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SYNTHESIS OF 17α-BROMOVINYL- AND 17α-IODOVINYLNORTESTOSTERONE DERIVATIVES

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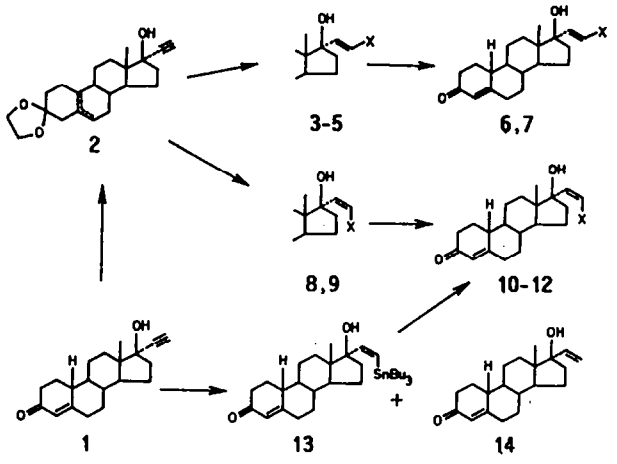
Summary - Depending upon the reaction conditions, norethisterone (**1**) and its ketal **2** can be transformed with tributyltin hydride to either the (E)- or (Z)-17α-(2-tributylstannylvinyl)-nortestosterone derivatives **3**, **8** and **13**. Further treatment with N-bromo- or N-iodosuccinimide yields the corresponding (E)- and (Z)-17α-halovinyl steroids **6**, **7**, **10** and **11**. Radio-labelled (Z)-17α-(2-iodovinyl)-nortestosterone was prepared by reaction of the 17α-stannylvinyl derivative **13** with $Na^{125}I$.

The use of 17α-bromoethynyl- and 17α-iodoethynylestradiols and especially their radioactivelly-labelled derivatives has become recently of importance for the diagnosis of steroid hormone-dependent tumors.[1] Analogously, it should be possible to perform such radiological investigations also with the radiohalogen ethynyl derivatives of nortestosterone. For this purpose there were prepared 17α-bromoethynyl- and 17α-iodoethynylnortestosterone according to a new procedure.[2] As these compounds are instable under in vitro test conditions, we investigated the synthesis of the 17α-bromovinyl and iodovinyl derivatives of nortestosterone[3] which, in analogy to the previously described 17α-iodovinyl derivatives of estradiol and 11ß-methoxy estradiol,[4-8] we expected to be stable under physiological conditions.

The starting material for (E)-17α-halovinyl derivatives **6** and **7** is the 3-ketal of norethisterone **2**.[9] When the ketal **2** is allowed to react with tri-n-butyltin hydride in the presence of azobisisobutyronitrile in tetrahydrofuran at 70°C, we obtained within 1 hour the (E)-17α-tributylstannylvinyl derivative **3** in 67% yield. The same reaction carried out in a polar solvent such as hexamethylphosphoric triamide in the absence of azobisisobutyronitrile yields **3** only in 8% after a reaction time of 20 hours. The main product is a somewhat less polar isomer, (Z)-17α-tributylstannylvinyl derivative **8**, mixed with starting material. The presumed ionic hydrostannylation of the triple bond which leads to the formation of **8** can be also performed without previously protecting the Δ^4-3-ketone as its ketal. Norethisterone (**1**) was found to react with tributyltin hydride in hexamethylphosphoric triamide at a temperature of 70°C within 30 hours to yield (Z)-17α-tributylstannylvinyl derivative **13** in 42% yield. The isomeric (E)-17α-stannylvinyl compound was not observed under this conditions. There can also be isolated starting material and the vinyl derivative **14**.[10]

The 17α-tributylstannylvinyl derivatives **3**, **8** and **13** were converted with retention of configuration into the corresponding (E)- and (Z)-17α-bromovinyl and 17α-iodovinyl compounds by reaction with N-bromo- or N-iodosuccinimide.[11-14] Starting from **3** there were obtained via ketals **4** and **5** the (E)-halovinyl derivatives **6** and **7**. The isomeric (Z)-halovinyl compounds **10** and **11** were prepared from the (Z)-stannylvinyl compounds **8** via **9** and from **13**.



