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Novel Regioselective Iodination of Estradiol 17β-Acetate[1)]

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Direct iodination of estradiol 17β-acetate (**3**) using iodine-copper(II) acetate in acetic acid afforded the 2-iodo derivative regioselectively in high yield. The iodination of **3** using several methods was discussed. On the other hand, the reaction of **3** with iodine-copper(II) bromide gave the 4-bromo derivative (**7**), not the 2-iodo compound. The reaction of 3-methoxy-17β-acetoxy-1,3,5(10)-estratriene (**4**) with iodine-copper(II) chloride-iron(III) chloride in acetic acid gave the 2- (**10**) and 4-iodo (**11**) derivative.

2-Iodoestradiols are important as synthethic intermediates and as possessors of biological activity, and also in making highly radioactive iodine isotopes. They are usually prepared either from diazotization of the corresponding 2- or 4-amino-3-methoxyestrone derivative, reduction with sodium borohydride, and then demethylation using boron tribromide,[2)] or from the reaction of estradiol (**1**) with mercury(II) acetate and iodine.[3)] However, recently the synthesis of 2-iodoestradiol (**5**) by the reaction of **1** with mercury(II) acetate and iodine in acetic acid has been questioned.[3)] More recently, Santaniello and Ferrabschi[4)] reported that the reaction of 3-methoxy-17β-acetoxy-1,3,5(10)-estratriene with mercury(II) acetate in dry acetonitrile gave the 2-iodo derivative. However, since these methods involve many steps and the demethylation results in low yield, we wished to find a method for the direct regioselective iodination of estradiol (**1**).

We have been investigating a novel iodination using iodine-copper(II) acetate, and as a first step in this research project, we reported earlier the α-iodination of ketone,[5)] the iodination of electron-rich aromatic compound,[6)] and synthesis of α-iodo carboxylic acid.[7)] Earlier, we described a novel regioselective iodination of estradiol, estriol, and estrone using iodine-copper(II) acetate to afford the 2-iodo derivative.[8)] In the present paper, we would like to report the details of this iodination. We have been now also investigated the reaction of estradiol (**1**) with iodine and some other copper(II) salts.

The reaction of **1** with iodine (1.5 mol equiv)-copper(II) chloride dihydrate (1.5 mol equiv) in acetic acid at 55°C for 35 h gave the diiodo compound **8** (mp 190—193°C) and the monoiodo compound **6** (mp 175—177°C). Compound **8** showed absorption at 1708 (C=O) and 1264 cm^{-1} (C-O) in its IR spectrum. The NMR spectrum showed a singlet at δ 7.60 (C_1-H) and a singlet at δ 2.06 ($C_{17\beta}$-OAc). Therefore, compound **8** was presumed to be 2,4-diiodoestradiol 17β-acetate. The IR spectrum of **6** showed absorption at 1708 (C=O), 1268 (C-O), and 880 cm^{-1} (-CH). This product **6** was presumed to be 2-iodoestradiol 17β-acetate, identification being based on the presence of two singlets in the NMR spectrum at δ 6.70 (C_4-H) and δ 7.50 (C_1-H), and a singlet at δ 2.06 ($C_{17\beta}$-OAc). In the case of the reaction using iodine (1.5 mol equiv)-copper(II) bromide (1.5 mol equiv), the bromo estrogen derivative **7**, mp 140—142°C was obtained. This product was presumed to be 4-bromoestradiol 17β-acetate, identification being based on the presence of two doublets in the NMR spectrum at δ 6.62 and δ 7.16. These results are summarized in Table 1 for the iodination of **1**.

On the basis of these results, it was found that (i) copper(II) acetate and copper(II) chloride were the best reagents for C_2-iodination, (ii) copper(II) chloride was more active than copper(II) acetate, and (iii) in the case of copper(II) bromide, bromination occurred at the C_4-position, not iodination at the C_2-position. Also, these results showed that copper(II) salts acted as a catalyst of acetylation of 17β-hydroxyl group.

Hence, we attempted acetylation of the hydroxyl group using copper(II) acetate-acetic acid. The reaction of **1** or **2** with copper(II) acetate in acetic acid under refluxing for 2 h gave 17β-acetoxy derivative (**3** or **4**) in good yield. The treatment of **3** with iodine-copper(II) acetate at 60°C for 10 h yielded the 2-iodo derivative **6** (89%). Moreover, the reaction of **3** with iodine-copper(II) chloride, iodine-copper(I) acetate, iodine-copper(I) chloride, iodine-thallium(I) acetate, iodine monochloride, iodine-morpholine complex, or iodine-copper(II) chloride-iron(III) chloride was carried out in a similar manner to the procedure mentioned above, and the results are presented in Table 2.

