Syntheses of Steroidal *trans*-Iodo Acetates

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Synopsis. The reaction of the following steroidal olefins with iodine–copper(II) acetate in acetic acid afforded the corresponding steroidal *trans*-iodo acetates: 5α-cholest-1-, -2-, and -3-ene; and 5β-cholest-1-, -2-, and -3-ene.

trans-1-Iodo-2-acetates are important as intermediates of Prévost reaction. There have been known many procedures for syntheses of *trans*-1-iodo-2-acetates, namely, *trans*-addition to olefins using iodine–silver(I) acetate,[1] *N*-iodosuccinimide–acetic acid,[2] iodine–mercury(II) acetate,[3] and iodine–thallium acetate.[4] Recently, Georgoulis and Valery[5] reported a convenient procedure for the preparation of vicinal alkoxy-iodoalkanes from alkene by means of copper(II) acetate and iodine. In part of the paper, they mentioned that the reaction of cyclohexene with iodine–copper(II) acetate in acetic acid yielded *trans*-iodo(acetoxy)cyclohexane.

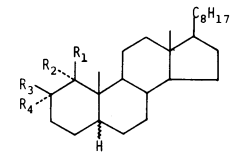
We have been investigating a novel iodination method using iodine–copper(II) acetate; and as early steps in this research project, we have already reported the α-iodination of ketones;[6] the regioselective iodination of estradiol, estriol, and estrone;[7a,7b] a convenient procedure for iodination of electron-rich aromatic compounds;[8] and α-iodination of carboxylic acid.[9]

Now in the present paper, we would like to report that the reaction of the following steroidal olefins readily yielded the corresponding steroidal *trans*-iodo acetates: 5α-cholest-1- (**1**), -2- (**2**), and -3-ene (**3**); and 5β-cholest-1- (**4**), -2- (**5**), and -3-ene (**6**).

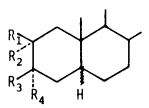
The reaction of 5α-cholest-1-ene (**1**) with iodine–copper(II) acetate in acetic acid at 60 °C for 10 h yielded the *trans*-iodo acetate (**7**), mp 113—114 °C. The NMR spectrum of **7** showed two multiplets due to the C_1- and C_2-proton at δ 4.46 (W/2=6.0 Hz) and 5.45 ppm (W/2=6.0 Hz), respectively. From this spectrum, however, it would not be determined the structure of **7**; and so the following procedure was carried out: The iodo acetate (**7**) was reduced with lithium aluminium hydride to give the 2β-hydroxyl derivative (**18**). By treating the iodo acetate (**7**) with potassium hydroxide, the 1β, 2β-epoxide (**13**) was obtained. From these results an acetoxyl group and an iodine atom of the iodo acetate were shown to be *trans*; this led to a 1α-iodo-2β-acetoxy-5α-cholestane structure for this iodo acetate. Similarly, 5α-cholest-2-ene (**2**) gave the 3α-iodo-2β-acetoxy derivative (**8**) (85%).[10] In the case of 5α-cholest-3-ene (**3**), a needle crystalline material (**9**), mp 83—85 °C was obtained. This product was presumed to be 3α-iodo-4β-acetoxy-5α-chlolestane on the basis of the NMR spectral data. The iodo acetate (**9**) was then converted to the 3β,4β-epoxide (**14**). The reaction of **9** with lithium aluminium hydride gave the 4β-ol derivative (**19**). Similarly, the reaction of 5β-cholest-1- (**4**) and -2-ene (**5**) gave 1β-iodo-2α-acetoxy- (**10**) and 3β-iodo-2α-acetoxy derivatives (**11**), respectively. These structures were determined from the NMR spectra and the chemical methods described above. The reaction of 5β-cholest-3-ene (**6**) gave *trans*-iodo acetate (**12**); mp 125—126 °C. The NMR spectrum showed a triplet (J=10.5 Hz) and a multiplet (W/2=15 Hz) at δ 4.50 and δ 5.02, respectively. By treating **12** with potassium hydroxide according to the method above, 3α, 4α-epoxide (**17**) was obtained. From this fact, *trans*-iodo acetate (**12**) was confirmed to be 4β-iodo-3α-acetoxy-5β-cholestane.

Moreover, the reaction is applicable to the synthesis of hindered *cis*-diols. The *trans*-iodo acetate (**8**) was converted with *m*-chloroperbenzoic acid to give 2β-acetoxy-5α-cholestan-3β-ol (**22**) (90%). Then the hydrolysis of **22** afforded the 2β,3β-diol (**23**) in good yield.

