Notes

Potential Antiandrogenic Antitumor Steroidal Lactones[1]

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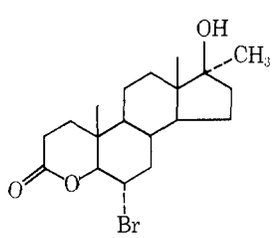
Steroids exhibiting antiandrogenic activity include 17α-hydroxyprogesterone caproate,[2] 17α-methyl-*B*-nortestosterone,[3] and cyproterone acetate.[4] These and most other antiandrogenic steroids suffer the disadvantage of also exhibiting varying degrees of progestational, estrogenic, and androgenic activity. An antiandrogenic steroid free of these undesirable activities is 6α-bromo-17β-hydroxy-17α-methyl-4-oxa-5α-androstan-3-one (**1**), having the special structural features of a 6α-bromine and a lactone ring.[5] Lactone rings, especially α-methylene lactone rings, are found in many naturally occurring antitumor compounds,[6] and in fact cytotoxic activity is reported for steroids having a lactone ring fused to the D ring, as in **2**.[7] Thus, the preparation of steroidal lactones takes on added significance in light of the numerous methods for converting γ-lactones into α-methylene-γ-lactones.[8-11]



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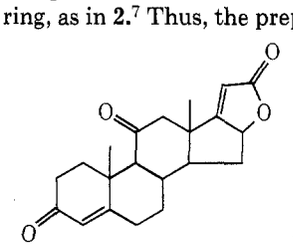

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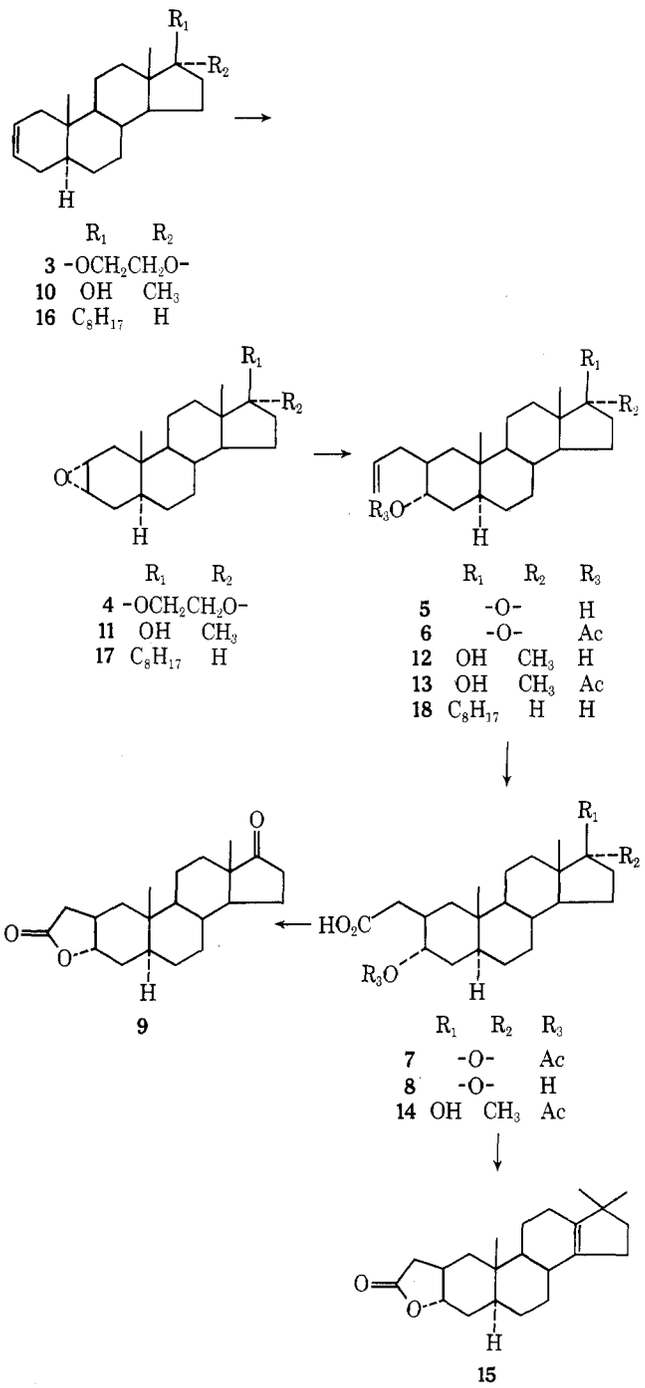
Lactones **9** and **15** were synthesized as outlined in Chart I. Thus, 2α,3-epoxy-5α-androstan-17-one ethylene ketal[12] (**4**) underwent normal ring opening[13] with allylmagnesium bromide to produce 2β-allyl-3α-hydroxy-5α-androstan-17-one (**5**) in 88% yield. Following the method of Huffman and Sobti,[14] oxidation of the acetate **6** with potassium permanganate, sodium periodate, and potassium carbonate in aqueous *tert*-butyl alcohol gave a 70% yield of 2-(3α-acetoxy-17-oxo-5α-androstan-2β-yl)acetic acid (**7**). Hydrolysis with potassium hydroxide in aqueous THF gave the hydroxy acid **8**, which was cyclized with perchloric acid in 78% yield to 2-(3α-hydroxy-17-oxo-5α-androstan-2β-yl)acetic acid lactone (**9**). The presence of the lactone ring is clearly shown by the 1780 cm^{-1} C=O band in the infrared spectrum.[15] The shape of the 3β-H (equatorial) resonance (3.85 ppm in **5**) suggests a narrow peak superimposed on a broad one,[16] and perhaps the presence of some 2β-H (axial), the result of C-2 attack by the allyl Grignard reagent, although all products (**5**, **7**, **8**, and **9**) gave single spots by TLC.

