INDIRECT IODINATION OF ESTROGENES VIA TRIAZENES

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Received October 5, 1992
Accepted October 27, 1992

Dedicated to Professor Otto Wichterle on the occasion of his 80th birthday.

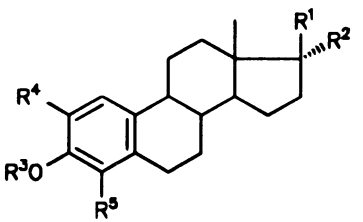
Triazene derivatives of estrone and estradiol in positions 2 and 4 were prepared. Their reaction with sodium iodide in an acid medium afforded the corresponding iodo derivatives. The ^{1}H NMR, ^{13}C NMR and mass spectra of the compounds prepared are discussed.

Estrogenes, particularly estrone and estradiol, labelled selectively in the ring A with radioactive isotopes of iodine, are in demand in many fields of medicine and biochemistry. Recently, a series of direct iodination methods (see e.g. refs[1-6]), as well as methods using the corresponding amino derivative as intermediate[7-10], have been published. Invariably, all the methods are laborious and time-consuming, moreover, in cases of direct iodination, they require separation of the arising isomers, and are thus not suitable for the work with high activities and short-living isotopes.

Therefore, we tried to prepare stable triazene derivatives of estrogenes which could be quantitatively and regiospecifically converted into the desired A-iodoestrogenes by a single, rapid and simple reaction. This approach has already been successfully applied to many aromatic ring-containing compounds of interest[11-13].

Our synthesis started from nitroestrones *I* and *II*, obtained by nitration of estrone with nitric acid in acetic acid[14]. The derivatives *I* and *II* were converted into 3-methyl ethers *III* and *IV* (ref.[15]) because in the diazotization step, aminoestrones unprotected in position 3 afforded unseparable mixtures of coloured products. In the next step, the nitroestrones *III* and *IV* were reduced to give amino derivatives *V* and *VI*. Instead of sodium dithionite in alkaline medium[16] (which gave yields of about 45%) we made use of catalytic hydrogenation over 10% palladium on carbon. This reduction was almost quantitative, the 17-keto group remaining intact. Diazotization of the obtained aminoestrones *V* and *VI*, followed by reaction with piperidine, afforded estrone triazenes *VII*

and *VIII*. Triazenes of 17β-estradiol were prepared by the following reaction scheme. The nitro methyl ethers *III* and *IV* were reduced by two procedures which reduced both the nitro and the oxo group simultaneously. Hydrogenation over platinum in methanol proceeded almost quantitatively to give the 17β-derivative but the reaction was very slow (several days). On the other hand, reaction with sodium borohydride in the presence of palladium in methanol was rapid and also yielded the 17β-isomer; however, the yield was lower. The obtained amino alcohols *IX* and *X* were diazotized with



I, $R^1 + R^2 = O$; $R^3 = R^5 = H$; $R^4 = NO_2$

II, $R^1 + R^2 = O$; $R^3 = R^4 = H$; $R^5 = NO_2$

III, $R^1 + R^2 = O$; $R^3 = CH_3$; $R^4 = NO_2$; $R^5 = H$

IV, $R^1 + R^2 = O$; $R^3 = CH_3$; $R^4 = H$; $R^5 = NO_2$

V, $R^1 + R^2 = O$; $R^3 = CH_3$; $R^4 = NH_2$; $R^5 = H$

VI, $R^1 + R^2 = O$; $R^3 = CH_3$; $R^4 = H$; $R^5 = NH_2$

VII, $R^1 + R^2 = O$; $R^3 = CH_3$; $R^4 = A$; $R^5 = H$

VIII, $R^1 + R^2 = O$; $R^3 = CH_3$; $R^4 = H$; $R^5 = A$

IX, $R^1 = OH$; $R^2 = R^5 = H$; $R^3 = CH_3$; $R^4 = NH_2$

X, $R^1 = OH$; $R^2 = R^4 = H$; $R^3 = CH_3$; $R^5 = NH_2$

XI, $R^1 = OH$; $R^2 = R^5 = H$; $R^3 = CH_3$; $R^4 = A$

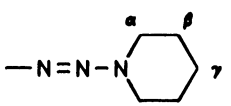
XII, $R^1 = OH$; $R^2 = R^4 = H$; $R^3 = CH_3$; $R^5 = A$

