Total Synthesis of Heterocyclic Steroids

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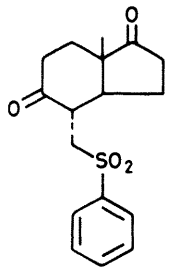
The total synthetic approach developed initially for natural steroids, and used for the preparation of *A*-nor compounds, has been extended to the preparation of novel heterocyclic steroids. The easily accessible 3,4-dinor-2,5-seco-9α-estrane-1,5,17-trione (9a) was treated with hydrazine hydrate, urea, and hydroxylamine hydrochloride to provide the 1-methyl-2,3-diaza steroid derivative (10a), the pyrimidone (11), and the isoxazole analogue (12a), respectively. The 17α-ethynyl steroids (10b) and (12b) were also prepared.

Whereas the preparation of some heterocyclic steroids has been mentioned in the literature, only very few papers report the synthesis of steroids containing a heteroatom in ring *A*.[1] Thus, we decided to try and adapt the previously described total synthetic scheme for *A*-nor-steroids [2] to the preparation of ring *A* heterocyclic analogues. The present report details the total synthesis of such heterocyclic steroids, emphasizing the flexibility of the scheme originally developed by Wiechert *et al.*[3]

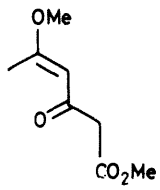
The initial step of the synthesis required condensation of the known sulphone (1) [3] with the oxo ester (2); the latter was prepared from pentane-2,4-dione in two steps. After a careful survey of several techniques, it was found that appropriate conditions for the preparation of the enol ether (3) were reaction of pentane-2,4-dione with trimethyl orthoformate, catalysed with toluene-*p*-sulphonic acid.[4] The enolate of the ketone (3), prepared either by reaction with lithium di-isopropylamide (LDA) or with sodium hydride,[5] was treated with dimethyl carbonate to yield the desired β-oxo ester (2).

In our initial approach, the enol ether group of the intermediate (4) was hydrolyzed before ring closure and decarboxylation occurred. Thus, acid-catalysed hydrolysis of the enol ether group in compound (4), followed by treatment with methanolic potassium hydroxide, not only led to cyclization and formation of ring *B*, but hydrolysis of the ester, decarboxylation, and cleavage of the β-diketo grouping were also achieved, thus furnishing the known enedione (5).[6] The structure of the enone (5) was confirmed by *X*-ray crystallography. The problem of cleavage of the β-diketone was circumvented by effecting the conversion of the intermediate (4) into the desired enetrione (8) in steps. Thus, compound (4) was first subjected to base-treatment with methanolic potassium hydroxide, which brought about saponification of the ester grouping, followed by decarboxylation, providing the trione (6). The enol ether group in compound (6) was then hydrolyzed with 1M-hydrochloric acid in acetone solution at room temperature. Under these conditions ring closure also occurred, thus affording the tertiary carbinol (7). Further treatment of the intermediate (7) in acidic conditions at *ca.* 55 °C brought about dehydration, and yielded the desired enone (8). After a systematic study of different reaction conditions, it was found that this process could be simplified by treatment of the crude product (6) in hydrochloric acid–acetone at 50 °C, thus providing directly the expected enone (8) in 52% overall yield from the trioxoester (4).

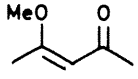
It is worth emphasizing that the intramolecular condensation of the intermediate (4) took place under substantially different conditions from those used for the synthesis of natural steroids [3] and *A*-nor-steroids.[2,3] Both diastereoisomers of compound (4) at position 6 have been isolated. As anticipated, when treated separately they led to the same enetrione (8) as obtained from the mixture (4) (see Experimental section).



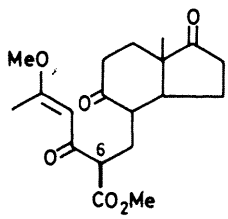
(1)



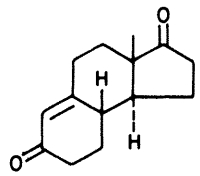
(2)



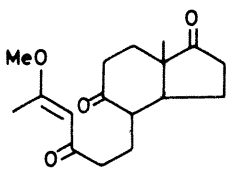
(3)



(4)



(5)



(6)