From these results, it was concluded that iodine-copper(II) acetate and iodine-copper(II) chloride are efficient and regioselective iodinating agents in com-

Table 1. Products and Isolated Yields (%) in the Iodination of Estradiol (**1**) at 60°C

Reagents (molar equiv)	Time/h	Products	Isolated yield/%
I_2-$CuCl_2 \cdot 2H_2O$	35	**6**	50
(1.5) (1.5)		**8**	11
I_2-$CuCl_2 \cdot 2H_2O$	20	**3**	39
(0.5) (1.0)			
I_2-$CuBr_2$	10	**3**	20
(1.5) (1.5)		**7**	45
$CuBr_2$	10	**3**	41
(2.0)		**7**	42
I_2-$Cu(OAc)_2 \cdot H_2O$	22	**5**	64
(1.5) (1.5)			

Table 2. Products and Isolated Yields (%) in the Iodination of Estradiol 17β-Acetate (**3**) at 60°C

Reagents (molar equiv)	Time/h	Products	Isolated yield/%
I_2–$Cu(OAc)_2 \cdot H_2O$ (1.5) (1.5)	10	**6**	89
I_2–$CuCl_2 \cdot 2H_2O$ (1.5) (1.5)	52	**6**	52
		8	6
		9	22
I_2–CuOAc (1.2) (1.2)	27	**6**	36
I_2–CuCl (1.2) (1.2)	65	**6**	25
I_2–TlOAc (1.2) (1.2)	8	**6**	30
$CuBr_2$ (2.0)	6	**7**	62
$CuCl_2 \cdot 2H_2O$ (2.0)	50	[no reaction]	
ICl (1.0)	1	**6**	50
		9	29
I_2–Morpholine/MeOH (1.0)	3	**6**	17
		8	27
		9	21
I_2–$CuCl_2 \cdot 2H_2O$– (1.5) (1.5) $FeCl_3 \cdot 6H_2O$ (1.5)	3	**6**	30
		8	35
		9	14

parison with the other reagents. Moreover, it was found that the iodination of estradiol 17β-acetate (**3**) gave 2-iodoestradiol 17β-acetate (**6**) in good yield (80—90%). This results is also supported by our earlier finding that the iodination using iodine–copper(II) acetate of phenol occurred at the ortho-position.[6]

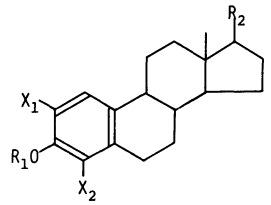
Thus, it is considered that in the reaction of **3** using iodine–copper(II) acetate, the copper is coordinated to the oxygen of the phenolic hydroxyl group, and then attacks at the less hindered C_2-position than the corresponding C_4-position.

We attempted the iodination of 3-methoxy-17β-acetoxy-1,3,5(10)-estratriene (**4**) with affecting the coordinating ability of the oxygen atom using iodine–copper(II) acetate or iodine–copper(II) chloride in acetic acid. The reaction resulted in the recovery of the starting material. The reaction of **4** with iodine–copper(II) chloride–iron(III) chloride in acetic acid gave the 2- (**10**) (56%) and the 4-iodo derivative (**11**) (18%).

From these results, it is considered that the iodination using iodine–copper(II) chloride–iron(III) chloride of the 3-methoxyestrogen (**4**) proceeds by an initial π-complex of iodine with the aryl ring and the more powerful Lewis acid, iron(III) chloride is no doubt attributable to the roles as a potent catalyst.

Experimental

All the melting points are uncorrected. The IR spectra were measured using a Hitachi Model 215 grating infrared spectrometer. The NMR spectra were measured using either Hitachi Model R-900 or JEOL FX200 Model Spectrometer in deuteriochloroform with TMS as an internal standard.



1 : $X_1=X_2=R_1=H$, $R_2=OH$
2 : $X_1=X_2=H$, $R_1=Me$, $R_2=OH$
3 : $X_1=X_2=R_1=H$, $R_2=OAc$
4 : $X_1=X_2=H$, $R_1=Me$, $R_2=OAc$
5 : $X_1=I$, $X_2=R_1=H$, $R_2=OH$
6 : $X_1=I$, $X_2=R_1=H$, $R_2=OAc$
7 : $X_1=R_1=H$, $X_2=Br$, $R_2=OAc$
8 : $X_1=X_2=I$, $R_1=H$, $R_2=OAc$
9 : $X_1=R_1=H$, $X_2=I$, $R_2=OAc$
10 : $X_1=I$, $X_2=H$, $R_1=Me$, $R_2=OAc$
11 : $X_1=H$, $X_2=I$, $R_1=Me$, $R_2=OAc$

The high-resolution mass spectra were recorded at 75 eV on a JEOL JMS-O1SG-2 instrument with a direct inlet.

