cis-Hydroxylation of Steroidal Olefins with Thallium Triacetate

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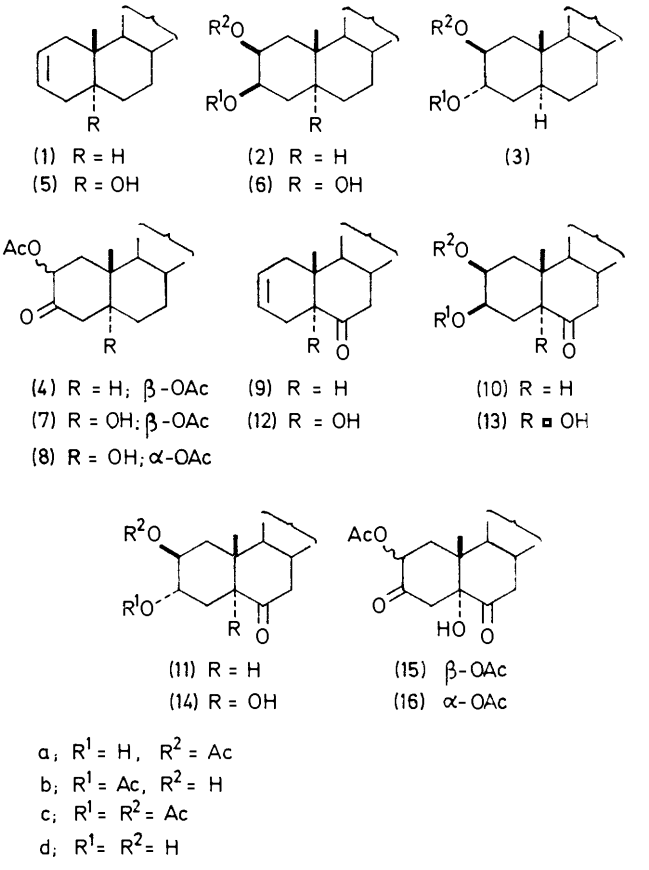
Treatment of 5α-cholest-2-ene (1) with thallium triacetate in acetic acid afforded, in good yield, following hydrolysis, the corresponding β-*cis*-diol. The reaction constitutes a convenient procedure for *cis*-hydroxylation of disubstituted olefins from the hindered side of the molecule and appears to be assisted by the presence of a homoallylic hydroxy-group. 5α-Cholest-2-en-5-ol and 5-hydroxy-5α-cholest-2-en-6-one are converted under milder conditions than compound (1) and 5α-cholest-2-en-6-one into the corresponding 2β,3β-diols.

ALTHOUGH the importance of thallium(III) reagents in organic chemistry is now well established,[1] relatively little attention has been paid to their potential use in the steroid field.[2] We report the first results in a study of the reactions of steroidal olefins with thallium triacetate. The reaction constitutes a convenient alternative to the well known *cis*-hydroxylation of olefins, from the more hindered side of the molecule, by means of silver acetate or benzoate and iodine [3] and of some other procedures recently developed.[4]

The reaction proceeds by initial electrophilic attack of thallium triacetate from the rear, less hindered side of the molecule. The intermediate organothallium derivative is either hydrolysed with inversion of configuration, or displaced by formation of a cyclic acetoxonium ion, as shown to occur in *cis*-hydroxylations by the Woodward procedure.[3]

Treatment of 5α-cholest-2-ene (1) with thallium tri-acetate in excess, in acetic acid solution at *ca.* 60 °C, afforded a mixture of 5α-cholestane-2β,3β-diol 2-acetate (2a), 3-acetate (2b), and 2,3-diacetate (2c),[5a] as well as small amounts of 5α-cholestane-2β,3α-diol 2-acetate (3a). Oxidation of the 2-acetate (2a) gave 2β-acetoxy-5α-cholestan-3-one (4), alternatively obtained from 2α,3α-epoxy-5α-cholestane by treatment with acetic acid and subsequent oxidation of the *trans*-diol acetate.[6] The latter was identical with compound (3a). Hydrolysis of the *cis*-diol acetates (2a and b) afforded the same 2β,3β-diol (2d),[5b] and acetylation gave the diacetate (2c).

