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SOME NEW RING-D SECO STEROIDS

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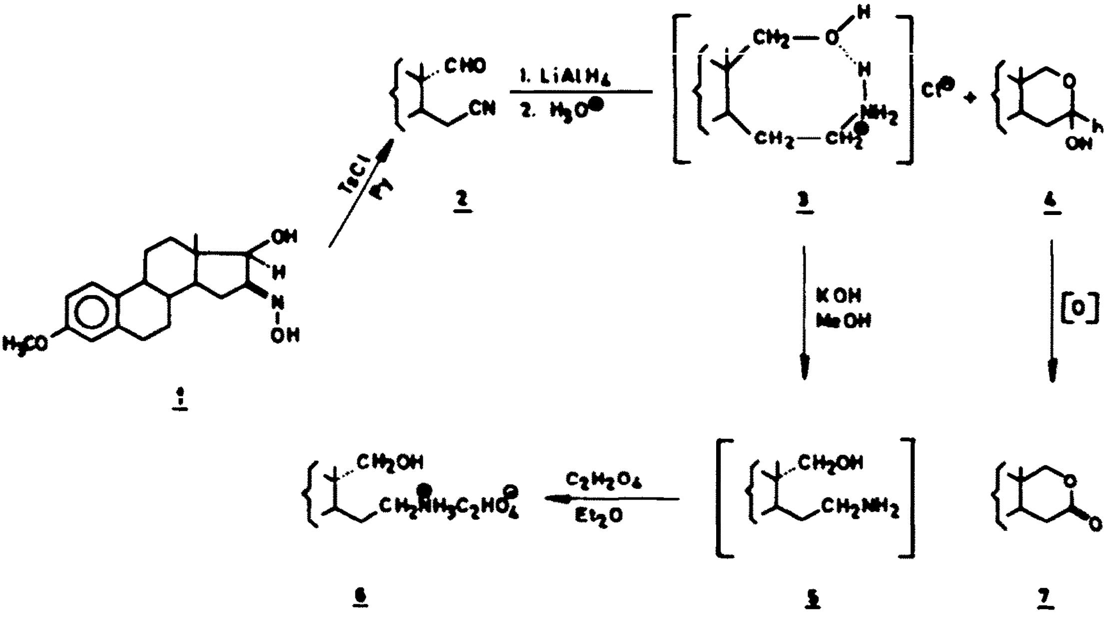
Abstract—The Beckmann fragmentation product, 3-methoxy-17-oxo-16,17-secoestra-1,3,5(10)-trien-16-nitrile (2) has been reduced by LAH giving the expected 3-methoxy-17-hydroxy-16,17-secoestra-1,3,5(10-trien-16-amine hydrochloride (3) and 3-methoxy-17-oxa-D-homoestra-1,3,5(10)-trien-16-ol (4), by a presumed neighbouring group participation of 17-OH group in the intermediary formed 16-imino derivative (A). The structure of 4 has been proved by an alternative synthetic route by reducing 3-methoxy-17-oxa-D-homoestra-1,3,5(10)-trien-16-one (7) with di-iso-butylaluminium hydride.

In our previous papers in the androstane[1] and estrone[2] series we reported the syntheses of two ring-D seco 16-cyano-17-aldehydes, as products of the Beckmann fragmentation reaction of the corresponding 17β-hydroxy-16-oximino derivatives. The primary fragmentation products can be used for syntheses of other ring-D seco steroids, as well as a certain number of D-hetero steroids. In addition, the investigations of Baran[3] showed that some ring-D seco steroids of the estrone series, and estrone derivatives with a heteroatom in ring D possess considerable hypocholesterolemic activity, while their estrogenic activity is quite depressed.

Having in mind these facts, we intended to synthesize the 16-amino-17-hydroxy-D-seco derivative of estrone 3-methyl ether, and to submit this compound to pharmacological examination, as a potential agent in therapy of atherosclerosis. We selected as a starting material the primary Beckmann fragmentation product of 3-methoxy-17 β-hydroxyestra-1,3,5(10)trien-16-one oxime (1): 3 - methoxy - 17 - oxo - 16,17 - socoestra - 1,3,5(10) - tiren-16-nitrile (2). However, reduction of 2 with LAH in absolute THF afforded two products (3 and 4, Scheme 1). Working up the reaction by $CHCl_3$-extraction of the acidified aqueous suspension of the products (pH = 1) we found, surprisingly, both reduction products quantitatively in the $CHCl_3$ layer. As the hydrochloride 3 could be chromatographed without any observable change, we assumed a strong intramolecular H-bond in 3.

