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HETEROCYCLIC STEROIDS—XVII[1]

TOTAL SYNTHESIS OF 6-THIA-ESTROGENS

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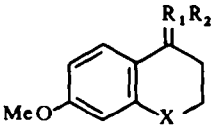
Abstract—The total synthesis of a series of 6-thia steroids, including *all trans*-6-thia-estrone is described. Structure proof has been based on NMR analysis, including the observation of a NOE in the spectrum of 8-H-iso-6-thia-estrone. Anomalous behaviour in the catalytic hydrogenation of thia-compounds is discussed.

IN THE synthesis of the various heterocyclic steroids obtained so far, the main emphasis has been put on the insertion of a hetero atom possessing its own electronic characteristics and at the same time leaving the geometry of the steroid skeleton unchanged. Yet the introduction of steric modifications of the rigid steroid framework has been recognized recently as a potential means to modify the structure profile of certain steroidal hormones. Therefore the insertion of other hetero atoms, for instance sulfur, combining the features of different size and electron distribution was anticipated to be of particular interest in our programme on the total synthesis of heterocyclic steroids.

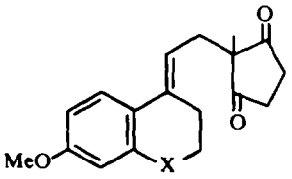
Although occasional reports on the total[3] and partial[4] synthesis of thiasteroids are available, it was not until recently that the synthesis of this class of compounds has been studied systematically,[5] thereby accentuating the influence of the S atom and its derived functionalities as sulfoxide and sulfone groups in ORD and CD spectroscopy.[6] To evaluate the potential hormonal activity of thia-steroids and also aiming at the investigation of the chemical influence of the sulfur atom in a number of reactions commonly used in the total synthesis of carbocyclic steroids the following study was undertaken. 7-Methoxythiachromanone-4 (**1a**), the synthesis of which could be considerably improved,* was converted via its vinyl-alcohol **2a** to the seco-steroid **3a** as was described earlier.[7] The latter compound could be synthesized also via a modification† of the procedure of Kuo *et al.*[8] Attempts to synthesize the corresponding sulfone **3b** via an analogous reaction series failed, although the diketonesulfone **3b** could be obtained via H_2O_2 oxidation of the sulfide **3a**. The failure of the vinyl alcohol **2b** to condense with methylcyclopentanedione is explained as a consequence of the intermediate charge development at the C_9 carbon atom in the mechanism of the condensation,[9] a process which is energetically unfavourable when strong electron attracting groups are present in the molecule. Cyclization of the sulfide **3a** occurred

* Direct ring closure of (*m*-methoxyphenyl-thio)-β-propionic acid[6] led to difficultly separable mixtures of isomeric ortho and para cyclization products. Use of PPA or $SnCl_4$ at controlled conditions afforded after distillation yields of ca. 60% pure 7-methoxythiachromanone-4 (**1**).

† Part of the forthcoming dissertation of J. M. B. Könst, University of Amsterdam.



1: R_1R_2 = O
2: R_1 = OH, R_2 = CH=CH_2



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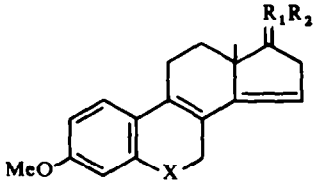
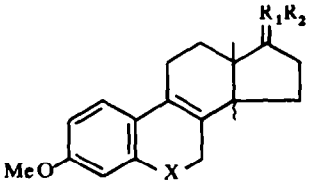
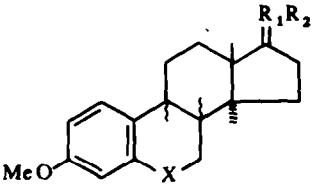


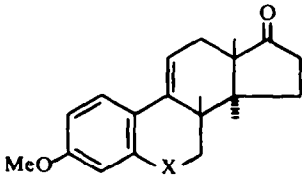
4: R_1R_2 = O
7: R_1 = H, R_2 = OH



5: 14αH, R_1R_2 = O
6: 14βH, R_1R_2 = O
8: 14αH, R_1 = H, R_2 = OH
15: 14αH, R_1 = OH, R_2 = C≡CH



9: 8βH, 9βH, R_1R_2 = O
10: 8αH, 9αH, R_1R_2 = O
12: 8βH, 9αH, R_1R_2 = O
13: 8βH, 9βH, R_1 = OH, R_2 = C≡CH
14: 8αH, 9αH, R_1 = OH, R_2 = C≡CH
16: 8βH, 9βH, R_1 = OH, R_2 = CH=CH_2
17: 8αH, 9αH, R_1 = OH, R_2 = CH=CH_2



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[a]: X = S
[b]: X = SO_2

smoothly upon p-TsOH treatment in benzene and the tetracyclic pentaene **4a**, although rather unstable, was obtained in crystalline form. Ring closure of the sulfone **3b** under a variety of conditions gave no cyclized material, presumably because of the aforementioned destabilization of the intermediate C_9^+ ion, which is a necessary intermediate in both isomerization and cyclization steps. Direct hydrogenation of **4a** produced a mixture of 14α-H and 14β-H isomers **5a** and **6a**, of which the former could also be obtained via the alternate $NaBH_4$ reduction of C_{17}-carbonyl to **7a**, catalytic hydrogenation of the latter leading to **8a**, and finally aluminium isopropide-cyclohexanone oxidation to afford **5a**. Spectral evidence confirmed the structure of the products. An important characteristic of the NMR-spectra is the separation of the C_7-methylene hydrogens from the hump, normally observed in the spectra of the homocyclic steroids. This proved to be a phenomenon of great help in later stereochemical assignments. The S-CH_2 signal in **7a** was found as a singlet, while in the spectrum of **4a** a doublet was noted for the corresponding methylene protons, which could be shown to arise as a result of the chemical shift difference between 7α- and 7β-H.* Furthermore, an extra splitting of (1·5 ±0·3) c/s in the spectra of compounds **5a**, **6a** and **8a** was attributed to a long-range coupling of $H_{7\alpha}$ and $H_{7\beta}$ with H_{14}.