The reaction with 5α-cholest-2-en-5-ol (5) proceeded even at room temperature to give a mixture of the β-*cis*-glycol monoacetates (6a and b) in the ratio 3 : 1, accompanied by small amounts of the diacetate (6c). Hydrolysis of both monoacetates gave 5α-cholestane-2β,3β,5-triol (6d). No traces of the corresponding *trans*-glycol acetates were detected. The structure of compound (6a) was proved by oxidation with Jones reagent to the 2β-acetoxy-3-one (7), which was quantitatively isomerised during chromatography on silica gel to the



thermodynamically more stable 2α-acetoxy-3-one (8). The structure of the acetoxy-ketone (7) was confirmed by its independent preparation from 2α,3α-epoxy-5α-cholestan-5-ol [7] following epoxide ring opening to 5α-

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cholestane-2β,3α,5-triol 2-acetate and subsequent oxidation.

It appears that the reaction with thallium triacetate is assisted by the homoallylic 5α-hydroxy-group; it proceeds under milder conditions and in better yields not only with compound (5) but also with 5-hydroxy-5α-cholest-2-en-6-one (12), in contrast to the more drastic conditions required by compound (1) as well as by 5α-cholest-2-en-6-one (9).

The reaction of compound (9) takes place at *ca.* 60 °C and requires a minimum of 24 h to give more than 80% conversion into a mixture of the corresponding *cis*-glycol monoacetates (10a and b) [8] and the diacetate (10c), accompanied by *ca.* 10% of an inseparable mixture of the *trans*-glycol acetates (11a and b).

The main products from 5-hydroxy-5α-cholest-2-en-6-one (12) were the *cis*-glycol monoacetates (13a) [9] and (13b) and the corresponding diacetate (13c) [more than 80% yield; the monoacetate (13a) alone accounts for 65% of the reaction product], again accompanied by *ca.* 10% of a mixture of the *trans*-glycol acetates (14a and b). Hydrolysis of the monoacetates (13a and b) gave the same triol (13d). Oxidation of compound (13a) afforded the 2β-acetoxy-3-one (15), which was isomerised during chromatography on silica gel into the 2α-acetoxy-3-one (16).

EXPERIMENTAL

M.p.s were taken on a Fisher–Johns apparatus. Optical rotations were recorded with an automatic Perkin-Elmer 141 polarimeter and refer to solutions in chloroform. I.r. spectra were recorded for solutions in chloroform with a Perkin-Elmer 237 grating spectrophotometer. N.m.r. spectra were determined with a Varian NV-14 instrument (60 MHz) for solutions in deuteriochloroform. T.l.c. was carried out on chromatoplates of silica gel G (Merck) and spots were developed with iodine vapour. Column chromatography was performed on silica gel 60 (Merck; 70—230 mesh) unless stated otherwise. Petroleum refers to the fraction of b.p. 60—80 °C. Analyses were performed in the microanalytical laboratory of the Weizmann Institute, under the direction of Mr. R. Heller.

5α-Cholest-2-ene (1).—To a solution of 5α-cholestan-3β-yl tosylate (10 g) in benzene (300 ml), alumina (Alcoa F_{20}) (100 g) was added and the slurry was heated to reflux with stirring for 1 h. After cooling, the mixture was introduced into a chromatographic column and the product washed out with ethyl acetate. The solvent was removed and the crude product (8 g) was chromatographed on alumina (200 g). Elution with petroleum gave compound (1) (5 g), m.p. 74° (from methanol) (lit.,[10] 74—75°); elution with chloroform gave 5α-cholestan-3α-ol (3 g), m.p. 187° (from methanol).

5-Hydroxy-5α-cholest-2-en-6-one (12).—The compound was obtained as reported,[11] with the exception of the last step, the conversion of 5-hydroxy-3β-tosyloxy-5α-cholestan-6-one into (12). This reaction was carried out on alumina as described above. Elution with dichloromethane gave compound (12) (5 g), m.p. 140—141° (lit.,[11] 140—141°). Further elution with ethyl acetate gave 3α,5-dihydroxy-5α-cholestan-6-one.