XIII, $R^1 + R^2 = O$; $R^3 = CH_3$; $R^4 = I$; $R^5 = H$

XIV, $R^1 + R^2 = O$; $R^3 = CH_3$; $R^4 = H$; $R^5 = I$

XV, $R^1 = OH$; $R^2 = R^5 = H$; $R^3 = CH_3$; $R^4 = I$

XVI, $R^1 = OH$; $R^2 = R^4 = H$; $R^3 = CH_3$; $R^5 = I$



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sodium nitrite in sulfuric acid; subsequent reaction with piperidine afforded triazenes *XI* and *XII*. Triazenes *VII*, *VIII*, *XI* and *XII* are yellow to orange crystalline compounds, stable in the solid state but unstable in solutions (particularly in chloroform).

Comparison of ^{1}H NMR spectra of the triazenes with those of the corresponding amines shows that, as expected, the signal of proton in position 1 is shifted downfield as the result of lower ability of the triazene group to increase electron density in the ortho and para positions. All other aromatic proton signals (as well as that of the OCH_3 group) retain their positions. The spectra of the triazenes further display signals at 3.75 and 3.77 ppm corresponding to piperidine protons adjacent to the nitrogen atom, and signals at 1.69 and 1.70 ppm due to the remaining $-CH_2-$ groups of the piperidine ring. Also ^{13}C NMR spectra confirmed the structure of the triazenes. The ^{13}C NMR signals for the triazenes, as well as the amino and nitro derivatives, are listed in Table I and II, together with their assignment.

TABLE I
^{13}C Chemical shifts of compounds *I* – *VI*

Carbon	*I*	*II*	*III*	*IV*	*V*	*VI*
1	121.4	127.4	122.1	127.6	110.9	114.4
2	133.0	114.4	137.2	109.9	133.8	107.8
3	152.7	156.1	151.0	148.5	145.7	145.1
4	118.8	146.4	113.5	142.4	112.2	132.7
5	148.8	130.9	144.4	133.2	126.2	121.3
6	29.5	23.7	29.7	23.9	29.1	24.6
7[a]	25.8	25.5	25.9	25.9	26.8	26.4
8	37.6	37.1	37.7	37.5	38.4	37.6
9	43.3	43.3	43.3	43.8	44.0	44.2
10	131.6	127.9	132.3	128.8	131.8	133.4
11[a]	25.6	25.0	25.6	25.4	26.0	26.0
12	31.2	31.2	31.2	31.4	31.6	31.6
13	47.7	47.3	47.7	47.8	48.0	47.9
14	50.2	49.5	50.1	50.1	50.4	50.5
15	21.4	21.1	21.4	21.5	21.5	21.6
16	35.7	35.4	35.7	35.8	35.9	35.9
17	220.2	219.5	220.1	220.3	221.0	220.0
18	13.7	13.5	13.7	13.8	13.8	13.8
$-OCH_3$	–	–	56.4	56.3	55.5	55.6

[a] The signals may be interchanged.

Mass spectra of triazenes *VII*, *VIII*, *XI* and *XII* are similar and very typical. Molecular ion *m/z* 395 (or 397) loses the radical $C_5H_{10}N^{\bullet}$ under formation of ion *m/z* 311 (313) which, upon loss of nitrogen molecule combined with hydrogen transfer, is converted into the base ion of *m/z* 284 (286). These ions are further split as described for the molecular ion of 3-methoxyestrone (or 3-methoxyestradiol)[17, 18].

