Aminosteroids. Part 5.[1] Synthesis of the Four Isomeric 3,11-Diamino-5α-pregnanes

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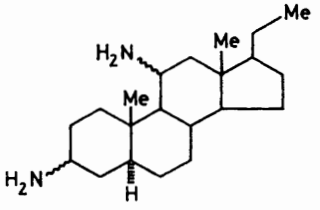
Preparation of the four isomeric 3,11-diamino-5α-pregnanes is reported. Three (3β,11α-, 3α,11α-, and 3α,11β-) were prepared from 5α-pregnane-11,20-dione obtained from 20-oxo-5α-pregnane-3β,11α-diyl diacetate. The fourth (3β,11β-) was prepared from 11-oxo-5α-pregnan-3β-yl acetate which is also available from 5α-pregnane-11,20-dione, though for convenience another source was used.

The equatorial amino-groups (3β- and 11α-) were formed by alkali-metal reduction of the oximes; the axial 3α-amino-group by reduction of the 3α-azide; and the axial 11β-amino-group by catalytic hydrogenation of the oxime.

In continuation of our studies investigating the biological activities of amino-steroids, the 3,11-diamino-5α-pregnanes (1)—(4) have been prepared by the routes described herein.

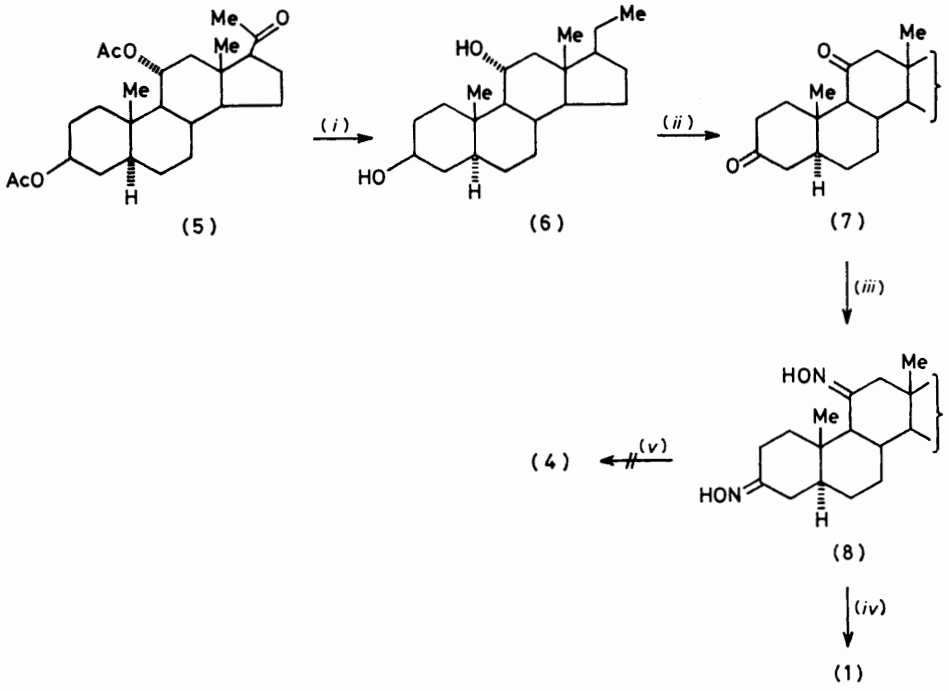


(1) 3β, 11α
(2) 3α, 11α
(3) 3β, 11β
(4) 3α, 11β

Huang-Minlon reduction[2] of the known[3] 20-oxo-5α-pregnane-3β,11α-diyl diacetate (5) afforded the diol (6) (77%) which was oxidised with Jones reagent to give the 3,11-dione (7) (62%). Treatment of this dione with hydroxylamine hydrochloride in refluxing aqueous pyridine[4,5] furnished the dioxime (8) (95%) which was reduced with sodium in propan-1-ol to give 3β,11α-diamino-5α-pregnane (1), isolated in 30% yield as the dihydrochloride salt. The equatorial configurations of the amino-groups were assigned on the basis of the known preference for equatorial amine formation with sodium in alcohols[4-9] and confirmed by the ^{1}H n.m.r. spectrum which displays broad signals at δ 2.55 and 3.0 (each $W_{\frac{1}{2}}$ 18 Hz) for the 3α and 11β axial protons.[10] These are in agreement with the values reported by Cowell[6] for 3β- and 11α-aminoandrostanes.

Hydrogenation of the dioxime (8) over platinum in acetic acid, which was expected[4-8] to afford the 3α,11β-diamine (4) with the amino-groups in the axial configurations, gave an intractable mixture. Consequently, an alternative route to (4) (Scheme 2) was devised.