Treatment of 5α-Cholest-2-ene (1) *with Thallium Triacetate.*—Thallium triacetate (2.2 g) was added to a solution of compound (1) (1 g) in glacial acetic acid (40 ml) and the solution was stirred for 6 h at 60 °C. After cooling to room temperature, N-hydrochloric acid (5 ml) was added to precipitate most of the thallium; the precipitate was filtered off and washed with ether. Water (100 ml) was added to the filtrate and the product was extracted with ether (3 × 100 ml). The combined extracts were washed with aqueous 5% sodium hydrogen carbonate until a test for thallium ions was negative (no colouration with 10% potassium iodide), then washed with water (3 × 50 ml), dried (Na_2SO_4), and evaporated. The crude product was chromatographed; elution with petroleum gave unchanged material (1) (150 mg). Elution with petroleum–dichloromethane (1 : 1) gave 5α-cholestane-2β,3β-diol 2,3-diacetate (2c) (150 mg), m.p. 116—117° (from aqueous methanol) (lit.,[5a] 121—123°; 108—110°). Elution with dichloromethane–ethyl acetate (9.5 : 0.5) gave *5α-cholestane-2β,3β-diol 3-acetate* (2b) (120 mg), followed by a mixture of the two *trans*-diol monoacetates (3a and b). Compound (2b) had m.p. 154—155° (from aqueous methanol), $[\alpha]_D$ +26° (*c* 0.8); $\nu_{max.}$ 1 724 cm^{-1} (Found: C, 78.05; H, 11.35. $C_{29}H_{50}O_3$ requires C, 77.95;

N.m.r. data *

Compd.	2-H	3-H	C(10)CH_3	Acetates
(2a)	5.13m ($W_{\frac{1}{2}}$ 6)	3.72m ($W_{\frac{1}{2}}$ 21)	0.90	2.07
(2b)	4.12m ($W_{\frac{1}{2}}$ 8)	4.8m ($W_{\frac{1}{2}}$ 22)	1.03	2.07
(2c)	5.25m ($W_{\frac{1}{2}}$ 9)	4.83m ($W_{\frac{1}{2}}$ 22)	0.95	1.98, 2.07
(2d)	3.9m		1.00	
(4)	5.37dd (10; 7)		0.85	2.12
(6a)	5.20m ($W_{\frac{1}{2}}$ 6)	4.26m ($W_{\frac{1}{2}}$ 22)	1.07	2.07
(6b)	4.20m ($W_{\frac{1}{2}}$ 8)	5.35m ($W_{\frac{1}{2}}$ 22)	1.20	2.09
(6c)	5.37m		1.13	1.98, 2.07
(6d)	4.10m		1.18	
(7)	5.77dd (10; 6)		0.95	2.12
(8)	5.33t (10)		1.27	2.15
(10a)	5.15m ($W_{\frac{1}{2}}$ 8)	3.65m ($W_{\frac{1}{2}}$ 20)	0.88	2.08
(10b)	4.12m ($W_{\frac{1}{2}}$ 9)	4.83m ($W_{\frac{1}{2}}$ 16)	1.02	2.08
(10c)	5.30m ($W_{\frac{1}{2}}$ 8)	4.83m ($W_{\frac{1}{2}}$ 18)	0.92	2.00, 2.08
(13a)	5.20m ($W_{\frac{1}{2}}$ 9)	4.13m ($W_{\frac{1}{2}}$ 22)	0.92	2.08
(13b)	4.13m ($W_{\frac{1}{2}}$ 10)	5.15m ($W_{\frac{1}{2}}$ (22)	1.03	2.08
(13c)	5.25m		0.97	1.98, 2.07
(15)	5.63dd (10; 5)		0.83	2.13
(16)	5.33t (9.5)		1.12	2.15

* Recorded at 60 MHz; solvent $CDCl_3$; δ values; coupling constants or signal widths (in Hz) in parentheses.