Estradiol 17β-Acetate (3). A mixture of estradiol (**1**) (3.0 g) and copper(II) acetate monohydrate (0.2 mol equiv) in acetic acid (80 ml) was stirred under refluxing for 4 h. The solvent was then removed under reduced pressure, and the residue was poured into water and extracted with ether. The ethereal solution was washed successively with aqueous sodium hydrogencarbonate and with water, dried, and concentrated. Crystallization of the residue from methanol gave plates of **3** (3.02 g, 87%), mp 216—218°C (lit,[9] 217—218°C). The IR and ^1H NMR spectra were identical with those of an authentic sample.

3-Methoxy-17β-acetoxy-1,3,5(10)-estratriene (4). A mixture of 3-methoxyestradiol (**2**) (1.0 g) and copper(II) acetate mono-

hydrate (0.2 mol equiv) in acetic acid (30 ml) was stirred under refluxing for 12 h. After a similar work-up, the resulting oil, on crystallization from methanol, gave **4** as plates (1.05 g, 92%), mp 102—103 °C (lit,[10] 103.5—104.5 °C). The IR and ^{1}H NMR spectra were identical with those of an authentic sample.

Reaction of Estradiol with Iodine and Copper(II) Chloride in Acetic Acid. Estradiol (**1**) (200 mg) in acetic acid (20 ml) was treated with iodine (280 mg) and copper(II) chloride dihydrate (188 mg) at 60 °C for 35 h. After a similar work-up, the resulting oil (322 mg) was purified by preparative TLC on silica-gel plates (2 mm layer) (Merck). Developement with benzene–ether (2:1) gave 2,4-diiodoestradiol 17β-acetate (**8**) as plates (44 mg) from methanol, mp 190—193 °C; IR (KBr): 3450, 1708, 1530, 1264, and 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ=0.82 (3H, s, C_{18}–H_3), 2.07 (3H, s, $C_{17\beta}$–$OCOCH_3$), 4.70 (1H, t, J=7.5 Hz, $C_{17\alpha}$–H), and 7.60 (1H, s, C_1–H).

Found: C, 42.51; H, 4.40%. HRMS m/z 565.9770. Calcd for $C_{20}H_{24}O_3I_2$: C, 42.43; H, 4.27%; M, 565.9816.

The less polar fraction on crystallization from methanol gave 2-iodoestradiol 17β-acetate (**6**) as needles (162 mg), mp 175—177 °C; IR (KBr): 3450, 1708, 1594, 1268, 880, and 865 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ=0.82 (3H, s, C_{18}–H_3), 2.06 (3H, s, $C_{17\beta}$–$OCOCH_3$), 4.68 (1H, t, J=7.5 Hz, $C_{17\alpha}$–H), 6.70 (1H, s, C_4–H), and 7.50 (1H, s, C_1–H).

Found: C, 54.74; H, 5.76%. HRMS m/z 440.0892. Calcd for $C_{20}H_{25}O_3I$: C, 54.56; H, 5.72%; M, 440.0850.

Reaction of Estradiol 17β-Acetate with Copper(II) Bromide in Acetic Acid. Estradiol (**1**) (100 mg) in acetic acid (10 ml) was treated with copper(II) bromide (82 mg) at 60 °C for 10 h. After a similar work-up, the resulting oil (127 mg) was purified by preparative TLC on silica-gel plates (2 mm layer) (Merck). Developement with benzene–ether (2:1) gave 4-bromoestradiol 17β-acetate (**7**) as needles (61 mg) from acetone, mp 213—215 °C; IR (KBr): 3430, 1705, 1605, 1561, 1274, and 793 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ=0.82 (3H, s, C_{18}–H_3), 2.07 (3H, s, $C_{17\beta}$–$OCOCH_3$), 4.71 (1H, t, J=7.5 Hz, $C_{17\alpha}$–H), 6.62 (1H, d, J=8.0 Hz, C_2–H), and 7.16 (1H, d, J=8.0 Hz, C_1–H).

Found: m/z 392.1019 (M^+); 394.0926 $(M+2)^+$. Calcd for $C_{20}H_{25}O_3Br$: M, 392.0986; M+2, 394.0966.

Reaction of Estradiol 17β-Acetate with Iodine–Copper(II) Acetate in Acetic Acid. A mixture of estradiol 17β-acetate (**13**) (200 mg), iodine (242 mg), and copper(II) acetate (116 mg) in acetic acid (20 ml) was stirred at 60 °C for 10 h. The precipitated copper(I) iodide was removed by filtration, and the filtrate was poured into water and extracted with ether. After a similar work-up, the resulting oil, on crystallization from methanol, gave **6** as needles (250 mg), mp 175—177 °C.

