THE SYNTHESIS OF ANDROSTANE DERIVATIVES WITH AN AROMATIC B-RING*

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Some analogues of steroidal hormones with aromatic B-ring were prepared by the degradation of the side chain in neoergosterol and corresponding functionalisation.

The appreciable planarity of the entire skeleton of steroids with an aromatic B-ring and the absence of the angular methyl group at $C_{(10)}$ could possibly have a certain effect on the pharmacodynamical activity of steroids with oxygen-containing functions at $C_{(17)}$ and $C_{(20)}$. Some of the derivatives prepared earlier were already tested but only 17β-hydroxy-17α-chloroethinyl-19-norpregna-5,7,9(10)-trien-3-one displayed a weak gonadotropin inhibiting activity[1]. In this paper we describe the preparation of further analogues of common pharmacodynamically active steroids.

Ergosterol was chosen as the most suitable starting material because of the presence of a double bond in its side chain permitting an easy degradation; on the other hand the presence of a diene system in the ring B enables the preparation of the B-aromatic steroids by photochemical dimerisation of ergosterol sensibilised with eosin, *via* 7,7'-bis(5,8,22-ergostatrien-3β-ol) (*II*) and 19-nor-5,7,9(10),22-ergostatetraen-3β-ol (neoergosterol) (*III*), according to a modified Windaus method[2].

On ozonization of the side chain double bond of compound *III* we obtained aldehyde[2] *V* that was acetylated to afford compound *VI*. Baeyer–Villiger oxidation of the product, and subsequent selective saponification of the resulting formate *VIII*, that was carried out either on alumina (method *A*) or with dilute hydrochloric acid in methanol (method *B*) afforded 20-alcohol *IX* characterised as acetate *X* or benzoate *XI*. 20*S* configuration follows from these facts: Baeyer–Villiger oxidation is known to take place with the retention of configuration of the migrating center. Therefore the 20-alcohol formed from the *S*-aldehyde must also have the configuration *S* (*i.e.* 20 α). The positive optical rotation shift observed between the alcohol *IX* and benzoate *XI* is also in agreement with this configuration (benzoate rule)[3]. Moreover, oxidation of alcohol *IX* with Jones' reagent gave the known[4] ketone *XIV*.

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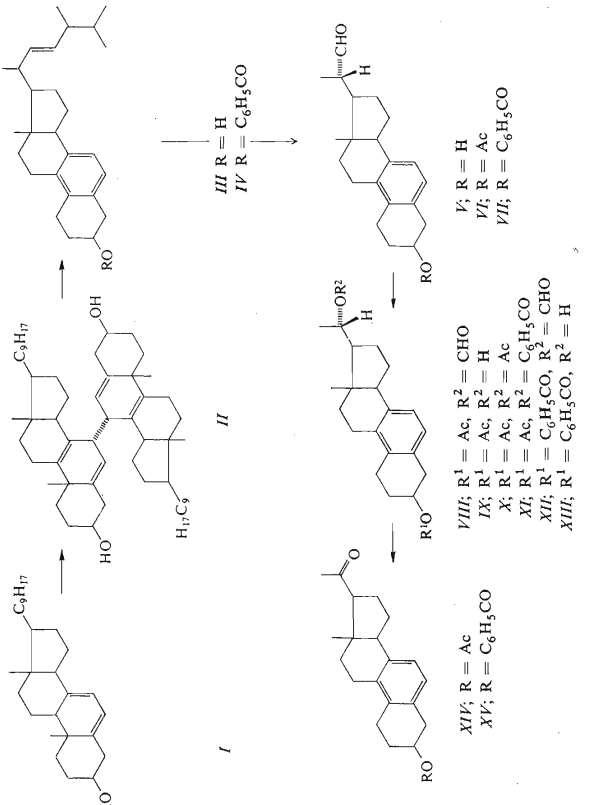
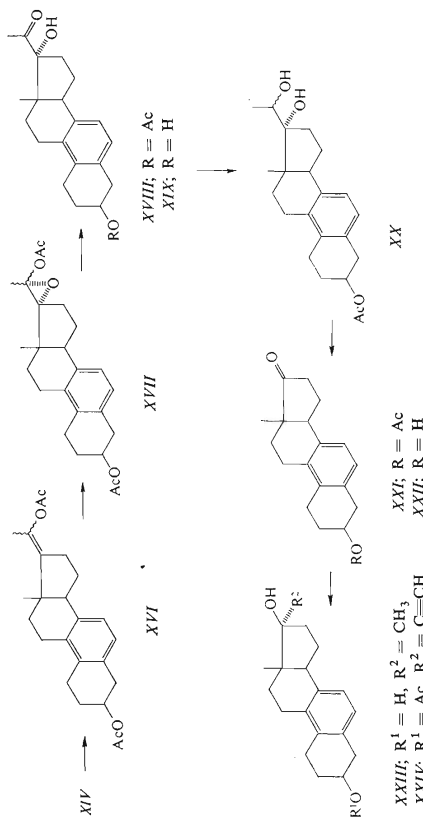