Attempts to remove the protecting methyl group in the synthesized triazenes were unsuccessful: under all conditions tried, also the triazene functionality was cleaved. Therefore, the triazenes *VII*, *VIII*, *XI* and *XII* were converted into iodo derivatives *XIII* – *XVI*, containing the iodine atom in the position of the original triazene, by reaction with sodium iodide in trifluoroacetic acid at room temperature in yields of 47 – 60%. The removal of the protecting methyl group in position 3 in the iodo derivatives has

TABLE II
^{13}C Chemical shifts of compounds *VII* – *XII*

Carbon	*VII*	*VIII*	*IX*	*X*	XI	*XII*
1	115.1	122.4	111.0	114.3	115.1	122.3
2	138.1	110.0	133.9	108.0	138.0	110.2
3	151.1	160.3	152.2	144.9	158.1	160.1
4	112.3	139.1	112.2	133.0	112.5	139.4
5	134.6	130.4	126.6	121.5	135.0	130.6
6	29.5	25.6[a]	29.3	25.1	29.7	26.1
7[b]	26.6	26.5[a]	27.5	27.1	27.3	27.2
8	38.3	37.7	38.9	38.1	38.8	38.2
9	44.1	44.2	44.0	44.2	44.1	44.2
10	132.0	132.7	132.4	133.8	132.6	133.1
11[b]	25.9	26.0[a]	26.4	26.4	26.3	26.4
12	31.5	31.6	36.8	36.8	36.7	36.8
13	48.0	47.9	43.2	43.1	43.2	43.1
14	50.4	50.4	50.1	50.2	50.1	50.1
15	21.5	21.5	23.1	23.2	23.1	23.1
16	35.8	35.8	30.7	30.6	30.6	30.5
17	221.0	221.0	81.8	81.0	81.9	81.9
18	13.8	13.8	11.2	11.1	11.1	11.1
$-OCH_3$	56.2	56.3	55.5	55.6	56.2	56.3
α	48.1	47.9	–	–	48.3	48.0
β	25.2	25.1	–	–	25.2	25.1
γ	24.3	24.5	–	–	24.4	24.5

[a,b] The signals with the same symbols may de interchanged.

already been described: as reagents were used boron tribromide etherate or boron trifluoride etherate[19], sodium salt of ethyl sulfide[20] or boron tribromide[21].

Our new method of selective introduction of iodine into the ring A is thus so far of advantage only for non-radioactive iodo derivatives. Removal of the protecting group in a radioactive iodo derivative would be difficult and therefore the method is conditioned by finding such a protecting group that could be removed under preservation of the triazene functionality.

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained with a Varian XL-200 instrument (200.057 MHz for ^{1}H, 50.309 MHz for ^{13}C) in deuteriochloroform. Chemical shifts are given in the δ-scale. Tetramethylsilane was used as internal standard for the ^{1}H NMR spectra, the ^{13}C NMR spectra were referenced to the $CDCl_3$ signal (77.0). The mass spectra were taken on an Incos 50 Finnigan MAT spectrometer, ionizing electron energy 70 eV, ionizing current 800 mA, ion source temperature 150 °C, direct inlet system temperature 100 °C. IR spectra were measured in chloroform on a Perkin–Elmer 684 instrument equipped with data station. Column chromatography was performed on silica gel L 40/100 (Lachema, Brno, The Czech Republic).

The usual work-up means evaporation of the solvent in vacuo to dryness, extraction with ether, washing the ethereal solution with water, drying over anhydrous sodium sulfate and evaporation to dryness.

