Aminosteroids. Part 8.[1] Synthesis of the Four Isomeric 3,7-Diamino-5α-pregnanes

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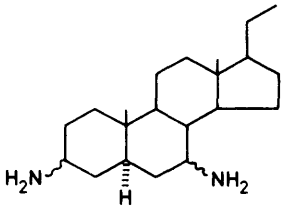
The preparation of the four isomeric 3,7-diamino-5α-pregnanes is reported. All four were prepared from pregnenolone by way of 7-oxo-5α-pregnan-3β-yl acetate. The equatorial amino-groups (3β- and 7β-) were formed by alkali-metal reduction of the oximes and the axial amino-groups by reduction of the azides with lithium aluminium hydride.

As part of a programme to evaluate the biological activity of aminosteroids, we have investigated 3,7-diamino-5α-pregnanes (1)—(4). The synthesis and the precursors of each compound and the intermediates involved are described herein. Structures of the compounds were deduced from their geneses and confirmed by ^{1}H n.m.r. spectroscopy.

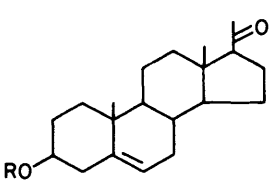


(1) 3α,7α
(2) 3β, 7β
(3) 3α,7β
(4) 3β, 7α

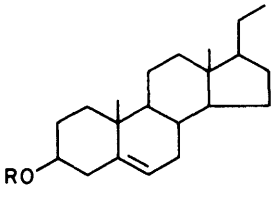
There are several methods [2-7] for introducing an oxygen function at the 7-position of the steroid and a modification of the method of Marshall and his co-workers [2] for converting pregnenolone acetate (6) into the 7-oxo-derivative was applied to the acetate (8). Thus, reduction of pregnenolone (5) by the Huang-Minlon procedure [8] gave the known pregn-5-en-3β-ol (7) [8,9] which, in turn, gave the acetate (8).[9] Treatment of the latter with anhydrous sodium chromate in acetic acid, acetic anhydride, and carbon tetrachloride furnished the 7-oxo-pregn-5-en-3β-yl acetate (9) in good yield. The observed values (δ 0.55 and 1.18) for the 18-H and 19-H respectively of compound (9) are in agreement with the Zurcher values [10] (δ 0.59 and 1.19) and a singlet at δ 5.65 confirms the presence of the C-6 olefinic proton. The u.v. absorption ($\lambda_{max.}$ 234 nm, ε 13 200) also agrees with the assigned structure.

Hydrogenation of the enone (9) over a palladium catalyst afforded the expected [11,12] 7-oxo-5α-pregnan-3β-yl acetate (10). The 5α-configuration was confirmed by the observed value of δ 1.07 for 19-H which is in agreement with the Zurcher value [10] of δ 1.11 and is significantly different from the calculated value of δ 1.25 for the 5β-isomer.

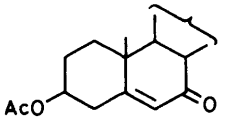
Reduction of the 7-ketone (10) with sodium and pentan-1-ol afforded a mixture of diols. Since this process is known to favour formation of the equatorial hydroxy-group,[13] the major component (53% after fractional crystallisation) was assigned the diequatorial 3β,7β-diol structure (11). This was confirmed by the ^{1}H n.m.r. spectrum in which the broad signal at δ 2.95—3.90 (2H) established the axial character of the hydrogen atoms at C-3 and C-7.[10] The minor component (16%), formulated as the 3β,7α-diol (12), shows a broad signal centred



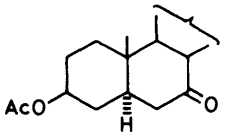
(5) R = H
(6) R = Ac



(7) R = H
(8) R = Ac

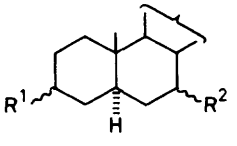


(9)

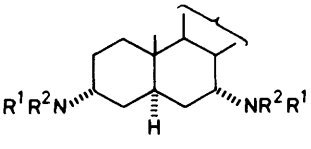


(10)

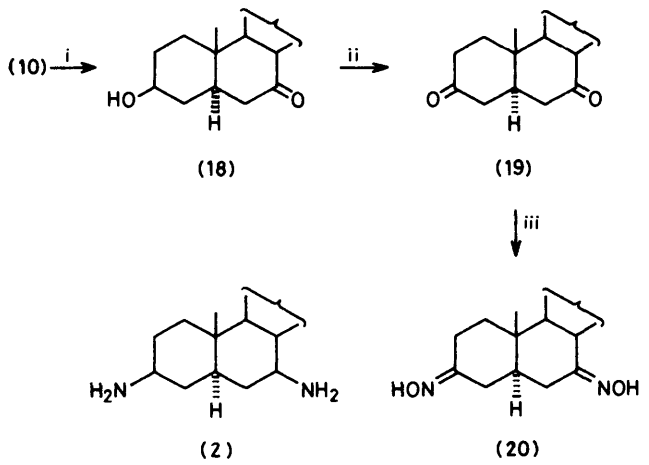
at δ 3.63 ($W_{\frac{1}{2}}$ *ca.* 26 Hz) and a sharper signal at δ 3.81 ($W_{\frac{1}{2}}$ *ca.* 7 Hz).[10] The diol (11) was converted into the ditosylate (13) and thence with sodium azide to the 3α,7α-diazido-5α-pregnane (14). The widths at half-height of the signals at δ 3.69 ($W_{\frac{1}{2}}$ 6 Hz) and δ 3.89 ($W_{\frac{1}{2}}$ 7 Hz) established that the hydrogen atoms at C-3 and C-7 were equatorial [10] and confirmed that replacement of the tosyloxy-groups was accompanied by inversion. Reduction of the diazide (14) with lithium aluminium hydride afforded 3α,7α-diamino-5α-pregnane (1) which was purified as the dihydrochloride salt. This diamine was converted into the bisdimethylamino-, diacetamido-, and



(11) $R^1 = R^2 = \beta$-OH
(12) $R^1 = \beta$-OH, $R^2 = \alpha$-OH
(13) $R^1 = R^2 = \beta$-OTs
(14) $R^1 = R^2 = \alpha$-N_3



(15) $R^1 = R^2$ = Me
(16) R^1 = H, R^2 = Ac
(17) R^1 = H, R^2 = CHO



SCHEME 1 *Reagents:* i, KOH–MeOH; ii, H_2CrO_4–Me_2CO; iii, $NH_2OH{\cdot}HCl$–C_5H_5N; iv, Na–Pr^nOH