C9H17
HO
I
OH
HO
H17C9
II
RO
III R = H
IV R = C6H5CO
RO
V; R = H
VI; R = Ac
VII; R = C6H5CO
CHO
H
OR2
R1O
VIII; R1 = Ac, R2 = CHO
IX; R1 = Ac, R2 = H
X; R1 = Ac, R2 = Ac
XI; R1 = Ac, R2 = C6H5CO
XII; R1 = C6H5CO, R2 = CHO
XIII; R1 = C6H5CO, R2 = H
O
RO
XIV; R = Ac
XV; R = C6H5CO


XIV
XVI
XVII
XVIII; R = Ac
XIX; R = H
XX
XXI; R = Ac
XXII; R = H
XXIII; R¹ = H, R² = CH₃
XXIV; R¹ = Ac, R² = C≡CH
XXV; R¹ = H, R² = C≡CH

The conversion of pregnane derivatives to androstane derivatives could start with the Baeyer-Villiger oxidation. However, the diacetate formed would hardly be convertible by saponification and oxidation to the required 3β-acetoxy-5,7,9(10)--trien-17-one. Therefore we made use of the derivative with the 3β-hydroxy group protected not by acetylation but in a different way. From the benzoate of 19-norergosta--5,7,9(10)-trien-3β-ol (*IV*) we obtained ketone *XV* analogously, *i.e.* by degradation *via* the aldehyde *VII* formate *XII* and alcohol *XIII*. However, this route gives a lower yield which is caused mainly by the formation of by-products during ozonization. In view of the fact that the ketone *XV* was resistent to perphthalic, *m*-chloroperbenzoic, and perbenzoic acids in the presence of *p*-toluenesulphonic acid, we chose another, longer route, but as was later found, a more effective one.

Ketone *XIV* was converted under the effect of acetic anhydride and catalysis with *p*-toluenesulfonic acid to enol acetate *XVI* which gave the acetate *XVIII* on epoxidation and subsequent opening of the epoxide *XVII* with sodium hydroxide[5,6]. When the epoxide *XVII* was opened with potassium hydrogen carbonate[7] in methanol we obtained hydroxy ketone *XIX* which on acetylation afforded acetate *XVIII*. Substance *XVIII* displays a positive Cotton effect from which it follows[8] that the hydroxyl at $C_{(17)}$ has configuration α. Reduction of compound *XVIII* with lithium tris-(tert--butoxy)hydridoaluminate gave a mixture of epimeric alcohols *XX* which was converted by cleavage with lead tetraacetate according to method[9,10] to the required 3β-acetoxy-19-norandrosta-5,7,9(10)-trien-17-one (*XXI*). Alkaline saponification of this acetoxy ketone led to the so-called Heard's ketone *XXII* prepared synthetically from equilenine[11] and also isolated from the urine of pregnant mares[12] and from human placenta[13].