2-Amino-3-methoxyestra-1,3,5(10)-trien-17-one (*V*)

A solution of 2-nitro derivative *III* (1 g) in anhydrous ethanol (150 ml) was hydrogenated over 10% palladium on carbon (150 mg) for 9 h. The catalyst was filtered off, the solvent evaporated and the product crystallized from benzene–methanol; yield 900 mg (98%) of amine *V*, m.p. 159 – 161 °C (reported[15] m.p. 160 – 161.5 °C). ^{1}H NMR spectrum: 0.90 s, 3 H (CH_3); 1.48 m, 6 H; 1.91 – 2.56 m, 7 H; 2.81 m, 2 H; 3.81 s, 3 H ($-OCH_3$); 6.51 s, 1 H (H-1); 6.67 s, 1 H (H-4). IR spectrum (cm^{-1}): 1 593, 1 620 (C=C), 1 731 (C=O), 2 858 ($-OCH_3$), 3 365, 3 458 (NH). Mass spectrum, *m/z* (%): 299 (M^+, 100), 284 (13), 174 (3), 160 (3), 136 (5), 97 (3), 71 (5), 57 (4). For $C_{19}H_{25}NO_2$ (299.4) calculated: 76.22% C, 8.42% H, 4.68% N; found: 76.31% C, 8.40% H, 4.71% N.

4-Amino-3-methoxyestra-1,3,5(10)-trien-17-one (*VI*)

The 4-nitro derivative *IV* (450 mg) was hydrogenated for 40 h and the reaction mixture was worked up as described for the compound *III*; yield 390 mg (96%) of amine *VI*, m.p. 187 – 189 °C (reported[15] m.p. 190.5 – 191.5 °C). ^{1}H NMR spectrum: 0.90 s, 3 H ($-CH_3$); 1.50 m, 6 H; 1.92 – 2.65 m, 9 H; 3.74 s, 2 H (NH_2); 3.84 s, 3 H ($-OCH_3$); 6.68 and 6.73 ABq, 2 H (H-1 and H-2, J = 8.1). IR spectrum (cm^{-1}): 1 574, 1 610 (C=C), 1 731 (C=O), 2 860 ($-OCH_3$), 3 395, 3 466 (NH). Mass spectrum, *m/z* (%): 299 (M^+, 100), 284 (16), 214 (3), 160 (6), 122 (10), 69 (8), 41 (14). For $C_{19}H_{25}NO_2$ (299.4) calculated: 76.22% C, 8.42% H, 4.68% N; found: 76.19% C, 8.37% H, 4.67% N.

2-Amino-3-methoxyestra-1,3,5(10)-trien-17β-ol (*IX*)

Palladium on carbon (10%, 50 mg) and sodium borohydride (500 mg) were added to a solution of 2-nitro derivative *III* (500 mg) in methanol (200 ml). The mixture was stirred at room temperature

for 5 h, diluted with water (100 ml) and the product was taken up in ether and worked up as usual. Crystallization from benzene–light petroleum afforded 370 mg (81%) of amino derivative *IX*, m.p. 124 – 127 °C. ^{1}H NMR spectrum: 0.76 s, 3 H (-CH_3); 3.71 m, 1 H; 3.80 s, 3 H (-OCH_3); 6.50 s, 1 H (H-1); 6.67 s, 1 H (H-4). IR spectrum (cm^{-1}): 1 593, 1 617 (C=C), 2 870 (-OCH_3), 3 375 (NH), 3 606 (OH). Mass spectrum, *m/z* (%): 301 (M^+, 100), 284 (40), 188 (6), 174 (11), 162 (7), 160 (5), 144 (6), 136 (20), 122 (15). For $C_{19}H_{27}NO_2$ (301.4) calculated: 75.71% C, 9.03% H, 4.65% N; found: 75.75% C, 9.08% H, 4.62% N.

4-Amino-3-methoxyestra-1,3,5(10)-trien-17β-ol (*X*)

Procedure A. Nitro derivative *IV* (410 mg) was reduced and isolated analogously as described for compound *III*; yield 205 mg (53%) of amine *X*, m.p. 90 – 91 °C.