* The assignment is based on a comparison of the 60 and 100 Mc spectra of compounds **4a–8a** and by studying the spectra of the C_{14}–C_{15} dideuterio compounds.

The problem then was to find a method via which the remaining 8,9 double bond could be hydrogenated in a stereoselective manner, without affecting the thia-ether function. Li-NH_3 reduction did produce exclusively thiols, indicating a facile C-S cleavage[10] under the reaction circumstances. Attempts to isomerize the $C_{8,9}$ double bond into the $C_{9,11}$ position prior to catalytic hydrogenation, failed as a result of the instability of the material under acid conditions. With no alternative method available, allowing for the direct formation of ring B/C *trans* product, the catalytic hydrogenation of ketone **5a** was studied. Recent information in the carbocyclic series indicated the exclusive formation of 8-H-isoestrone upon Pd/C hydrogenation of 8,9-dehydroestrone,[11] while in the B-nor[12] and D-homo[13] series the predominant product is also the 8-iso-compound. Both the steric effects of the C_{13} methyl and C_7 axial hydrogen were apparently involved in the unique stereoselectivity of the reaction. Contrary to the latter reduction course, a slow hydrogen uptake* was observed in the hydrogenation of the keton **5a**. Upon fractional crystallization of the reaction mixture two isomeric products were obtained in a ratio of 1:1, presumably the B/C *cis* fused ketones **9a** and **10a**. To account for this behaviour it was originally postulated that the presence of the sulfur atom affected the catalyst in such a way so as to diminish the rate of the reduction, thereby experiencing a loss in the stereoselectivity of the α-approach. Although this hypothesis could be valid in the reduction of the thiaestrone **5a** a hydrogenation of the sulfone **5b** in which a direct interaction between the sulfur electrons and the catalyst is less likely, gave identical results, a slow reduction process combined with the formation of equal amounts of the isomeric ketones **9b** and **10b**. Whether this behaviour is due to steric and/or electronic interaction is under investigation.† The interrelationship between sulfides **9a** and **10a** and sulfones **9b** and **10b** was established by H_2O_2 oxidation of the former compounds.

Stereochemical assignments were deduced from a NMR analysis of the splitting pattern of C_7-methylene hydrogens and the position of the C_1 aromatic proton and were supported by the observation of a NOE in the spectrum of the 8-iso compound **10a**. The NMR spectrum of ketone **9a** (Fig 1) showed three separated signals for the C_7 ax, C_9 and C_7 eq hydrogens, respectively at δ 2·74, δ 3·05 and δ 3·31 from which the following coupling constants were deduced: J 7α, 7β = 13 c/s, J 7ax, 8 = 4·5 c/s and J 7eq, 8 = 3·5 c/s. These values indicate an equatorial position for the C_8 hydrogen atom, compatible with an 8β-H structure. On the other hand in the spectrum of the second isomer **10a** (Fig 2) solely the presence of two large couplings (13 c/s each) in the signal of one of the C_7 methylenes could be observed, thus pointing to the presence of a large J ax,ax and clearly revealing the 8α-H structure of ketone **10a**. Additional evidence was taken from the position of the C_1 aromatic hydrogen, which is known to be influenced by steric interaction with the C_{11} hydrogen atoms.[14] A large downfield shift for C_1-H in the spectrum of ketone **9a** is also indicative for the in-plane structure of the C_{11} eq-H and C_1-H, in agreement with a 8β-H, 9β-H structure for isomer **9a**. A final proof for the stereochemistry of the ring B/C fusion in ketone **10a** was taken from a NOE experiment. Model studies of 8-iso-steroids indicated a proximity effect to be possible between the axial C_7-H and the C_{13} Me group, the interjacent distance

* The reaction time at room temp (50 hr) could be shortened by working at higher temp, f.i. at 50° 5 hr were necessary to complete the hydrogen take-up.

† Similar effects were noted in the syntheses of a series of 7-thiasteroids, F. J. M. Deckers, forthcoming dissertation, University of Amsterdam.