The cross-conjugated enetrione (8) proved to be fairly unstable, probably being oxidised to phenolic materials in the presence of air. Catalytic hydrogenation in acidic conditions (traces of hydrochloric acid in ethanol) did not provide the desired saturated trione (9); similarly, in alkaline medium (ethanol in the presence of triethylamine) catalytic reduction gave a complex mixture. Moreover, Birch reduction (Li or Na in liquid ammonia) only yielded *ca.* 20% of the desired product (9), mixed with other components which were difficult to separate. Conversely, when catalytic hydrogenation of the enetrione (8) was performed in ethanol solution under neutral conditions and pressure, in the presence of 5% palladium on charcoal, an 8 : 5 mixture of isomeric 9α- (9a) and 9β- (9b) triones was obtained; these were then separated by column chromatography. The saturated ketones (9a) and (9b) were isolated in 37 and 23% yields, respectively, after recrystallization. It is interesting to note that, contrary to the observations made in other series,[2,3] the catalytic reduction of

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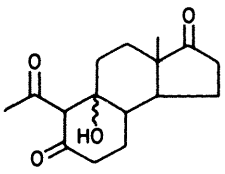
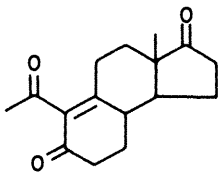
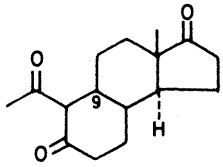


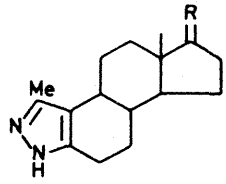
(7)



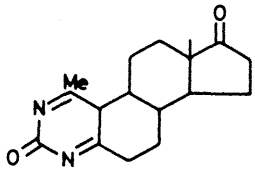
(8)



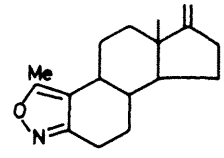
(9)
a; 9α–H
b; 9β–H



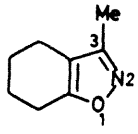
(10)
a; R = O
b; R = 



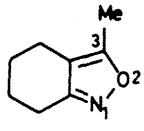
(11)



(12)
a; R = O
b; R = 



(13a)



(13b)

the enone (8) was not stereoselective, perhaps because of the cross-conjugated enedione system.

Both the correct structure and the stereochemistry of the 9α-isomer (9a), a key intermediate in this synthesis, were confirmed by *X*-ray crystallographic analysis. This compound (9a) was then used for the preparation of novel steroids.

On the one hand, reaction of the trione (9a) with 95% hydrazine hydrate in refluxing ethanol [7] afforded selectively the 1-methyl-2,3-diaza steroid derivative (10a), in 90% yield. Surprisingly, the 17-ketone was not affected under these conditions. Treatment of the 17-oxo group in (10a) with lithium acetylide in tetrahydrofuran (THF)–hexane at −78 °C then provided the 17α-ethynyl steroid (10b).

On the other hand, reaction of the ketone (9a) with urea in absolute ethanol [7,8] afforded the pyrimidone steroid (11) as a pale yellow crystalline material. The structure of this novel heterocyclic steroid is supported by its physical properties (see Experimental section).

Finally, when the trione (9a) was treated with hydroxylamine hydrochloride in aqueous ethanol at 70 °C [9] the steroidal isoxazole (12a) was obtained in 83% yield. Ethynylation of the oxo group in compound (12a) also provided the corresponding 17α-ethynyl carbinol (12b) in good yield. Because of the somewhat conflicting reports on the interpretation of the ^{13}C n.m.r. properties of isoxazoles,[10] the known model compounds (13a) and (13b) were prepared [9] and examined by ^{13}C n.m.r. spectroscopy. From the coupling pattern observed in the spectrum of 3-methyl-4,5,6,7-tetrahydro-1,2-benzisoxazole (13a), the signal at δ 167.431 p.p.m. was assigned to the carbon attached to the nitrogen, and the signal at δ 158.664 p.p.m. was attributed to the carbon adjacent to the oxygen. The ^{13}C n.m.r. spectrum of the isomeric 3-methyl-4,5,6,7-tetrahydro-2,1-benzisoxazole (13b) exhibited a signal at δ 162.936 p.p.m., attributed to the carbon linked to the nitrogen, and a signal at δ 160.995 p.p.m., assigned to the carbon vicinal to the oxygen atom. The difference between the chemical shifts of the carbon atom linked to nitrogen (δ 162.710 p.p.m.) and that attached to oxygen (δ 160.744 p.p.m.) in compound (12a) is *ca.* 2 p.p.m., *i.e.* similar to that observed in compound (13b), and thus a correlation can be established between these compounds, supporting structure (12a) for the new steroid.

