THE CHEMISTRY OF 9α-HYDROXY STEROIDS. 2. EPIMERIZATION AND FUNCTIONALIZATION OF 17α-ETHYLNYLATED 9α-HYDROXY STEROIDS

Jacobus N.M. Batist, Adrianus F.M. Slobbe, and Arthur F. Marx

Research & Development, Gist-brocades, P.O. Box 1, 2600 MA Delft, The Netherlands

Corresponding author: Jacobus N.M. Batist
Received September 6, 1988
Revised February 10, 1989

ABSTRACT

Practical routes to 9α-hydroxypregnenes were developed by epimerization and hydration of 17α-ethynyl-9α,17β-dihydroxyandrost-4-en-3-one. In the three different methods of epimerization which were used, the C-9α hydroxy group was not susceptible to rearrangement or other side reactions. C-21 functionalized 9α-hydroxypregnenes were obtained by introducing a 17α-halogenated ethynyl group into 9α-hydroxyandrost-4-ene-3,17-dione. Epimerization and hydration by the 17β-nitrooxy method produced 21-halogenated 9α-hydroxypregnenes, which were further converted into 21-acetoxy-9α-hydroxypregn-4-ene-3,20-dione.

INTRODUCTION

Although the preparation of 9α-hydroxy steroids by microbiological hydroxylation of 9-unsubstituted steroids has been known for years (1), most of the scarce literature concerning their chemistry is limited to their instability (2) or their direct dehydration (1,3) to $\Delta^{9(11)}$ steroids, which were believed to be more stable. 9α-Hydroxyandrost-4-ene-3,17-dione, recently produced on a large scale by the microbiological degradation of sterols*, such as sitosterol, has - as a starting compound - the advantage of providing 9α-halogen- and 11β-hydroxy corticoids without any

additional microbiological process step.

The preceding publication of this series (4) described the successful ethynylation of 9α-hydroxyandrost-4-ene-3,17-dione 1.

By proper protection of the reactive Δ^4-3-ketone as its 3,5-dienol methyl ether 2, 17α-ethynyl-9α,17β-dihydroxyandrost-4-en-3-one 3 was obtained without rearrangement of the steroid A ring.

We investigated epimerization of the 17α-ethynyl group and successive functionalization of the ethynyl group in order to create new routes for corticosteroid production. The objective of our study was to prove that, starting from 17α-ethynyl-9α,17β-dihydroxyandrost-4-en-3-one 3, the synthesis of different pregnane side chains can be carried out, while keeping C-9α hydroxy group intact. Dehydration to 9(11)dehydro steroids was postponed to a later stage of the synthetic route.

EXPERIMENTAL

9α-Hydroxyandrost-4-ene-3,17-dione used as the starting material in this study is manufactured at Gist-brocades. Melting points were determined on a Dr. Tottoli apparatus (Büchi) and are uncorrected. Optical rotations [α] were measured on a Perkin Elmer 241 polorimeter at 20 C at 589 nm and are given in degrees.

Infrared spectra are recorded in KBr on a Perkin-Elmer 521 spectrophotometer. Adsorption frequencies are reported in reciprocal centimeters. Proton NMR and ^{13}C-NMR are measured on a Bruker AM 360 MHz spectrophotometer. NMR spectra are taken in $CDCl_3$ unless otherwise mentioned and chemical shifts were reported on the δ scale in parts per million downfield from Me_4Si as internal standard.

Notations C^α and C^β refer to the α and β carbon atoms of the ethynyl group. Characteristic ^{13}C-NMR chemical shifts of isolated 9α-hydroxy steroids are presented in Table 1.

Silica gel 60 (grain size 0.063-0.2 mm, Merck) was used for ordinary column chromatography. Preparative high-performance liquid chromatography (HPLC) was performed using prepacked silica gel columns (Merck). Usual workup means washing extracts with water, drying ($MgSO_4$ or Na_2SO_4), filtration, and evaporation of the solvent under reduced pressure.