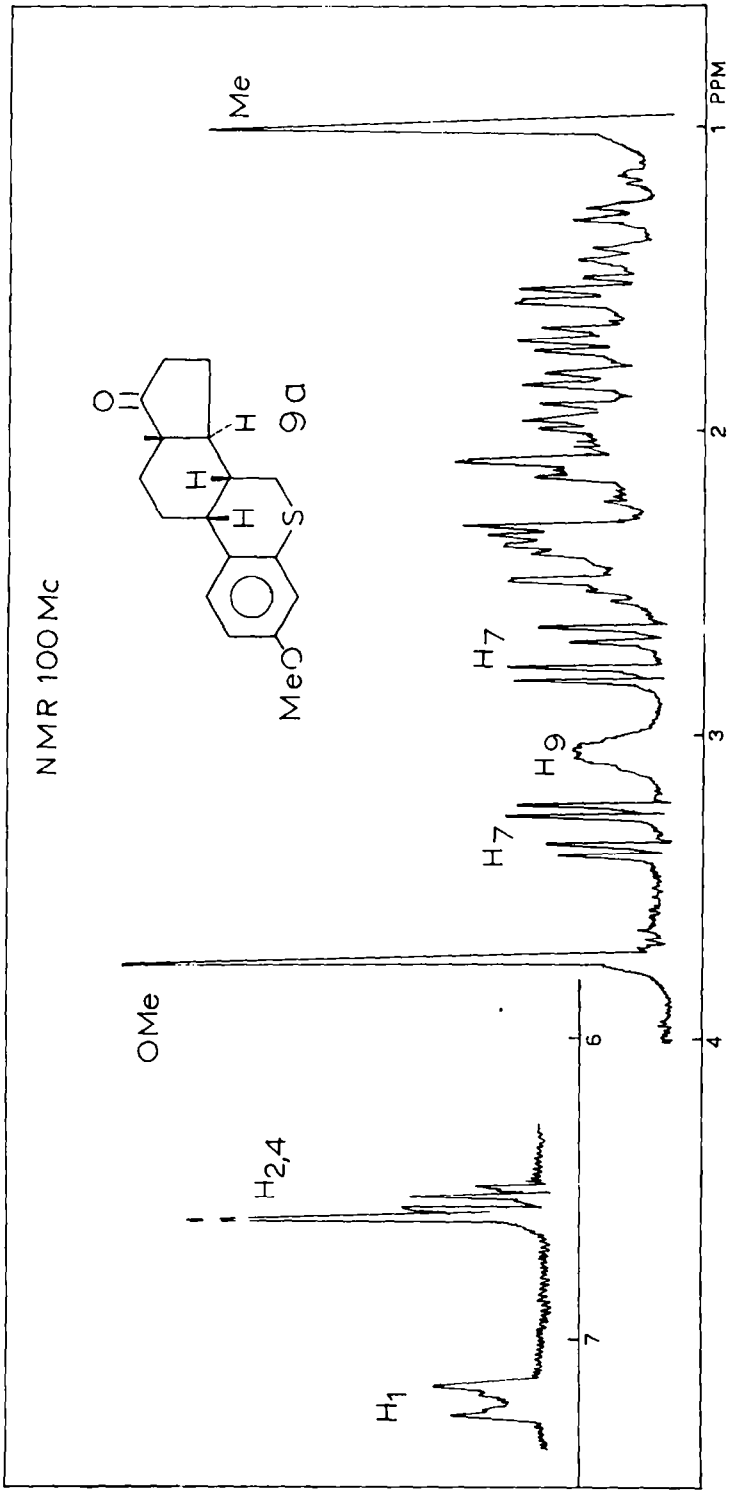


FIG. 1

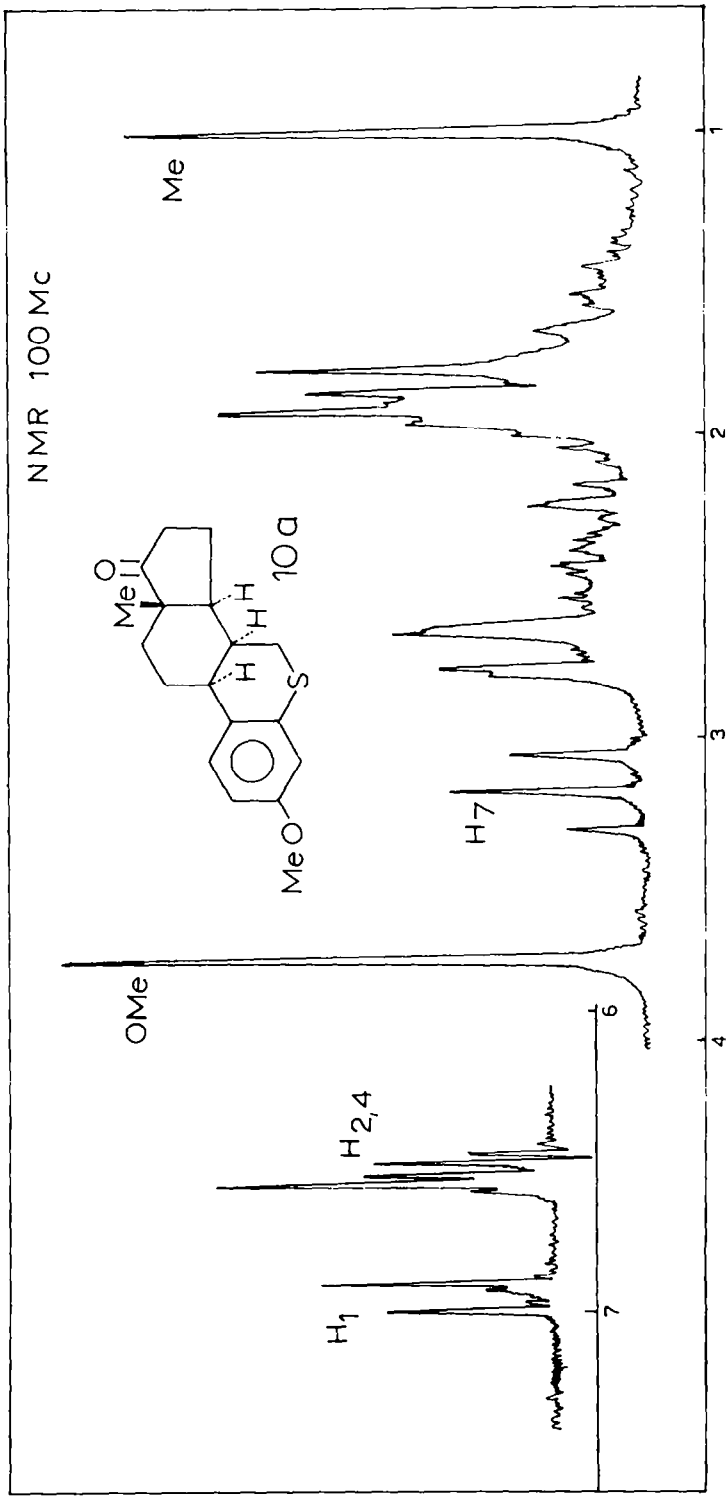


FIG. 2

being less than 3·2 Å. The C_7-axial-H is separately visible in the spectrum of ketone **10a**, and indeed it was found that irradiation of the C_{13}-methyl signal produced a 12% enhancement of the integrated intensity of the C_7-ax-H signal (Fig 3).