Selective reduction of dione (7) with sodium boro-



SCHEME 1 $N_2H_4 \cdot H_2O$,NaOH; (*ii*) H_2CrO_4, Me_2CO; (*iii*) $NH_2OH \cdot HCl$, pyridine, H_2O; (*iv*) Na,n-C_3H_7OH; (*v*) PtO_2, H_2, AcOH

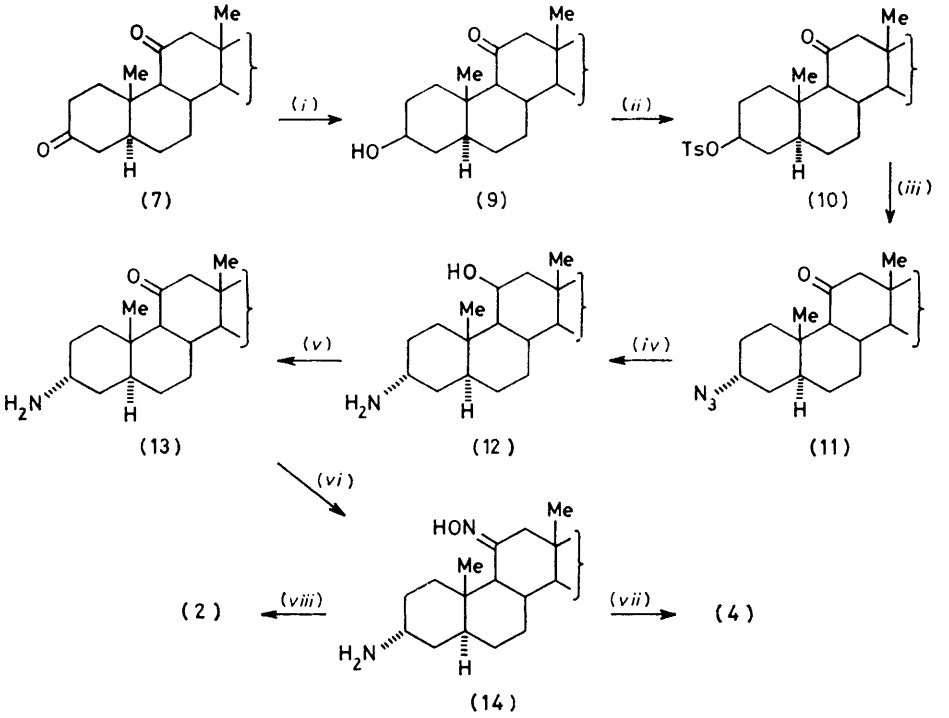
hydride[11] in tetrahydrofuran at room temperature afforded 3β-hydroxy-5α-pregnan-11-one (9) (80%). A broad signal at δ 3.55 ($W_{\frac{1}{2}}$ 20 Hz) in the ^{1}H n.m.r.

spectrum establishes the C-3 proton as axial.[10] Tosylation of this alcohol in pyridine with toluene-*p*-sulphonyl chloride gave the 3β-toluene-*p*-sulphonate (10) which, on treatment with sodium azide in *N*-methyl-2-pyrrolidone, furnished 3α-azido-5α-pregnan-11-one (11) in 83% overall yield from (9). Inversion at C-3 on formation of the azide is confirmed by the width of the signal at δ 3.81 ($W_{\frac{1}{2}}$ 9 Hz) for the 3β-proton.[10]

Reduction of the foregoing azido-ketone (11) with lithium aluminium hydride afforded 3α-amino-5α-pregnan-11β-ol (12) (86%) which showed characteristic signals at δ 3.12 and 4.29 (each $W_{\frac{1}{2}}$ 8 Hz) for the 3β- and 11α-protons.[10] Oxidation of this alcohol with Kiliani reagent [12] yielded the unstable amino-ketone (13) which was immediately treated with hydroxylamine hydrochloride in refluxing aqueous pyridine to afford, in 77% yield from alcohol (12), the amino-oxime (14) [$\nu_{max.}$ 3 380 (OH and NH_2) and 1 625 cm^{-1} (C=N)].