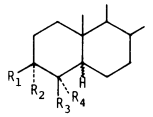
Thus, on the basis of all of the foregoing results, it can be concluded that the reagent used in this work [iodine–copper(II) acetate in acetic acid] is applicable to the steroidal olefins. In the reactions of 5α- and 5β-steroidal olefins with this reagent, the products in the case of the 5α-steroidal olefins were the α-iodo-β-acetoxy derivatives, in which the iodine attacked from the α-face; while the products in the case of the 5β-olefins were the β-iodo-α-acetoxy derivatives, in which the iodine attacked from the β-face. These results are also in agreement with the facts that the



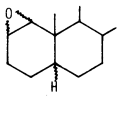
7: 5α-H, R_1=R_4=H, R_2=I, R_3=OAc
10: 5β-H, R_1=I, R_2=R_3=H, R_4=OAc



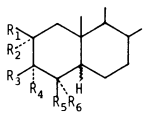
8: 5α-H, R_1=OAc, R_2=R_3=H, R_4=I
11: 5β-H, R_1=R_4=H, R_2=OAc, R_3=I



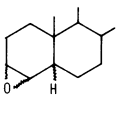
9: 5α-H, R_1=R_4=H, R_2=I, R_3=OAc
12: 5β-H, R_1=R_4=H, R_2=OAc, R_3=I



13: 5α-H, 1β,2β-O-
15: 5β-H, 1α,2α-O-



18: 5α-H, R_1=OH, R_2=R_3=R_4=R_5=R_6=H
19: 5α-H, R_1=R_2=R_3=R_4=R_6=H, R_5=OH
20: 5β-H, R_1=R_3=R_4=R_5=R_6=H, R_2=OH
21: 5β-H, R_1=R_2=R_3=R_5=R_6=H, R_4=OH
22: 5α-H, R_1=OAc, R_3=OH, R_2=R_4=R_5=R_6=H
23: 5α-H, R_1=R_3=OH, R_2=R_4=R_5=R_6=H



14: 5α-H, 3β,4β-O-
17: 5β-H, 3α,4α-O-

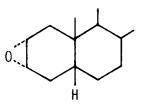


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Table 1. Yields and Physical Data of *trans*-Iodo Acetates (**7**—**12**)

Materials	Products	Isolated yields/%	Mp θ_m/°C	IR (KBr, cm^{-1})	NMR (CCl_4, δ, ppm)	Elemental analysis/%	
1	**7**	80	113—114	1741 1240	2.05 (3H, s) 4.46 (1H, m, W/2=6.0 Hz) 5.45 (1H, m, W/2=6.0 Hz)	Found (Calcd for $C_{29}H_{49}O_2I$)	
						C	H
						63.03	9.05
						(62.58)	(8.87)
2	**8**	85	96—98 (lit, 96—97[10])	1744 1233	2.03 (3H, s) 4.54 (1H, m, W/2=7.0 Hz) 5.18 (1H, m, W/2=8.0 Hz)	62.60	8.92
3	**9**	76	83—85	1741 1231	2.03 (3H, s) 4.54 (1H, m, W/2=7.5 Hz) 5.18 (1H, m, W/2=7.5 Hz)	62.71	8.93
4	**10**	85	75—76	1740 1235	2.07 (3H, s) 4.99 (1H, m, W/2=6.0 Hz) 5.45 (1H, m, W/2=6.0 Hz)	62.39	8.89
5	**11**	79	87—88	1740 1233	2.06 (3H, s) 4.55 (1H, m, W/2=9.0 Hz) 5.10 (1H, m, W/2=9.0 Hz)	62.59	8.90
6	**12**	83	125—126	1741 1231	2.11 (3H, s) 4.50 (1H, t, J=10.5 Hz) 5.02 (1H, m, W/2=15.0 Hz)	62.42	8.84

α-face of 5α-steroidal olefins is less hindered than the β-face, and that the β-face of 5β-steroidal olefins is less hindered than the α-face.

Experimental

All the melting points are uncorrected. The IR and NMR spectra were measured using a Hitachi model 215 grating infrared spectrometer and a nuclear magnetic resonance spectrometer, Hitachi-Perkin Elmer R-20A, in carbon tetrachloride and deuteriochloroform, with TMS as the internal standard.

General Procedure. A mixture of steroidal olefin (1.349×10^{-3} mol), copper(II) acetate monohydrate (1.349×10^{-3} mol), iodine (1.349×10^{-3} mol), and acetic acid (50 ml) was stirred at 55—60 °C. After 10—30 h, the reaction mixture turned to brown; and then it was filtered to remove copper(I) iodide produced. The filtrate was taken up in ether, and the ether extracts were washed with sodium hydrogencarbonate solution and with water, and then dried and evaporated. Crystallization of the residue from ethanol gave *trans*-iodo acetate.