It is noteworthy that the heterocyclic steroids (10a) and (12a) could be obtained in high yield, in spite of the potential competitive formation of the 17-hydrazone and oxime. This seems to indicate that the reactivity of the 5-oxo group is higher than that at C-17. Moreover, the almost exclusive formation of the steroidal benzisoxazole (12a) is unexpected, since a mixture of isomers might have been expected.

Preliminary testing indicates that compounds (10a), (10b), (12a), and (12b) do not show a significant increase in uterine weight after administration at different levels (up to 100 μg).*

However, in the rat, compounds (10a) and (12b) show a high affinity for androgen binding protein (ABP), and it is known that ligands that bind with high affinity to ABP but do not interact with the androgen receptor are potential inhibitors of male fertility.†

Experimental

M.p.s were determined with a Fisher-Johns apparatus and are corrected. I.r. spectra were obtained with a Beckman infrared spectrometer model IR-10. U.v. spectra were taken with a Perkin-Elmer 576 ST spectrophotometer. Rotations were taken in chloroform solution (*c* 1.0), between 16 and 22 °C a 1 dm tube at the sodium D-line, with a Carl-Zeiss 42017 polarimeter. ^1H N.m.r. spectra were recorded with a Varian EM-360 60 MHz spectrometer and a Nicolet NT-300 WB instrument at 300 MHz, for 5—8% w/v solutions in deuteriochloroform containing tetramethylsilane as internal reference. Coupling constants are accurate to ±1 Hz. ^{13}C N.m.r. were recorded with a Nicolet instrument at 75.45 MHz (20-mm tube). Mass spectra were recorded with a Dupont instrument, model 21-490, ionizing energy 70 eV.

X-Ray data were collected on an Enraf-Nonius CAD4 diffractometer using Mo-K_α radiation from a graphite monochromator; the structures were solved using MULTAN.

Column chromatography was carried out using silica gel (Kieselgel 60, Art 9385, 230—400 mesh, Merck Darmstadt). T.l.c. was carried out with Camlab 'Polygram' pre-coated silica plates, and Merck 2-mm thickness preparative plates were used for preparative t.l.c.

* Personal communication from Dr. G. Bialy, Contraceptive Development Branch, Centre for Population Research, National Institute of Child Health and Human Development, National Institute of Health, Bethesda, Maryland, U.S.A. We thank Dr. Bialy for this information.

† Personal communication from Dr. G. Rousseau, University of Louvain, Belgium, gratefully acknowledged. See: G. Rousseau, J. Quivy, and P. Crabbé, *Steroids*, 1981, **37**, 383.

Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, U.S.A.

Ether refers to diethyl ether.

4-*Methoxypent*-3-*en*-2-*one* (3).—Pentane-2,4-dione (50 g), trimethyl orthoformate (80 g), toluene-*p*-sulphonic acid (obtained by azeotropic distillation from benzene and toluene-*p*-sulphonic acid) (0.95 g), dry benzene (450 ml), and absolute methanol (100 ml) were stirred for 24 h at 20 °C.[4] The reaction mixture was then fractionally distilled through a Vigreux column to remove part of the solvent (*ca.* 100 ml). The remaining solution was neutralized with triethylamine (2 ml), washed with water, and dried (Na_2SO_4). After the solvent had been removed, the oily residue was fractionally distilled through a column packed with glass helices and the enone (3) (14.2 g, 25%) was obtained, b.p. 70—72 °C/18 mmHg; $\nu_{max.}$ (neat) 1 680, 1 585, and 1 065 cm^{-1}; $\lambda_{max.}$ (EtOH) 256—257 nm (ε 12 800); δ (CCl_4) 2.05 (s, 3 H, COMe), 2.19 (s, 3 H, vinylic Me), 3.60 (s, 3 H, OMe), and 5.38 (s, 1 H, vinylic H).