Assignment of the α-configuration to the 11-amino-group was confirmed by the signals for the C-18 and C-19 protons at δ 0.57 and 0.92 in the ^1H n.m.r. spectrum of the amino-alcohol, which are in agreement with the values calculated by application of Zurcher's additivity constants [14] to 11α-amino-5α-androstane.[6]

Catalytic hydrogenation of oxime (16) followed by hydrolysis of the 3β-acetate (18) afforded 11β-amino-5α-pregnan-3β-ol (19) (52%). The signal for the 11α-proton was not clearly discernible in the ^1H n.m.r. spectrum, because it was superimposed on the signal due to the axial 3α-proton. However, the shapes and widths of the overlapping signals are consistent with the assigned equatorial configuration of the 11α-proton.[6]

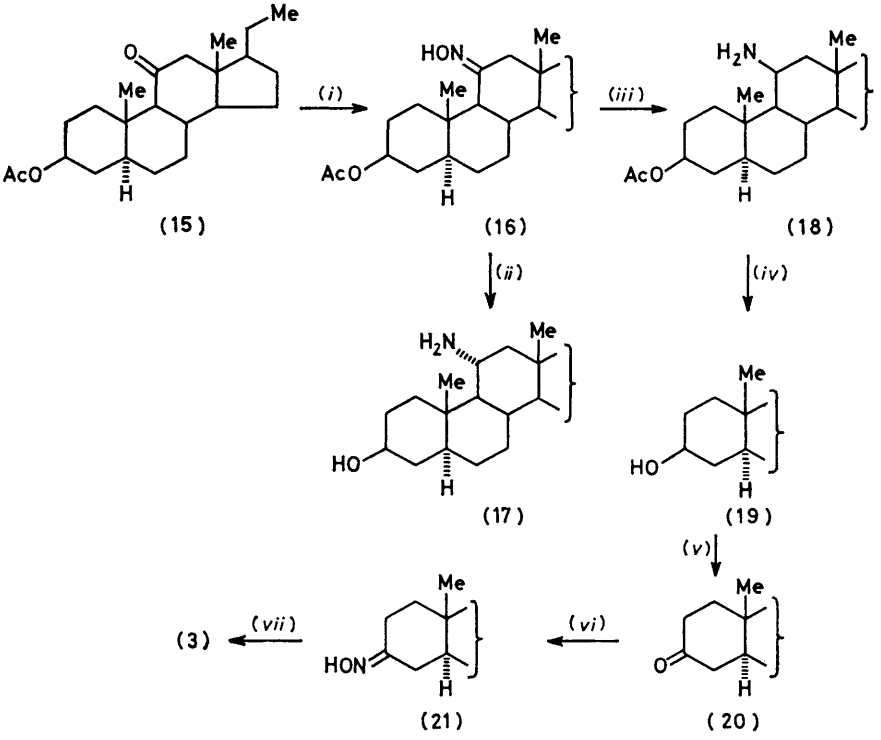


SCHEME 2 (*i*) $NaBH_4$; (*ii*) *p*-$MeC_6H_4SO_2Cl$, pyridine; (*iii*) NaN_3; (*iv*) $LiAlH_4$; (*v*) H_2CrO_4, AcOH; (*vi*) $NH_2OH{\cdot}HCl$, pyridine, H_2O; (*vii*) PtO_2, H_2, AcOH; (*viii*) Na,n-C_3H_7OH

Reduction of the oxime (14) with sodium in propan-1-ol and hydrogen over platinum catalyst in acetic acid gave the desired 11α- and 11β-amino-derivatives (2) (δ 3.02, $W_{\frac{1}{2}}$ 19 Hz, 11β-H) and (4) (δ 3.48, $W_{\frac{1}{2}}$ 9 Hz, 11α-H) respectively, the former being isolated as the dihydrochloride salt.

Heating the known 11-oxo-5α-pregnan-3β-yl acetate (15) [13] with hydroxylamine hydrochloride in refluxing aqueous pyridine gave the 11-oxime (16) (52%) [$\nu_{max.}$ 3 590, 3 400 (OH), and 1 642 cm^{-1} (C=N)] which was reduced with sodium in propan-1-ol to 11α-amino-5α-pregnan-3β-ol (17) (δ 3.02, $W_{\frac{1}{2}}$ 20 Hz, 11β-H) isolated in 34% yield as the hydrochloride monohydrate salt. Moreover, the singlets at δ 0.79 and 1.02 for the C-18 and C-19 protons respectively, are close to the values (δ 0.84 and 1.05) predicted by Zurcher's additivity constants [14] applied to 11β-amino-5α-androstane.[6]

Oxidation of the amino-alcohol (19) with Kiliani reagent [12] gave the unstable amino-ketone (20). This was immediately treated with hydroxylamine hydrochloride and aqueous methanolic potassium bicarbonate to furnish the 3-oxime (21) [$\nu_{max.}$ 3 450 (OH) and 1 650 cm^{-1} (C=N)] which was then reduced with sodium in propan-1-ol to give 3β,11β-diamino-5α-pregnane (3), isolated in 28% overall yield from the alcohol (19) as the dihydrochloride monohydrate salt. The ^1H n.m.r. spectrum is consistent with this structure, displaying a broad signal at δ 2.64 ($W_{\frac{1}{2}}$ 19 Hz) and a sharp singlet at δ 3.48 ($W_{\frac{1}{2}}$ 9.5 Hz) for the axial 3α-proton and the equatorial 11α-proton respectively.[10]