Procedure B. Nitro derivative *IV* (500 mg) was dissolved in methanol (200 ml) and hydrogenated over platinum oxide (25 mg) for 70 h. The product was crystallized from benzene–light petroleum; yield 450 mg (98%) of amine *X*, m.p. 88 – 90 °C. ^{1}H NMR spectrum: 0.77 s, 3 H (-CH_3); 3.72 m, 1 H; 3.84 s, 3 H (-OCH_3); 6.71 s, 2 H (H-1, H-2). IR spectrum (cm^{-1}): 1 573, 1 609 (C=C), 2 873 (-OCH_3), 3 376 (NH), 3 615 (OH). Mass spectrum, *m/z* (%): 301 (M^+, 100), 286 (18), 227 (3), 174 (7), 160 (7), 122 (11), 78 (17), 43 (9). For $C_{19}H_{27}NO_2$ (301.4) calculated: 75.71% C, 9.03% H, 4.65% N; found: 75.70% C, 9.06% H, 4.70% N.

3-Methoxy-2-(3,3-(1,5-pentadiyl)triazenyl)estra-1,3,5(10)-trien-17-one (*VII*)

A solution of sodium nitrite (535 mg) in water (12 ml) was added dropwise at 0 – 5 °C to a stirred suspension of 2-amino derivative *V* (700 mg) in 40% sulfuric acid (11.5 ml), and the mixture was stirred for 20 min. Piperidine (550 μl) was added to the yellow reaction mixture and stirring was continued for 45 min under cooling. After dilution with water (200 ml), the mixture was adjusted to pH 10 – 11 with 10% solution of potassium hydroxide and extracted with ether (3 × 60 ml). The ethereal extract was worked up as usual and the solvent was evaporated to dryness. Column chromatography on alumina in benzene, followed by crystallization from ether–light petroleum, afforded 390 mg (42%) of triazene *VII*, m.p. 166 – 168 °C. ^{1}H NMR spectrum: 0.91 s, 3 H (-CH_3); 1.52 m, 6 H; 1.69 bs, 6 H (3 × CH_2, piperidine); 1.92 – 2.56 m, 7 H; 2.88 m, 2 H; 3.77 m, 4 H (-$N(CH_2)_2$); 3.86 s, 3 H (-OCH_3); 6.64 s, 1 H (H-4); 7.26 s, 1 H (H-1). IR spectrum (cm^{-1}): 1 453, 1 499, 1 574, 1 602 (C=C, N=N), 1 731 (C=O), 2 858 (-OCH_3). Mass spectrum, *m/z* (%): 395 (M^+, 17), 311 (18), 284 (100), 283 (30), 253 (35), 199 (31), 186 (18), 160 (25), 149 (21), 129 (11), 97 (15), 84 (22). For $C_{24}H_{33}N_3O_2$ (395.5) calculated: 72.87% C, 8.41% H, 10.62% N; found: 72.90% C, 8.53% H, 10.39% N.

Analogously were prepared:

3-Methoxy-4-(3,3-(1,5-pentadiyl)triazenyl)estra-1,3,5(10)-trien-17-one (*VIII*)

Yield 37%, m.p. 114 – 117 °C. ^{1}H NMR spectrum: 0.90 s, 3 H (-CH_3); 1.50 m, 6 H; 1.70 s, 6 H (3 × CH_2, piperidine); 1.93 – 2.81 m, 9 H; 3.75 s, 7 H (-OCH_3, -$N(CH_2)_2$); 6.77 d, 1 H (H-2, J = 8.3); 7.06 d, 1 H (H-1, J = 8.3). IR spectrum (cm^{-1}): 1 463, 1 483, 1 577, 1 594 (C=C, N=N), 1 731 (C=O), 2 858 (-OCH_3). Mass spectrum, *m/z* (%): 395 (M^+, 27), 311 (86), 284 (100), 283 (71), 253 (60), 199 (30), 186 (17), 160 (23), 129 (15), 97 (18), 84 (29). For $C_{24}H_{33}N_3O_2$ (395.5) calculated: 72.87% C, 8.41% H, 10.62% N; found: 72.69% C, 8.51% H, 10.67% N.