Acetoxy ketone *XXI* served as starting material for the preparation of 17α-methyl and 17α-ethinyl derivatives. Reaction with methyl magnesium iodide in ether gave 17α-methyl derivative *XXIII*, while on addition of acetylene in toluene in the presence of potassium tert-butoxide 17α-ethinyl derivative *XXIV* was obtained which on saponification of the 3β-acetoxy group afforded diol *XXV*.

EXPERIMENTAL

The melting points were determined on a Kofler block. Analytical samples were dried at 25°C/0·2 Torr. Optical rotations were carried out in chloroform with a ±1° error. The infrared spectra were measured with a Zeiss UR 10 spectrophotometer in tetrachloromethane or in chloroform. The mass spectral measurements were carried out on an AEI MS 902 spectrometer. The NMR spectra were recorded on a Varian HA-100 instrument in deuteriochloroform with tetramethylsilane as internal reference. The CD curves were recorded on a Dichrographe II (Jouan-Roussel) in methanol. The identity of the samples prepared by different routes was checked by mixture melting point determinations, by thin-layer chromatography, and by IR spectra. Neutral alumina of activity II was supplied by Reanal (Budapest), while silica gel according to Pitra was prepared in our Service Laboratories.

7,7′-Bis(ergosta-5,8,22-trien-3β-ol) (*II*)

To a solution of eosin (50 g) in ethanol (1 500 ml) a solution of ergosterol (50 g) in tetrahydrofuran (750 ml) was added and the mixture stirred and saturated with a stream of nitrogen at 70°C in

darkness for 30 minutes. The well closed flask with the mixture was exposed to the effects of the sun for 1 to 2 weeks, depending on the weather. The precipitated product was filtered off under suction, washed with ethanol and dried in air. The yields were in the 50–60% range. The product contained traces of eosin, but this did not disturb further operations.

19-Norergosta-5,7,9(10),22-tetraen-3β-ol (*III*)

The dimer *II* (100 g) was refluxed in 1,2-propanediol (1 000 ml) until the dissolution was complete (approximately one hour). The solvent was distilled off in a vacuum and the residue dissolved in ether. The solution was washed several times with 5% sodium hydrogen carbonate and water, dried over sodium sulfate and evaporated. The residue was dissolved in benzene and chromatographed on alumina (1 kg) with benzene. The corresponding fractions were combined and evaporated. The product obtained was used for further steps. Yield 60%. A sample was crystallised twice from methanol; m.p. 152–154°C (reported[2] m.p. 151–153°C), $[\alpha]_D^{20}$ −11° (*c* 1·8) (reported value[2] $[\alpha]_D$ −10°).

19-Norpregna-5,7,9(10),22-tetraen-3β-ol 3-Benzoate (*IV*)

A mixture of neoergosterol (*III*) (7·0 g), pyridine (100 ml), and benzoyl chloride (30 ml) was allowed to stand at room temperature overnight, then decomposed with ice and worked up in the conventional manner. Crystallisation from chloroform–methanol mixture gave 7·2 g of benzoate, m.p. 135–136°C, $[\alpha]_D^{2C}$ −2·8° (*c* 2·2). For $C_{34}H_{44}O_2$ (484·7) calculated: 84·25% C, 9·15% H; found: 84·30% C, 9·18% H.

(20*S*)-3β-Acetoxy-19-norpregna-5,7,9(10)-triene-20-carbaldehyde (*VI*)

Hydroxy aldehyde[2] *V* (25 g) was acetylated with acetic anhydride (60 ml) in pyridine (100 ml) at room temperature for 5 hours and worked up in the usual manner. The acetate obtained (24 g) was used directly for further operations. A sample crystallised from chloroform–methanol mixture had m.p. 132–133°C (reported[3]: 128–130°C), $[\alpha]_D^{20}$ −12·3° (reported[3]: $[\alpha]_D$ −11·9°). IR (CCl_4): 1 247, 1 731, 2 700 cm^{-1}. For $C_{23}H_{30}O_3$ (354·5) calculated: 77·93% C, 8·53% H; found: 77·96% C, 8·53% H.