Compound	X
3, 8	$SnBu_3$
4, 6, 10	Br
5, 7, 9, 11	I
12	^{125}I

The synthesis of a mixture of (E)- and (Z)-iodovinylnortestosterones, in which the (E)-iodovinyl derivative predominates, has appeared recently in a publication by Hochberg et al.[15]

For biological investigations the (Z)-configurated radioisotopic iodo steroid **12** is of interest.[16,17] This compound was prepared from the stannyl derivative **13** by reaction with sodium-[^{125}I]-iodide in 2-butanone at room temperature.

Experimental

^{1}HNMR spectra (in $CDCl_3$, coupling constants (J) in Hz, TMS as internal standard): Bruker HX 90. Optical rotation (c=0.5, in $CHCl_3$): Perkin Elmer polarimeter 141. Melting points (uncorrected): Büchi melting point apparatus. Column chromatography was performed on silica gel (Merck 0.040-0.063 mm) using the gradient method.

(E)-3,3-Ethylenedioxy-17α-(2-tributylstannylvinyl)-5- and 5(10)estren-17ß-ol (**3**)

A solution of **2** (25.0 g, 72.9 mmol) in 500 ml THF and 75 ml (278 mmol) tributyltin hydride were heated at 70°C in the presence of 2.5 g (15.2 mmol) azobisisobutyronitrile for 1 h. The solvent was evaporated. After chromatography of the residue with toluene-ethyl acetate, 31.0 g (67%) **3** were obtained as colorless oil. $[\alpha]_D^{20}$ = -8.4°. ^{1}HNMR: δ 0.91 (s, 3H, H-18), 3.91-3.99 (m, 4H, 3-ketal), 5.47 (d, J=5.5, 1H, H-6), 6.00 (d, J=20, 1H, H-21), 6.15 (d, J=20, 1H, H-20). Anal. Calcd for $C_{34}H_{58}O_3Sn$ (633.5): C, 64.46; H, 9.23. Found: C, 64.47; H, 9.35.

(E)-17α-(2-Bromovinyl)-17ß-hydroxy-4-estren-3-one (**6**)

To a solution of **3** (1.5 g, 2.4 mmol) in 30 ml THF 540 mg (3.0 mmol) N-bromosuccinimide were added at room temperature. After 30 min the reaction mixture was diluted with ethyl acetate, washed with water and concentrated. The residue (1.3 g **4**) was heated with 1.3 g oxalic acid on a steam bath for 45 min. The solution was poured into ice water. The precipitate was filtered off, redissolved in ethyl acetate and washed with water. The solvent was evaporated. Recrystallization of the crude product from acetone-hexane yielded 590 mg (64%) **6**, m.p. 132°C (dec.);

$[\alpha]_D^{20}$ = -4.9°. ^{1}HNMR: δ 0.95 (s, 3H, H-18), 1.93 (s, 1H, 17β-OH), 5.82 (s, 1H, H-4), 6.21 (d, J=13, 1H, H-21), 6.40 (d, J=13, 1H, H-20). Anal. Calcd for $C_{20}H_{27}BrO_2$ (379.4): C, 63.32; H, 7.17; Br, 21.07; O, 8.43. Found: C, 62.98; H, 7.18; Br, 21.13; O, 8.30.

(E)-17β-Hydroxy-17α-(2-iodovinyl)-4-estren-3-one (7)

The preparation of **7** from **3** (1.5 g, 2.4 mmol) with N-iodosuccinimide (775 mg, 3.5 mmol) was analogous to the procedure described for **6**. Yield: 680 mg (66%) **7**; m.p. 130°C (dec.); $[\alpha]_D^{20}$ = -19°. ^{1}HNMR: δ 0.95 (s, 3H, H-18), 5.82 (s, 1H, H-4), 6.24 (d, J=14, 1H, H-21), 6.71 (d, J=14, 1H, H-20). Anal. Calcd for $C_{20}H_{27}IO_2$ (426.3): C, 56.34; H, 6.38; I, 29.77; O, 7.50. Found: C, 55.98; H, 6.46; I, 29.86; O, 7.08.

