under the reaction conditions. On the basis of spectral properties, possible structures **4a**–**4f** can be discarded, since none of them possesses an isolated methylene group adjacent to a carbonyl function as required by the NMR spectrum (δ 2.9d and 2.3d). An unresolved singlet at δ 5.6 (1H) in NMR spectrum of **4** was ascribed to C_{7a}-βH[2]. The strong bands at 1798 and 920 cm^{-1} in IR spectrum of **4** can be assigned to C=O and C–O–C linkage of the oxetalactone moiety.[6]

Hydroxy compound **2**, when subjected to perbenzoic acid (1 mole equiv) oxidation afforded **4**. Thus **2** appears to be an intermediate in the transformation of **1** to **4**. A possible mechanism for the formation of oxetalactone **4** from **1** involving the intermediacy of **2** is being proposed (Scheme), in view of the established routes for Baeyer- Villiger oxidation of unsaturated ketones.[7]

Compound **5** ($C_{27}H_{42}O_5$) showed strong bands in IR spectrum at 1795 and 920 cm^{-1} which indicated the presence of oxetalactone moiety[6] in this compound as observed in **4**. The NMR spectrum of **5** was found to be very similar to **4** with an additional signal at δ 4.4 (2H) which is ascribable to $\underline{H_2}C_2$–OCO. The close similarity between the spectral properties of the compounds **4** and **5** suggested strong structural resemblance between the two. Evidently there is a difference of only an oxygen atom between **4** and **5** and it was suspected that insertion of an oxygen atom to **4** has taken place during the reaction. Chemical evidence in support of this proposal came from the perbenzoic oxidation of **4** to afford **5**.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were determined in Nujol with a Perkin-Elmer 237 spectrophotometer and UV spectra were obtained in methanol with a Beckman DK2 spectrophotometer. NMR spectra were run in



Scheme

$CDCl_3$ on a Varian A60 instrument with Me_4Si as the internal standard. TLC plates were coated with silica gel. A 20% aqueous solution of perchloric acid was used as the spraying agent. Light petroleum refers to a fraction of b.p. 60–80°. Anhydrous Na_2SO_4 was used as drying agent.

Bayer-Villiger Oxidation of 1

(i) *With* 1 *mole equiv of perbenzoic acid.* To a solution of **1**[8] (2 g) in chloroform (30 ml) was added a chloroform solution of perbenzoic acid (1 mole equiv) and a few crystals of *p*-toluene- sulphonic acid monohydrate as catalyst. The reaction mixture was allowed to stand at room temp for 60 h. The solvent was removed by distillation under reduced pressure and the residue extracted with ether. The ethereal solution was washed with water, $NaHCO_3$ solution (5%) and water and dried. Removal of the solvent provided a residue (ca 2.1 g) which was chromatographed over silica gel (40 g) (each fraction of about 30 ml was collected). Elution with light petroleum-ether (10:1) gave 4-hydroxy-6-methoxycholesta-4,6-dien-3-one **3**, which crystallized from light petroleum (85 mg), m.p. 100°, ν_{max} 3400, 1650, 1608, 1200, 1060, 1030 cm^{-1}; δ 5.76 (broad s, 1H, C7-$\underline{H}$; Dihedral angle between C7-H and C8-βH was found to be almost 90°), 3.71 (s, 3H, OC$\underline{H}_3$), 2.3 (m, 3H, O$\underline{H}$ and C2$\underline{H}_2$; after D_2O shake, m, 2H, C2$\underline{H}_2$), 1.1 (s, 3H, C10-C$\underline{H}_3$), 0.73 (s, 3H, C13-C$\underline{H}_3$), 0.91 and 0.81 (other methyls). (Found: C, 78.66; H, 10.41. Calc. for $C_{28}H_{44}O_3$: C, 78.50; H, 10.28%). Elution with light petroleum-ether (5:1) yielded unchanged **1** (500 mg), m.p.[8] and m.m.p. 122°. Continued elution with the same solvent combination afforded oxetalactone, 5α,7aα-oxido-6-oxa-B-homocholestane-3,7-dione **4**, which crystallized from light petroleum (210 mg), m.p. 115°, ν_{max} 1798, 1720, 1180, 1140, 920 cm^{-1}; δ 5.6 (broad s, 1H, C_{7a}-$\beta\underline{H}$), [2.9 (d, 1H, J = 15 Hz), 2.3 (d, 1H, J = 15 Hz); gem coupling, $C_4\underline{H}_2$], 1.10 (s, 3H, C10- CH$_3$), 0.70 (s, 3H, C13-C$\underline{H}_3$), 0.9 and 0.8 (other methyls). (Found: C, 75.50; H, 9.84. Calc. for $C_{27}H_{42}O_4$: C, 75.34; H, 9.76%). Further elution with light petroleum-ether (2:1) furnished 7α-hydroxycholest-4-ene-3,6-dione **2**, which crystallized from light petroleum (680 mg), m.p. 165°, ν_{max} 3330, 1700, 1680, 1625, 1040 cm^{-1}; δ 6.1 (s, 1H, C4-$\underline{H}$), 3.98 (broad s, 1H, C7-βH), 2.35 (m, 3H, O-$\underline{H}$ and C2$\underline{H}_2$; on D_2O shake, m, 2H, C2H$_2$), 1.15 (s, 3H, C10-C$\underline{H}_3$), 0.7 (s, 3H, C13-C$\underline{H}_3$), 0.9 and 0.81 (other methyls). (Found: C, 78.31; H, 10.08. Calc. for $C_{27}H_{42}O_3$: C, 78.26; H, 10.14%.)