(20*S*)-3β-Benzoyloxy-19-norpregna-5,7,9(10)-triene-20-carbaldehyde (*VII*)

A solution of benzoate *IV* (7·0 g) in dichloromethane (600 ml) and pyridine (1·65 ml) was ozonized at −50°C. The reaction was followed by thin-layer chromatography. When the reaction was over the ozonide was decomposed with zinc (9·0 g) and acetic acid (42·0 ml) by one hour's stirring at 0°C. The mixture was filtered and the solution washed with 5% sodium hydrogen carbonate and water, dried, evaporated and crystallised from methanol. Yield 2·9 g, m.p. 183–185°C, $[\alpha]_D^{20}$ −1·8° (*c* 2·3). For $C_{28}H_{32}O_3$ (416·5) calculated: 80·73% C, 7·74% H; found: 80·65% C, 7·76% H.

(20*S*)-19-Norpregna-5,7,9(10)-triene-3β,20-diol 3-Acetate 20-Formate (*VIII*)

To a solution of aldehyde *VI* (20 g) in chloroform (120 ml) formic acid (100 ml) and 30% hydrogen peroxide (55 ml) were added and the mixture vigorously stirred at room temperature for 5 hours. After dilution with chloroform it was washed with water, sodium hydrogen carbonate solution, again with water, then dried and evaporated. For saponification by method *A* the obtained product

was sufficiently pure, but for method *B* it had to be chromatographed with benzene on a 50-fold amount of silica gel. The yield of the pure compound *VIII* after chromatography was 60–65%. The crystallisation of the chromatographed product from methanol gave formate *VIII*, m.p. 93–95°C, $[\alpha]_D^{20}$ −9·5° (*c* 1·7), IR (CCl_4): 1 040, 1 187, 1 245, 1 725 cm^{-1}. For $C_{23}H_{30}O_4$ (370·5) calculated: 74·56% C, 8·16% H; found: 74·60% C, 8·21% H.

(20*S*)-Norpregna-5,7,9(10)-triene-3β,20-diol 3-Monoacetate (*IX*)

Method A: A benzene solution of the crude product *VIII* was adsorbed on a column containing a 40-fold amount of alumina and allowed to stand overnight. The alcohol formed was eluted from the column with a mixture of benzene and ether (9 : 1). The corresponding fractions were combined, evaporated and the residue crystallised from a mixture of chloroform and methanol. The yield was almost quantitative, m.p. 145–146°C, $[\alpha]_D^{20}$ −4·8° (*c* 2·1). For $C_{22}H_{30}O_3$ (342·5) calculated: 77·15% C, 8·83% H; found: 77·17% C, 8·82% H.

Method B: To a solution of formate *VIII* (1·9 g) in chloroform (10 ml) hydrochloric acid (1·9 ml) in methanol (100 ml) was added and the mixture allowed to stand at room temperature for 30 minutes. After dilution with ether it was washed with water, 5% sodium hydrogen carbonate solution, water, then dried and evaporated. Chromatography on 80 g of silica gel with benzene–ether (95 : 5) gave 1·75 g of product. A sample crystallised from chloroform–methanol had the same properties as that from method *A*.

(20*S*)-19-Norpregna-5,7,9(10)-triene-3β,20-diol Diacetate (*X*)

Alcohol *IX* (130 mg) was acetylated with acetic anhydride (1·5 ml) in boiling pyridine (2·0 ml) for 10 minutes and worked up in the usual manner. Crystallisation from methanol gave a product (70 mg) of m.p. 164–166°C, $[\alpha]_D^{20}$ −2·1° (*c* 1·9). For $C_{24}H_{32}O_4$ (384·5) calculated: 74·96% C, 8·39% H; found: 75·08% C, 8·29% H.