(Z)-3,3-Ethylenedioxy-17α-(2-tributylstannylvinyl)-5-estren-17β-ol (8)

A solution of **2** (10.5 g, 30.7 mmol) in 50 ml hexamethylphosphoric triamide and 25 ml (92.7 mmol) tributyltin hydride were stirred at 70°C for 20 h. The reaction mixture was diluted with ethyl acetate, washed with water, dried and concentrated. Chromatography of the crude product with hexane-ethyl acetate gave 6.0 g (31%) **8** as colorless oil. $[\alpha]_D^{20}$ = -3.6°. ^{1}HNMR: δ 0.90 (s, 3H, H-18), 3.92-4.00 (m, 4H, 3-ketal), 5.47 (d, J=5.5, 1H, H-6), 5.82 (d, J=13, 1H, H-21), 6.72 (d, J=13, 1H, H-20). Anal. Calcd for $C_{34}H_{58}O_3Sn$ (633.5): C, 64.46; H, 9.23. Found: C, 64.54; H, 9.11.

(Z)-17α-(2-Bromovinyl)-17β-hydroxy-4-estren-3-one (10)

A solution of **13** (1.5 g, 2.5 mmol) in 25 ml THF was stirred with 530 mg (2.9 mmol) N-bromosuccinimide at room temperature. After 30 min the reaction mixture was diluted with ethyl acetate, washed with water, dried and concentrated. Chromatography of the crude product with hexane-acetone and recrystallization from acetone-hexane afforded 770 mg (81%) **10**; m.p. 127°C (dec.); $[\alpha]_D^{20}$ = +62°. ^{1}HNMR: δ 0.98 (s, 3H, H-18), 2.86 (s, 1H, 17β-OH), 5.83 (s, 1H, H-4), 6.26 (d, J=8, 1H, H-21), 6.43 (d, J=8, 1H, H-20). Anal. Calcd for $C_{20}H_{27}BrO_2$ (379.4): C, 63.32; H, 7.17; Br, 21.07; O, 8.43. Found: C, 63.32; H, 7.14; Br, 21.02; O, 7.96.

(Z)-17β-Hydroxy-17α-(2-iodovinyl)-4-estren-3-one (11)

a) From **8**: The preparation of **11** from **8** (4.9 g, 7.7 mmol) with N-iodosuccinimide (2.4 g, 10.6 mmol) was analogous to the procedure described for **6**. Yield: 1.8 g (54%) **11**; m.p. 125°C (dec.); $[\alpha]_D^{20}$ = +70°. ^{1}HNMR: δ 0.99 (s, 3H, H-18), 2.47 (s, 1H, 17β-OH), 5.82 (s, 1H, H-4), 6.34 (d, J=8, 1H, H-21), 6.77 (d, J=8, 1H, H-20). Anal. Calcd for $C_{20}H_{27}IO_2$ (426.3): C, 56.34; H, 6.38; I, 29.77; O, 7.50. Found: C, 56.56; H, 6.73; I, 29.65; O, 7.39.

b) From **13**: The preparation of **11** from **13** (2.3 g, 3.9 mmol) with N-iodosuccinimide (1.1 g, 4.8 mmol) was analogous to the procedure described for **10**. Yield: 1.2 g (71%) **13**; m.p. 113°C (dec.); $[\alpha]_D^{20}$ = +69°.

(Z)-17β-Hydroxy-17α-(2-[^{125}I]iodovinyl)-4-estren-3-one (12)

To a solution of **13** (0.5 mg, $8.4 \cdot 10^{-4}$ mmol) in 0.25 ml 2-butanone 37 MBq of sodium-[^{125}I]-iodide were added. (IMS.30, Amersham international plc). The reaction mixture was stirred for 10 min, applied to a HPTLC plate (10 x 10 cm, Merck, 5628), and developed in hexane-ethyl acetate 70:30. The radio active zone was measured, scraped off and extracted with ethyl acetate to afford the [^{125}I]-labelled **12**.

(Z)-17β-Hydroxy-17α-(2-tributylstannylvinyl)-4-estren-3-one (13)

The preparation of **13** from **1** (5.0 g, 16.7 mmol) was analogous to the procedure described for **8**. Yield: 4.1 g (42%) **13** as colorless oil. A sample which was recrystallized from acetone-hexane melted at 117°C; $[\alpha]_D^{20}$ = +72°. ^{1}HNMR: δ 0.94 (s, 3H, H-18), 5.83 (s, 1H, H-4), 5.83 (d, J=13, 1H, H-21), 6.69 (d, J=13, 1H, H-20). Anal. Calcd for $C_{32}H_{54}O_2Sn$ (589.5): C, 65.20; H, 9.23. Found: C, 65.28; H, 9.55.

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References and Notes

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