Methyl 5-*Methoxy*-3-*oxohex*-4-*enoate* (2).—*Method A.* To anhydrous THF (10 ml; distilled over lithium aluminium hydride) and dry di-isopropylamine (1.95 ml; distilled over sodium hydride), n-butyl-lithium in hexane (2.3M; 5.75 ml) was added dropwise under nitrogen at −78 °C with a syringe during 45 min. The solution was stirred for 0.5 h at −78 °C. 4-Methoxypent-3-en-2-one (3) (1.425 g) in anhydrous THF (7 ml) was added dropwise during 30 min, the mixture was stirred for an additional 1 h and then the reaction temperature was raised to 0 °C. Dry dimethyl carbonate (6.5 ml; distilled over sodium hydride) was added and stirring was continued for 9 h at 0 °C, followed by 12 h at 20 °C. The reaction mixture was cooled to −78 °C and neutralized with 50% acetic acid in dry THF (2 ml). Ether (50 ml) and brine (50 ml) were added and the aqueous layer was separated and extracted with more ether. After the combined organic solution had been dried and the solvents removed the residue was chromatographed on a silica gel column. Methyl 5-methoxy-3-oxohex-4-enoate (2) [0.406 g, 28% based on the consumed (3) and unchanged 4-methoxypent-3-en-2-one (0.466 g)] was obtained, $\nu_{max.}$ (neat) 3 010, 1 745, 1 735, 1 680, and 1 580 cm^{-1}; $\lambda_{max.}$ (EtOH) 260 nm (ε 13 720); δ 2.23 (s, 3 H, vinylic Me), 3.27 (s, 2 H, $COCH_2CO_2Me$), 3.66 (s, 6 H, OMe and CO_2Me), and 5.49 (s, 1 H, vinylic H); *m/z* 172 (M^+), and 99 ($M^+ - CH_2CO_2Me$).

Method B.[5] To anhydrous dimethyl carbonate (300 ml; freshly distilled from sodium hydride) and 50% sodium hydride dispersion (24 g; washed three times with n-pentane), 4-methoxypent-3-en-2-one (3) (22.8 g) was added dropwise under nitrogen at 20 °C during 15 min. The exothermic reaction mixture was stirred for 11 h at 20 °C and then cooled to 0 °C. The mixture was neutralized with anhydrous acetic acid, washed with 5% sodium hydrogen carbonate and brine, then dried, and the dimethyl carbonate removed under reduced pressure. The residue was fractionally distilled through a 30-cm column and methyl 5-methoxy-3-oxohex-4-enoate (2) [9.79 g, 42% based on the consumed (3)], b.p. 75—78 °C/0.8 mmHg, and unchanged (3) (7.2 g), b.p. 68 °C/0.8 mmHg, were obtained.

(+)-4-(5-*Methoxy*-2-*methoxycarbonyl*-3-*oxohex*-4-*enyl*)-7a-*methylperhydroindan*-1,5-*dione* (4).—To potassium hydride (2.22 g; washed three times with n-pentane) and dry toluene (300 ml; dried over sodium wire) methyl 5-methoxy-3-oxohex-4-enoate (2) (3.152 g) in dry toluene (50 ml) was added dropwise during 15 min under nitrogen at 20 °C. The suspension was stirred for 15 min and then (+)-7a-methylperhydro-4-phenylsulphonylmethylindan-1,5-dione (1) (5.236 g) in dry toluene (50 ml) was added during 1 h at 20 °C. Stirring was continued for 11 h at 20 °C and the solution was cooled to 0 °C, neutralized with acetic acid (3.7 ml), washed with sodium hydrogen carbonate solution, and dried (Na_2SO_4). The solvents were removed under reduced pressure and the residue was crystallized in ethyl acetate–hexane to give one of the diastereoisomers of the title compound, (4a) (1.52 g), m.p. 144—145 °C. After recrystallization in ethyl acetate–hexane colourless crystals of *compound* (4a) were obtained, m.p. 145—146 °C, $[\alpha]_D$ +80°; $\nu_{max.}$ ($CHCl_3$) 1 735, 1 700, and 1 675 cm^{-1}; $\lambda_{max.}$ (MeOH) 262 nm (ε 14 962); δ 1.13 (s, 3 H, 7a-Me), 2.29 (s, 3 H, vinylic Me), 3.65 (s, 3 H, OMe), 3.70 (s, 3 H, CO_2Me), and 5.54 (s, 1 H, vinylic H); *m/z* 350 (M^+) and 319 ($M^+ - OMe$) (Found : C, 64.9; H, 7.6. $C_{19}H_{26}O_6$ requires C, 65.12; H, 7.48%).