17α-Ethynyl-9α-hydroxy-17β-nitrooxyandrost-4-en-3-one 4

To a stirred suspension of 17α-ethynyl-9α,17β-dihydroxyandrost-4-

en-3-one 3 (411 mg) in acetic anhydride (3.1 mL), fuming nitric acid (HNO_3, 0.31 mL) was added dropwise at -25 C under nitrogen. After stirring at -20 C for 1 h, the reaction mixture was poured into 25 mL of ice water. The resulting precipitate was filtered and dissolved in CH_2Cl_2, followed by the usual workup to afford the nitro ester 4 (0.44 g, yield 94%).
IR: 3391 (OH), 3315 (C^{8}H), 2143 (C≡C), 1650 (CO), 1628, 1308, 1289 (ONO_2).
NMR: ($CDCl_3$/DMSO-d6 (3:1)): 0.963 (C$^{18}H_3$), 1.310 (C$^{19}H_3$), 3.08 (C^{8}H), 3.69 (OH), 5.75 (C^{4}H).

17β-Ethynyl-9α,17α-dihydroxyandrost-4-en-3-one 5 (from 4)
To a solution of 4 (0.40 g) in tetrahydrofuran (THF, 1.2 mL), water (1.2 mL) and silver nitrate ($AgNO_3$, 46 mg) were added. The reaction mixture was stirred at room temperature for 72 h, after which THF was evaporated under reduced pressure. HNO_3 (65%, 0.6 mL) was added, and the mixture was extracted with CH_2Cl_2. The usual workup gave 340 mg (96%) of the epimerized ethynyl compound 5. Recrystallization from THF/hexane afforded an analytical sample.
Mp: 236 C (decom); [α]: +102° (c=1, DMSO).
NMR ($CDCl_3$): 0.923 (C$^{18}H_3$), 1.335 (C$^{19}H_3$), 2.51 (C^{8}H), 5.88 (C^{4}H).
NMR (DMSO-d6): 0.790 (C$^{18}H_3$), 1.233 (C$^{19}H_3$), 3.19 (C^{8}H), 4.02 (OH), 5.07 (OH), 5.62 (C^{4}H).

9α,17α-Dihydroxypregn-4-ene-3,20-dione 6 (from 5)
To a stirred suspension of 5 (80 mg) in a mixture of acetic acid, water and 30% aqueous H_2SO_4 (0.48 mL, 20:4:0.5 v/v/v), mercury (II) oxide (HgO, 9.6 mg) was added and the mixture was stirred at 35 C for 105 min. After neutralizing with one drop of 2 N aqueous NaOH, water (0.4 mL) was added. Extraction with CH_2Cl_2 followed by the usual workup afforded 70 mg (83%) of the 9α,17α-dihydroxypregnene 6.
Mp: 235-239 C; [α]: +91.1° (c=1, $CHCl_3$).
IR: 3485 (2xOH), 1700 (CO), 1665 (CO), 1614 (C=C).
NMR: 0.737 (C$^{18}H_3$), 1.317 (C$^{19}H_3$), 2.27 (C$^{21}H_3$), 3.15 (OH), 5.87 (C^{4}H).

17α-Hydroxypregna-4,9(11)-diene-3,20-dione 7
A mixture of 6 (50 mg) in 70% aqueous H_2SO_4 (1.5 mL) was stirred at room temperature for 40 min and then poured into ice water. Extraction with CH_2Cl_2 and usual workup gave 37 mg (78%) of the crude 9,11-dehydrated pregnene 7.
Proton NMR and ^{13}C-NMR could not detect undesired 8,9-dehydro isomer.
NMR: 0.725 (C$^{18}H_3$), 1.341 (C$^{19}H_3$), 2.04 (C$^{21}H_3$), 5.54 (C^{11}H), 5.74 (C^{4}H).