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H, 11.30%). Elution with dichloromethane–ethyl acetate (3 : 1) gave 5α-*cholestane*-2β,3β-*diol* 2-*acetate* (2a) (500 mg), m.p. 136—138° (from aqueous methanol), $[\alpha]_D$ +36.5° (*c* 0.9); $\nu_{max.}$ 1 724 cm^{-1} (Found: C, 75.4; H, 11.45. $C_{29}H_{50}O_3,CH_3OH$ requires C, 75.25; H, 11.35%). Elution with ethyl acetate–methanol (4 : 1) gave 5α-cholestane-2β,3β-diol (2d) (30 mg), m.p. 175—176° (from aqueous methanol) (lit.,[5b] 178—180°).

When the reaction was performed at room temperature, more than 90% of the starting material was recovered.

Treatment of 5α-*Cholest*-2-*en*-5-*ol* (5) [12] *with Thallium Triacetate.*—The reaction was carried out as above, for 24 h at room temperature. The crude product was separated by chromatography. Elution with dichloromethane gave 5α-*cholestane*-2β,3β,5-*triol* 2,3-*diacetate* (6c), m.p. 162—163° (from aqueous methanol); $[\alpha]_D$ +25° (*c* 1.0); $\nu_{max.}$ 1 732 cm^{-1} (Found: C, 73.6; H, 10.2. $C_{31}H_{52}O_5$ requires C, 73.75; H, 10.4%). Elution with dichloromethane–ethyl acetate (4 : 1) gave 5α-*cholestane*-2β,3β,5-*triol* 3-*acetate* (6b) (280 mg), m.p. 186—188° (methanol), $[\alpha]_D$ +8.0° (*c* 0.8); $\nu_{max.}$ 1 722 cm^{-1} (Found: C, 75.1; H, 11.0. $C_{29}H_{50}O_4$ requires C, 75.3; H, 10.9%). Elution with dichloromethane–ethyl acetate (1 : 1) gave 5α-*cholestane*-2β,3β,5-*triol* 2-*acetate* (6a) (560 mg), m.p. 170—171° (methanol), $[\alpha]_D$ +33.5° (*c* 0.8); $\nu_{max.}$ 1 722 cm^{-1} (Found: C, 75.1; H, 10.9%. $C_{29}H_{50}O_4$ requires C, 75.3; H, 10.9%).

The reaction performed at 50 °C for 4 h gave compounds (6a) (640 mg), (6b) (220 mg), and (6c) (120 mg).

Treatment of 5α-*Cholest*-2-*en*-6-*one* (9) [8] *with Thallium Triacetate.*—The reaction was performed as above, at 60 °C for 24 h (after 6 h 40% of the starting material was unchanged; almost no reaction took place at room temperature). The product was separated by chromatography. Elution with dichloromethane gave unchanged material (9) (180 mg). Elution with dichloromethane–ethyl acetate (9.5 : 0.5) gave 2β,3β-diacetoxy-5α-cholestan-6-one (10c), m.p. 189—190° (from aqueous methanol) (lit.,[8] 191—192°). Elution with dichloromethane–ethyl acetate (9 : 1) gave 3β-acetoxy-2β-hydroxy-5α-cholestan-6-one (10b) (100 mg), m.p. 172—173° (from methanol) (lit.,[8] 178—179°), followed by a mixture of the *trans*-diol monoacetates (11a and b) (80 mg). Elution with dichloromethane–ethyl acetate (2 : 1) gave 2β-acetoxy-3β-hydroxy-5α-cholestan-6-one (10a) (420 mg), m.p. 219—220° (from methanol) (lit.,[8] 218—219°).

Treatment of 5-*Hydroxy*-5α-*cholest*-2-*en*-6-*one* (12) *with Thallium Triacetate.*—The reaction was performed as above, at 50 °C for 6 h. Separation was achieved by chromatography. Elution with dichloromethane gave unchanged material (12) (120 mg). Elution with dichloromethane–ethyl acetate (9.5 : 0.5) gave 2β,3β-diacetoxy-5-hydroxy-5α-cholestan-6-one (13c) (80 mg), m.p. 178—179° (methanol) (lit.,[9] 179°), followed by a mixture of *trans*-diol monoacetates (14a and b) (80 mg). Elution with dichloromethane–ethyl acetate (4 : 1) gave 3β-*acetoxy*-2β,5-*dihydroxy*-5α-*cholestan*-6-*one* (13b) (120 mg), m.p. 198—199° (methanol), $[\alpha]_D$ −44.6° (*c* 0.7), $\nu_{max.}$ 1 710 and 1 740 cm^{-1} (Found: C, 72.8; H, 10.3. $C_{29}H_{48}O_5$ requires C, 73.05; H, 10.15%). Elution with ethyl acetate gave 2β-acetoxy-3β,5-dihydroxy-5α-cholestan-6-one (13a) (680 mg), m.p. 200—201° (methanol) (lit.,[9] 201°).