The residue of the crude product was chromatographed on silica gel (hexane-ethyl acetate, 3 : 2) and the other diastereoisomer (4b) (3.313 g), was obtained as an oil, $[\alpha]_D$ +160°; $\nu_{max.}$ (neat) 1 740, 1 710, and 1 680 cm^{-1}; δ 1.16 (s, 3 H, 7a-Me), 2.30 (s, 3 H, vinylic Me), 3.71 (s, 6 H, OMe and CO_2Me), and 5.67 (s, 1 H, vinylic H); *m/z* 350 (M^+) and 319 ($M^+ - OMe$). The total yield of (4) was 82.1%.

Formation of the Tricyclic Enedione (5).—To a solution of compound (4) (180 mg) in acetone (30 ml), 1M-hydrochloric acid (1.5 ml) was added at room temperature and the reaction mixture was stirred for 1 h. After being cooled to 0 °C the mixture was neutralized with 5% sodium hydrogen carbonate solution and the solvent was evaporated under reduced pressure. The residue was extracted with methylene dichloride and the extracts dried (Na_2SO_4). After the solvent had been removed the residue was dissolved in methanol (60 ml) and 10% potassium hydroxide (8 ml) was added at 0 °C. The reaction mixture was stirred for 4 h at room temperature, then cooled to 0 °C and neutralized with 1M-hydrochloric acid to pH *ca.* 3—4. After the solvent had been removed through a rotavapor the residue was extracted twice with methylene dichloride and dried (Na_2SO_4). The solvents were evaporated and the residue was taken up in toluene and refluxed for 3 h; the toluene was then removed under reduced pressure with a rotavapor. The residue was chromatographed on silica gel (3 : 2 hexane–ethyl acetate) and a yellow crystalline material (5) (106 mg) was obtained. After recrystallization from ethyl acetate–hexane it showed m.p. 137 °C; $[\alpha]_D$ +80°; $\lambda_{max.}$ (EtOH) 238 nm (ε 12 890) {lit.,[6] m.p. 137 °C; $[\alpha]_D$ +85° (MeOH); $\lambda_{max.}$ 237 nm}.

(+)-4-(5-*Methoxy*-3-*oxohex*-4-*enyl*)-7a-*methylperhydroindan*-1,5-*dione* (6).—Compound (4a) (1.50 g) in methanol (125 ml) was saponified in the presence of 10% sodium hydroxide (10 ml) at 0 °C for 2 h and the mixture was neutralized with acetic acid (3 ml). The reaction mixture was then heated for 1 h at 60—70 °C. After the methanol had been removed under reduced pressure, the residue was taken up in methylene dichloride, washed with 5% sodium hydrogen carbonate solution and dried (Na_2SO_4). After the solvent had been removed the crude product was chromatographed on a silica gel column (hexane–ethyl acetate, 3 : 2) to provide compound (6) (0.826 g, 66%), $[\alpha]_D$ +135°; $\nu_{max.}$ (neat) 1 740, 1 705, and 1 680 cm^{-1}; $\lambda_{max.}$ (EtOH) 256 nm (ε 14 142); δ 1.16 (s, 3 H, 7a-Me), 2.28 (s, 3 H, vinylic Me), 3.66 (s, 3 H, OMe), and 5.48 (s, 1 H, vinylic H); *m/z* 292 (M^+), 260 ($M^+ - MeOH$), 247, and 196.

In the same manner, compound (4b) (3.250 g) was saponified with 10% sodium hydroxide at 0 °C and decarboxylated at 60—70 °C. After purification a product identical with compound (6) (1.792 g) was obtained (66%).

