Steroid Amines. Part V.[1] 20-Pyrrolidin-1-ylpregnane Derivatives

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The Leuckart reaction with pyrrolidine has been applied to 3β-hydroxypregn-5-en-20-one and to 3β-hydroxy-5α-pregnan-20-one. Mixtures of (20*S*)-20-pyrrolidin-1-yl-17β-pregnanes and 20ξ-pyrrolidin-1-yl-17α-pregnanes were obtained; the expected (20*R*)-20-pyrrolidin-1-yl-17β-pregnanes were not isolated.

(20*S*)-20-AMINOPREGNANES † occur widely in nature,[2] and synthetic 20-amines have been the subject of considerable interest because of their diverse biological properties.[3] We have applied to the pregnane series methods developed for the synthesis of 3-pyrrolidin-1-yl-[4] and 17-pyrrolidin-1-yl-androstanes,[5,6] and record here the preparation of certain 20-pyrrolidin-1-yl-pregnane derivatives required for biological testing and for the preparation of some stereoisomeric 3,20-diamines.

The reaction under Leuckart–Wallach conditions of 3β-hydroxypregn-5-en-20-one (2) with pyrrolidine and formic acid was expected to give a mixture containing both (20*S*)-20-pyrrolidin-1-yl- (6) and (20*R*)-20-pyrrolidin-1-ylpregn-5-en-3β-ol (4), of which the less polar 20*R*-epimer should be eluted faster from chromatographic columns or plates. The mixture obtained was indeed readily separated chromatographically, and configurations were tentatively assigned to the two principal products (combined yield 65%) on the basis of their order of elution. However, certain molecular rotation data appeared to be anomalous (Table 1), and attempts to prepare authentic specimens gave equivocal results because of the impurity of the samples of the corresponding primary amines (1) and (3) available at the time (1963—1964).

Complete separation of the epimeric (20*S*)-20-amino- (1) and (20*R*)-20-amino-pregn-5-en-3β-ol (3) formed by sodium–propanol reduction of the oxime of 3β-hydroxypregn-5-en-20-one (2) was later achieved by Van de Woude and van Hove [7] and by Goutarel *et al.*[8] We subsequently treated samples of the pure primary amines (1) and (3) obtained in this way separately with 1,4-dibromobutane to provide reference specimens of the (20*S*)- (6) and (20*R*)-20-pyrrolidin-1-yl derivatives (4). Comparison with the amines derived from the Leuckart reaction confirmed that the more polar product (23%) was the expected 20*S*-compound (6), but the less polar, more easily eluted product (42%) differed from the authentic 20*R*-isomer (4).

Similar results were obtained when the Leuckart reaction was extended to 3β-hydroxy-5α-pregnan-20-one (14). The more polar product (18%) was identical with (20*S*)-20-pyrrolidin-1-yl-5α-pregnan-3β-ol (10) prepared by catalytic reduction of the pregn-5-en-3β-ol (6) and also from the known (20*S*)-20-amino-5α-pregnan-3β-ol (13) [7] and 1,4-dibromobutane. The less polar product (33%), eluted first in chromatography, was identical with the saturated amine formed by similar reduction of the less polar Leuckart product from pregnenolone.

TABLE 1

Molecular rotations (M_D/°) [a]

Series	20*S*	20*R*	ΔM_D (20*S* − 20*R*)
20-Aminopregn-5-en-3β-ol	−200	−234	34
	−208 [b]	−241 [b]	33
20-Methylaminopregn-5-en-3β-ol	−109 [b]	−178 [b]	69
20-Dimethylaminopregn-5-en-3β-ol	−176 [b]	−218 [b]	42
20-Pyrrolidin-1-ylpregn-5-en-3β-ol	−164	−310	146
20-Amino-5α-pregnan-3β-ol	44 [b]	10 [b]	34
20-Methylamino-5α-pregnan-3β-ol	80 [b]	3 [b]	77
20-Dimethylamino-5α-pregnan-3β-ol	83 [b]	44 [b]	39
20-Pyrrolidin-1-yl-5α-pregnan-3β-ol	−10		
20-Pyrrolidin-1-yl-17α-pregn-5-en-3β-ol	−315 [c]		151 [d]
20-Pyrrolidin-1-yl-5α,17α-pregnan-3β-ol	−154 [e]		144 [f]

[a] Values to nearest integer. [b] Ref. 7. [c] 17α,20ξ-Isomer (7). [d] ΔM_D for compounds (6) and (7) [(6) − (7)]. [e] 17α,20ξ-Isomer (11). [f] ΔM_D for compounds (10) and (11)] [(10) − (11)].