SCHEME 3 (*i*) NH_2OH·HCl,pyridine,H_2O; (*ii*) Na,n-C_3H_7OH; (*iii*) PtO_2,H_2,AcOH; (*iv*) KOH,H_2O,CH_3OH; (*v*) H_2CrO_4, AcOH; (*vi*) NH_2OH·HCl,$KHCO_3$; (*vii*) Na,n-C_3H_7OH

EXPERIMENTAL

Unless otherwise stated, m.p.s were determined with a Kofler hot-stage apparatus; i.r. spectra were recorded on solutions in methylene chloride with a Perkin-Elmer 457 spectrophotometer; and ^1H n.m.r. spectra were measured for solutions in [^2H]chloroform with a Perkin-Elmer R12B instrument. Specific rotations were determined for solutions in chloroform unless otherwise indicated. Concentrations (*c*) are quoted in g per 100 ml. G.l.c. analyses were performed with a Pye–Unicam 105 gas chromatograph and quoted reference times are relative to cholestane (t_R = 1 on 3% SE 30 column at 229 °C; gas flow rate 35 ml min^{-1}).

5α-Pregnane-3β,11α-diol (6).—20-Oxo-5α-pregnane-3β,11α-diyl diacetate (5) [3] (80 g) was reduced by the method of Huang-Minlon.[2] The crude product in methylene chloride–ethyl acetate was passed through a short alumina column and recrystallised from ether–hexane to give the *diol* (6) (47 g) as needles, m.p. 143—147 °C; $[\alpha]_D$ −8° (*c* 0.8); $\nu_{max.}$ (KCl) 3 370 and 1 025 cm^{-1} (OH); δ 0.56 and 0.92 (each 3 H, s, 13- and 10-Me) and 3.2—4.2 (2 H, m, 3α-H and 11β-H) (Found: C, 78.45; H, 11.3. $C_{21}H_{36}O_2$ requires C, 78.7; H, 11.3%).

5α-Pregnane-3,11-dione (7).—Jones reagent (6.24N; 45 ml) was added dropwise to a stirred solution of the diol (6) (20 g) in acetone (500 ml) at 0 °C and the stirred mixture was set aside until conversion to the dione was complete (t.l.c.). The mixture was poured into water at 0 °C and the precipitated solid was removed by filtration and dissolved in ether. The solution was washed with water until neutral, dried (Na_2SO_4), and the solvent removed. Recrystallisation of the crude product (17.4 g) from ether–hexane gave the *dione* (7) (12.3 g) as needles, m.p. 143—148 °C; $[\alpha]_D$ +83° (*c* 1.2); $\nu_{max.}$ 1 715 and 1 705 cm^{-1} (C=O); δ 0.57 and 1.21 (each 3 H, s, 13- and 10-Me) (Found: C, 79.8; H, 10.25. $C_{21}H_{32}O_2$ requires C, 79.7; H, 10.2%).

5α-Pregnane-3,11-dione oxime (8).—Hydroxylamine hydrochloride (10 g) was added to a solution of the dione (7) (6.7 g) in pyridine (150 ml) and water (15 ml) and the solution was refluxed for 25 h. The reaction was poured into water at 0 °C and the precipitated solid was washed well with water and then dried to afford the *dioxime* (8) (7 g) as a colourless solid, m.p. 119—123 °C; $\nu_{max.}$ (KCl) 3 600 and 3 350 (OH) and 1 655 cm^{-1} (C=N). Recrystallisation from methanol afforded a pure sample as fine needles, m.p. 122—125 °C; $[\alpha]_D$ +94° (*c* 0.8); $\nu_{max.}$ (KCl) 3 600, 3 400 (OH), and 1 655 cm^{-1} (C=N); δ 0.53 and 1.14 (each 3 H, s, 13- and 10-Me) and 7.6 (1 H, m, $W_{\frac{1}{2}}$ 19 Hz, O*H*) (Found: C, 72.95; H, 10.1; N, 8.2. $C_{21}H_{34}N_2O_2$ requires C, 72.8; H, 9.9; N, 8.1%).