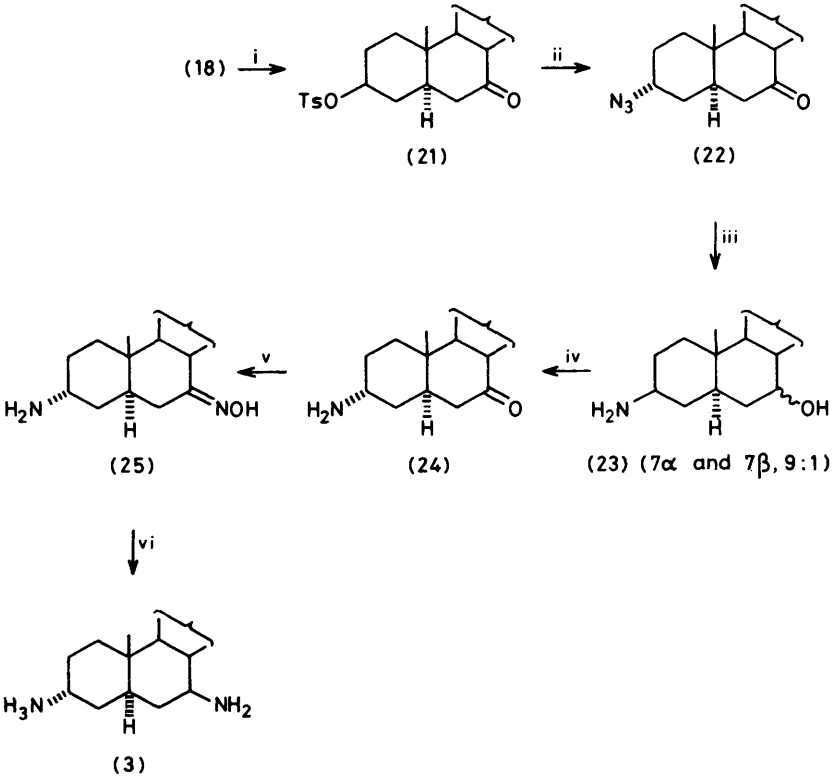
diformamido-derivatives (15)—(17) by standard procedures.

3β,7β-Diamino-5α-pregnane (2) was prepared by the route described in Scheme 1. The diamine was assigned the 3β,7β-diequatorial structure on the basis of the known preference for equatorial amine formation when oximes are reduced with sodium and alcohol,[14] and this was confirmed by the ^{1}H n.m.r. spectrum. When the methine proton of the >CHNH$_2$ grouping is equatorial, it is subject to smaller coupling and resonates at lower field than the axial proton.[10,15,16] For the diamine (2), the broad signals for the C-3 and C-7 methine protons over δ 2.22—2.82 occur upfield of the corresponding signals [δ 2.95 ($W_{\frac{1}{2}}$ 8 Hz) and 3.15 ($W_{\frac{1}{2}}$ 9 Hz)] in the spectrum of the 3α,7α-diamine (1).

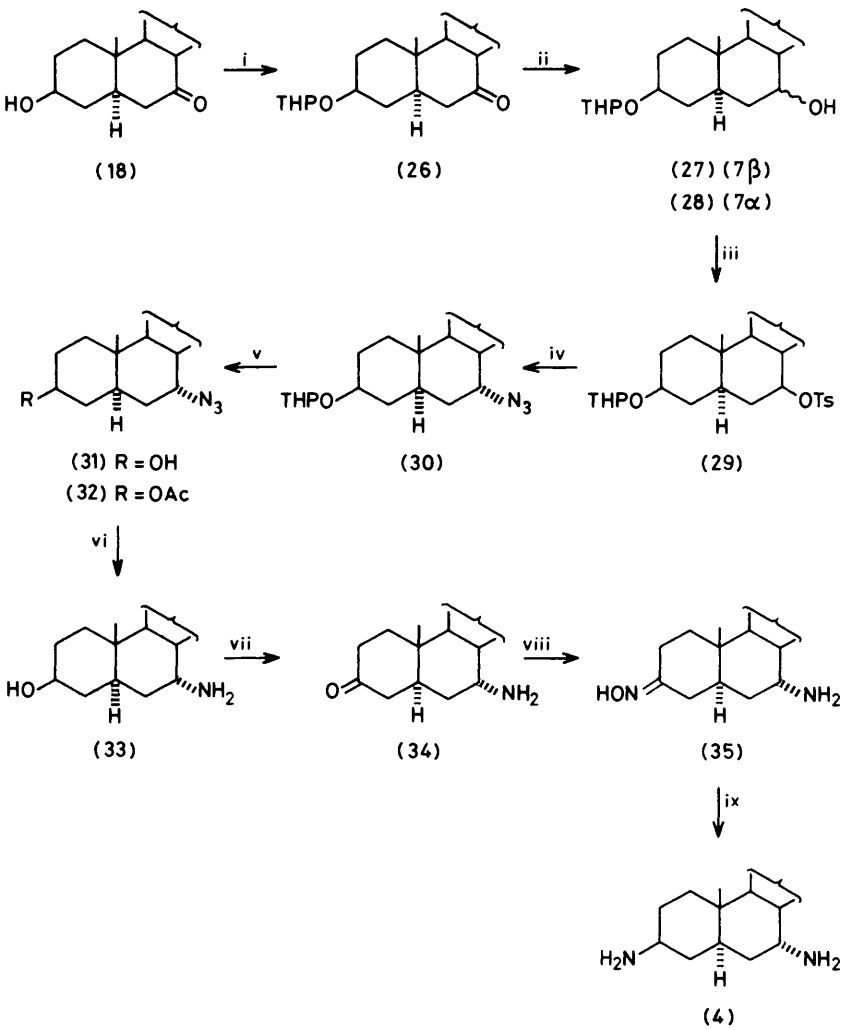
The route employed for the preparation of 3α,7β-diamino-5α-pregnane (3) is outlined in Scheme 2. The half-band width (8 Hz) of the signal for 3-H (δ 3.90) in the ^{1}H n.m.r. spectrum of the azide (22) confirmed that inversion occurred during replacement of the tosyloxy-group of (21) by azide. The 3-amino-group in structure (3) is therefore designated as axial. The 7-amino-function in compound (3) was derived from the oximino-group of compound (25) by reduction with sodium and alcohol and is assigned the β-configuration.[14] Confirmation of these assignments to the diamine (3) was obtained from the ^{1}H n.m.r. spectrum. Signals at δ 3.20 ($W_{\frac{1}{2}}$ 9 Hz) and δ 2.40 ($W_{\frac{1}{2}}$ 33 Hz) are due to the C-3 equatorial and C-7 axial hydrogen atoms respectively.