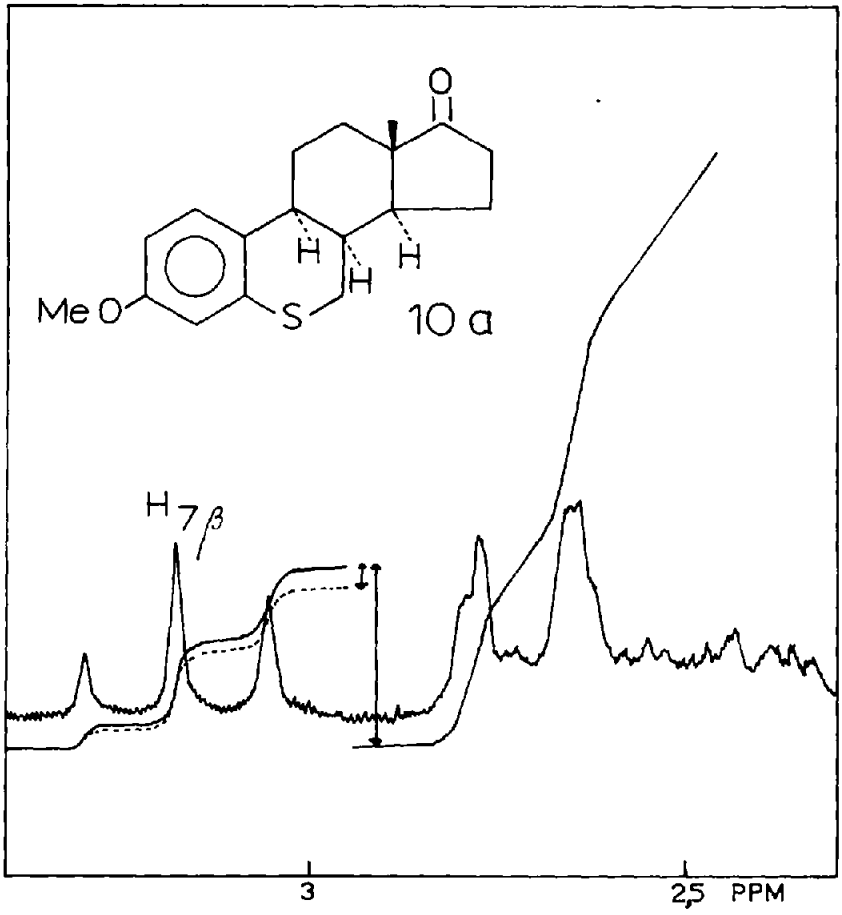


FIG. 3

Lastly the synthesis of all *trans* 6-thia estrone methyl ether could be achieved via the following route: model studies indicated the $C_{9,11}$ bond in thiaketone **9a** to be situated almost in a plane with the aromatic ring, implying a perpendicular position for the C_9-H, with respect to this plane. This is a favourable stereochemistry for hydride abstraction by means of DDQ.[15] Dehydrogenation of ketone **9a** indeed occurred smoothly* and the resulting $C_{9,11}$ dehydroisomer **11a** was finally hydrogenated to yield a mixture of two 6-thia-steroids, the starting material **9a** (25%) and the all-*trans* isomer **12a** (75%). In contrast to the slow hydrogenation rate of the $C_{8,9}$ double bond, the hydrogen uptake occurred quickly and in a stereoselective manner. In the NMR spectrum of **12a** the C_{13}-CH_3 signal was found at the same δ (0·91) value as compared to estrone and 6-aza-estrone.[16] The mass spectra of both *cis*-isomers **9a**

* The 9α-isomer was recovered unchanged upon treatment with DDQ.

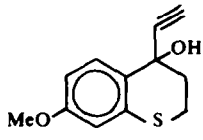
and **10a** showed also a close resemblance with the spectra of the corresponding homocyclic compounds.[17] In particular the intensity of the *m/e* 178 fragment, corresponding to a rupture of the $C_{9,11}$ and $C_{8,14}$ bonds, is far more pronounced in the spectra of the *cis* isomers **9a** and **10a**, as compared to the spectrum of the all-*trans* isomer **11a**.

Reactions at the C_{17}*-carbonylgroup.* To conclude the first part of this work a number of reactions at the C_{17} ketone function was carried out. In general the reaction of alkali-acetylides in liquid NH_3 or as the ethylenediamine-complex proved not very successful. Although some addition occurred, the results indicated always the remaining of a considerable amount of starting material, while substantial decomposition also occurred. Satisfactory results, however, were obtained upon use of alkynylmagnesium halides.[18] Reaction of ketones **9a** and **10a** produced the corresponding carbinols **13a** and **14a**. At low temperature the 8,9-dehydroketone **5a** could also be converted to the ethynylhydroxy compound **15a**, albeit in lesser yields. A remarkable influence of the sulfur-atom again was noted in the catalytic hydrogenation of carbinols **13a** and **14a**. Use of partially poisoned $Pd/CaCO_3$* did not lead to any uptake of hydrogen, while with $Pd/CaCO_3$ itself the process occurred extremely slowly. Use of Pd/C led to a partial saturation of the ethynyl moiety and the vinylhydroxy compounds **16a** and **17a** were obtained in good yields. When ethynyl sulfones **13b** and **14b** were reacted, a similar behaviour was observed, hydrogenation proceeding until one mole of hydrogen was consumed and affording the vinylhydroxysulfones **16b** and **17b**.

TABLE 1

Derivative / Compound No.	acetylene	ethylene		
		Ha, Hb, Hc		
	$\delta \equiv CH$	δH_a	δH_b	δH_c
6-thiaestrone **12a**	2·6			
8-dehydro-6-thiaestrone **5a**	2·6			
8-iso-6-thiaestrone **10a**	2·6	6·13	5·17	5·16
9-iso-6-thiaestrone **9a**	2·3	5·83	4·90	5·05

In the NMR spectra of the carbinols **13a**, **14a** and **15a** a marked difference in the δ value (0·3 ppm) for the signals of the acetylenic and ethylenic hydrogen (Table 1) was explained in terms of a shielding effect exerted by the aromatic nucleus (Fig 4). The unique stereochemistry, necessary to observe this effect, is found in the β-*cis* junction of rings B and C, which allows for the bent shape of ketone **9a**. On the other hand, however, an α-position for the ethynyl function is also a necessary feature, thereby determining the stereochemistry at C_{17}. The corresponding chemical shift differences

* Reduction of 

with the same catalyst proceeded without difficulties and afforded the vinylhydroxy compound **2**.

of the signals of the ethylene protons (0·3 ppm) confirm this assignment. The precise cause of the anomal hydrogenation effects observed in some thia-steroidal molecules is still uncertain. Further work on this interesting aspect is in progress.