Hydrolysis of Monoacetates.—To a solution of monoacetate (50 mg) in methanol (5 ml), methanolic 5% potassium hydroxide (3 ml) was added. After 24 h at room temperature, water was added, the solution neutralised with dilute hydrochloric acid, and the product isolated by filtration. Compounds (2a and b) afforded 5α-cholestane-2β,3β-diol (2d), m.p. 175—176°. Compounds (6a and b) gave 5α-*cholestane*-2β,3β,5-*triol* (6d), m.p. 218—220° (from methanol), $[\alpha]_D$ +29° (*c* 0.8) (Found: C, 76.8; H, 11.5. $C_{27}H_{48}O_3$ requires C, 77.1; H, 11.5%). Compounds (13a and b) gave 2β,3β,5-trihydroxy-5α-cholestan-6-one (13d), m.p. 278—280° (from methanol) (lit.,[9] 281°).

Acetylation of Monoacetates.—The monoacetate (50 mg) was treated with acetic anhydride (1 ml) and pyridine (1 ml) overnight at room temperature. The diacetates (2c), (6c), (10c), and (13c) were thus obtained.

Oxidation of Monoacetates.—To a solution of monoacetate (100 mg) in acetone (40 ml), a solution of Jones reagent was added dropwise, with stirring, at 15 °C. After 20 min, the excess of reagent was destroyed with a few drops of methanol, most of the solvent was removed, water was added, and the product was filtered off.

Compound (2a) gave 2β-acetoxy-5α-cholestan-3-one (4), m.p. 143—144° (from methanol) (lit.,[6] 145—146°). Compound (6a) gave 2β-*acetoxy*-5-*hydroxy*-5α-*cholestan*-3-*one* (7), m.p. 190—192° (from aqueous methanol), $[\alpha]_D$ +75.6° (*c* 0.7); $\nu_{max.}$ 1 724 and 1 740 cm^{-1} (Found: C, 75.7; H, 10.55. $C_{29}H_{48}O_4$ requires C, 75.6; H, 10.5%). Compound (13a) gave 2β-*acetoxy*-5-*hydroxy*-5α-*cholestane*-3,6-*dione* (15), m.p. 197—199° (from methanol), $[\alpha]_D$ +29° (*c* 0.7); $\nu_{max.}$ 1 712, 1 724, and 1 740 cm^{-1} (Found: C, 73.2; H, 9.9. $C_{29}H_{46}O_5$ requires C, 73.4; H, 9.75%).

Isomerisation of the Acetoxy-ketones (7) *and* (15).—A solution of compound (7) in benzene was introduced into a column filled with dry silica gel (10 g); after 24 h the product was eluted with benzene–ethyl acetate (4 : 1), the solvent was removed and the product crystallised from aqueous methanol to give 2α-*acetoxy*-5-*hydroxy*-5α-*cholestan*-3-*one* (8), m.p. 184—186°, $[\alpha]_D$ +19° (*c* 0.7); $\nu_{max.}$ 1 724 and 1 742 cm^{-1} (Found: C, 75.8; H, 10.6. $C_{29}H_{48}O_4$ requires C, 75.6; H, 10.5%). Similarly, compound (15) was isomerised into 2α-*acetoxy*-5-*hydroxy*-5α-*cholestane*-3,6-*dione* (16), m.p. 224—225° (from methanol), $[\alpha]_D$ +1.5° (*c* 0.7); $\nu_{max.}$ 1 715, 1 730, and 1 744 cm^{-1} (Found: C, 73.3; H, 9.9. $C_{29}H_{46}O_5$ requires C, 73.4; H, 9.75%).

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