Scheme 3 outlines the route used to prepare the 3β,7α-diamine (4). Protection of the ketol (18) as the tetrahydropyranyl ether (26) and then reduction with sodium and pentan-1-ol[13] furnished a mixture of epimeric 7-hydroxy-derivatives (27) and (28). Tosylation of the mixture and crystallisation of the product gave the required 7β-tosylate (29) which was converted into the 7α-azido-derivative (30). The inversion was confirmed by the half-height width of the ^{1}H n.m.r. signal for the C-7 proton (δ 3.68, $W_{\frac{1}{2}}$ *ca.* 7 Hz).

Hydrolysis of the tetrahydropyranyl ether (30) in



SCHEME 2 *Reagents:* i, *p*-$MeC_6H_4{\cdot}SO_2Cl$–C_5H_5N; ii, NaN_3; iii, $LiAlH_4$; iv, H_2CrO_4–AcOH; v, $NH_2OH{\cdot}HCl$–$NaHCO_3$–MeOH–H_2O; vi, Na–Pr^nOH



SCHEME 3 *Reagents:* i, dihydropyran–*p*-$MeC_6H_4{\cdot}SO_3H$–C_6H_6; ii, Na–Pent^{n}OH; iii, *p*-$MeC_6H_4SO_2Cl$–C_5H_5N; iv, NaN_3; v, AcOH–H_2O; vi, $LiAlH_4$; vii, H_2CrO_4–AcOH; viii, $NH_2OH{\cdot}HCl$–$NaHCO_3$–MeOH–H_2O; ix, Na–Pr^{n}OH

aqueous acetic acid gave the 3β-hydroxy-derivative (31) accompanied by the 3-acetate (32) (i.r.). Reduction of the mixture with lithium aluminium hydride gave 7α-amino-5α-pregnan-3β-ol (33) which was elaborated by treatment with Kiliani reagent,[17] hydroxylamine and then sodium and propan-1-ol to the diamine (4). The structural assignment of compound (4) was supported by the resonances for the C-3 and C-7 methine protons at δ 2.65 ($W_{\frac{1}{2}}$, 19 Hz) and δ 2.97 ($W_{\frac{1}{2}}$, 7 Hz) respectively.

EXPERIMENTAL

Unless otherwise stated, m.p.s were determined with a Kofler hot-stage apparatus i.r. spectra were measured for solutions in methylene dichloride 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 indicated to the contrary. Concentrations (*c*) are quoted in g per 100 ml. Ether refers to diethyl ether throughout.

Pregn-5-en-3β-ol (7).—The alcohol (7) was prepared from pregnenolone (5) in 71% yield by the method described by Huang-Minlon,[8] m.p. 133—134 °C, $[\alpha]_D$(EtOH) −45.5° (lit.,[8] m.p. 133—134 °C, $[\alpha]_D$ −46°).

Pregn-5-en-3β-yl Acetate (8).—Acetylation of the alcohol (7) with acetic anhydride and pyridine gave, in 75% yield, the acetate (8), m.p. 148—150 °C, $[\alpha]_D$ −61.05° (*c* 1.55) [lit.,[9] m.p. 147—148 °C, $[\alpha]_D$ −62° (*c* 3.66)].

7-*Oxopregn-5-en-3β-yl Acetate* (9).—The acetate (8) (76 g) was dissolved in carbon tetrachloride at 35 °C. Acetic acid (500 ml) and acetic anhydride (200 ml) were added and then anhydrous sodium chromate (130 g) was added portionwise with stirring at such a rate that the temperature of the solution did not exceed 40 °C. The reaction mixture was maintained at 40 °C with stirring for 18 h and then poured into water (2 l). Isolation with methylene dichloride gave a solid (66.4 g) which was chromatographed on a column of alumina. Elution with methylene dichloride afforded a colourless solid which recrystallised from methylene dichloride–methanol to furnish the *ketone* (9) (46.9 g) as needles, m.p. 212—213.5 °C; $[\alpha]_D$ −108° (*c* 0.99); $\lambda_{max.}$ 234 nm (ε 13 200); $\nu_{max.}$ 1 735 (OAc), 1 670 (C=O) and 1 636 cm^{-1} (C=C); δ 0.55 and 1.18 (each 3 H, s, 13- and 10-Me), 1.99 3 H, s, 3β-OAc), 4.70 (1 H, m, $W_{\frac{1}{2}}$ 21 Hz, 3α-H), and 5.65

(1 H, s, 6-H) (Found: C, 76.8; H, 9.7. $C_{23}H_{34}O_3$ requires C, 77.05; H, 9.6%).

7-Oxo-5α-pregnan-3β-yl Acetate (10).—A solution of the ketone (9) (48 g) in tetrahydrofuran (2.09 l) and methanol (110 ml) was hydrogenated with 5% palladium on charcoal as catalyst (10 g) at room temperature until 3.14 l of hydrogen had been absorbed. The catalyst was removed and the solution was evaporated to dryness. The residual solid (47.5 g) was recrystallised from methylene dichloride–methanol to furnish the *ketone* (10) (40.4 g) as plates, m.p. 187—188.5 °C; $[\alpha]_D$ +46.8° (*c* 2.41); $\nu_{max.}$ 1 730 (OAc) and 1 710 cm^{-1} (C=O); δ 0.53 and 1.07 (each 3 H, s, 13- and 10-Me), 1.96 (3 H, s, 3β-OAc) and 4.60 (1 H, m, $W_{\frac{1}{2}}$ 20 Hz, 3α-H) (Found: C, 76.45; H, 10.1. $C_{23}H_{36}O_3$ requires C, 76.6; H, 10.1%).