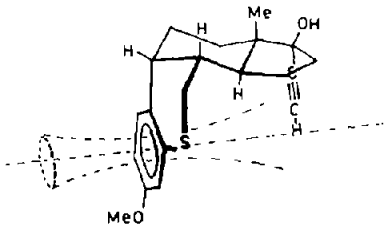


FIG. 4

EXPERIMENTAL

7-Methoxy thiachromanone-4 **1a**. 21·2 g (0·1 mole) 5-(3-methoxyfenyl)-3-thiopropionic acid was stirred with 75 g polyphosphoric acid at 50° during 4 hr. The reaction mixture was diluted with 300 cc water and extracted with ether. The organic layer was washed with a $NaHCO_3$ aq and water and dried on $MgSO_4$. The solvent was removed by distillation and the residue was distilled under diminished press. The fraction boiling at 148–153°/0·4 mm Hg (16·2 g yellow oil) was recrystallized from MeOH and 10 g (52%) colourless crystalline product, m.p. 56–57° was obtained; IR (KBr) C=O: 1670 cm^{-1}; Ar: 1590 and 1490 cm^{-1}; NMR ($CDCl_3$) 100 Mc, $O\underline{CH_3}$: δ = 3·78; $\underline{H_5}$: δ = 7·96, 8·04. (Found: C, 61·7; H, 5·3; S, 16·4. $C_{10}H_{10}O_2S$ (M = 194·25). Calc: C, 61·85; H, 5·19; S, 16·48%).

2-[7-Methoxythiachromylidene-ethyl]-2-methylcyclopentanedione-1,3 **3a**. To 6 g (0·25 mole) Mg and a crystal I_2 in 50 cc THF a soln of 33 g (0·28 mole) vinylbromide in 50 ml of THF was added with stirring. The addition took place at such a rate that the temp of the mixture did not rise above 45°. The soln was subsequently refluxed on a waterbath during ½ hr, diluted with 50 cc THF and cooled to −10°. At this temp a soln of 14 g (0·072 mole) 7-methoxy-thiachromanon-4 in 30 ml THF and 50 ml ether was slowly added. The mixture was allowed to warm up to room temp during 1 hr and refluxed for an additional hr, after which the soln was poured into a mixture of 400 g ice and 200 g NH_4Cl. The organic layer was separated, diluted with ether and washed with a sat NH_4Cl aq and water, dried on $MgSO_4$ and evaporated *in vacuo*. The vinylic alcohol was obtained as a light yellow oil and was not purified further. The reaction was carried out in a N_2 atm; IR (cap.) −OH: 3470 cm^{-1}; Ar: 1600, 1500 cm^{-1}; NMR ($CDCl_3$) 60 Mc, H_1: 7·24, 7·10; —$O\underline{CH_3}$: 3·60. A soln of 8 g (0·036 mole) **2a**, 6 g 2-methyl-cyclopentane-1,3-dione and 0·5 g KOH in 200 cc dry MeOH was refluxed on a waterbath during 4 hr in a N_2 atm. The MeOH was evaporated *in vacuo* and the residue was treated with benzene. After filtration of the unreacted dione the benzene soln was diluted with ether and washed 3 times with a 5%-KOH aq and with water. Drying on $MgSO_4$ and evaporation of the solvent resulted in a brown oil, which was recrystallized from ether or MeOH, yield 6·7 g (55%) white needles, m.p. 92–94°; IR (KBr), C=O 1715, 1755 cm^{-1}, Ar 1600, 1490 cm^{-1}; NMR ($CDCl_3$) 100 Mc, $\underline{H_1}$: 7·28, 7·19; —$O\underline{CH_3}$: 3·74; $\underline{H_{11}}$: 5·50, 5·58, 5·66; —$\underline{CH_3}$: 1·16. (Found: C, 68·1; H, 6·4; S, 10·0. $C_{18}H_{20}O_3S$ (M = 316·41. Calc: 68·34; H, 6·37; S, 10·11%).

3-Methoxy-8,14-bisdehydro-6-thiaestrone **4a**. 0·5 g (2·8 mmole) *p*-toluenesulfonic acid was heated in 250 cc benzene at a Dean Stark watertrap during 20 min (bath temp 115°) after which a soln of 10·5 g (33 mmole) of **3a** in 60 ml benzene was added. The mixture was heated during 10 min, cooled in ice and diluted with 100 cc ether. After washing with sat $NaHCO_3$ aq and water, the organic layer was dried over $MgSO_4$ and the solvent was evaporated. The reaction and working up took place in a N_2 atm. The resulting brown oil was not purified but reduced immediately. An analytical sample could be obtained by crystallization from benzene; m.p. 111–113°. IR ($CHCl_3$) C=O 1735 cm^{-1}, Ar 1595, 1495 cm^{-1}; NMR ($CDCl_3$) 60 Mc, $\underline{H_1}$: 7·37, 3·24; $O\underline{CH_3}$: 3·77; $\underline{H_{11}}$: 5·84, 5·88, 5·92; $\underline{H_7}$: 3·45; $\underline{CH_3}$: 1·14. (Found: C, 72·2; H, 5·9; S, 10·6. $C_{18}H_{18}O_2S$ (M = 298·39). Calc: C, 72·45; H, 6·08; S, 10·75%).

3-Methoxy-8-dehydro-6-thiaestrone **5a**; *3-methoxy-8-dehydro-14-iso-6-thiaestrone* **6a**. A suspension of 2 g Pd/$CaCO_3$ 10% in 30 ml THF was saturated with H_2 and a soln of 2 g (6·6 mmole) 3-methoxy-8,14-bisdehydro-6-thiaestrone in 15 ml THF was added. After a reaction time of 3 hr 130 ml H_2 was taken up and the catalyst was filtered off. The solvent was removed *in vacuo* and the residue dissolved in hot MeOH.