17α-Formyloxy-9α-hydroxypregn-4-ene-3,20-dione 9
Trifluoroacetic anhydride (1.29 mL) was added dropwise to a stirred solution of 3 (1.00 g) in dimethylformamide (DMF, 10 mL) at 2 C. The reaction mixture was stirred at 5 C for 10 min after which TLC indicated conversion into the 17β-trifluoroacetate 8 to be complete. Formic acid (HCOOH, 10 mL) and HgO (140 mg) were added and stirring was continued at 55 C for 9 h. The reaction mixture was extracted with CH_2Cl_2. The crude product (1.5 g), obtained after usual workup, was subjected to preparative HPLC (Lobar Size C, toluene/acetone (4:1)), which afforded 470 mg of the 9α-hydroxy pregnene 9 (40% from 3). Mp: 237-240 C;
[α]: +76,4 ° (c=1, $CHCl_3$).
IR: 3400 (OH), 1730 (CO), 1651 (CO), 1620 (C=C), 1162 (COC).
NMR: 0.701 ($C^{18}H_3$), 1.332 ($C^{19}H_3$), 2.09 ($C^{21}H_3$), 2.43 (OH), 5.89 (C^4H), 8.09 (formyl-H).
A less polar by-product was isolated and identified by IR and NMR to be the 16,17-dehydrated compound 9α-hydroxypregna-4,16-diene-3,20-dione 10 (170 mg; 17% from 3). Mp: 177-181 C; [α]: +144.9 (c=1, $CHCl_3$).
IR: 3468 (OH), 1660 (CO), 1620 (C=C), 1581 (C=C).
NMR: 0.948 ($C^{18}H_3$), 1.347 ($C^{19}H_3$), 2.26 ($C^{21}H_3$), 2.41 (OH), 5.86 (C^4H), 6.73 ($C^{16}H$).

9α,17α-Dihydroxypregn-4-ene-3,20-dione 6 (from 9)
To a stirred solution of 9 (100 mg) in a mixture of MeOH (10 mL) and water (1.6 mL), $KHCO_3$ (94 mg) was added at room temperature. After stirring was continued for 20 h, MeOH was evaporated under reduced pressure. The residue was extracted with CH_2Cl_2, followed by the usual workup which gave 80 mg (85%) of the 9α,17α-dihydroxypregnene 6. NMR and IR were identical with the spectra of the product obtained using the nitrate method.

17α-Ethynyl-3-methoxyandrosta-3,5-diene-9α,17β-diol 11
A solution of 9α-hydroxy-3-methoxyandrosta-3,5-dien-17-one 2 (3.16 g) in dry THF (25 mL) was added dropwise to a stirred solution of lithium acetylide ethylenediamine complex (90%, 5.11 g) in ethylenediamine (15 mL) at 5 C. The reaction mixture was stirred at room temperature for 2.5 h after which TLC indicated the reaction to be complete. The reaction mixture was poured into ice water and extracted with CH_2Cl_2. The usual workup afforded 4.0 g of the 17α-ethynylated compound 11, which, without purification, was used for the next step.

17α-Ethynyl-17β-methanesulfonyloxy-3-methoxyandrosta-3,5-dien-9α-ol 12
A mixture of 11 (4.0 g), anhydrous LiBr (0.87 g), and anhydrous THF (35 mL) was cooled to -60 C. After addition of a 15% solution

of n-butyllithium (n-Buli) in hexane (7 mL), the reaction mixture was stirred at -60 C for 45 min. Next, methanesulfonylchloride (CH_3SO_2Cl, 0.77 mL) was added and stirring was continued at -60 C for 45 min. The mixture was poured into an aqueous NH_4Cl solution and extracted twice with CH_2Cl_2. The combined organic layers were dried and, after the addition of pyridine (1 mL), concentrated under reduced pressure at 0 C. The crude product was washed with diethyl ether and filtered to afford the sulfonated compound 12 which, without purification, was used for the next step.

17β-Ethynyl-9α,17α-dihydroxyandrost-4-en-3-one 5 (from 12)
To a stirred solution of 12 (2.0 g), as prepared above, in THF (15 mL), water (2.5 mL) and AgNO3 (150 mg) were added. After stirring was continued for 2 h, the mixture was poured into an aqueous NH_4Cl solution (100 mL), containing NaCN (1 g), and extracted twice with CH_2Cl_2, followed by the usual workup. In order to hydrolyze the 3,5-dienol ether, the residue was dissolved in a mixture of MeOH (50 mL) and water (5 mL) and then 4 M aqueous HCl (2 mL) was added. After stirring at room temperature for 15 min, the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with water, and dried and concentrated under reduced pressure to afford 1.07 g of the crude epimerized ethynyl compound 5 (overall yield of 32% from 2).
In the extraction procedure some insoluble material was filtered, combined with the aqueous layer and extracted with CH_2Cl_2. This extract was worked up as usual to afford 0.62 g of the 17α-ethynyl compound 3.