5α-Pregnane-3β,7β-diol (11) *and 5α-Pregnane-3β,7α-diol* (12).—Freshly cut sodium (5.5 g) was added portionwise during 1 h to a gently boiling solution of the ketone (10) (10 g) in n-pentyl alcohol (1 l) and the mixture was heated under reflux for a further 1 h. Water was added, the n-pentyl alcohol was removed as an azeotrope under reduced pressure, and the product was isolated in the usual manner *via* ether extraction. Recrystallisation of the resultant solid (9 g) from ether afforded the *diol* (11) (5.34 g) as needles, m.p. 165—168 °C; $[\alpha]_D$ +52° (*c* 0.57); $\nu_{max.}$ 3 640 and 3 610 cm^{-1} (OH); δ 0.55 and 0.81 (each 3 H, s, 13- and 10 Me) and 2.95—3.90 (2 H, m, $W_{\frac{1}{2}}$ 29 Hz, 3α- and 7α-H) (Found: C, 78.8; H, 11.5. $C_{21}H_{36}O_2$ requires C, 78.7; H, 11.3%). Further crystallisations from ether of the mother-liquor afforded the *diol* (12) (1.6 g) as plates, m.p. 195—197 °C, $[\alpha]_D$ −2° (*c* 1.0); $\nu_{max.}$ 3 610 and 3 530—3 330 cm^{-1} (OH); δ 0.52 and 0.78 (each 3 H, s, 13- and 10-Me), 3.63 (1 H, m, $W_{\frac{1}{2}}$ 26 Hz, 3α-H), and 3.81 (1 H, m, $W_{\frac{1}{2}}$ 7 Hz, 7β-H) (Found: C, 78.6; H, 11.4. $C_{21}H_{36}O_2$ requires C, 78.7; H, 11.3%).

5α-Pregnane-3β,7β-diyl Ditosylate (13).—A solution of the diol (11) (2.5 g) and toluene-*p*-sulphonyl chloride (5 g) in pyridine (30 ml) was allowed to stand at 5 °C for 18 h; it was then poured onto ice and the precipitated solid was filtered off. The dried solid (4.88 g) was recrystallised from acetone–hexane to give the ditosylate (13) (3.9 g) as needles, m.p. 93—126 °C (decomp); δ 0.50 and 0.78 (each 3 H, s, 13- and 10-Me) and 4.12—4.58 (2 H, m, $W_{\frac{1}{2}}$ 24 Hz, 3α- and 7α-H).

3α,7α-Diazido-5α-pregnane (14).—Sodium azide (4.64 g) was added to a solution of the ditosylate (13) (2.9 g) in *N*-methyl-2-pyrrolidone (29 ml) and the mixture was stirred at 90 °C for 2 h. The cooled reaction mixture was poured into water, and the product was isolated *via* ether extraction. The crude solid (1.58 g) on recrystallisation from ether–methanol gave the *diazide* (14) (1.38 g) as needles, m.p. 151—154 °C; $[\alpha]_D$ −100° (*c* 0.9); $\nu_{max.}$ 2 100 cm^{-1} (azides); $\nu_{max.}$ (KCl) 2 110 and 2 058 cm^{-1} (azides); δ 0.55 and 0.80 (each 3 H, s, 13- and 10-Me), 3.69 (1 H, m, $W_{\frac{1}{2}}$ 7 Hz, 7β-H) and 3.89 (1 H, m, $W_{\frac{1}{2}}$ 7 Hz, 3β-H) (Found: C, 68.15; H, 9.3; N, 22.4. $C_{21}H_{34}N_6$ requires C, 68.1; H, 9.25; N, 22.7%).

3α,7α-Diamino-5α-pregnane (1) *and 3α,7α-Diamino-5α-pregnane Dihydrochloride Monohydrate*.—A solution of the diazide (14) (1.3 g) in dry tetrahydrofuran (40 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1 g) in dry tetrahydrofuran (25 ml). When the effervescence had subsided the mixture was heated under reflux for 2 h, and then water–tetrahydrofuran (10% v/v) was added dropwise to the cooled mixture to destroy excess of hydride. After filtration, the solvent was removed under reduced pressure and the residual gum was dissolved in ether, washed with brine, and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded the diamine (1) (980 mg) as a non-crystallisable gum, δ 0.56 and 0.79 (each 3 H, s, 13- and 10-Me), 1.53 (4 H, s, 3α- and 7α-NH_2), 2.95 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, 7β-H), and 3.15 (1 H, m, $W_{\frac{1}{2}}$ 9 Hz, 3β-H).

Dry hydrogen chloride was bubbled slowly through a solution of the diamine (900 mg) in methylene dichloride (100 ml) for 30 min. The solution was concentrated under reduced pressure and dry ether was added. The precipitated solid was recrystallised from methylene dichloride–ether to give the *diamine dihydrochloride monohydrate* (1.16 g) as needles, m.p. >260 °C (decomp.); $[\alpha]_D$ −4.2° (*c* 1.06); $\nu_{max.}$ 2 000, 1 600, and 1 510 cm^{-1} (NH_3^+); $\nu_{max.}$ (KCl) 2 560, 1 990, 1 600, and 1 515 cm^{-1} (NH_3^+) (Found: C, 61.9; H, 10.5; Cl, 17.1; N, 6.2. $C_{21}H_{38}N_2 \cdot 2HCl \cdot H_2O$ requires C, 61.6; H, 10.3; Cl, 17.3; N, 6.8%).

3α,7α-Bisdimethylamino-5α-pregnane (15) *and 3α,7α-Bisdimethylamino-5α-pregnane Dihydrochloride·0.50 Water*.—Formic acid (3 ml) was added to a solution of the diamine (1) (2.5 g) in formalin (3 ml) and the solution was boiled under reflux for 4 h. The mixture was poured into water and filtered. The filtrate was made strongly alkaline by addition of aqueous potassium hydroxide and the resultant precipitate was filtered off, washed with water, and dried. Hydrogen chloride was bubbled through a cooled, stirred solution of the crude diamine (2.7 g) in methylene dichloride–methanol (100 ml, 9 : 1) for several minutes. The solution was concentrated under reduced pressure, ether was added, and the precipitated solid was recrystallised from methanol–ether to yield the *diamine dihydrochloride·0.50 water* (2.2 g) as needles, charring above 240 °C; $[\alpha]_D$ (EtOH) − 6.6° (*c* 0.97); $\nu_{max.}$ (KCl) 3 400 (H_2O), 2 850 (N–CH_3), 2 680 (NH^+) and 1 630 cm^{-1} (H_2O) (Found: C, 65.7; H, 10.55; Cl, 15.2; N, 6.1. $C_{25}H_{46}N_2 \cdot 2HCl \cdot 0.5H_2O$ requires C, 65.7; H, 10.8; Cl, 15.5; N, 6.15%).