3β,11α-Diamino-5α-pregnane (1) *and 3β,11α-Diamino-5α-pregnane Dihydrochloride.*—Sodium (45 g) was added portionwise to a solution of the dioxime (8) (6.7 g) in propan-1-ol (650 ml) at a rate which maintained the solution at gentle reflux. The mixture was boiled for a further 1 h, then cooled and washed with saturated sodium chloride solution (2 × 250 ml). The organic phase was concentrated to low volume under reduced pressure and ether was added. The ether solution was washed with water until neutral, dried (Na_2SO_4), and hydrogen chloride was bubbled through the solution. The precipitate was filtered off, suspended in ether, aqueous potassium hydroxide solution was added, and the suspension was shaken. The ether layer was washed to neutrality with water and dried (Na_2SO_4). Removal of solvent under reduced pressure gave the diamine (1) (4.8 g) as a gum, t_R 0.63, δ 0.55 and 0.89 (each 3 H, s, 13- and 10-Me), 2.55 (1 H, m, $W_{\frac{1}{2}}$ 18 Hz, 3α-H), and 3.00 (1 H, m, $W_{\frac{1}{2}}$ 18 Hz, 11β-H).

Hydrogen chloride was bubbled through a cooled solution of this gum (3.0 g) in methanol–water (2 : 1; 30 ml) for several minutes, and the solution was concentrated to low volume by distillation to afford the *diamine dihydrochloride* (1.4 g) as needles, sublimes; too insoluble to measure the rotation; $\nu_{max.}$ (KCl) 3 450, 3 320—2 500, and 1 970 cm^{-1} (NH_3^+) (Found: C, 64.1; H, 10.35; N, 6.9; Cl, 18.4. $C_{21}H_{40}Cl_2N_2$ requires C, 64.4; H, 10.3; N, 7.15; Cl, 18.1%). Regeneration of the free diamine gave an intractable gum comparable (n.m.r.) to that described above.

3β-*Hydroxy*-5α-*pregnan*-11-*one* (9).—Sodium borohydride (5 g) was added portionwise during 10 min to a stirred solution of dione (7) (25 g) in tetrahydrofuran (700 ml) and the suspension was stirred at room temperature for 6 h. Acetic acid was added cautiously and the reaction mixture was poured into water. The precipitate was removed by filtration, dissolved in ether, and washed with sodium hydrogencarbonate solution and then with water until neutral. The solution was dried and the solvent removed under reduced pressure. Recrystallisation from methanol–water afforded the *keto-alcohol* (9) (20 g) as needles, m.p. 132—136 °C; $[\alpha]_D$ +60° (*c* 1.1); $\nu_{max.}$ 3 610, 3 450 (OH), and 1 700 cm^{-1} (C=O); δ 0.50 and 0.99 (each 3 H, s, 13- and 10-Me), 1.50 (1 H, m, O*H*), and 3.55 (1 H, m, $W_{\frac{1}{2}}$ 20 Hz, 3α-H) (Found: C, 79.1; H, 11.0. $C_{21}H_{34}O_2$ requires C, 79.2; H, 10.8%).

11-*Oxo*-5α-*pregnan*-3β-*yl Toluene*-p-*sulphonate* (10).—A solution of the keto-alcohol (9) (12 g) and toluene-*p*-sulphonyl chloride (13 g) in pyridine (150 ml) was set aside for 40 h at 4 °C, and then poured into water at 0 °C. After stirring for 2 h, the gummy precipitate solidified. It was filtered off, dried, and recrystallised from methanol to give the *toluene*-p-*sulphonate* (10) (16 g) as needles, m.p. 139—142 °C; $[\alpha]_D$ +27° (*c* 0.9); $\nu_{max.}$ 1 705 (C=O), 1 599 (aromatic), 1 355, 1 190, and 1 175 cm^{-1} (SO_2); δ 0.50 and 0.98 (each 3 H, s, 13- and 10-Me), 2.42 (3 H, s, C_6H_4-*Me*), 4.35 (1 H, m, $W_{\frac{1}{2}}$ 18 Hz, 3α-H), and 7.29 and 7.75 (4 H, AB quartet, *J* 7 Hz, C_6H_4) (Found: C, 71.4; H, 8.75; O, 13.8. $C_{28}H_{40}O_4S$ requires C, 71.15; H, 8.55; O, 13.55%).

3α-*Azido*-5α-*pregnan*-11-*one* (11).—Sodium azide (15 g) was added to a solution of the tosylate (10) (15.7 g) in *N*-methyl-2-pyrrolidone (125 ml) and the mixture was stirred at 100 °C for 2.5 h, then cooled and poured into water at 0 °C. The product (10.8 g), m.p. 93—96 °C, was isolated *via* ether in the usual way. Recrystallisation of a sample from acetone–hexane gave the *azide* (11) as needles, m.p. 96—98 °C; $[\alpha]_D$ +58° (*c* 1.0); $\nu_{max.}$ 3 350, 2 100 (azide), and 1 705 cm^{-1} (C=O); δ 0.52 and 1.01 (each 3 H, s, 13- and 10-Me) and 3.81 (1 H, m, $W_{\frac{1}{2}}$ 9 Hz, 3β-H) (Found: C, 73.45; H, 9.85; N, 12.05. $C_{21}H_{33}N_3O$ requires C, 73.4; H, 9.7; N, 12.25%).