17α-Bromoethynyl-9α-hydroxy-17β-nitrooxyandrost-4-en-3-one 13
To a stirred solution of 4 (373 mg) in acetone (7 mL), N-bromosuccinimide (0.22 g) and $AgNO_3$ (18 mg) were added at room temperature. After stirring was continued for 30 min, ice water was added. The resulting precipitate was filtered and dissolved in a mixture of ethyl acetate and CH_2Cl_2. The usual workup gave 0.42 g (93%) of the brominated 9α-hydroxy steroid 13.
IR: 3328 (OH), 2202 (C≡C), 1664 (CO), 1630, 1301, 1287 (ONO_2).
NMR: 0.969 ($C^{18}H_3$), 1.331 ($C^{19}H_3$), 2.42 (OH), 5.88 (C_4H).

21-Bromo-17α-formyloxy-9α-hydroxypregn-4-ene-3,20-dione 14
To a stirred solution of 13 (360 mg) in HCOOH (3.05 mL) and 1-methyl-2-pyrrolidinone (0.61 mL), $AgNO_3$ (15.3 mg) was added at room temperature. After stirring was continued for 7 h, the reaction mixture was poured into a mixture of ice water and CH_2Cl_2, followed by the usual workup. The crude product (0.50 g) was purified by preparative HPLC (Lobar size B) using toluene/acetone (3:1) as the eluent to afford 0.19 g (52%) of the 17α-formyloxy 9α-hydroxypregnene 14. Mp: 190-192 C (decomp).
IR: 3400 (OH), 1720 (CO), 1636 (CO), 1150 (COC).

NMR: 0.758 ($C^{18}H_3$), 1.337 ($C^{19}H_3$), 2.42 (OH), 3.98, 4.07 ($C^{21}H_2$), 5.89 (C^4H), 8.09 (formyl-H).

17α-Chloroethynyl-9α,17β-dihydroxyandrost-4-en-3-one 15

A solution of 1,2-trans-dichloroethene (3.1 mL) in anhydrous diethyl ether (10 mL) was added dropwise to a stirred solution of 15% n-Buli in hexane (50 mL) at -5 C under nitrogen. The temperature was allowed to raise to 20 C, after which a solution of 2 (3.10 g) in anhydrous toluene (70 mL) was added dropwise in 20 min. The reaction mixture was stirred at room temperature for 16 h and then poured into water. The aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water to neutral pH, dried, and concentrated under reduced pressure to dryness. A solution of this crude intermediate (17α-chloroethynyl-3-methoxyandrosta-3,5-diene-9α,17β-diol; 4.0 g) in a mixture of MeOH (100 mL) and water (10 mL) was acidified to pH 1 with 6 N aqueous HCl (2 mL). After stirring for 15 min, the mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of CH_2Cl_2 and water, followed by the usual workup. Purification of the crude product (4.0 g) by HPLC (Lobar size A; toluene/acetone (3:1) afforded 0.56 g (16%) of the 17α-chloroethynylated 9α-hydroxyandrostene 15. Mp: 216-222 C (decomp).
IR: 3507 (OH), 3377 (OH), 2218 (C≡C), 1642 (CO), 1608 (C=C).
NMR: 0.897 ($C^{18}H_3$), 1.330 ($C^{19}H_3$), 2.43 (OH), 5.87 (C^4H).

17α-Chloroethynyl-9α-hydroxy-17β-nitrooxyandrost-4-en-3-one 16

To a stirred suspension of 15 (0.56 g) in acetic anhydride (4.7 mL), fuming HNO_3 (0.64 mL) was added dropwise at -20 C under nitrogen. After stirring for 45 min, the reaction mixture was poured into water. The resulting precipitate was filtered and dissolved in CH_2Cl_2, followed by the usual workup to afford 0.52 g (84%) of the nitrate 16.
IR: 3415 (OH), 2221 (C≡C), 1660 (CO), 1626, 1298, 1284 (ONO_2).
NMR: 0.967 ($C^{18}H_3$), 1.332 ($C^{19}H_3$), 2.42 (OH), 5.88 (C^4H).