9-*Hydroxy*-3,4-*dinor*-2,5-*secoestrane*-1,5,17-*trione* (7).—(+)-4-(5-Methoxy-3-oxohex-4-enyl)-7a-methylperhydroindan-1,5-dione (6) (2.374 g) in acetone (200 ml; redistilled) and 1M-hydrochloric acid (10 ml) were stirred at 20 °C for 1 h. After being cooled to 0 °C, the mixture was neutralized with a 5% sodium hydrogen carbonate solution. The solvent was evaporated under reduced pressure and the residue was taken up in methylene dichloride, dried, and the solvent removed under reduced pressure to give the crude product which was crystallized in ethyl acetate. The crystalline pure *compound* (7) (1.33 g, 59%) obtained had m.p. 150—153 °C; $[\alpha]_D$ +25°; $\nu_{max.}$ (KBr) 3 500, 1 740, 1 710, and 1 690 cm^{-1}; δ 0.94 (s, 3 H, 18-Me), 2.20 (s, 3 H, COMe), 3.66 (s, 1 H, 10-CH), and 4.01 (s, 1 H, OH); *m/z* 278 (M^+) and 260 ($M^+ - H_2O$) (Found: C, 69.2; H, 7.95. $C_{16}H_{22}O_4$ requires C, 69.03; H, 7.97%).

3,4-*Dinor*-2,5-*secoestr*-9-*ene*-1,5,17-*trione* (8).—9-Hydroxy-3,4-dinor-2,5-secoestrane-1,5,7-trione (7) (1.942 g) in acetone (200 ml) and 1M-hydrochloric acid (10 ml) was stirred for 0.5 h at 60—70 °C. After being cooled to 0 °C the mixture was neutralized with 5% sodium hydrogen carbonate solution. The solvent was evaporated under reduced pressure and the residue was taken up in methylene dichloride, dried, and the solvent removed. The residue was then chromatographed on a silica gel column (hexane–ethyl acetate, 3 : 2). The title compound (8) (1.101 g, 61%) was obtained and proved to be unstable at room temperature; $[\alpha]_D$ +100°; $\nu_{max.}$ (neat) 1 740, 1 705, and 1 665 cm^{-1}; $\lambda_{max.}$ (EtOH) 241 mm (ε 7 570); δ 1.04 (s, 3 H, 18-Me) and 2.32 (s, 3 H, COMe); *m/z* 260 (M^+) and 245 ($M^+ - Me$).

Because of its instability no attempt was made to crystallize this compound (8), which was used directly for the next step.

3,4-*Dinor*-2,5-*secoestr*-9-*ene*-1,5,17-*trione* (8) *from the Oxo-ester* (4).—(+)-4-(5-Methoxy-2-methoxycarbonyl-3-oxohex-4-enyl)-7a-methylperhydroindan-1,5-dione (4a) (1.579 g) in methanol (135 ml) and aqueous 10% sodium hydroxide (10.5 ml) were stirred for 2 h at 0 °C. Acetic acid (10 ml) was added and the reaction mixture was heated for 45 min at 70 °C. The solvent was removed under reduced pressure and the residue was taken up in methylene dichloride, washed with 5% sodium hydrogen carbonate, and dried. The solvent was then removed under reduced pressure and the residue was dissolved in acetone (110 ml) and stirred with 1M-hydrochloric acid (5.5 ml) for 0.5 h at 20 °C. The solvent was removed by a rotavapor at 25—30 °C and the residue was dissolved in methylene dichloride, then washed with 5% sodium hydrogen carbonate solution and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (methylene dichloride–ethyl acetate, 12 : 1), affording the title compound (8) (0.608 g, 52%), identical with the sample obtained above.

Catalytic Hydrogenation of the Enone (8) *and Obtention of* 3,4-*Dinor*-2,5-*seco*-9α-*estrane*-1,5,17-*trione* (9a) *and its Isomer* (9b).—3,4-Dinor-2,5-secoestr-9-ene-1,5,17-trione (8) (2.162 g) in absolute ethanol (245 ml) and 5% Pd–C (400 mg) were shaken with hydrogen under 30 lb in^{-2} pressure for 4 h. After the catalyst had been filtered off and the solvent removed under reduced pressure the residue was chromatographed on a silica gel column (methylene dichloride–ethyl acetate, 20 : 1), allowing the separation of the 9α-saturated trione (9a) (792 mg, 37%), m.p. 114—116 °C (after recrystallization from ethyl acetate–hexane) and the 9β-trione (9b) (495 mg, 23%), m.p. 139—140 °C (recrystallized from ethyl acetate–hexane). *Compound* (9a) had m.p. 114—116 °C; $[\alpha]_D$ +62°; $\nu_{max.}$ (KBr) 1 740, 1 720, and 1 700 cm^{-1}; δ 0.97 (s, 3 H, 18-Me), 2.19 (s, 3 H, COMe), and 3.27 (d, *J* 10 Hz, 1 H, 10-CH); *m/z* 262 (M^+), 247 ($M^+ - Me$), and 219 ($M^+ - COMe$) (Found: C, 73.4; H, 8.65. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%). *Compound* (9b) showed m.p. 139—140 °C; $[\alpha]_D$ +47°; $\nu_{max.}$ (KBr) 1 738, 1 720, and 1 700 cm^{-1}; δ 0.97 (s, 3 H, 18-Me), 2.19 (s, 3 H, COMe), and 3.36 (d, *J* 12 Hz, 1 H, 10-CH); *m/z* 262 (M^+), 247 ($M^+ - Me$), and 219 ($M^+ - COMe$) (Found: C, 73.3; H, 8.4. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%).