Treatment of the dihydrochloride salt with aqueous potassium hydroxide regenerated in quantitative yield the free diamine (15), δ 0.54 and 0.80 (each 3 H, s, 13- and 10-Me) and 2.19 and 2.33 (each 6 H, s, 3α- and 7α-NMe_2).

3α,7α-Diacetamido-5α-pregnane·0.26 Water (16).—A solution of the diamine (1) (2.5 g) in pyridine (25 ml) and acetic anhydride (1.5 ml) was allowed to stand at 0 °C for 20 min; it was then poured into water and the aqueous mixture was extracted first with ether then with toluene. The combined extracts were washed successively with hydrochloric acid, water, aqueous sodium hydrogen carbonate and water and then dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a solid (2.5 g) which was recrystallised from aqueous methanol to yield the *diacetamide* (16) (2.32 g) as needles, m.p. 303.5—306 °C (crystalline form changed above 240 °C); $[\alpha]_D$ −29.5° (*c* 1.23); $\nu_{max.}$ 3 660 (H_2O), 3 450, 3 400, 1 670, 1 510 (CONH), and 1 375 cm^{-1} ($COCH_3$); δ 0.55 and 0.81 (each 3 H, s, 13- and 10-Me), 1.94 and 1.96 (each 3 H, s, 3α- and 7α-$NHCOCH_3$), 3.85—4.35 (2 H, m, 3β- and 7β-H), and 5.90 (2 H, m, 3α- and 7α-$NHCOCH_3$) (Found: C, 73.7; H, 10.6; N, 6.75. $C_{25}H_{42}N_2O_2 \cdot 0.26H_2O$ requires C, 73.7; H, 10.5; N, 6.8%).

3α,7α-Diformamido-5α-pregnane·0.876 Water (17).—A solution of diamine (1) (2.5 g) in formic acid (98%; 15 ml) and formamide (25 ml) was refluxed for 5 h and then cooled and poured into water. The precipitated solid was filtered off, washed with water, and recrystallised from aqueous methanol to afford the *diformamide* (17) (2.6 g) as needles, m.p. 143—146 °C; $[\alpha]_D$ −40.6° (*c* 0.8); $\nu_{max.}$ 3 690 (H_2O),

3 440 and 3 410 (CONH), 3 300 (CONH and H_2O), 1 685 (CONH), 1 610 (H_2O), and 1 530 and 1 500 cm^{-1} (CONH); δ(C_5D_5N) 0.52 and 0.77 (each 3 H, s, 13- and 10-Me), 4.15—4.60 (2 H, m, 3β- and 7β-H), 8.15 (2 H, m, 3α- and 7α-N*H*COH), and 8.40 (2 H, s, 3α- and 7α-NHCO*H*) (Found: C, 70.8; H, 10.3; N, 7.2; O, 11.55. $C_{23}H_{38}N_2O_2 \cdot 0.875H_2O$ requires C, 70.8; H, 10.3; N, 7.2; O, 11.8%).

3β-*Hydroxy*-5α-*pregnan*-7-*one* (18).—A solution of potassium hydroxide (10 g) in methanol (200 ml) was added dropwise to a boiling solution of the ketone (9) (30 g) in tetrahydrofuran (200 ml) and methanol (100 ml) under an atmosphere of nitrogen. The mixture was boiled for a further 1 h and then concentrated under reduced pressure and diluted with water. The resultant precipitate was filtered off and isolated *via* ether extraction to afford a solid (26 g), which on recrystallisation from ether–hexane gave the *ketol* (18) (25.26 g) as needles, m.p. 178.5—179.5 °C; $[\alpha]_D$ −50.5° (*c* 1.13); $\nu_{max.}$ 3 610 and 3 460 (OH) and 1 705 cm^{-1} (C=O); δ 0.52 and 1.05 (each 3 H, s, 13- and 10-Me), 1.74 (1 H, s, 3β-OH), and 3.55 (1 H, m, $W_{\frac{1}{2}}$ 24 Hz, 3α-H) (Found: C, 79.5; H, 10.9. $C_{21}H_{34}O_2$ requires C, 79.2; H, 10.8%).

5α-*Pregnane*-3,7-*dione* (19).—Jones reagent (6.24 N; 11.2 ml) was added dropwise to a stirred solution of the ketol (18) (10 g) in acetone (250 ml) at 0 °C and the stirred mixture was set aside until conversion into the dione was complete (t.l.c.). Methanol was added to destroy the excess of reagent and the solution was concentrated under reduced pressure and then poured into water. The precipitate was filtered off, dissolved in ether, and the solution washed with aqueous sodium carbonate and then with water till neutral; it was then dried (Na_2SO_4). Removal of the solvent and recrystallisation of the crude product (10 g) from acetone–hexane gave the *dione* (19) (9.1 g) as platelets, m.p. 170—172 °C; $[\alpha]_D$ −27.4° (*c* 1.15); $\nu_{max.}$ 1 712 cm^{-1} (C=O); δ 0.59 and 1.26 (each 3 H, s, 13- and 10-Me) (Found: C, 79.6; H, 10.3. $C_{21}H_{32}O_2$ requires C, 79.7; H, 10.2%).

5α-*Pregnane*-3,7-*dione Dioxime* (20).—Hydroxylamine hydrochloride (3.3 g) was added to a solution of the dione (19) (6 g) in pyridine (100 ml) and the stirred mixture was heated on a steam-bath for 4 h. The solution was poured into water and the precipitated solid was washed thoroughly with water and then dried. The colourless solid (6.4 g) was recrystallised from methanol to give the *dioxime* (20) (4.7 g) as needles, m.p. 262—264.5 °C (decomp.); $[\alpha]_D$ (pyridine) −24.4° (*c* 1.14); $\nu_{max.}$ (KCl) 3 530 (OH), 1 670, and 1 655 cm^{-1} (C=N); δ (C_5D_5N) 0.64 and 1.05 (each 3 H, s, 13- and 10-Me), and 12.03 and 12.16 (each 1 H, s, 3- and 7-NOH) (Found: C, 72.9; H, 9.85; N, 7.8. $C_{21}H_{34}N_2O_2$ requires C, 72.8; H, 9.9; N, 8.1%).