We believe the less polar amines produced in the Leuckart reaction are 17α-epimers.

The mechanism of the Leuckart reaction has not been fully elucidated, but the most widely held view is that an intermediate immonium ion, *e.g.* (17), formed by dehydration of the carbinolamine (15) is subsequently reduced by formate (as anion or ester).[9] The immonium

† The sequence rule procedure is used for defining stereochemistry at C-20. Compounds previously referred to as 20α-amines have the 20*S*-configuration, and 20β-amines have the 20*R*-configuration.

[1] Part IV, M. Davis, E. W. Parnell, and J. Rosenbaum, *J. Chem. Soc.* (*C*), 1967, 1045.

[2] R. Goutarel, 'Les acaloides stéroidiques des Apocynacées,' Hermann, Paris, 1964.

[3] M. Alauddin and M. Martin-Smith, *J. Pharm. Pharmacol.* 1962, **14**, 469; M. Martin-Smith and M. F. Sugrue, *ibid.*, 1964, **16**, 569.

[4] Part III, M. Davis, E. W. Parnell, and J. Rosenbaum, *J. Chem. Soc.* (*C*), 1966, 1983.

[5] Part I, M. Davis, E. W. Parnell, and D. Warburton, *J. Chem. Soc.* (*C*), 1966, 1688.

[6] Part II, M. Davis, E. W. Parnell, and D. Warburton, *J. Chem. Soc.* (*C*), 1966, 1698.

[7] G. Van De Woude and L. Van Hove, *Bull. Soc. Chim. belges.*, 1967, **76**, 566.

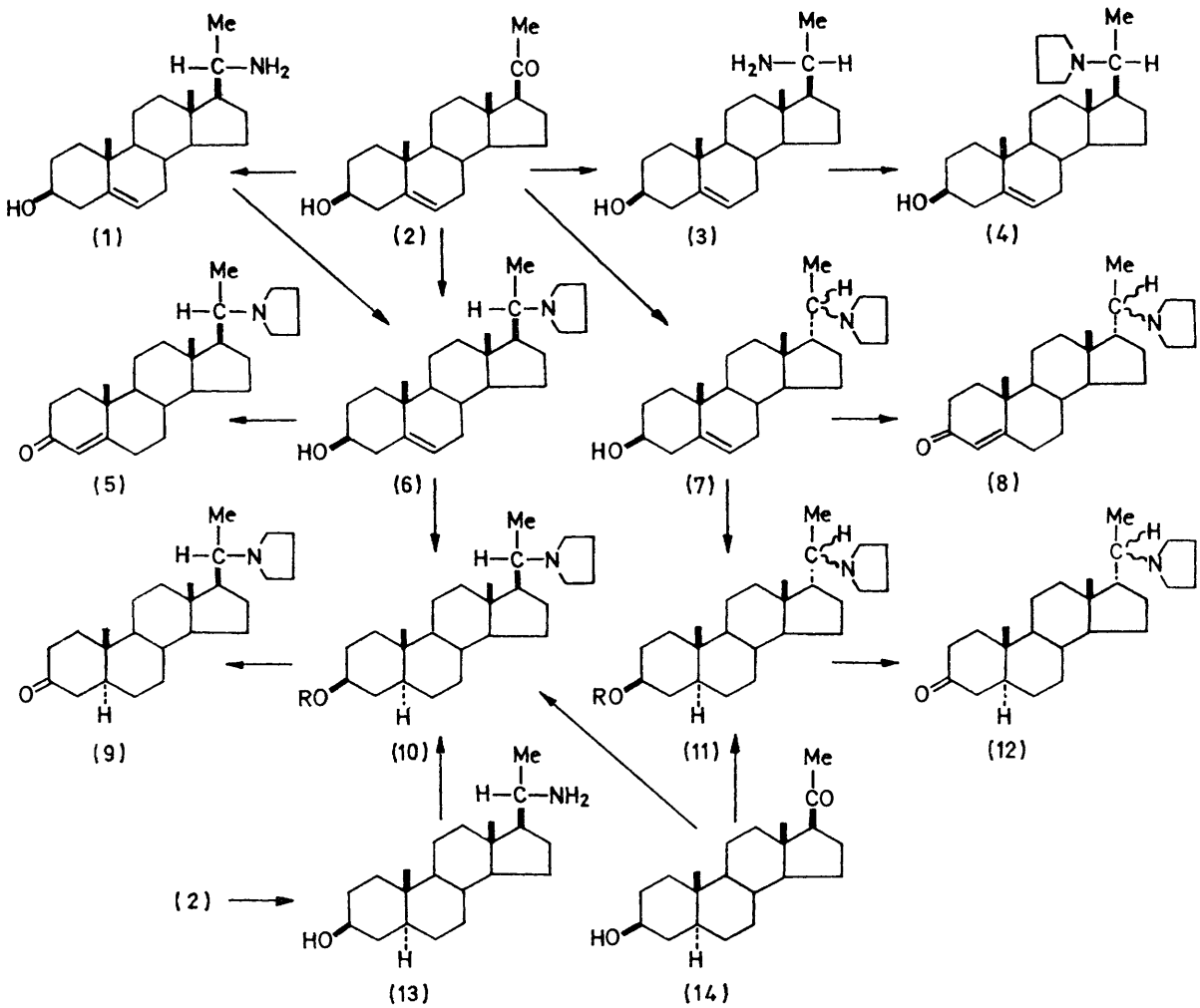
[8] R. Goutarel, H. R. Mahler, G. Green, Q. Khuong-Huu, A. Cavé, C. Conreur, F. X. Jarreau, and J. Hannart, *Bull. Soc. chim. France*, 1967, 4575.