After cooling the ppt was filtered off and recrystallized from MeOH/EtOAc, yielding 0·6 g (30%) **5a**, m.p. 150–153°. The filtrate was concentrated *in vacuo* to 10 ml and 1 ml EtOAc was added. At cooling in ice the 14β-isomer, **6a** precipitated. Recrystallization twice from MeOH gave a product which contained less than 3% of the 14α-isomer, yield 0·37 g (18%), m.p. 95–97°. (**5a**) IR (KBr) C=O 1735 cm^{-1}; Ar 1590, 1495 cm^{-1}; NMR ($CDCl_3$) 100 Mc, $\underline{H}_1$: 7·23, 7·14; $-O\underline{CH}_3$: 3·75; $\underline{H}_7$: 3·27, 3·29, $-\underline{CH}_3$: 0·89. (Found: C, 71·8; H, 6·7; S, 10·7. $C_{18}H_{20}O_2S$ (M = 300·40). Calc: C, 71·98; H, 6·71; S, 10·65%). (**6a**) IR (KBr) C=O, 1735 cm^{-1}; NMR ($CDCl_3$) 100 Mc, $\underline{H}_1$: 7·21, 7·12; $-O\underline{CH}_3$: 3·76; $\underline{H}_7$: 3·25; $-\underline{CH}_3$: 1·08. (Found: C, 62·0; H, 5·8; S, 9·1. $C_{18}H_{20}O_5S$ (M = 348·40). Calc: C, 62·06; H, 5·79; S, 9·18%).

3-*Methoxy*-8,14-*bisdehydro*-6-*thiaestradiol* **7a**. 10 g (33 mmole) of **4a** was dissolved in 300 cc MeOH in 15 cc benzene and an ice cold soln of 10 g (270 mmole) $NaBH_4$ in 100 cc EtOH and 40 cc water was added. The reaction mixture was stirred at room temp during 2 hr and then acidified with AcOH to pH = 5. Most of the solvent was removed by evaporation *in vacuo* and the residue was treated with ether and water. The organic layer was washed with a sat $NaHCO_3$ aq and water, dried over $MgSO_4$ and the solvent was removed by distillation *in vacuo*. The residue was crystallized from MeOH, resulting in 5·9 g (60%) yellow needles, m.p. 94–101°; IR ($CHCl_3$) —OH: 3500 cm^{-1}; Ar 1595, 1490 cm^{-1}; NMR ($CDCl_3$) 60 Mc, $\underline{H}_1$: 7·31, 7·16; $-O\underline{CH}_3$: 3·76; $\underline{H}_7$: 3·35; $\underline{H}_{11}$: 5·54, 5·49, 5·44; $-\underline{CH}_3$: 0·96. Determination of the exact mass weight* gave M = 300·1190, required for $C_{18}H_{20}O_2S$ 300·11839.

3-*Methoxy*-8-*dehydro*-6-*thiaestradiol* **8a**. 5 g Pd/$CaCO_3$ 10% was sat with H_2 in 100 ml THF, after which a soln of 5·9 g (20 mmole) 3-methoxy-8,14-bisdehydro-6-thiaestradiol in 35 ml THF was added and hydrogenated during 6 hr (420 cc H_2 was taken up). The reaction mixture was filtered and the filtrate evaporated *in vacuo*. The residue was crystallized from MeOH, yield 4·4 g (88%) 3-methoxy-8-dehydro-6-thiaestradiol, m.p. 101–107°; IR ($CHCl_3$) —OH: 3500 cm^{-1}; Ar: 1600, 1495 cm^{-1}; NMR ($CDCl_3$) 100 Mc, δ $\underline{H}_1$: 7·23, 7·14; $-O\underline{CH}_3$: 3·76; $-\underline{CH}_3$: 0·80; $\underline{H}_7$: 3·21, 3·22, 3·25, 3·26. Determination of the exact mass weight gave M = 302·1336, required for $C_{18}H_{22}O_2S$ 302·13404.

3-*Methoxy*-8-*dehydro*-6-*thiaestrone*, **5a**, *via Oppenauer oxidation of* **8a**. 0·8 g (2·7 mmole) 3-methoxy-8-dehydro-6-thiaestradiol was dissolved in 60 ml dry toluene and 1·1 g (5·3 mmole) Al-isopropoxide and 2·0 cc (19·4 mmole) cyclohexanone were added. The reaction mixture was heated on an oil bath (150°) whereby solvent was distilled off and toluene was added via a dropping funnel at the same rate. After 2 hr the mixture was cooled, diluted with ether and extracted 3 times with a 5% KOH aq. The organic layer was washed with water, dried on $MgSO_4$ and evaporated *in vacuo*. The residue was crystallized from MeOH yielding 0·56 g (70%) 3-methoxy-8-dehydro-6-thiaestrone, m.p. 152–154°.

3-*Methoxy*-9-*iso*-6-*thiaestrone* **9a**; 3-*Methoxy*-8-*iso*-6-*thiaestrone* **10a**. To a H_2-sat suspension of 2 g Pd/C (10%) in 50 cc benzene, a soln of 1 g (3·3 mmole) **5a** in 30 cc benzene was added. After 5 hr hydrogenation at 50°, the catalyst was filtered off and the residue was crystallized from EtOAc. The ppt mainly consisted of **10a** which could be purified by recrystallizing from MeOH and EtOAc, yield 0·31 g (31%), m.p. 167–168°. The filtrate was evaporated and the residue extracted with hot MeOH. On cooling the 9-iso compound precipitated and was further purified by crystallizing twice from MeOH, yielding 0·28 g (28%), m.p. 128–131°. (**9a**) IR ($CHCl_3$) C=O 1725 cm^{-1}; Ar 1600, 1500 cm^{-1}. (Found: C, 71·3; H, 7·5; S, 10·6. $C_{18}H_{22}O_2S$ (M = 302·42). Calc: C, 71·50; H, 7·33; S, 10·59%). (**10a**) IR ($CHCl_3$) C=O, 1725 cm^{-1}. (Found: C, 71·3; H, 7·4; S, 10·7. $C_{18}H_{22}O_2S$ (M = 302·42). Calc: C, 71·50; H, 7·33; S, 10·59%).