3α-*Amino*-5α-*pregnan*-11β-*ol* (12).—A solution of the azide (11) (4 g) in dry ether (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (3 g) in ether (150 ml) under an atmosphere of nitrogen. When the effervescence had subsided, the mixture was stirred at reflux for 2.5 h, cooled, and then water (5 ml) was added dropwise to the mixture to destroy excess of hydride. After filtration, the ether solution was washed with water and dried (Na_2SO_4). Removal of solvent afforded a colourless solid, which was triturated with ether, and then recrystallised from methanol to furnish the *amino-alcohol* (12) (3.2 g) as needles, m.p. 194—204 °C; $[\alpha]_D$ +38° (*c* 1.0); $\nu_{max.}$ (KCl) 3 210 (NH_2 and OH) and 1 575 cm^{-1} (NH_2); δ ($CDCl_3$–CD_3OD) 0.79 and 1.04 (each 3 H, s, 13- and 10-Me), 3.01 (2 H, s, NH_2), 3.12 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, 3β-H), and 4.29 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, 11α-H) (Found: C, 78.85; H, 11.8; N, 4.1. $C_{21}H_{37}NO$ requires C, 78.95; H, 11.65; N, 4.4%).

3α-*Amino*-5α-*pregnan*-11-*one* (13).—Kiliani reagent [12] (4N; 8 ml) was added dropwise to a stirred solution of the amino-alcohol (12) (3 g) in acetic acid (35 ml) at room temperature, and stirring was continued for a further 30 min. The mixture was poured into a slight excess of potassium hydroxide solution at 0 °C and the precipitated gum was isolated *via* ether in the usual manner to give the crude amino-ketone (13) (2.8 g) as an unstable gum, δ 0.53 and 1.00 (each 3 H, s, 13- and 10-Me), 1.35 (2 H, m, NH_2), 2.15 (2 H, m, C-12 protons), and 3.12 (1 H, m, $W_{\frac{1}{2}}$ 9 Hz, 3β-H), which was immediately converted to the oxime.

3α-*Amino*-5α-*pregnan*-11-*one Oxime* (14).—Hydroxylamine hydrochloride (4 g) was added to a solution of the ketone (13) (2.8 g) in pyridine (45 ml) and water (4.5 ml). The solution was heated at reflux temperature for 22 h, then cooled and poured into water at 0 °C. The precipitate was isolated by filtration and dissolved in methylene chloride–methanol (4 : 1). On washing with water, crystallisation occurred from the organic layer and this was filtered and dried to afford the oxime (14) (2.4 g), m.p. >180 °C (decomp.); $\nu_{max.}$ (KCl) 3 380 (NOH and NH_2) and 1 625 cm^{-1} (C=N); δ (CD_3OD) 0.52 and 1.13 (each 3 H, s, 13- and 10-Me).

3α,11β-*Diamino*-5α-*pregnane* (4).—A solution of the oxime (14) (3.1 g) in acetic acid (150 ml) containing platinum oxide was hydrogenated at room temperature at 150 lb in^{-2} for 24 h. After removal of the catalyst, the solution was concentrated to low volume and poured into an excess of potassium hydroxide solution at 0 °C. The precipitate was filtered off and dissolved in methylene chloride. The solution was washed with brine, and then dried (Na_2SO_4). Removal of solvent under reduced pressure and recrystallisation from ether–hexane gave the *diamine* (4) (2 g) as needles, m.p. 105—118 °C; $[\alpha]_D$ +38.5° (*c* 0.75); $\nu_{max.}$ 1 612 and 1 580 cm^{-1} (NH_2); δ 0.78 and 0.99 (each 3 H, s, 13- and 10-Me), 1.15 (4 H, s, 2 NH_2), 3.16 (1 H, m, $W_{\frac{1}{2}}$ 9 Hz, 3β-H), and 3.48 (1 H, m, $W_{\frac{1}{2}}$ 9 Hz, 11α-H) (Found: C, 79.1; H, 12.0; N, 8.8. $C_{21}H_{38}N_2$ requires C, 79.2; H, 12.0; N, 8.8%).