Separating the products by chromatography on silica gel, we isolated 3 and 4 in a pure form. Based on spectral data, we assumed the more polar compound (yield 46%) be 3-methoxy-17-hydroxy-16,17-secoestra-1,3,5(10)-trien-16-amine hydrochloride (3). Treating 3 with KOH in methanol the free base: 3-methoxy-17-hydroxy-16,17-secoestra-1,3,5(10)-trien-16-amine (5) was prepared, but due to its instability we did not suceed in getting a satisfactory elemental microanalysis. However, the IR spectrum of freshly prepared aminoalcohol 5 showed a noticable band for the free amino group at 3360 cm^{-1}, and disappearance of bands at 3270 and 2700-2400 cm^{-1} (for NH_3^+). The crude aminoalcohol 5 was also converted to the corresponding oxalate 6.

For the less polar reduction product, isolated in 13% yield, we assumed the structure 4, based on spectral



Scheme 1.

data, as well as the reaction with Fehling solution. Namely 3-methoxy-17-oxa-D-homoestra-1,3,5(10)-trien-16-one (7) was formed as the main product upon heating the ethanol solution of 4 with Fehling reagent. We assumed the compound 4 to be the partial reduction product of the nitrile function,[4] including the participation of the neighbouring C_{17}-OH group. Namely, we first supposed the addition of C_{17}-OH group to the intermediary formed 16-imino group (A, Scheme 2), followed by the formation of a nonreducable product (A'). Subsequent hydrolysis of A' gave the cyclic hemiacetal 4.

The structure of 4 was finally proved by a selective reduction of lactone 7 with di-iso-butylaluminium hydride, according to the procedure of Schmidlin and Wettstein[5] (Scheme 3 and Experimental).

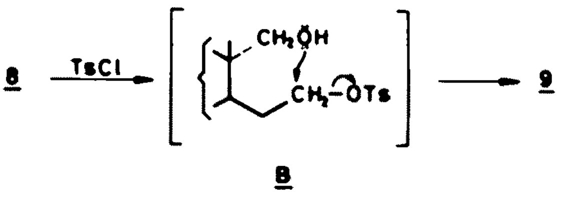
The crude reduction product was purified affording the cyclic hemiacetal 4 (79% yield) and the cyclic ether 9 (11% yield), as a side-product.

Ether 9 was also prepared from lactane 7 as follows: LAH reduction of 7 afforded diol 8, which on treatment with *p*-toluenesulfonyl chloride led to the formation of 3-methoxy-17-oxa-D-homoestra-1,3,5(10)-triene (9). The cyclization of 8 to 9 has been explained by the participation of the neighbouring C_{17}-OH group (of neopentyl type) in the intermediary formed C_{16}-monotosilate B (Scheme 4).

Compounds 8 and 9 were previously synthesised by Baran,[3] starting from 3-methoxy-17-oxa-D-homoestra-1,3,5(10)-trien-17a-one. The experimental procedure we used provided, however, a higher yield of the ether 9. Also, the synthesis of lactone 7 directly from 3-methoxy-17β-hydroxyestra-1,3,5(10)-trien-16-one oxime (1),[2] is more convenient than that described earlier.[6]

EXPERIMENTAL

The m.p. are uncorrected. The IR spectra were recorded in KBR pellets with a Perkin-Elmer IR spectrophotometer, Model 457, and NMR spectra with a Varian 60A spectrometer with TMS as the internal standard. Chemical shifts (δ) are expresed in parts per million. Mass spectra were recorded with a Varian CH-5 spectrometer.

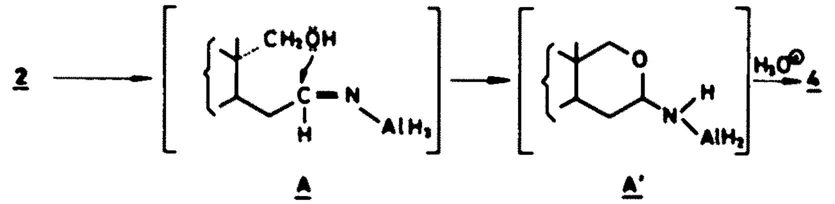


Scheme 4.