21-Chloro-17α-formyloxy-9α-hydroxypregn-4-ene-3,20-dione 17

The nitro ester 16 (0.45 g) was converted to the 21-chloro-9α-hydroxy-17α-formyloxy pregnene 17, as described for its bromo analog 14, with 21 mg of $AgNO_3$ in HCOOH (4.2 mL) and 1-methyl-2-pyrrolidinone (0.84 mL). Chromatography (Lobar size B, toluene/acetone (3:1) gave 0.20 g (44%) of the epimerized 21-chloro pregnene 17. Mp: 223-225 C; [α]: +98.0 (c=1, $CHCl_3$).
IR: 3400 (OH), 1740 (CO), 1725 (CO), 1625 (CO), 1150 (COC).
NMR: 0.743 ($C^{18}H_3$), 1.334 ($C^{19}H_3$), 2.42 (OH), 4.14, 4.25 ($C^{21}H_2$), 5.88 (C^4H).

Table 1. Characteristic ^{13}C-NMR chemical shifts of prepared 9α-hydroxy steroids[a]

Carbon No.	Compounds					
	4	5	6	9	19	13
C^4	124.74	125.03	126.57	126.84	126.67	126.86
C^5	168.79	171.05	168.82	167.96	168.59	167.74
C^9	74.24	74.01	76.21	75.82	76.43	75.94
C^{17}	90.76	87.35	89.82	96.91	154.70	92.12
C^{18}	11.25	15.54	14.36	13.34	14.68	12.26
C^{19}	18.82	19.55	19.84	19.77	19.66	19.79
C^{20}	-	-	211.08	203.21	196.50	-
C^{21}	-	-	27.64	26.36	26.92	-
C^{α}	79.67	76.55	-	-	-	76.98
C^{β}	76.90	75.35	-	-	-	49.72
C^{16}	[b]	[b]	[b]	[b]	144.24	[b]
	14	15	16	17	18	19
C^4	126.96	126.63	126.87	126.93	124.97	126.61
C^5	167.73	168.55	167.84	167.67	169.46	168.92
C^9	75.79	76.34	75.96	75.78	74.83	76.40
C^{17}	96.49	79.98	91.72	96.06	89.49	90.00
C^{18}	13.65	11.82	12.27	13.54	13.52	13.57
C^{19}	19.78	19.82	19.80	19.78	19.13	19.87
C^{20}	196.98	-	-	197.01	202.60	204.96
C^{21}	[b]	-	-	45.52	[b]	66.06
C^{α}	-	72.20	67.81	-	-	-
C^{β}	-	64.54	66.31	-	-	-
formyl-C	160.66	-	-	160.58	-	-
acetyl-C	-	-	-	-	-	20.52
acetyl-CH_3	-	-	-	-	-	170.66

[a] Spectra are taken up in $CDCl_3$ except for 4 ($CDCl_3$/DMSO-d6 (3:1)), 5 (DMSO-d6), and 18 ($CDCl_3$/DMSO-d6 (1:1).
[b] Present but difficult to assign.

21-Bromo-9α,17α-dihydroxypregn-4-ene-3,20-dione 18

A suspension of 14 (100 mg) and $KHCO_3$ (78 mg) in a mixture of MeOH (8.1 mL) and water (1.3 mL) was stirred at room temperature for 4 h. MeOH was then evaporated under reduced pressure and the residue was dissolved in a mixture of CH_2Cl_2 and water. The organic phase was worked up as usual to give 93 mg (100%) of the

hydrolyzed 21-bromo-9α-hydroxypregnene 18. Mp: 200-201 C (decom); [α]: +111.5° (c=1, $CHCl_3$).
IR: 3460 (OH), 3400 (OH), 1732 (CO), 1655 (CO), 1622 (C=C).
NMR: 0.726 ($C^{18}H_3$), 1.325 ($C^{19}H_3$), 2.43 (OH), 4.20, 4.40 ($C^{21}H_2$), 5.87 (C^4H).