A similar sequence began with 17α-methyl-5α-androst-2-en-17β-ol (**10**), prepared by dehydrotosylation of 17α-methyl-5α-androstane-3β,17β-diol 3-tosylate in refluxing 2,6-lutidine (see Table I). *m*-Chloroperbenzoic acid produced the epoxide **11** in 76% yield. The Grignard reaction produced the 2β-allyl-3α-hydroxy derivative **12**; its acetate **13** was not purified but was used directly to prepare the acid **14**. Alkaline hydrolysis followed by acid-catalyzed ring closure gave 2-(3α-hydroxy-10,17,17-trimethyl-5α-gon-13-en-2β-yl)acetic acid lactone (**15**), a result of concomitant dehydration of the 17β-hydroxyl and rearrangement.[17] Either alternate structure, Δ^{16} unrearranged or Δ^{12} rearranged, would exhibit NMR resonance in the 6.1–5.5-ppm region, which **15** does not.

Chart I



Experimental Section[19]

2β-Allyl-3α-hydroxy-5α-androstan-17-one (5). Tosylation of isoandrosterone with tosyl chloride in pyridine gave a 90% yield of 3β-tosyloxy-5α-androstan-17-one, white crystals out of MeOH, mp 165–166 °C (lit.[12] 163–164 °C). Dehydrotosylation in refluxing lu-

Table I. Synthesis of a Steroidal Lactone

No.	Name	Yield, %	Mp, °C (solvent)	Ir, cm^{-1}	Anal., % Calcd	Anal., % Found
10	17α-Methyl-5α-androst-2-en-17β-ol[a]	67	154–155 (acetone)	3330 (OH), 1150, 935, 720, 660	C 83.27 H 11.18	83.24 11.22
11	2α,3-Epoxy-17α-methyl-5α-androstan-17β-ol[b]	76	206–208 (MeOH–H_2O)	3400 and 3330 (OH), 1155, 1076, 972, 936, 800	C 78.90 H 10.60	78.80 10.60
12	2β-Allyl-17α-methyl-5α-androstane-3α,17β-diol[c]	54	200–202 (acetone)	3390 (OH), 1632 (C=C), 1002 and 920 (–C=CH_2)	C 79.71 H 11.05	79.93 10.70
14	2-(3α-Acetoxy-17β-hydroxy-17α-methyl-5α-androstan-2β-yl)acetic acid	71	216–217 (benzene–hexane)	3425 (OH), 1738 (acetate C=O), 1698 (acid C=O), 1240 (acetate C=O)	C 70.90 H 9.42	71.08 9.51
15	2-(3α-Hydroxy-10,17,17-trimethyl-5α-gon-13-en-2β-yl)acetic acid lactone[d]	70	172–177 (dioxane–H_2O)	1795 (lactone C=O) 1210, 1199, 1139, 1059, 1000	C 80.44 H 9.82	80.31 10.01
18	2β-Allyl-5α-cholestan-3α-ol[e]	70	87–90 (amorphous, out of acetone)		C 84.04 H 12.28	84.43 12.23

[a] Prepared by dehydrotosylation of 17α-methyl-5α-androstane-3β,17β-diol 3-tosylate, mp 108–113 °c)lit.[20] 105–108 °C); compound **10** NMR δ 5.60 (s, 2 H, olefinic H at C-2 and C-3), 1.20 (s, 3 H, Me), 0.85 (s, 3 H, Me), 0.77 (s, 3 H, Me). [b] NMR δ 3.12 (m, 2 H, H's on C-2 and C-3), 1.18 (s, 3 H, Me), 0.82 (s, 3 H, Me), 0.77 (s, 3 H, Me). [c] NMR δ 6.1–5.4 (m, 1 H, βH of allyl group), 5.10 (broad s, 1 H, γ-H of allyl group), 4.88 (broad s, 1 H, γ-H of allyl group), 3.80 (broad s, 1 H, 3β-H), 1.17 (s, 3 H, Me), 0.82 (s, 6 H, Me's). [d] NMR δ 4.4–4.05 (m, 1 H, 3β-H), 0.95 (s, 6 H, Me's), 0.88 (s, 3 H, Me). [e] Prepared from 2α,3-epoxycholestane, mp 106–107 °C (lit.[21] 100–108 °C).