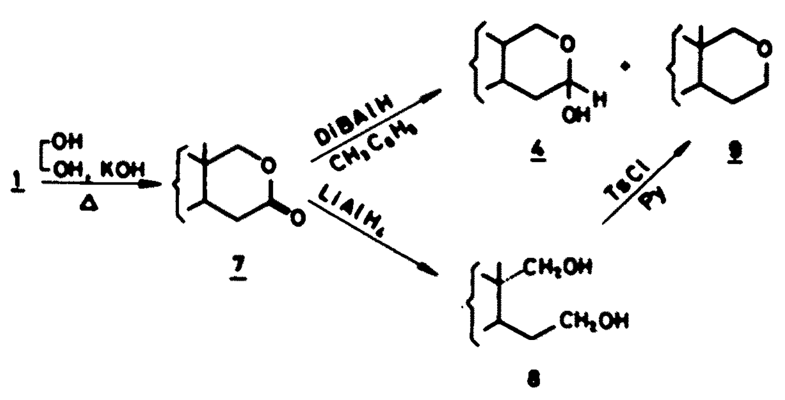
3-Methoxy-17-oxo-16,17-secoestra-1,3,5(10)-trien-16-nitrile(2).[2] Compound 1 (1 g, 3.17 mmol, finely ground and dried for 3 hr at 120°) and *p*-toluenesulfonyl chloride (1 g, 5.25 mmol) were dissolved in absolute pyridine (20 ml). The mixture was kept at room temp. for 3 hr, and then poured into an excess of cold dil. HCl. The ppt of the crude 2 was washed with water, and dried (0.94 g; 98% yield, m.p. 142°). Recrystallization from methylene chloride-hexane afforded pure 2: 0.78 g; 82% yield, m.p. 158–60°.

LAH reduction of 2. Compound 2 (1 g, 3.37 mmol) was dissolved in absolute THF (20 ml) and added dropwise to a suspension of LAH_4 (1 g, 26.4 mmol) in absolute THF (10 ml). The mixture was stirred, in a stream of N_2, for 1 hr at room temp., and for another 2 hr at the bp. The mixture was diluted with MeOH (20 ml), followed by water (500 ml), acidified with dilute HCl to pH = 1, and extracted with $CHCl_3$. After drying the extract, the $CHCl_3$ removed *in vacuo* and the residue was further purified by column chromatography on silica gel (100 g; $CHCl_3$ MeOH/9:1/), affording 0.53 g (46% yield) of 3, m.p. 212°, and 0.26 g of an oily product, which by rechromatography on silica gel (20 g; benzene–EtOAc/2:1) gave 0.13 g (13%) of 4, m.p. 156–8°. Compound 3: IR 3400, 3270, 2700–2400, 1605, 1525, 1500, 1250, 1150, 1070, 1050 and 820 cm^{-1}; mass spectrum *m/e* 304 (/M–Cl/$^+$, 13), 303 (13), 273 (55), 256 (34), 45 (100) and 31 (27). Found: C, 66.86; H, 8.64; N, 4.22. $C_{19}H_{30}ClNO_2$ requires: C, 67.06; H, 8.53: N, 4.12%. Compound 4: IR 3400, 2940, 2870, 1610, 1500, 1260, 1140, 1120, 1030, and 780 cm^{-1}; NMR ($CDCl_3$) 1.0 (s; 3H), 2.8 (m; 2H), 3.35 (quartet; 2H), 3.75 (s; 3H), 4.55 (m; 1H), 6.45 (d; 1H), 6.60 (quartet; 1H), and 7.10 (d; 1H); mass spectrum *m/e* 302 (M^+, 100), 174 (31), 173 (34), 147 (34), 55 (38), 43 (43) and 31 (53). (Found: C, 75.81; H, 8.36. $C_{19}H_{26}O_3$ requires C, 75.50; H, 8.61).

3-Methoxy-17-hydroxy-16,17-secoestra-1,3,5(10)-trien-16-amine (5) *and 5-oxalate* (6). KOH (0.2 g, 3.56 mmol) was dissolved in



Scheme 2.



Scheme 3.

MeOH (50 ml) and 4 (1 g, 2.94 mmol) was added. After 30 min the soln was diluted with water (500 ml), the solid was collected, washed thoroughly with water and air dried (0.85 g; 96% yield, m.p: 158°). Recrystallization from methylene chloride–hexane (1:2) gave 0.76 g (85%) 5, m.p. 164–6°. IR 3360, 2950, 1605, 1500, 1260, 1060 and 1030 cm^{-1}; mass spectrum *m/e* 303 (M^+, 25), 273 (100), 256 (75), 178 (60), 44 (98) and 30 (85).