3α,11α-*Diamino*-5α-*pregnane* (2) *and* 3α,11α-*Diamino*-5α-*pregnane Dihydrochloride*.—Sodium (23 g) was added portionwise to a solution of the oxime (14) (3.4 g) in propan-1-ol (400 ml) at a rate which maintained the reaction at gentle reflux. The mixture was boiled for a further 3 h, then cooled and washed with saturated sodium chloride solution (2 × 50 ml). The organic phase was concentrated under reduced pressure to near dryness and the product isolated *via* ether in the usual manner to afford the diamine (2) (2.6 g) as a colourless solid, t_R 0.60, δ 0.57 and 0.94 (each 3 H, s, 13- and 10-Me).

Hydrogen chloride was bubbled through a solution of the foregoing crude amine in methanol to give, on crystallisation from methanol–ether, the *diamine dihydrochloride* (1.9 g) as prisms, m.p. >300 °C; $[\alpha]_D^{H_2O}$ +10° (*c* 0.9); $\nu_{max.}$ (KCl) 3 400, 1 890, and 1 605 cm^{-1} (NH_3^+); δ (D_2O) 0.56 and 0.96 (each 3 H, s, 13- and 10-Me); δ (free base) (100 MHz; Varian XL-100) 0.57 and 0.94 (each 3 H, s, 13- and 10-Me), 3.02 (1 H, m, $W_{\frac{1}{2}}$ 19 Hz, 11β-H), and 3.16 (1 H, m, $W_{\frac{1}{2}}$ 9 Hz, 3β-H) (Found: C, 64.05; H, 10.45; N, 7.1; Cl, 18.3. $C_{21}H_{40}Cl_2N_2$ requires C, 64.45; H, 10.3; N, 7.15; Cl, 18.1%).

11-*Hydroxyimino*-5α-*pregnan*-3β-*yl Acetate* (16).—Treatment of 3β-acetoxy-5α-pregnan-11-one (15) [13] (2 g) with hydroxylamine hydrochloride (3 g) in pyridine–water (10 : 1; 27.5 ml) as previously described for 3α-amino-5α-pregnan-11-one (13), followed by isolation of the product *via* ether in the usual manner and recrystallisation from methanol, gave the *oxime* (16) (1.08 g) as needles, m.p. 184—190 °C; $[\alpha]_D$ +89° (*c* 1.1); $\nu_{max.}$ 3 590, 3 400 (OH), 1 728 (C=O), and 1 642 cm^{-1} (OH); δ 0.52 and 1.06 (each 3 H, s, 13- and 10-Me), 1.97 (3 H, s, COMe), 4.62 (1 H, m, $W_{\frac{1}{2}}$ 15 Hz, 3α-H), and 6.87 (1 H, s, OH) (Found: C, 73.4; H, 9.75; N, 3.4. $C_{23}H_{37}NO_3$ requires C, 73.55; H, 9.9; N, 3.7%).

11β-*Amino*-5α-*pregnan*-3β-*yl Acetate* (18).—A solution of the oxime (16) (4.5 g) in acetic acid (200 ml) containing platinum oxide was hydrogenated at room temperature at 140 lb in^{-2} for 7 h. After removal of the catalyst, the solution was concentrated to low volume and poured into an excess of potassium hydroxide solution at 0 °C. The gummy precipitate was isolated *via* ether in the usual way to afford the amine (18) (4.1 g) as a gummy solid, t_R 1.00; δ 0.79 and 1.05 (each 3 H, s, 13- and 10-Me), 1.99 (3 H, s, COMe), 3.45 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, 11α-H), and 4.73 (1 H, m, $W_{\frac{1}{2}}$ 20 Hz, 3α-H).

11β-*Amino*-5α-*pregnan*-3β-*ol* (19).—To a solution of the amino-acetate (18) (4 g) in methanol (100 ml) was added potassium hydroxide solution (10N; 100 ml) and the mixture was refluxed for 40 min. The reaction mixture was concentrated under reduced pressure to low volume and the residue partitioned between ether and saturated sodium chloride solution. The ether layer was washed to neutrality with brine and dried (Na_2SO_4). Removal of solvent afforded the crude product (3.8 g). G.l.c. showed a main peak (t_R 0.61) and several percent of each of two impurities (t_R 0.57 and 0.97).

Hydrogen chloride was bubbled through a solution of the crude product in tetrahydrofuran (20 ml) for 10 min, followed by dropwise addition of water. The finely divided solid which precipitated was separated by filtration and found (g.l.c. analysis) to consist of the two impurities. Treatment of the filtrate with sodium hydroxide solution gave the *amino-alcohol* (19) (2 g), m.p. 182—184 °C. Recrystallisation from ether–methanol–hexane furnished an analytical sample as needles, m.p. 183—185 °C; $[\alpha]_D$ +32° (*c* 1.0); $\nu_{max.}$ 3 602 (OH and NH_2) and 1 610 cm^{-1} (NH_2); δ 0.79 and 1.02 (each 3 H, s, 13- and 10-Me), 1.27 (2 H, s, NH_2), and 3.3—3.8 (2 H, m, 3α-H and 11α-H) (Found: C, 78.75; H, 11.7; N, 4.45. $C_{21}H_{37}NO$ requires C, 78.95; H, 11.65; N, 4.4%).