tidine for 2.5 h and recrystallization of the crude product from MeOH gave an 85% yield of 5α-androst-2-en-17-one, white plates, mp 108–109 °C (lit.[12] 104–111 °C). The latter was converted in 88% yield to the corresponding ethylene ketal **3**, white platelets: mp 117–118 °C (lit.[12] 112–113 °C); ir 3000 (olefinic CH), 1646 (C=C), 1300, 1165, 1110, 1052 cm^{-1}. Oxidation with *m*-chloroperbenzoic acid (85%) gave a 76% yield of 2α,3-epoxy-5α-androstan-17-one ethylene ketal (**4**), recrystallized from MeOH–H_2O: mp 152–156 °C (lit.[12] 151–152 °C); ir 1300, 1170, 1050, 1007, 948, 903, 800 cm^{-1}. Allylmagnesium bromide [prepared from 94 g (0.78 mol) of allyl bromide and 24.3 g (1 g-atom) of Mg] in 500 ml of Et_2O was added to a solution of 19.95 g (0.060 mol) of **4** in 400 ml of Et_2O. The mixture was refrigerated overnight, then excess reagent was destroyed with H_2O. The ethereal layer was washed and dried (Na_2SO_4); evaporation left an oil which was hydrolyzed in MeOH (500 ml) and H_2O (200 ml) containing 10 drops of concentrated HCl at reflux for 10 min. Cooling gave crude **5**, which was recrystallized in MeOH–H_2O to give an 88% yield of **5**: mp 142–147 °C; ir 3460 (OH), 3060 (olefinic CH), 1712 (C=O), 1632 (C=C), 1260, 1000, 896 cm^{-1}; NMR δ 6.0–5.5 (m, 1 H, β-H in allyl group), 5.08 (broad s, 1 H, γ-H in allyl group), 4.93 (broad s, 1 H, γ-H in allyl group), 3.85 (broad s, 1 H, 3β-H), 0.85 (s, 3 H, Me), 0.83 (s, 3 H, Me).

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.82; H, 10.46.

2-(3α-Acetoxy-17-oxo-5α-androstan-2β-yl)acetic Acid (7). Acetylation of 4.627 g (0.014 mol) of **5** with acetic anhydride and pyridine at room temperature, followed by the usual work-up, gave **6**, an oil, which was oxidized without purification. A solution of 336 mg of $KMnO_4$, 29.96 g of $NaIO_4$, and 23.0 g of K_2CO_3 in 450 ml of H_2O was added to the oily **6** in 450 ml of *t*-BuOH, and the mixture was refrigerated overnight. Filtering, extraction with Et_2O, and acidification of the filtrate precipitated the crude product, which was recrystallized from benzene–petroleum ether to give 3.84 g (70%) of **7**, small needles: mp 263–264 °C; ir 1720 (acetate and ketone C=O), 1695 (acid C=O), 1240 (acetate C–O), 1200 cm^{-1}.

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.89; H, 8.68.

2-(3α-Hydroxy-17-oxo-5α-androstan-2β-yl)acetic Acid (8). Hydrolysis of 3.84 g of **7** with KOH in aqueous THF at 45–50 °C for 24 h, acidification, extraction into $HCCl_3$, washing, and drying gave the crude product, which was recrystallized from benzene–hexane to give 2.23 g (65%) of **8**: mp 240–242 °C; ir 3460 and 3370 (OH), 1720 (ketone C=O), 1685 (acid C=O), 1250, 1020 cm^{-1}.

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.29. Found: C, 72.51; H, 9.25.

2-(3α-Hydroxy-17-oxo-5α-androstan-2β-yl)acetic Acid Lactone (9). A solution of 1.74 g of **8** in 15 ml of THF and 75 ml of benzene containing 2 drops of $HClO_4$ was heated to reflux for 10 min, then concentrated to 25 ml volume, cooled, and diluted with 150 ml of hexane. Overnight refrigeration produced a crude product which was recrystallized in dioxane–H_2O to give 1.24 g (78%) of **9**: mp 172–173 °C; ir 1780 (lactone C=O), 1736 and 1720 (ketone C=O), 1208, 1141, 1094, 1022, 998 cm^{-1}; NMR δ 4.4–4.0 (m, 1 H, 3β-H), 0.91 (s, 3 H, 19-Me), 0.86 (s, 3 H, 18-Me).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.10; H, 9.24.

Registry No.—**3**, 14935-92-3; **4**, 10429-04-6; **5**, 57901-43-6; **7**, 57901-44-7; **8**, 57901-45-8; **9**, 57901-46-9; **10**, 3275-64-7; **11**, 968-54-7; **12**, 57901-47-0; **14**, 57901-48-1; **15**, 57901-49-2; **18**, 57901-50-5; isoandrosterone, 481-29-8; allyl bromide, 106-95-6; acetic anhydride, 108-24-7; 17α-methyl-5-α-androstane-3β,17β-diol, 1921-53-5; 2α-3-epoxycholestane, 1753-61-3.

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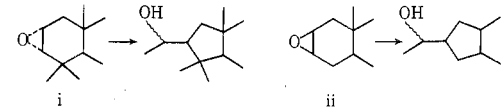

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