(20*S*)-19-Norpregna-5,7,9(10)-triene-3β,20-diol 3-Acetate 20-Benzoate (*XI*)

Alcohol *IX* (40 mg) was benzoylated with benzoyl chloride (0·3 ml) in pyridine (1·0 ml) at room temperature for 6 hours. The reaction mixture was worked up in the conventional manner. Crystallisation from methanol afforded 18 mg of benzoate, m.p. 135–136°C, $[\alpha]_D^{20}$ +47·1° (*c* 2·2). IR (CCl_4) : 1 245, 1 275, 1 715 1 733 cm^{-1}. For $C_{29}H_{34}O_4$ (446·6) calculated: 77·99% C, 7·67% H; found: 78·04% C, 7·64% H.

(20*S*)-19-Norpregna-5,7,9(10)-triene-3β,20-diol 3-Monobenzoate (*XIII*)

A mixture of aldehyde *VII* (1·4 g) and *m*-chloroperbenzoic acid (1·4 g) was refluxed in dichloroethane (30 ml) for 4 hours, the solution was diluted with chloroform, washed with a 5% sodium hydrogen carbonate solution and water, dried, and evaporated. The residue was dissolved in benzene, adsorbed on a column of alumina and allowed to stand overnight. The alcohol formed was washed with a benzene–ether (9 : 1) mixture, the fractions containing the required product were combined and evaporated. Yield 650 mg. Crystallisation from a mixture of chloroform and methanol afforded a substance (410 mg) of m.p. 209–210°C, and $[\alpha]_D^{20}$ −13·4° (*c* 2·3). For $C_{27}H_{32}O_3$ (404·5) calculated: 80·16% C, 7·97% H; found: 80·09% C, 7·90% H.

3β-Acetoxy-19-norpregna-5,7,9(10)-trien-20-one (*XIV*)

Alcohol *IX* (10 g) dissolved in acetone (350 ml) was oxidised with Jones' reagent at 5°C under nitrogen for 10 minutes. The excess reagent was decomposed with methanol and the mixture worked up in the usual manner. The dried residue weighed 9·6 g and it was used as such for further reactions. The sample was crystallised twice from n-heptane; m.p. 106–107°C, $[\alpha]_D^{20}$ +53° (*c* 2·1); IR spectrum (CCl_4): 1245, 1485, 1707, 1736, 3035, 3065 cm^{-1}. For $C_{22}H_{28}O_3$ (340·4) calculated: 77·61% C, 8·29% H; found: 77·63% C, 8·26% H.

3β-Benzoyloxy-19-norpregna-5,7,9(10)-trien-20-one (*XV*)

Alcohol *XIII* (300 mg) dissolved in acetone (30 ml) was oxidised with Jones' reagent in the same manner as above. The residue (290 mg) when crystallised from a chloroform–methanol mixture gave 183 mg of ketone *XV*, m.p. 182–184°C, $[\alpha]_D^{20}$ +37·5° (*c* 1·9). For $C_{27}H_{30}O_3$ (402·5) calculated: 80·56% C, 7·51% H; found: 80·46% C, 7·49% H.

19-Norpregna-5,7,9(10),17(20)-tetraene-3β,20-diol Diacetate (*XVI*)

From a mixture of ketone *XIV* (10 g), *p*-toluenesulfonic acid (3 g) and acetic anhydride (200 ml) 130 ml of distillate were distilled off over 3 hours and the remaining acetic anhydride was distilled off in a vacuum. The residue was dissolved in a light petroleum–ether mixture (2 : 1) and filtered through 100 g of alumina. After evaporation the residue weighed 10 g and it was used for further reaction directly. A sample was crystallised from methanol, m.p. 136–138°C. For $C_{24}H_{30}O_4$ (382·5) calculated: 75·36% C, 7·91% H; found: 75·38% C, 7·91% H.

17α,20ξ-Epoxy-19-norpregna-5,7,9(10)-triene-3β,20ξ-diol Diacetate (*XVII*)

To a solution of enol acetate *XVI* (9·0 g) in benzene (200 ml) 150 ml of an ethereal perphthalic acid solution (110 mg/l ml) were added and allowed to stand overnight at room temperature. The mixture was diluted with ether, washed with 5% sodium hydrogen carbonate and water, dried and evaporated. The oily residue (8·0 g) was used immediately for further reactions. For $C_{24}H_{30}O_5$ (398·5) calculated: 72·33% C, 7·59% H; found: 72·30% C, 7·55% H.