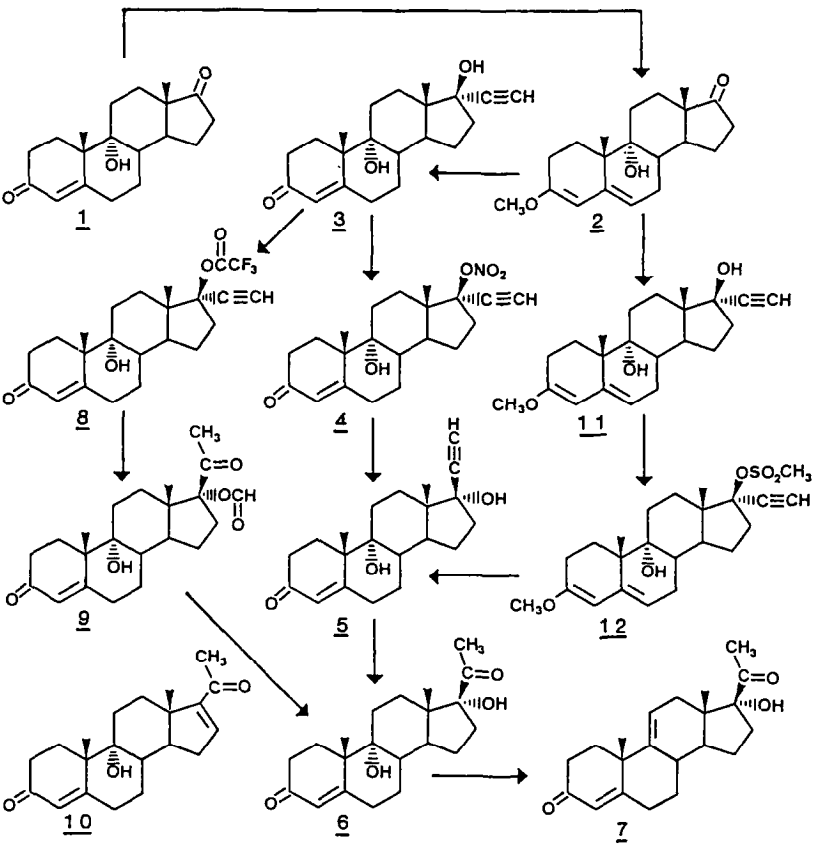
21-Acetoxy-9α,17α-dihydroxypregn-4-ene-3,20-dione 19
A suspension of 18 (30 mg) and potassium acetate (30 mg) in acetone (0.75 mL) was heated in a sealed bottle at 60 C for 1 h. The reaction mixture was cooled to room temperature and extracted with a mixture of CH_2Cl_2 and water, followed by the usual workup to afford 27 mg (95%) of the 21-acetoxylated 9α-hydroxy pregnene 19. Mp: 231-234 C (decomp).
IR: 3470 (OH), 1750 (CO), 1720 (CO), 1649 (CO).
NMR: 0.716 ($C^{18}H_3$), 1.318 ($C^{19}H_3$), 2.17 ($COCH_3$), 4.89, 5.05 ($C^{21}H_2$), 3.1 (OH), 5.86 (C^4H).

DISCUSSION

Epimerization of the 17α-ethynyl group can be accomplished by metal ion catalyzed hydrolysis of 17β-esters of 17α-ethynyl steroids. In our hands, epimerization was carried out by the following three methods, which are summerized in scheme 1:

1. Nitration of the 17β-hydroxy group, followed by treatment with $AgNO_3$ (5,6).
2. Trifluoroacetylation of the 17β-hydroxy group and subsequent treatment with mercury (II) acetate (7).
3. Methanesulfonylation of the 17β-hydroxy group, followed by reaction with $AgNO_3$ (8).

In the first method 17α-ethynyl-9α,17β-dihydroxyandrost-4-en-3-one 3 was nitrated with fuming HNO_3 at -25 C. Despite the lability of the 9α-hydroxy group to strong oxygenated acids (3), nitration of the 17β-hydroxy group was achieved in high yield (94%). Treatment of the 17β-nitrate 4 with $AgNO_3$ afforded the epimerized 17β-ethynyl-9α,17α-dihydroxy steroid 5 in 96% yield. The ethynyl group of 5 was converted into the pregnane side chain of 6 with HgO in 83% yield. The 9α-17α-dihydroxypregnene 6 was