1,18-*Dimethyl*-4-*nor*-2,3-*diazaestra*-1,5(10)-*dien*-17-*one* (10a).—The trione derivative (9a) (218 mg) in 95% ethanol (10 ml) and 95% hydrazine (150 mg) was refluxed for 2 h. Levulinic acid–1M-hydrochloric acid (12 ml, 8 : 1 v/v) [7] and chloroform (12 ml) were then added and the mixture stirred for 24 h at 20 °C. The reaction mixture was diluted with water and extracted with methylene dichloride. The extracts were washed with 5% sodium hydrogen carbonate solution to remove the levulinic acid, then dried and the solvent removed. The residue was chromatographed on silica gel (methylene dichloride–ethyl acetate–methanol, 40 : 3 : 1), thus affording the *title compound* (10a) (193 mg, 90%), m.p. 183—185 °C. Recrystallization from ethyl acetate gave an analytical sample, m.p. 188—189 °C; $[\alpha]_D$ +200°; $\nu_{max.}$ ($CHCl_3$) 3 470, 1 735, and 1 580 cm^{-1}; $\lambda_{max.}$ (EtOH) 204 (ε 3 544) and 226 nm (4 285); δ 0.93 (s, 3 H, 18-Me) and 2.30 (s, 3 H, 1-Me); *m/z* 258 (M^+), 243 ($M^+ - Me$), and 230 ($M^+ - CH_2CH_2$) (Found: C, 73.25; H, 8.85; N, 10.6. $C_{16}H_{22}N_2O \cdot \frac{1}{4}H_2O$ requires C, 73.11; H, 8.61; N, 10.65%).

17α-*Ethynyl*-1-*methyl*-4-*nor*-2,3-*diazaestra*-1,5(10)-*dien*-17β-*ol* (10b).—A stream of acetylene was bubbled into 2.3M-n-butyl-lithium–hexane (8 ml) in dry THF (20 ml) for 1 h at −78 °C. The 17-ketone (10a) (373 mg) in dry THF (5 ml) was added dropwise, and the reaction mixture was stirred for 3.5 h at −78 °C and then warmed to −10 °C in 0.5 h. Aqueous ammonium chloride was added to remove the excess of ethynyl-lithium. The aqueous layer was extracted twice with ethyl acetate, dried and the solvent removed. The residue was chromatographed on silica gel (methylene dichloride–ethyl acetate–methanol). Besides some starting material (10a) (54 mg), the *title compound* (10b) (298 mg, 85% based on consumed product) was obtained. Recrystallization from methanol–water furnished the pure compound (10b), m.p. 205—206 °C; $[\alpha]_D$ +20°; $\nu_{max.}$ ($CHCl_3$) 3 600, 3 470, 3 310, 2 410, and 1 585 cm^{-1}; $\lambda_{max.}$ (EtOH) 203 (ε 3 267) and 226 nm (3 416); δ 0.89 (s, 3 H, 18-Me), 2.27 (s, 3 H, 1-Me), 6.31 (br s, OH and NH), and 2.59 (s, 1 H, C≡CH); *m/z* 284 (M^+), 269 ($M^+ - Me$), 258 ($M^+ - HC{\equiv}CH$), and 256 (Found: C, 76.0; H, 8.55; N, 9.8. $C_{18}H_{24}N_2O$ requires C, 76.02; H, 8.51; N, 9.85%).