Confirmation of Configuration of 1α-Iodo-2β-acetoxy-5α-cholestane (7). The *trans*-iodo acetate (**7**) (180 mg) in dry ether (18 ml) was treated with lithium aluminium hydride (13 mg). After the usual work-up, the resulting oil, on crystallization from ethanol, gave 5α-cholestan-2β-ol (**18**) (140 mg), mp 161—163 °C (154—155 °C[16]).

The *trans*-iodo acetate (**7**) (20 mg) in ethanol was treated with potassium hydroxide. After the usual work-up, the resulting oil, on crystallization from ethanol, yielded 1β,2β-epoxy-5α-cholestane (**13**) (9 mg), mp 93—94 °C (94—95 °C[16]).

Confirmation of Configuration of 3α-Iodo-4β-acetoxy-5α-cholestane (9). By practically the same method as that in the case of **7** above, **9** (40 mg) was converted to 5α-cholestan-4β-ol (**19**) (17 mg), mp 131—133 °C (132—135 °C[17]) and 3β,4β-epoxy-5α-cholestane (**14**) (16 mg), mp 96—98 °C (98—99 °C[18]) respectively.

Confirmation of Configuration of 1β-Iodo-2α-acetoxy-5β-cholestane (10). The *trans*-iodo acetate (**10**) (70 mg) in dry ether was treated with lithium aluminium hydride. After the usual work-up, the resulting oil, on crystallization from ethanol, gave 5β-cholestan-2α-ol (**20**) (41 mg), mp 105—106 °C (106—107 °C[19]).

The *trans*-iodo acetate (**10**) (70 mg) in ethanol (10 ml) was treated with potassium hydroxide (76 mg). After the usual work-up, the resulting oil, on crystallization from ethanol, gave 1α,2α-epoxy-5β-cholestane (**15**) (45 mg); IR (KBr): 847 cm^{-1}, ^1H NMR (CCl_4) δ=2.63 (1H, d, J=3.6 Hz) and 3.05 (1H, m, W/2=6.75 Hz).

Found: C, 83.43; H, 11.89%. Calcd for $C_{27}H_{46}O$; C, 83.87 H, 11.99%.

Confirmation of Configuration of 3β-Iodo-2α-acetoxy-5β-cholestane (11). The *trans*-iodo acetate (**11**) (30 mg) in dry ether was treated with lithium aluminium hydride. After the usual work-up, the resulting oil, on crystallization from ethanol gave 5β-cholestan-2α-ol (**20**) (17 mg), mp 105—106 °C (106—107 °C[19]). The *trans*-iodo acetate (**11**) (70 mg) in ethanol was treated with potassium hydroxide. After the usual work-up, crystallization of the residue from ethanol gave 2α,3α-epoxy-5β-cholestane (**16**) (38 mg), mp 74—76 °C; IR (KBr): 810 and 800 cm^{-1}, ^1H NMR (CCl_4) δ=2.75—3.10 (2H, m).

Found: C, 83.50; H, 11.90%. Calcd for $C_{27}H_{46}O$; C, 83.87 H, 11.99%.

Confirmation of Configuration of 4β-Iodo-3α-acetoxy-5β-cholestane (12). By practically the same method as that in the case of **11** above, **12** (40 mg) was converted to 5β-cholestan-3α-ol (**21**) (14 mg), mp 113—115 °C (107—108 °C[20]) and 3α,4α-epoxy-5β-cholestane (**17**) (18 mg), mp 53—55 °C (55—56 °C[21]), respectively.

The Reaction of 2β-Acetoxy-3β-iodo-5α-cholestane (8) with *m*-Chloroperbenzoic Acid. A mixture of **8** (200 mg) in

methylene dichloride (20 ml) and *m*-chloroperbenzoic acid (137 mg) was stirred at room temperature for 4 h. After the usual work-up, the resulting oil, on crystallization from ethanol, 2β-acetoxy-5α-cholestan-3β-ol (**22**) (144 mg), mp 136—137 °C (136—138 °C[22]).

Hydrolysis of 2β-Acetoxy-5α-cholestan-3β-ol (22). A mixture of **22** (100 mg) in methanol (10 ml) and potassium hydroxide (10 mg) in water (0.5 ml) was refluxed for 0.5 h. After evaporation of the reaction mixture, the residue was dissolved in ether. The ethereal solution was washed with water, dried, and evaporated. Crystallization of the residue from methanol gave plates of **23** (90 mg), mp 174—177 °C (175—176 °C[22]).

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