3β,7β-*Diamino*-5α-*pregnane* (2) *and* 3β,7β-*Diamino*-5α-*pregnane Dihydrochloride*.—Sodium (12 g) was added portionwise to a warm solution of the dioxime (20) (6.1 g) in propan-1-ol (600 ml) at a rate which maintained the solution at gentle reflux. The mixture was boiled for a further 2 h and then cooled and diluted with saturated aqueous sodium chloride (300 ml). The aqueous layer was extracted with ether, and the solvent was removed from the combined organic extracts under reduced pressure. The residue was dissolved in ether, and the solution washed to neutrality with brine and then dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a non-crystallisable gum (5.5 g). Hydrogen chloride was bubbled through a cooled solution of this gum (5 g) in methylene dichloride–methanol (1 : 3 v/v; 800 ml) for several minutes. Removal of the solvent under reduced pressure afforded an orange solid which was recrystallised four times from methanol–ether to yield the *dihydrochloride* salt (1.89 g) as needles, charring above 300 °C; $[\alpha]_D$ (MeOH : H_2O 1 : 1) +40.5° (*c* 0.76); $\nu_{max.}$ (KCl) 3 100, 2 560, 1 965, 1 600, 1 590, 1 509, and 1 502 cm^{-1} (NH_3^+); δ(D_2O) 0.47 and 0.65 (each 3 H, s, 13- and 10-Me) (Found: C, 64.3; H, 10.5; Cl, 18.4; N, 7.25. $C_{21}H_{40}N_2Cl_2$ requires C, 64.4; H, 10.3; Cl, 18.1; N, 7.2%).

Treatment of the dihydrochloride salt with aqueous potassium hydroxide regenerated in quantitative yield the free diamine (2), δ 0.56 and 0.78 (each 3 H, s, 13- and 10-Me) and 2.22—2.82 (2 H, m, $W_{\frac{1}{2}}$ 32 Hz, 3α- and 7α-H).

7-*Oxo*-5α-*pregnan*-3β-*yl Tosylate* (21).—A solution of the ketol (18) (10 g) and toluene-*p*-sulphonyl chloride (9 g) in pyridine (120 ml) was allowed to stand for 7 days at 4 °C and then poured into water at 0 °C. The product was isolated *via* methylene dichloride extraction and recrystallised from methylene dichloride–hexane to give the *tosylate* (21) (14 g) as needles, m.p. 165—168 °C; $[\alpha]_D$ −32.1° (*c* 0.7); $\nu_{max.}$ 1 710 (C=O) and 1 600 and 1 590 cm^{-1} (aromatic); δ 0.53 and 1.05 (each 3 H, s, 13- and 10-Me), 2.42 (3 H, s, C_6H_4–C*H*$_3$), 4.36 (1 H, m, $W_{\frac{1}{2}}$ 24 Hz, 3α-H), 7.35 and 7.77 (4 H, ABq, *J* 8 Hz, C_6H_4) (Found: C, 71.35; H, 8.5; S, 7.0. $C_{28}H_{40}O_4S$ requires C, 71.15; H, 8.5; S, 6.8%).

3α-*Azido*-5α-*pregnan*-7-*one* (22).—Sodium azide (22 g) was added to a solution of the tosylate (21) (20 g) in *N*-methyl-2-pyrrolidone (325 ml) and the mixture was heated under reflux for 4.5 h; it was then cooled and poured into water at 0 °C. The product (14.2 g) was isolated *via* ether extraction. Recrystallisation of the product from ether–methanol gave the *azide* (22) (12.6 g) as needles, m.p. 116—117 °C; $[\alpha]_D$ −52.5° (*c* 0.7); $\nu_{max.}$ 2 105 (N_3) and 1 710 cm^{-1} (C=O); $\nu_{max.}$ (KCl) 2 095 (N_3) and 1 710 cm^{-1} (C=O); δ 0.55 and 1.05 (each 3 H, s, 13- and 10-Me), and 3.90 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, 3β-H) (Found: C, 73.4; H, 9.4; N, 12.5. $C_{21}H_{33}N_3O$ requires C, 73.4; H, 9.7; N, 12.2%).

3α-*Amino*-5α-*pregnan*-7-*ols* (23).—A solution of the azide (22) (6 g) in dry tetrahydrofuran (200 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1 g) in dry tetrahydrofuran under an atmosphere of nitrogen. When the effervescence had subsided the mixture was heated under reflux for 4 h and then water–tetrahydrofuran (10% v/v; 5 ml) was added dropwise to the cooled mixture to destroy excess of hydride. After filtration, the solvent was removed under reduced pressure, and the residual gum was dissolved in ether–benzene and the solution was washed with brine. Removal of the solvent under reduced pressure gave the crude amino-ols (23) (5.5 g) as a gum, $\nu_{max.}$ (KCl) 3 600—3 050 cm^{-1} (OH); δ 0.54 and 0.76 (each 3 H, s, 13- and 10-Me), 1.85 (2 H, s, NH_2), 3.15 (1 H, m, $W_{\frac{1}{2}}$ 9 Hz, 3β-H), 3.44 (0.1 H, m, $W_{\frac{1}{2}}$ 20 Hz, 7α-H), and 3.79 (0.9 H, m, $W_{\frac{1}{2}}$ 6 Hz, 7β-H).

3α-*Amino*-5α-*pregnan*-7-*one* (24).—Kiliani reagent (4N; 10.9 ml) was added dropwise to a stirred solution of the foregoing crude mixture of the alcohols (23) (5.4 g) in acetic acid (125 ml) at room temperature and stirring was continued for a further 30 min. The mixture was poured into a slight excess of aqueous potassium hydroxide at 0 °C and the precipitated solid was isolated *via* ether extraction to give the crude amino-ketone (24) (4.8 g), m.p. 118—123 °C; $\nu_{max.}$ 3 380 (NH_2) and 1 710 cm^{-1} (C=O); $\nu_{max.}$ (KCl) 3 380 (NH_2), 1 710 (C=O), and 1 610 cm^{-1} (NH_2); δ 0.53 and 1.02 (each 3 H, s, 13- and 10-Me), 1.17 (2 H, s, NH_2), and 3.20 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, 3β-H).