3-*Methoxy*-9,11-*dehydro*-6-*thiaestrone* **11a**. A soln in 200 mg (0·67 mmole) of **9a** and 180 mg (0·8 mmole) 2,3-dichloro-5,6-dicyano-quinone in 30 ml benzene was heated on a waterbath during 30 min. The mixture was cooled and the ppt of hydroquinone was filtered off. The filtrate was diluted with ether and washed twice with a 5% KOH aq and water. Drying over $MgSO_4$ and evaporating the solvent resulted in a yellow residue, which was crystallized from EtOAc, yield 68 mg (35%), m.p. 203–206°; IR ($CHCl_3$) C=O 1720 cm^{-1}, Ar 1600, 1500 cm^{-1}; NMR ($CDCl_3$), 100 Mc, $\underline{H}_1$: 7·43, 7·53; $O\underline{CH}_3$: 3·74; $\underline{H}_{11}$: 6·10–6·25 (mult.), $\underline{H}_7$: 2·80–3·00 (mult), $\underline{CH}_3$: 0·93. (Found: C, 71·9; H, 6·8; S, 10·7. $C_{18}H_{20}O_2S$ (M = 300·40). Calc: C, 71·98; H, 6·71; S, 10·65%).

3-*Methoxy*-6-*thiaestrone* **12a**. 80 Mg Pd/C (10%) in 20 cc benzene was sat with H_2, after which a soln of 80 mg (0·27 mmole) of **11a** in 10 cc benzene was added. After 40 min the hydrogenation was complete and the catalyst filtered off. The solvent was removed *in vacuo* and the product crystallized from MeOH, yielding 51 mg (64%) 3-methoxy-6-thiaestrone, m.p. 199–201°; IR ($CHCl_3$) C=O, 1725 cm^{-1}; Ar 1605, 1500 cm^{-1}; NMR ($CDCl_3$) 100 Mc, $\underline{H}_1$: 7·16, 7·25; $O\underline{CH}_3$: 3·74, $\underline{H}_7$: 2·80–3·00 (mult), $\underline{CH}_3$: 0·91. (Found: C, 71·5; H, 7·3; S, 10·8. $C_{18}H_{22}O_2S$ (M = 302·42). Calc: C, 71·50; H, 7·33; S, 10·59%).

* The mass spectrum was taken on an AEI Ms-9 instrument.

3-Methoxy-9-iso-17-ethynyl-6-thiaestradiol **13a**. To 2·4 (0·1 mole) Mg and a crystal of I_2 in 30 cc THF, a soln of 11 g (0·1 mole) EtBr in 40 cc THF was added at such a rate that the mixture was refluxing gently. When the Mg was dissolved the mixture was slowly added (20 min) to 40 ml THF which was saturated with acetylene. During the addition a fast stream of acetylene was led through the mixture. (The acetylene was purified by cooling to −80°). After cooling to 0° a soln of 400 mg (1·33 mole) of **9a** in 20 ml THF was added and the suspension was stirred for 2 hr at this temp. The Grignard compound was decomposed by adding a sat NH_4Cl aq. The organic layer was diluted with ether, washed with NH_4Cl aq and water. Drying on $MgSO_4$ and evaporation of the solvent resulted in a yellow oil, which was crystallized from tetra, yield 283 mg (65%), m.p. 165–168°; IR ($CHCl_3$) ≡CH: 3320 cm^{-1}, —OH: 3470, 3610 cm^{-1}; Ar: 1595, 1495 cm^{-1}; NMR ($CDCl_3$) 60 Mc, $\underline{H}_1$: 7·20, 7·35; —O$\underline{CH}_3$: 3·74; ≡$\underline{CH}$: 2·28; $\underline{CH}_3$: 1·00. The determination of the exact mass weight gave M = 328·149, required for $C_{20}H_{24}O_2S$ 328·14969.

3-Methoxy-8-iso-17-ethynyl-6-thiaestradiol **14a**. Prepared according to the procedure for **13a**. The reaction product was crystallized from MeOH, yield 67%, m.p. 117–119°; IR ($CHCl_3$) ≡CH: 3340 cm^{-1}, —OH: 3450, 3640 cm^{-1}; Ar 1595, 1490 cm^{-1}; NMR ($CDCl_3$) 60 Mc, $\underline{H}_1$: 6·92, 7·08, —O$\underline{CH}_3$: 3·72, ≡$\underline{CH}$: 2·61, —$\underline{CH}_3$: 0·97. Determination of the exact mass weight gave M = 328·149, required for $C_{20}H_{24}O_2S$ 328·14969.

3-Methoxy-8-dehydro-17-ethynyl-6-thiaestradiol **15a**. Prepared according to the procedure for **13a**. The product was crystallized from MeOH/water and from tetra, yield 44%, m.p. 140–144°; IR ($CHCl_3$) ≡CH: 3340, —OH: 3450, 3640 cm^{-1}; Ar: 1595, 1495 cm^{-1}; NMR ($CDCl_3$) 60 Mc, H_1: 7·12, 7·26, —OCH_3: 3·76, H_7: 3·22, ≡CH: 2·56, —CH_3: 0·90. Determination of the exact mass weight gave M = 326·134, $C_{20}H_{22}O_2S$ requires 326·13404.