Reaction of Estradiol 17β-Acetate with Iodine–Copper(II) Chloride in Acetic Acid. A mixture of estradiol 17β-acetate (**3**) (200 mg), iodine (242 mg), and copper(II) chloride (163 mg) in acetic acid (20 ml) was stirred at 60 °C for 50 h. After a similar work-up, the resultant oil was chromatographed on silica gel (30 g). Elution with benzene (250 ml) gave 2,4-diiodoestradiol 17β-acetate (**8**) as plates (23 mg) from methanol, mp 190—193 °C. The next fraction, eluted by the same solvent (30 ml), on crystallization from methanol gave plates of **6** (146 mg), mp 175—177 °C. The third fraction, eluted by the same solvent (30 ml), on crystallization from methanol gave plates of 4-iodoestradiol 17β-acetate (**9**) (61 mg), mp 161—164 °C; IR (KBr): 3430, 1705, 1595, 1557, 1267, and 790 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=0.82 (3H, s, C_{18}–H_3), 2.06 (3H, s, $OCOCH_3$), 4.69 (1H, t, J=8.9 Hz, $C_{17\alpha}$–H), 7.20 (1H, d, J=8.8 Hz, C_1–H), and 6.84 (1H, d, J=8.8Hz, C_2–H).

Found: C, 54.24; H, 5.72%; HRMS m/z 440.0840. Calcd for $C_{20}H_{25}O_3I$: C, 54.56; H, 5.72%; M, 440.0850.

Reaction of Estradiol 17β-Acetate with Iodine Monochloride. A mixture of estradiol 17β-acetate (**3**) (200 mg) and iodine monochloride (103 mg) in acetic acid (20 ml) was stirred at 60 °C for 1 h. After a similar work-up, crystallization from methanol afforded plates of **9** (81 mg), mp 161—164 °C. From the mother liquor, recrystallization from methanol gave plates of **6** (139 mg), mp 175—177 °C.

Reaction of Estradiol 17β-Acetate with Iodine–Morpholine. A mixture of estradiol 17β-acetate (**3**) (200 mg), iodine (161 mg), and morpholine (166 mg) in methanol (40 ml) was stirred at 0 °C for 2 h. After a similar work-up, the resultant oil was chromatographed on silica gel (30 g). Elution with benzene–ether (10:1) (60 ml) gave 2,4-diiodoestradiol 17β-acetate (**8**) as plates (99 mg) from methanol, mp 190—193 °C. The second fraction, eluted by the same solvent (24 ml), on crystallization from methanol gave plates of **6** (48 mg), mp 175—177 °C. The third fraction, eluted by the same solvent (8 ml), on crystallization from methanol gave plates of **9** as plates (59 mg), mp 161—164 °C.

Reaction of 3-Methoxy-17β-acetoxy-1,3,5(10)-estratriene with Iodine, Copper(II) Chloride Dihydrate, and Iron(III) Chloride Hexahydrate. Estradiol 17β-acetate 3-methyl ether (**4**) (200 mg) in acetic acid (20 ml) was treated with iodine (232 mg), copper(II) chloride dihydrate (156 mg), and iron(III) chloride hexahydrate (247 mg) under stirring at 60 °C for 5 h. After a similar work-up, the resultant oil was chromatographed on silica gel (30 g). Elution with benzene (130 ml) gave 2-iodoestradiol 17β-acetate 3-methyl ether (**10**) as plates (154 mg) from methanol, mp 138—141 °C; IR (KBr): 1738, 1590, 1240, 878, and 860 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=0.82 (3H, s, C_{18}–H_3), 2.06 (3H, s, $C_{17\beta}$–$OCOCH_3$), 3.83 (3H, s, OCH_3), 4.69 (1H, t, J=9.4 Hz, $C_{17\alpha}$–H), 6.54 (1H, s, C_4–H), and 7.64 (1H, s, C_1–H).

Found: C, 55.35; H, 5.97%; HRMS: m/z 454.1003. Calcd for $C_{21}H_{27}O_3I$: C, 55.52; H, 5.99%; M, 454.1006. The second fraction, eluted by the same solvent (40 ml) gave 4-iodoestradiol 17β-acetate 3-methyl ether (**11**) as plates (51 mg) from methanol, mp 165—167 °C; IR (KBr): 1734, 1590, 1556, 1260, 1245, and 786 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=0.82 (3H, s, C_{18}–H_3), 2.06 (3H, s, $C_{17\beta}$–$OCOCH_3$), 3.87 (3H, s, OCH_3), 4.69 (1H, t, J=7.6 Hz, $C_{17\alpha}$–H), 7.25 (1H, d, J=8.50 Hz, C_1–H), and 6.66 (1H, d, J=8.50 Hz, C_2–H).

Found: C, 55.80; H, 6.12%; HRMS: m/z 454.1008. Calcd for $C_{21}H_{27}O_3I$: C, 55.52; H, 5.99%; M, 454.1006.

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