3-Methoxy-2-(3,3-(1,5-pentadiyl)triazenyl)estra-1,3,5(10)-trien-17β-ol (*XI*)

Yield 21%, m.p. 126 – 128 °C. ^{1}H NMR spectrum: 0.78 s, 3 H (CH_3); 1.30 – 1.56 m, 6 H; 1.69 bs, 6 H (3 × CH_2, piperidine); 1.91 – 2.48 m, 9 H; 3.73 m, 4 H ($N(CH_2)_2$, piperidine); 3.86 s, 3 H (OCH_3); 4.17 t, 1 H (H-17, J = 5.2); 6.64 s, 1 H (H-4); 7.26 s, 1 H (H-1). IR spectrum (cm^{-1}): 1 454, 1 499(C=C, N=N), 2 855 (–OCH_3), 3 608 (OH). Mass spectrum, *m/z* (%): 397 (M^+, 11), 313 (12), 286 (100), 255 (20), 199 (17), 186 (29), 160 (24), 115 (16), 84 (25), 41 (26). For $C_{24}H_{35}N_3O_2$ (397.5) calculated: 72.51% C, 8.87% H, 10.57% N; found: 72.54% C, 8.84% H, 10.50% N.

3-Methoxy-4-(3,3-(1,5-pentadiyl)triazenyl)estra-1,3,5(10)-trien-17β-ol (*XII*)

Yield 25%, m.p. 157 – 158 °C. ^{1}H NMR spectrum: 0.78 s, 3 H (–CH_3); 1.19 – 1.61 m, 6 H; 1.69 bs, 6 H (3 × CH_2, piperidine); 1.75 – 2.74 m, 9 H; 3.75 m, 4 H ($N(CH_2)_2$, piperidine); 3.85 s, 3 H (OCH_3); 4.18 t, 1 H (H-17, J = 5.1); 6.84 d, 1 H (H-2, J = 8.5); 7.34 d, 1 H (H-1, J = 8.5). IR spectrum, (cm^{-1}): 1 573, 1 612 (C=C, N=N), 2 874 (–OCH_3), 3 608 (OH). Mass spectrum, *m/z* (%): 397 (M^+, 13), 313 (17), 286 (100), 255 (19), 199 (18), 186 (35), 160 (31), 115 (32), 84 (23), 41 (20). For $C_{24}H_{35}N_3O_2$ (397.5) calculated: 72.51% C, 8.87% H, 10.57% N; found: 72.54% C, 8.83% H, 10.56% N.

2-Iodo-3-methoxyestra-1,3,5(10)-trien-17-one (*XIII*)

A solution of triazene *VII* (56 mg) in acetone (2 ml) was added to a stirred mixture of sodium iodide (21 mg) and trifluoroacetic acid (2 ml). The mixture was stirred at room temperature for 20 min, diluted with water (30 ml) and the precipitate extracted with ether. The ethereal layers were combined, washed with 10% solution of sodium sulfite and with water, and dried over anhydrous sodium sulfate. After evaporation, the residue was crystallized from ether, affording 16 mg (28%) of iodo derivative *XIII*, m.p. 156 – 158 °C (reported[1] m.p. 158 – 159 °C). Mass spectrum, *m/z* (%): 410 (M^+, 45), 325 (4), 284 (100), 256 (5), 227 (12), 200 (16), 199 (61), 160 (37), 115 (15).

The following compounds were obtained in an analogous manner:

4-Iodo-3-methoxyestra-1,3,5(10)-trien-17-one (*XIV*)

Yield 47.5%, m.p. 208 – 210 °C (reported[1] m.p. 209 – 212 °C).

2-Iodo-3-methoxyestra-1,3,5(10)-trien-17β-ol (*XV*)

Yield 58%, m.p. 162 – 164 °C (reported[1] m.p. 162 – 165 °C).

4-Iodo-3-methoxyestra-1,3,5(10)-trien-17β-ol (*XVI*)

Yield 60%, m.p. 153 – 155 °C (reported[1] m.p. 153 – 156 °C).

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Translated by M. Tichý.