3α-*Amino*-5α-*pregnan*-7-*one Oxime* (25).—Hydroxylamine hydrochloride (2 g) and sodium hydrogen carbonate (4.7 g) were added to a solution of the above amino-ketone (24) (4.7 g) in methanol (145 ml) and water (5 ml). The stirred mixture was heated under reflux under an atmosphere of nitrogen for 1.5 h and then cooled, concentrated under reduced pressure, and diluted with water. Recrystallisation of the precipitated solid from aqueous methanol gave the *oxime* (25) (4.22 g) as needles, m.p. 204—207 °C (decomp.); $[\alpha]_D$ −144° (*c* 1.2); $\nu_{max.}$ 3 580 (OH), 1 640 (C=N), and 1 580 cm^{-1} (NH_2); $\nu_{max.}$ (KCl) 3 370 (OH), 3 200 and 3 080 (NH_2), 1 650 (C=N), and 1 580 cm^{-1} (NH_2); δ 0.56 and 0.92 (each 3 H, s, 13- and 10-Me), 2.94 (1 H, m, $W_{\frac{1}{2}}$ 5 Hz, 3β-H), and 4.0 (1 H, m, $W_{\frac{1}{2}}$ 32 Hz, N-OH) (Found: C, 75.95; H, 11.2; N, 8.5. $C_{21}H_{36}N_2O$ requires C, 75.85; H, 10.9; N, 8.4%).

3α,7β-*Diamino*-5α-*pregnane* (3) *and* 3α,7β-*Diamino*-5α-*pregnane Dihydrochloride*.—Sodium (6 g) was added portionwise during 4 h to a boiling solution of the oxime (25) (3.2 g) in propan-1-ol (160 ml) under an atmosphere of nitrogen. The mixture was cooled, diluted with brine, and the aqueous layer extracted with ether. The solvent was removed from the combined organic extracts under reduced pressure and the residue was dissolved in ether and the solution washed with brine and dried (Na_2SO_4). Removal of the solvent gave a non-crystallisable gum (3.1 g) which contained some 3α,7α-diamino-5α-pregnane (1) as impurity. Hydrogen chloride was bubbled through a cooled solution of this gum (3 g) in methylene dichloride for several minutes. The solution was concentrated under reduced pressure, diluted with methanol, and dry ether was added. The precipitated salt was recrystallised from methanol–ether to give a salt (2.6 g), which was converted into the diamine (3) [contaminated with the diamine (1) (^{1}H n.m.r.)]. This mixture (2 g) was chromatographed on basic alumina to afford the *diamine* (3) (470 mg) as a gum, δ 0.58 and 0.78 (each 3 H, s, 13- and 10-Me), 2.40 (1 H, m, $W_{\frac{1}{2}}$ 33 Hz, 7α-H), and 3.20 (1 H, m, $W_{\frac{1}{2}}$ 9 Hz, 3β-H). Treatment with hydrogen chloride as before and recrystallisation from methanol–ether gave the *dihydrochloride monohydrate* (320 mg) as needles, charred above 260 °C; $[\alpha]_D$ (EtOH) +32.6° (*c* 0.65); $\nu_{max.}$ (KCl) 3 400 (H_2O), 2 950, 2 870, 2 000, 1 605, 1 525, and 1510 cm^{-1} (NH_3^+) (Found: C, 61.3; H, 10.1; N, 6.55; O, 4.0. $C_{21}H_{38}N_2{\cdot}2HCl{\cdot}H_2O$ requires C, 61.6; H, 10.3; N, 6.8; O, 3.9%).

7-*Oxo*-5α-*pregnan*-3β-*yl Tetrahydropyranyl Ether* (26).—A mixture of the ketol (18) (24 g) and toluene-*p*-sulphonic acid (960 mg) in dry benzene (500 ml) and dihydropyran (50 ml) was stirred at room temperature for 1.5 h. Potassium hydrogen carbonate (*ca.* 5 g) was added to the mixture which was then washed with water till neutral and dried (Na_2SO_4). Removal of the solvent afforded the tetrahydropyranyl ether (26) (48 g) as a gummy solid, δ 0.55 and 1.08 (each 3 H, s, 13- and 10-Me).

3-*Tetrahydropyranyloxy*-5α-*pregnan*-7β-*yl* 7-*Tosylate* (29).—Sodium (15 g) was added portionwise during 1.5 h to a boiling solution of the ether (26) (48 g) in n-pentyl alcohol (600 ml) under an atmosphere of nitrogen. The cooled mixture was diluted with water and the alcohol was removed as an azeotrope under reduced pressure. The residue was isolated *via* ether extraction to give a mixture (t.l.c.) of the alcohols (27) and (28) (43.5 g), δ 0.56 and 0.72 (each 3 H, s, 13- and 10-Me), 3.20—4.10 (2 H, m, 2-H and 6-H of tetrahydropyran), 3.55 (7α-H), and 3.70 (7β-H). A solution of this mixture (43.5 g) and toluene-*p*-sulphonyl chloride (84 g) in pyridine (450 ml) was maintained at 0 °C for 48 h and poured into water (2 l) at 0 °C; the product was isolated *via* ether extraction to afford a colourless solid (49 g). Recrystallisation of this from acetone–hexane gave a solid (11.3 g) which was washed with methanol to give the *tosylate* (29) (9.2 g), δ 0.53 and 0.80 (each 3 H, s, 13- and 10-Me), 2.42 (3 H, s, $C_6H_4CH_3$), 3.20—4.10 (3 H, m, 2-H and 6-H of tetrahydropyran), 4.50 (2 H, m, $W_{\frac{1}{2}}$ 24 Hz, 3α- and 7α-H), and 7.31 and 7.78 (4 H, ABq *J* 8 Hz, ArH). The mother-liquor contained a substantial quantity of the tosylate (29). The solvent was removed and the residual gum (A) (33 g) was retained for further treatment (see later).

7α-*Azido*-5α-*pregnan*-3β-*yl Tetrahydropyranyl Ether* (30).—A mixture of the tosylate (29) (9 g) and sodium azide (10 g) in *N*-methyl-2-pyrrolidone (250 ml) was stirred at 90 °C for 5 h and was then cooled and poured into water (1 l) at 0 °C. The precipitated solid was isolated *via* ether extraction to give a crude bi-component mixture (6.8 g), which recrystallised from ether–methanol to afford the *azide* (30) (4.87 g) as needles, m.p. 140—144 °C; $\nu_{max.}$ 2 870 (CH–O–CH), 2 100 (N_3), and 1 025 cm^{-1} (C–O–C); δ 0.54 and 0.80 (each 3 H, s, 13- and 10-Me), 3.68 (1 H, m, $W_{\frac{1}{2}}$ *ca.* 7 Hz, 7β-H), and 4.05 (1 H, m, $W_{\frac{1}{2}}$ 20 Hz, 3α-H).