11β-*Amino*-5α-*pregnan*-3-*one* (20).—Kiliani reagent [12] (4N; 5 ml) was added dropwise to a stirred solution of the amino-alcohol (19) (2 g) in acetic acid (20 ml) at room temperature and stirring was continued for a further 10 min. The mixture was poured into a slight excess of potassium hydroxide solution at 0 °C, and the product was isolated *via* methylene chloride in the usual manner to give the unstable amino-ketone (20) (1.7 g) as an amorphous solid which decomposed on heating; $\nu_{max.}$ 1 710 cm^{-1} (C=O); δ 0.82 and 1.26 (each 3 H, s, 13- and 10-Me).

11β-*Amino*-5α-*pregnan*-3-*one Oxime* (21).—To a solution of the above ketone (20) (1.7 g) in methanol (150 ml) and water (10 ml) was added hydroxylamine hydrochloride (560 mg) and potassium hydrogencarbonate (700 mg) and the mixture was stirred at reflux under nitrogen for 1.5 h. The reaction mixture was concentrated under reduced pressure and poured into water at 0 °C. The precipitate obtained was filtered off and isolated *via* ether in the usual manner to afford the *oxime* (21) (1.7 g); m.p. 128—145 °C; two spots on t.l.c. [dichloroethane–ether–methanol–water (77 : 15 : 8 : 1) on alumina] due to the *syn* and *anti* forms of the oxime; $\nu_{max.}$ (KCl) 3 450 (OH and NH_2) and 1 650 cm^{-1} (C=N).

3β,11β-*Diamino*-5α-*pregnane* (3) *and* 3β,11β-*Diamino*-5α-*pregnane Dihydrochloride*.—A solution of oxime (21) (1.6 g) in propan-1-ol (100 ml) was treated with sodium (6 g) as described for oxime (14) and the product was isolated by partitioning between ether and saturated sodium chloride solution to afford, on removal of solvent, the crude diamine (3) (1.35 g). This was dissolved in methanol and hydrogen chloride was bubbled through for 5 min. Concentration of the solution to low volume gave the *diamine dihydrochloride monohydrate* (720 mg), sublimes above 300 °C; $[\alpha]_D^{H_2O}$ +21° (*c* 0.9); $\nu_{max.}$ (KCl) 3 440 and 1 605 cm^{-1} (NH_3^+); δ (free base) (100 MHz; Varian XL-100) 0.81 and 1.02 (each 3 H, s, 13- and 10-Me), 2.64 (1 H, m, $W_{\frac{1}{2}}$ 19 Hz, 3α-H), and 3.48 (1 H, m, $W_{\frac{1}{2}}$ 9.5 Hz, 11α-H) (Found: C, 61.8; H, 10.05; N, 6.8; Cl, 17.4. $C_{21}H_{42}Cl_2N_2O$ requires C, 61.6; H, 10.35; N, 6.85; Cl, 17.3%).

11α-*Amino*-5α-*pregnan*-3β-*ol* (17) *and* 11α-*Amino*-5α-*pregnan*-3β-*ol Hydrochloride Monohydrate*.—A solution of the oxime (16) (14 g) in propan-1-ol (1.5 l) was treated with sodium (90 g) as described above to afford crude amino-alcohol (17) (12 g) as an amorphous solid, t_R 0.63; δ 0.57 and 0.92 (each 3 H, s, 13- and 10-Me), 1.46 (2 H, s, NH_2), and 3.02 (1 H, m, $W_{\frac{1}{2}}$ 20 Hz, 11β-H).

Hydrogen chloride was passed through a solution of the above amino-alcohol (3 g) in methanol (30 ml) and the resultant hydrochloride was recrystallised twice from methanol–ether to afford analytically pure *amine hydrochloride, monohydrate* (1.2 g), sublimes; $[\alpha]_D$ [$CHCl_3$–MeOH (1 : 1)] −1° (*c* 0.9); $\nu_{max.}$ (KCl) 3 360 and 3 250 cm^{-1} (NH_3^+ and OH); δ ($CDCl_3$–CD_3OD) 0.59 and 0.97 (each 3 H, s, 13- and 10-Me) (Found: C, 67.75; H, 11.05; N, 3.7; Cl, 9.15. $C_{21}H_{40}ClNO_2$ requires C, 67.45; H, 10.8; N, 3.75; Cl, 9.5%).

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