3β-Acetoxy-17α-hydroxy-19-norpregna-5,7,9(10)-trien-20-one (*XVIII*)

A) To a solution of epoxide *XVII* (1·8 g) in methanol (200 ml) a NaOH (1·0 g) solution in water (5 ml) and methanol (10 ml) was added and the mixture allowed to stand at room temperature for one hour. After neutralisation with dilute sulfuric acid and filtering off of sodium sulfate the filtrate was evaporated to one fourth of its volume, diluted with ether, washed with water, dried and evaporated. As during this reaction a partial hydrolysis of the acetyl group in the position 3 also took place the residue was acetylated to completion with acetic anhydride (6 ml) in pyridine (10 ml) at room temperature (5 hours) and the mixture worked up in the conventional manner. On crystallisation from methanol 0·9 g of substance were obtained, m.p. 142–144°C, $[\alpha]_D^{20}$ −43·9° (*c* 2·3). CD (methanol):Δε +2·46, 298 nm. IR spectrum ($CHCl_3$): 1257, 1358, 1367, 1380, 1484, 1600, 1690, 1708, 1724, 3500, 3610 cm^{-1}. For $C_{22}H_{28}O_4$ (356·4) calculated: 74·13% C, 7·92% H; found: 74·22% C, 8·02% H.

B) Dihydroxy ketone *XIX* (2·0 g) was acetylated with acetic anhydride (6·0 ml) in pyridine (10·0 ml) at room temperature for 5 hours and then worked up in the usual manner. Crystallisation from methanol gave 1·4 g of acetate which had the same properties as the compound obtained by method *A*) (m.p. and IR spectra).

3β,17α-Dihydroxy-19-norpregna-5,7,9(10)-trien-20-one (*XIX*)

A solution of epoxide *XVII* (3·0 g) and potassium hydrogen carbonate (1·0 g) in a mixture of methanol (30 ml) and water (3·0 ml) was refluxed for 3 hours, concentrated to one quarter of its volume, diluted with ethyl acetate, washed with water, dried and evaporated. Crystallisation from benzene gave 1·9 g of product, m.p. 192—193°C, $[\alpha]_D^{20}$ −59·1° (*c* 1·9). IR spectrum ($CHCl_3$): 1358, 1484, 1690, 1704, 3450, 3605 cm^{-1}. For $C_{20}H_{26}O_3$ (314·4) calculated: 76·40% C, 8·34% H; found: 76·48% C, 8·29% H.

19-Norpregna-5,7,9(10)-triene-3β,17α,20ξ-triol 3-Monoacetate (*XX*)

Ketone *XVIII* (3·0 g) was reduced in tetrahydrofuran (60 ml) with lithium tris(tert-butoxy)hydridoaluminate (6·0 g) for 15 minutes at room temperature. The solution was diluted with ether, the excess hydride decomposed with 5% HCl, washed with 5% sodium hydrogen carbonate and water, dried and evaporated. The residue (2·7 g) was used for further reactions; m.p. 134—138°C; For $C_{22}H_{30}O_4$ (358·5) calculated: 73·71% C, 8·44% H; found: 73·62% C, 8·41% H.

3β-Acetoxy-19-norandrosta-5,7,9(10)-trien-17-one (*XXI*)

A mixture of diols *XX* (2·0 g) and lead(IV) acetate (6·0 g) in acetic acid (150 ml) was stirred at room temperature for one hour and the excess reagent decomposed with ethylene glycol (15 ml) by stirring for 30 minutes. The mixture was diluted with water, neutralised with solid sodium hydrogen carbonate, extracted with dichloromethane, washed with water, dried and evaporated. On crystallisation from a chloroform–methanol mixture 1·35 g of crystals were obtained, m.p. 167—169°C (reported[11,12] 158°C). IR spectrum (CCl_4): 1035, 1245, 1407, 1484, 1738, 3010, 3030, 3060 cm^{-1}. For $C_{20}H_{24}O_3$ (312·4) calculated: 76·89% C, 7·74% H; found: 76·83% C, 7·84% H.