Compound 5 (0.76 g, 2.51 mmol; m.p. 164–6°) was dissolved in abs Et_2O (10 ml) and a soln of oxalic acid (0.3 g, 3.33 mmol) in abs Et_2O (5 ml) was added, whereupon 0.90 g (93%) of 6 separated. Crystallization from MeOH-Et_2O afforded 0.75 g (77% yield) of pure 6, m.p. 220° (Found: C, 64.00; H, 7.68; N, 3.63. $C_{21}H_{31}NO_6$ requires C, 64.10; H, 7.94; N, 3.56%).

Reduction of 3-methoxy-17-oxa-D-homoestra-1,3,5(10)-trien-16-one (7) with di-iso-butylaluminium hydride (DIBAlH) Compound 7 (1 g, 3.33 mmol) was dissolved in abs toluene (200 ml) in a 3-necked flask, fitted with a mechanical stirrer, thermometer, and dropping funnel. Argon, passed through wash bottles, containing an alkaline soln of pyrogallol and sulphuric acid, resp., was streaming through the apparatus during the reaction. The soln was cooled at −22° and a 15% soln of DIBAlH in abs toluene (3.5 ml; 0.525 g, 3.70 mmol) was added through a syringe. After stirring the mixture for 1 hr, MeOH (20 ml), followed by water (200 ml) was added. The organic layer was dried and the solvent evaporated *in vacuo*. The oily product (0.98 g) was further purified by column chromatography on silica gel (100 g; benzene–EtOAc (2:1)), affording 0.80 g (79%) of 4, m.p. 156–8° and 0.105 g (11%) of 9, m.p. 95°. Compounds 4 and 9 were crystallized from methylene chloride–hexane (1:2).

3-Methoxy-16,17-secoestra-1,3,5(10)-trien-16,17-diol (8). To a suspension of LAH (1 g, 26.4 mmol) in abs THF (10 ml) a soln of 7 (1 g, 3.33 mmol) in abs THF (10 ml) was added dropwise. After stirring the mixture for 1 hr at room temp. and for another hr at the bp, MeOH (20 ml) and then water (1000 ml) was added and the suspension acidified with dil. HCl to pH = 5. The separated solid was washed thoroughly with water and air dried (0.89 g; 86% yield, m.p. 146–8°). Recrystallization from methylene chloride–hexane (1:2) afforded 0.62 g (61% yield) of pure 8, m.p. 151–3° (lit mp[3] 147°). IR 3260, 2960, 2865, 2830, 1600, 1500, 1240, 1030, and 820 cm^{-1}; NMR ($CDCl_3$) 0.70 (s; 3H), 2.70–4.20 (11H), 6.45 (d; 1H), 6.60 (quartet; 1H), and 7.10 (d; 1H); mass spectrum *m/e* 304 (M^+, 87), 241 (69), 174 (100), 173 (50), 147 (45), 41 (36), 36 (46) and 31 (33).

3-Methoxy-17-oxa-D-homoestra-1,3,5(10)-triene (9). Compound 8 (1 g, 3.26 mmol) and *p*-toluenesulfonyl chloride (0.75 g, 3.94 mmol) were dissolved in abs pyridine (20 ml). The mixture was kept at room temp. for 48 hr, then poured into an excess of cold dil HCl, and extracted with $CHCl_3$. From the dried extract $CHCl_3$ was removed *in vacuo* and the oily product purified by column chromatography (100 g silica gel; benzene–EtOAc/98:2/); the yield of 9: 0.79 g (84%), m.p. 95° (lit. m.p.[3] 95°). IR 2970, 2850, 1610, 1575, 1500, 1260, 1150, 1130, 1100, 1080, 1040, 1030, 970, 880, 815, and 780 cm^{-1}; NMR ($CDCl_3$) 1.00 (s; 1H), 3.20 (quartet; 2H), 3.70 (s; 3H), 3.75 (quartet; 2H), 6.45 (d; 1H), 6.60 (quartet; 1H), and 7.10 (d; 1h); mass spectrum *m/e* 286 (M^+, 12), 31 (100), 30 (39) and 29 (71).

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