1-*Methyl*-2,4-*diazaestra*-1,5(10)-*diene*-3,17-*dione* (11).—The trione (9a) (41 mg), urea (9.46 mg), absolute ethanol (160 μl), and concentrated hydrochloric acid (16 μl) were stirred at 80 °C for 20 h in a small tube,[8] then cooled to room temperature. A 10% sodium carbonate solution was added to neutralize the acid, followed by methylene dichloride, and the organic layer was dried (Na_2SO_4) and filtered. After the solvent had been removed, the residue was chromatographed on silica gel (methylene dichloride–methanol, 10 : 1) to give the yellow crystalline pyrimidone derivative (11) (25 mg), m.p. 174—175 °C (decomp.); $[\alpha]_D$ −32°; $\nu_{max.}$ ($CHCl_3$) 1 735, 1660, 1 640, 1 610, and 1 540 em^{-1}; $\lambda_{max.}$ (EtOH) 204 (ε 67 640), 223 (74 720), and 312 nm (32 960); δ 0.95 (s, 3 H, 18-Me) and 2.41 (s, 3 H, 1-Me); *m/z* 286 (M^+) and 271 ($M^+ - Me$).

1-*Methyl*-4-*nor*-2,3-*oxazaestra*-1,5(10)-*dien*-17-*one* (12a).—The trione (9a) (35.3 mg) in ethanol (0.09 ml) and water (0.10 ml) was stirred with hydroxylamine hydrochloride (9.3 mg) for 1.5 h at 70 °C.[8] The reaction mixture was cooled to room

temperature and the crystalline material which formed was filtered off and washed with 50% ethanol, then with aqueous 5% sodium hydrogen carbonate and water. It was then dried and the *title compound* (12a) (29 mg, 83%) was obtained, m.p. 157—158 °C. The mother-liquors were extracted with methylene dichloride, the extracts were dried and the solvent was removed under reduced pressure to give a second crop of the isoxazole (12a) (4.5 mg), m.p. 144—148 °C. An analytical sample (12a) showed m.p. 157—158 °C; $[\alpha]_D$ +180°; $\nu_{max.}$ ($CHCl_3$) 1 735 and 1 632 cm^{-1}; $\lambda_{max.}$ (EtOH) 205 (ε 2 386) and 227 nm (5 019); δ 0.91 (s, 3 H, 18-Me) and 2.42 (s, 3 H, 1-Me); δ(^{13}C) ($CHCl_3$) 12 648, 13 973, 21 508, 21 875, 25.171, 25.916, 31.282, 35.515, 39.397, 48.108, 49.331, 113.309, 160.744, 162.710, and 220.047 p.p.m.; *m/z* 259 (M^+), 244 (M^+ − Me), and 231 (Found: C, 73.9; H, 8.2; N, 5.35. $C_{16}H_{21}NO_2$ requires C, 74.10; H, 8.16; N, 5.40%).

1-*Ethyl*-17α-*ethynyl*-4-*nor*-2,3-*oxazaestra*-1,5(10)-*dien*-17β-*ol* (12b).—A stream of acetylene was bubbled into 2.3M-n-butyl-lithium–hexane (3.4 ml) in dry THF (5 ml) for 1 h at −78 °C. The steroid (12a) (109 mg) in dry THF (1.5 ml) was added dropwise. The reaction mixture was stirred for 4 h at −78 °C and then warmed to −10 °C during 1 h. Aqueous ammonium chloride was added and the aqueous layer was extracted twice with ethyl acetate. After the extract had been dried and the solvent removed the residue was crystallized in ethanol, thus affording the *title compound* (12b) (69 mg). The mother-liquors were chromatographed on silica gel (methylene dichloride–ethyl acetate, 20 : 1) furnishing a second crop of compound (12b) (28 mg; 81% total yield). An analytical sample (12b) had m.p. 206—207 °C; $[\alpha]_D$ +20°; $\nu_{max.}$ ($CHCl_3$) 3 600, 3 310, 2 410, and 1 635 cm^{-1}; $\lambda_{max.}$ (EtOH) 205 (ε 1 470) and 227 nm (5 125); δ 0.90 (s, 3 H, 18-Me), 2.41 (s, 3 H, 1-Me), and 2.56 (s, 1 H, C≡CH); *m/z* 285 (M^+), 270 (M^+ − Me), 259 (M^+ − HC≡CH), and 257 (Found: C, 75.85; H, 8.35; N, 4.75. $C_{18}H_{23}NO_2$ requires C, 75.75; H, 8.12; N, 4.91%).

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