3β-Hydroxy-19-norandrosta-5,7,9(10)-trien-17-one (*XXII*)

Acetate *XXI* (500 mg) was refluxed in methanol (42 ml) and water (7 ml) in the presence of potassium carbonate (500 mg) for 2 hours. The mixture was worked up in the usual manner and the residue chromatographed on silica gel (50 g) with benzene–ether (9 : 1). The fractions containing the required product were combined and evaporated to give a residue weighing 450 mg. Crystallisation from ether gave a substance (295 mg), m.p. 145—147°C, (reported[11,12] 138—139·5°C); IR spectrum (CCl_4): 1407, 1484, 1740, 3010, 3030, 3060, 3460, 3615 cm^{-1}. For $C_{18}H_{22}O_2$ (270·4) calculated: 79·96% C, 8·20% H; found: 80·01% C, 8·23% H.

17α-Methyl-19-norandrosta-5,7,9(10)-triene-3β,17β-diol (*XXIII*)

A solution of ketone *XXI* in a mixture of ether (5 ml) and benzene (5 ml) was added to a boiling solution of methyl magnesium iodide in ether (prepared from 600 mg of magnesium) with stirring over 15 minutes. Ether was distilled off gradually and substituted by benzene and the mixture was refluxed for 5 hours. It was decomposed with a saturated ammonium chloride solution, diluted with ethyl acetate, washed with 5% hydrochloric acid and 5% sodium hydrogen carbonate and water, dried and evaporated. Crystallisation from a mixture of acetone and light petroleum gave 275 mg of a product melting at 186—188°C, $[\alpha]_D^{20}$ −34·7° (*c* 2·0); IR spectrum (nujol): 1487, 3375 cm^{-1}. For $C_{19}H_{26}O_2$ (286·4) calculated: 79·68% C, 9·15% H; found: 79·66% C, 9·13% H.

17α-Ethynyl-19-norandrosta-5,7,9(10)-triene-3β,17β-diol 3-Monoacetate (*XXIV*)

Acetylene was introduced for 10 minutes into a solution of ketone *XXI* (700 mg) in toluene (30 ml). Freshly sublimated potassium tert-butoxide (200 mg) was then added to the mixture and acetylene introduced for another 24 hours. Fresh potassium tert-butoxide portions (50 mg each) were added at 4 hour intervals. Finally the reaction mixture was decomposed with 30% sulfuric acid, the product was extracted with benzene and the organic layer washed with 5% sodium hydrogen carbonate and water, dried and evaporated. The residue was chromatographed on silica gel (150 g) with benzene which eluted the unreacted ketone, and with a benzene–ether mixture (9 : 1), which eluted the required product. Respective fractions were combined and evaporated. The residue of the unreacted ketone weighed 330 mg, the residue of the required ethynyl derivative 290 mg. Ethynyl derivative was crystallised from a mixture of acetone and light petroleum, m.p. 145–147°C, $[\alpha]_D^{20}$ −78° (*c* 2·2). NMR spectrum: 0·785 s (18-H), 2·55 s (acetylenic proton). For $C_{22}H_{26}O_3$ (338·4) calculated: 78·07% C, 7·74% H; found: 78·13% C, 7·83% H.

17α-Ethynyl-19-norandrosta-5,7,9(10)-triene-3β,17β-diol (*XXV*)

A solution of acetate *XXIV* (85 mg) was refluxed in a mixture of methanol (8·5 mg) and water (1·5 ml) and potassium carbonate (100 mg) for 2 hours. The solution was worked up in the conventional manner and the dried residue (75 mg) was crystallised from a mixture of acetone and light petroleum to afford diol *XXV* (58 mg), m.p. 129–131°C, $[\alpha]_D^{20}$ −90° (*c* 2·0). For $C_{20}H_{24}O_2$ (296·4) calculated: 81·04% C, 8·16% H; found: 81·07% C, 8·23% H.

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