(ii) *With* 2.5 *mole equiv of perbenzoic acid.* The ketone **1** (2 g), on treatment with an excess of perbenzoicacid (2.5 mole equiv) for 96 hr under similar reaction conditions as described above, followed by column chromatography provided **4** (790 mg), m.p. and m.m.p. 115° and oxetabislactone, 5α,7aα-oxido-3,6- dioxa-A,B-bishomocholestane-4,7-dione **5** (from solvent system light petroleum-ether 5:4), which crystallized from light petroleum (470 mg), m.p. 193°. ν_{max} 1795, 1735, 1200, 1142, 920 cm^{-1}; δ 5.6 (broad s, 1H, C7a-$\beta\underline{H}$), 4.4 (m, 2H, C2$\underline{H}_2$), [3.2 (d, 1H, J = 15 Hz), 2.6 (d, 1H, J = 15 Hz); gem coupling, C4a-$\underline{H}_2$], 1.05 (s, 3H, C10-CH$_3$), 0.78 (s, 3H, C13-CH$_3$), 0.9 and 0.8 (other methyls). (Found: C, 72.85; H, 9.47. Calc. for $C_{27}H_{42}O_5$: C, 72.64; H, 9.41%.)

6,7-*Diacetoxycholesta*-4,6-*dien*-3-*one* 6

A mixture of **2** (200 mg), purified pyridine (0.4 ml) and distilled acetic anhydride (0.3 ml) was heated on a steam bath for 15 h under anhydrous conditions. The solution was poured into cold water and extracted with ether. The ethereal solution was washed with water, dil. HCl, water, $NaHCO_3$ solution (5%) and water and dried. Removal of solvent provided **6**, which crystallized from light petroleum (170 mg), m.p. 125°, λ max 320 nm (ε 21 704); ν_{max} 1765, 1750, 1680, 1650, 1570, 1200, 1210, 1020 cm^{-1}; δ 6.11 (d, 1H, J = 1.5 Hz, C4-$\underline{H}$), 2.2 (s, 3H, C$\underline{H}_3$COO), 2.15 (s, 3H, C$\underline{H}_3$COO), 1.2 (s, 3H, C10- C$\underline{H}_3$), 0.7 (s, 3H, C13-C$\underline{H}_3$), 0.9 and 0.8 (other methyls). (Found: C, 74.58; H, 9.31. Calc. for $C_{31}H_{46}O_5$: C, 74.70; H, 9.23%.)

6-*Acetoxycholesta*-4,6-*dien*-3-*one* 7

Ketone **1** (200 mg) was subjected to acetylation in the manner described for **2**. Usual work up and removal of solvent yielded **7**, which crystallized from light petroleum (160 mg), m.p. 112°. λ_{max} 298 nm (ε 23 200); ν_{max} 1765, 1680, 1640, 1590, 1210, 1190 cm^{-1}; δ 5.78 (d, 1H, J = 1.5 Hz, C4-$\underline{H}$), 5.75 (broad s, 1H, C7-$\underline{H}$), 2.18 (s, 3H, C$\underline{H}_3$COO), 1.18 (s, 3H, C10-C$\underline{H}_3$), 0.76 (s, 3H, C13-C$\underline{H}_3$), 0.9 and 0.81 (other methyls). (Found: C, 79.28; H, 10.11. Calc for $C_{29}H_{44}O_3$: C, 79.10; H, 10.0%.)

Reaction of 2 *with perbenzoic acid*

Hydroxy ketone **2** (150 mg) was subjected to perbenzoic acid (1.2 mole equiv) oxidation under similar conditions as described before and progress of the reaction was monitored by TLC. After 8 h, the reaction mixture was worked up in usual manner. Removal of solvent gave a residue which was chromatographed over silica gel (2 g) (each fraction of ~ 5 ml was collected). Elution with light petroleum-ether (10:3) afforded **4** (110 mg), m.p. and m.m.p. 115° (TLC and IR identical with **4** obtained from **1**).

Reaction of 4 *with perbenzoic acid*

Treatment of **4** (100 mg) with perbenzoic acid (1.5 mole equiv) for 60 h in usual manner and followed by column chromatography over silica gel provided **5** (from solvent system petroleum-ether 5:4), (60 mg), m.p. and m.m.p. 193° (TLC and IR identical with **5** obtained from **1**).

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