Scheme 1

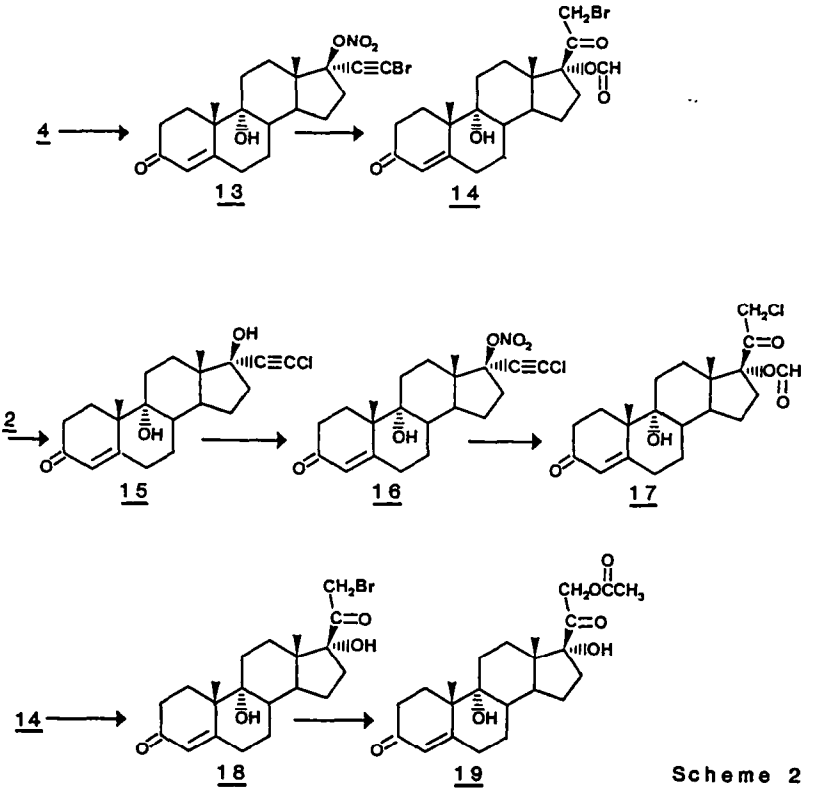
selectively dehydrated with 70% aqueous H_2SO_4 into the known 17α-hydroxypregna-4,9(11)-diene-3,20-dione 7 (9) in 78% crude yield. The second method of epimerization started with esterification of the 17β-hydroxy group of 3 with trifluoroacetic anhydride in DMF at 2 C. Without isolation of the 9α-hydroxy-17β-trifluoroacetate 8 formed, treatment with mercury acetate and HCOOH gave the

epimerized 17α-formyloxy-9α-hydroxypregnene 9, which was obtained, after chromatography, in 32% overall yield from 3. As expected from the literature (6), the 16,17-dehydrated pregnene 10 was isolated as a by-product in this reaction. The 17α-formyl ester 9 was easily hydrolyzed into 6 with $NaHCO_3$ in 85% yield.

In the third approach protection of the Δ^4-3-ketone, as used in the ethynylation of 9α-hydroxyandrost-4-ene-3,17-dione 1, was maintained during epimerization. Ethynylation of 2 was achieved as described by Kapur et al (4) except that the intermediate 17α-ethynyl-3-methoxyandrosta-3,5-diene-9α,17β-diol 11 was isolated and treated with CH_3SO_2Cl and n-BuLi to prepare the 17β-methanesulfonyl ester 12. Treatment of 12 with $AgNO_3$ and subsequent acid hydrolysis gave the epimerized 17β-ethynyl-9α,17α-dihydroxypregnene 5 in an overall yield of 32% from 2. The yield can probably be improved by the use of 2 equivalents of BuLi in the sulfonylation step. Due to concurrent metalation of the 9α-hydroxy group, sulfonylation of the 17β-hydroxy group and successive epimerization at C-17 were incomplete. For that reason the 17α-ethynyl epimer was isolated as a by-product in the reaction exemplified under the heading Experimental.