3-Methoxy-9-iso-17-vinyl-6-thiaestradiol **16a**. 100 Mg Pd/C (10%) in 10 cc EtOH was saturated with H_2 and a soln of 180 mg (0·55 mmole) of **13a** in 20 ml EtOH was added. After 30 min no more H_2 was taken up and the catalyst was filtered off. The solvent was evaporated and the residue crystallized from MeOH/water, yielding 140 mg (78%), m.p. 76–82°; IR: —OH: 3500, 3650 cm^{-1}; Ar: 1600, 1495 cm^{-1}; NMR ($CDCl_3$) 60 Mc, $\underline{H}_1$: 7·14, 7·28, O$\underline{CH}_3$: 3·75, $\underline{CH}_3$: 1·04, $\underline{H}_{20}$: 6·07, 5·90, 5·78, 5·61. $\underline{H}_{21}$: 4·80–5·25 (mult). Determination of the exact mass weight gave M = 330·165, $C_{20}H_{26}O_2S$ requires 330·16534.

3-Methoxy-8-iso-17-vinyl-6-thiaestradiol **17a**. This compound was synthesized in the same way as the corresponding 9-iso compound. The product was crystallized from EtOH, yield 75%, m.p. 85–91°; IR ($CHCl_3$): —OH: 3500, 3650 cm^{-1}; Ar: 1600, 1495 cm^{-1}; NMR ($CDCl_3$) 60 Mc, $\underline{H}_1$: 6·92, 7·07, —O$\underline{CH}_3$: 3·73; $\underline{CH}_3$: 1·03, $\underline{H}_{20}$: 6·37, 6·19, 6·07, 5·90, $\underline{H}_{21}$: 4·95–5·35 mult. Determination of the exact mass weight gave M = 330·165, required for $C_{20}H_{26}O_2S$ 330·16534.

Sulfones (general procedure). The sulfones could be synthesized by dissolving 1 mmole of the thioether in a mixture of 2·5 ml AcOH and 1·5 ml Ac_2O. The soln was cooled in ice and 1 ml 30% H_2O_2 soln was added. After standing overnight in the darkness at room temp 10 ml water was added and the ppt was filtered off and crystallized.

7-Methoxy-thiachromanon-4-1,1'-dioxide **1b**. Crystallized from MeOH, m.p. 128–130°; IR (KBr) C=O: 1680 cm^{-1}, SO_2: 1270, 1125, 1155 cm^{-1}; ($CDCl_3$) 60 Mc O$\underline{CH}_3$: 3·96; $\underline{H}_5$: 7·98, 8·14. (Found: C, 53·0; H, 4·5; S, 14·1. $C_{10}H_{10}O_4S$ (M = 226·25). Calc: C, 53·10; H, 4·46; S, 14·15%).

2-[7-Methoxy-1,1'-dioxide-thiachromylidene-ethyl-2-methylcyclopentane-dione-1,3 **3b**. Crystallized from MeOH, m.p. 151–154°; IR (KBr) C=O: 1720, 1760 cm^{-1}, SO_2: 1315, 1130, 1150 cm^{-1}; NMR ($CDCl_3$) 100 Mc, $\underline{H}_1$: 7·49, 7·40, —O$\underline{CH}_3$: 3·84; $\underline{CH}_3$: 1·20, H_{11}: 5·79, 5·87, 5·95. (Found: C, 62·0; H, 5·8; S, 9·1; $C_{18}H_{20}O_5S$ (M = 348·40). Calc: C, 62·06; H, 5·79; S, 9·18%).

3-Methoxy-8-dehydro-6-thiaestrone-6,6'-dioxide **5b**. Crystallized from MeOH/EtOAc, m.p. 198–201°; IR ($CHCl_3$) C=O, 1730 cm^{-1}, SO_2: 1295, 1130 cm^{-1}; NMR ($CDCl_3$) 100 Mc $\underline{H}_1$: 7·39, 7·48, $\underline{H}_2$: 7·04, 7·07, 7·13, 7·16, $\underline{H}_4$: 7·47, 7·50, O$\underline{CH}_3$: 3·86, $\underline{H}_7$: 3·86, $\underline{CH}_3$: 0·94. (Found: C, 65·0; H, 6·2; S, 9·7. $C_{18}H_{20}O_4S$ (M = 332·40). Calc: C, 65·05; H, 6·07; S, 9·63%).

3-Methoxy-9-iso-thiaestrone-6,6'-dioxide **9b**. Crystallized from MeOH 198–200°; IR (KBr) C=O: 1730 cm^{-1}; SO_2: 1310, 1140 cm^{-1}; NMR ($CDCl_3$) HA 100 Mc, $\underline{H}_1$: 7·38, 7·47, $\underline{H}_2$: 7·06, 7·09, 7·15, 7·18, $\underline{H}_4$: 7·47, 7·50, —O$\underline{CH}_3$: 3·85, $\underline{H}_7$: 3·68, 3·62, 3·54, 3·48, $\underline{H}_{7'}$: 3·32, 3·27, 3·18, 3·13, $\underline{H}_9$: 3·35–3·55 (mult), —$\underline{CH}_3$: 1·00. (Found: C, 64·6; H, 6·5; S, 9·7. $C_{18}H_{22}O_4S$ (M = 334·42). Calc: C, 64·65; H, 6·63; S, 9·57%).

3-Methoxy-8-iso-6-thiaestrone-6,6'-dioxide **10b**. Crystallized from EtOAc, m.p. 238–240°; IR (KBr) C=O: 1730 cm^{-1}, SO_2: 1300, 1140 cm^{-1}; NMR ($CDCl_3$) 100 Mc, $\underline{H}_1$: 7·24, 7·33, $\underline{H}_2$: 7·04, 7·07, 7·13, 7·16, $\underline{H}_4$: 7·40, 7·43, —O$\underline{CH}_3$: 3·85, —$\underline{CH}_3$: 0·98. (Found: C, 64·4; H, 6·6; S, 9·7. $C_{18}H_{22}O_4S$ (M = 334·42). Calc: C, 64·65; H, 6·63; S, 9·57%).

All m.ps are uncorrected. Analyses were carried out by Messrs. H. Pieters and W. J. Buis of the Microanalytical Department of this laboratory. IR and Mass spectra were recorded on Unicam SP 200 and AEI MS3-9 spectrometers, respectively. NMR spectra were measured on Varian Associates Model A-60 and HA-100 instruments.

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