7α-*Amino*-5α-*pregnan*-3β-*ol* (33) *and* 7α-*Amino*-5α-*pregnan*-3β-*ol Hydrochloride*.—A solution of the azide (30) (4.69 g) and toluene-*p*-sulphonic acid (50 mg) in acetic acid (94 ml) and water (19 ml) was heated at 90 °C for 2 h, and then cooled and poured into water (500 ml). The precipitated solid was isolated *via* ether extraction to give a bi-component mixture (t.l.c. and g.l.c.) (4.2 g) of the alcohol (31) (70%) and the acetate (32) (30%), $\nu_{max.}$ 3 580 (OH), 2 100 (N_3) and 1 710 cm^{-1} (OAc); δ 0.52 and 0.80 (each 3 H, s, 13- and 10-Me), 1.99 (0.3 × 3 H, s, OAc), 3.45 (0.7 H, m, $W_{\frac{1}{2}}$ 24 Hz, 3β-H of alcohol), 3.69 (1 H, m, $W_{\frac{1}{2}}$ 7 Hz, 7β-H), and 4.75 (0.3 H, m, $W_{\frac{1}{2}}$ 24 Hz, 3β-H of acetate). A solution of this mixture (4 g) in dry tetrahydrofuran (70 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (2.5 g) in dry tetrahydrofuran (60 ml) at 0 °C under an atmosphere of nitrogen. When the effervescence subsided the mixture was refluxed for 2.5 h. Isolation of the product *via* n-butyl alcohol extraction gave a glass (3 g). Hydrogen chloride was bubbled through a cooled solution of this solid in methylene dichloride (100 ml) at 0 °C for a few minutes. Removal of some of the solvent and addition of dry ether gave a precipitate (2.47 g) which was recrystallised thrice to give the *hydrochloride* (1.7 g) as needles, subliming above 225 °C; $[\alpha]_D$ ($CHCl_3$–MeOH, 1 : 1) −0.9° (*c* 0.53); $\nu_{max.}$ (KCl) 3 350 (OH), 3 020, 2 020, 1 630, and 1 540 cm^{-1} (NH_3^+) (Found: C, 70.6; H, 10.7; Cl, 9.9; N, 4.1. $C_{21}H_{37}NO{\cdot}HCl$ requires C, 70.85; H, 10.7; Cl, 9.95; N, 3.95%).

Treatment of the hydrochloride salt with aqueous potassium hydroxide regenerated in quantitative yield the free *amine* (33) as an amorphous solid δ 0.53 and 0.80 (each 3 H, s, 13- and 10-Me), 1.48 (3 H, s, with shoulder at δ 1.45, NH_2 and OH), 2.97 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, 7β-H), and 3.63 (1 H, m, $W_{\frac{1}{2}}$ 29 Hz, 3α-H).

A further quantity of the amine (33) was obtained from the gum (A). (A) (33 g) was treated with sodium azide (30 g) in *N*-methyl-2-pyrrolidone (600 ml) in the manner previously described, and the product (18.4 g) was reduced with lithium aluminium hydride (6 g) to give the amine (33) (6.5 g) purified by way of the hydrochloride salt.

7α-*Amino*-5α-*pregnan*-3-*one* (34).—Kiliani reagent (4N; 5 ml) was added dropwise to a stirred solution of the amine

(33) (3.1 g) in acetic acid (100 ml) at room temperature and stirring was continued for a further 30 min. Isolation of the product gave the unstable ketone (34) (2.7 g) as needles, charred above 235 °C; $\nu_{max.}$ 1 710 (C=O) and 1 650 cm^{-1} (NH_2).

7α-Amino-5α-pregnan-3-one Oxime (35).—A mixture of the ketone (34) (2.2 g), methanol (68 ml), water (1.9 ml), hydroxylamine hydrochloride (0.9 g), and sodium hydrogen carbonate (2.2 g) was heated under reflux under an atmosphere of nitrogen for 4 h with stirring; it was then concentrated under reduced pressure and poured into water (500 ml). The precipitated solid (2.2 g) was recrystallised from aqueous methanol to furnish the *oxime* (35) (1.7 g) as needles, m.p. 202—206 °C (decomp.); $[\alpha]_D$ −16.5° (*c* 0.95); $\nu_{max.}$ 3 590 (OH), 1 650 (C=N), and 1 580 cm^{-1} (NH_2); δ 0.58 and 0.90 (each 3 H, s, 13- and 10-Me), 3.05 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, 7β-H), and 3.85—4.65 (1 H, m, N-OH) (Found: C, 75.7; H, 10.7; N, 8.3. $C_{21}H_{36}N_2O$ requires C, 75.85; H, 10.9; N, 8.4%).

3β,7α-Diamino-5α-pregnane (4) *and 3β,7α-Diamino-5α-pregnane Dihydrochloride·1.50 Water*.—Sodium (3.6 g) was added portionwise during 4 h to a solution of the oxime (35) (2 g) in boiling propan-1-ol (100 ml) under an atmosphere of nitrogen. The cooled mixture was poured into brine, and the aqueous layer was extracted with ether. The combined organic extract was evaporated to dryness under reduced pressure and the residue was dissolved in ether, washed with brine, and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded the diamine (4) (1.8 g) as a non-crystallisable gum, δ 0.55 and 0.78 (each 3 H, s, 13- and 10-Me), 1.30 (4 H, s, 3β- and 7α-NH_2), 2.65 (1 H, m, $W_{\frac{1}{2}}$ 19 Hz, 3α-H), and 2.97 (1 H, m, $W_{\frac{1}{2}}$ 7 Hz, 7β-H). Hydrogen chloride was bubbled through a solution of this diamine (2.1 g) in methyl dichloride (150 ml) for 10 min. The mixture was concentrated under reduced pressure and dry ether was added. The precipitated salt was recrystallised from methanol–ether to give the *dihydrochloride hydrate* (2.24 g) as needles, charred above 240 °C; $[\alpha]_D$ (EtOH) −3.5° (*c* 1.0); $\nu_{max.}$ (KCl) 3 400 (H_2O), 2 560, 2 000, 1 600, and 1 510 cm^{-1} (NH_3^+) (Found: C, 60.6; H, 10.1; N, 6.6. $C_{21}H_{38}N_2 \cdot 2HCl \cdot 1.5H_2O$ requires C, 60.3; H, 10.35; N, 6.7%).

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