Efficient methods to convert the ethynyl group into a halogenated side chain were published recently (10). Within the context of our studies with 9α-hydroxylated steroids, we prepared 21-bromo-17α-formyloxy-9α-hydroxypregn-4-ene-3,20-dione 14 and its 21-chloro analog 17 by the two methods, shown in scheme 2 and discussed below:

1. Bromination of 17α-ethynyl-9α-hydroxy-17β-nitrooxyandrost-4-en-3-one 4 with N-bromosuccinimide gave the 17α-bromoethynyl androstene 13 in 93% yield. Successive treatment with $AgNO_3$ and 1-methyl-2-pyrrolidinone in HCOOH gave the 21-bromo-17α-formyloxy-9α-hydroxypregn-4-ene-3,20-dione 14 in 52% yield.



Scheme 2

2. This method started with the 3-keto-Δ^4 protected 9α-hydroxy-androst-4-ene-3,17-dione 2 which was chloroethynylated in one step with 1,2-dichloroethene and n-BuLi by a slightly modified procedure described by Burgess et al (11). The 17α-chloroethynyl steroid 15, obtained after chromatography in 10% yield, was nitrated with fuming HNO_3 to the 17β-nitrate 16 in 84% yield and epimerized in the same way as its bromo analog to the formyl ester 17 in 44% yield.

Further functionalization was demonstrated with the 21-bromo pregnane 14, which was quantitatively hydrolyzed with $KHCO_3$ to its 21-bromo-9α,17α-dihydroxy analog 18, and then treated with

potassium acetate to give 21-acetoxy-9α,17α-dihydroxypregnene 19 from 14 in 95% yield.

ACKNOWLEDGMENTS

The authors wish to thank Mr. M.M. Poot for recording and interpretation of IR and NMR spectra.

NOTES AND REFERENCES

* Not yet published European patent Application 87202619.0 by Gist-brocades.

1. Sih CJ, and Weisenborn FL. Process for preparing 9α-hydroxy steroids. US PATENT 3065146 (1962).
2. Bergstrom CG, and Dodson RM (1961). Acid-catalysed rearrangement of 9α-hydroxy-4-androstene-3,17-dione. CHEM & IND: 1530-1531.
3. Henkel G, Kern RM, Feiler L, and Hänzel W. Saure Dehydration von 9α-Hydroxyandrostendionen. GERMAN PATENT PUBLICATION DE 2814747 (1978).
4. Kapur JC, Marx AF, and Verweij J (1989). The chemistry of 9α-hydroxy steroids. 1. Preparation of 9α,17β-dihydroxy-17α-ethynylandrost-4-en-3-one. STEROIDS 52:181-186.
5. Hofmeister H, Annen K, Laurent H, and Wiechert R (1978). Überführung von 17α-Ethinyl-17β-nitrooxy-Steroiden in 17α-Hydroxy-20-oxopregnan-Derivate. CHEM BER 111: 3086-3093.
6. Nitta I, Fujimori S, Haruyama T, Inoue S, and Ueno H (1985). A new synthesis of 17α,21-dihydroxypregna-1,4-diene-3,20-dione 17,21-diacetate from androsta-1,4-diene-3,20-dione. BULL CHEM SOC JPN 58: 981-986.
7. Richter Gedeon Vegyeszeti Gyar: Verfahren zur Herstellung von 17α-Athinyl-17β-trifluoracetoxygon-4-en-3-on derivaten. EUROPEAN PATENT SPECIFICATION 0063369 (1984).
8. Westmijze H, Kleijn H, and Vermeer P (1980). Ag(I)-assisted hydrolysis of mestranol methanesulphonate into epimestranol. TETRAHEDRON LETT 21: 2665-2666.
9. Bucourt R, Nedelec L, Gasc JC, and Pierdet A. 17α-Hydroxy-pregna-4,9(11)-dien-3,20-dion. GERMAN PATENT PUBLICATION 2110140 (1971); CA 75-151986.
10. Hofmeister H, Annen H, Laurent H, and Wiechert R (1987). Aufbau der Corticoid-Seitenkette aus 17α-(Halogenethinyl)-17β-(nitrooxy)androstenen. LIEBIGS ANN CHEM: 423-426.
11. Burgess C, Burn D, Ducker JW, Ellis B, Feather P, Hiscock AK Leftwick AP, Mills JS, and Petrow V (1962). Some 17α-chloroethynyl-17β-hydroxy-derivatives. J CHEM SOC: 4995-5004.