[9] P. F. Coe, B. C. Uff, and J. W. Lewis, *J. Chem. Soc.*, 1968, 2265.

ion (19) is the protonated form of the enamine (18), which is an alternative primary product from a steroid ketone and pyrrolidine, and conceivably an intermediate in the formation of the ion (19).[10] Enamines can be reduced directly by formic acid to the saturated amines,[5,11] but this is considered to be preceded by protonation [*e.g.* to (17)].[12]

Leuckart reactions with the pregnan-20-ones (2) and (14) were in both cases 65% 17α : 35% 17β. This may reflect the greater degree of crowding by the 13β-methyl group in the immonium ion (17).

Each of the two intermediate ions (17) and (19) could give rise to two saturated amines on reduction. Approach of the formate ion from the relatively unhindered



The intervention of any equilibrium involving the enamine (18) (or its geometrical isomer) means that subsequent protonation would probably produce both the 17β- (16) and 17α-pregnane immonium ion (19), for which the most likely rotamers are shown. Such an equilibrium would parallel that occurring with pregnan-20-ones *via* the enolic 20-hydroxypregn-17(20)-ene (16).[13,14] However, whereas the normal equilibrium ratio for pregnan-20-ones is 25—18% 17α : 75—82% 17β,[13] the proportions of the amines isolated from the 'right-hand' side of the molecule would lead to reduction of the $C=\overset{+}{N}$ bond, giving rise to the 17β,20*S*-isomer (6). A preferential attack from the same side on the 17α-compound (19) would give rise to the 17α,20*R*-isomer (20), although insufficient evidence is available to support this assignment unequivocally.

The n.m.r. data (Table 2) show that compounds (7) and (11) exhibit a small downfield shift for the C-18 protons compared with the 17β-epimers (6) and (10),

[10] D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 186; J. Elguero, R. Jacquier, and G. Tarrago, *Tetrahedon Letters*, 1965, 4719.

[11] N. J. Leonard and R. R. Sauers, *J. Amer. Chem. Soc.*, 1957, **79**, 6210.

[12] J. Szmuszkovicz, *Adv. Org. Chem.*, 1963, **4**, 80.

[13] D. N. Kirk in 'Terpenoids and Steroids' (Chemical Society Specialist Periodical Report), **1**, 265.

[14] M. B. Rubin and E. C. Blossey, *J. Org. Chem.*, 1964, **29**, 1932.

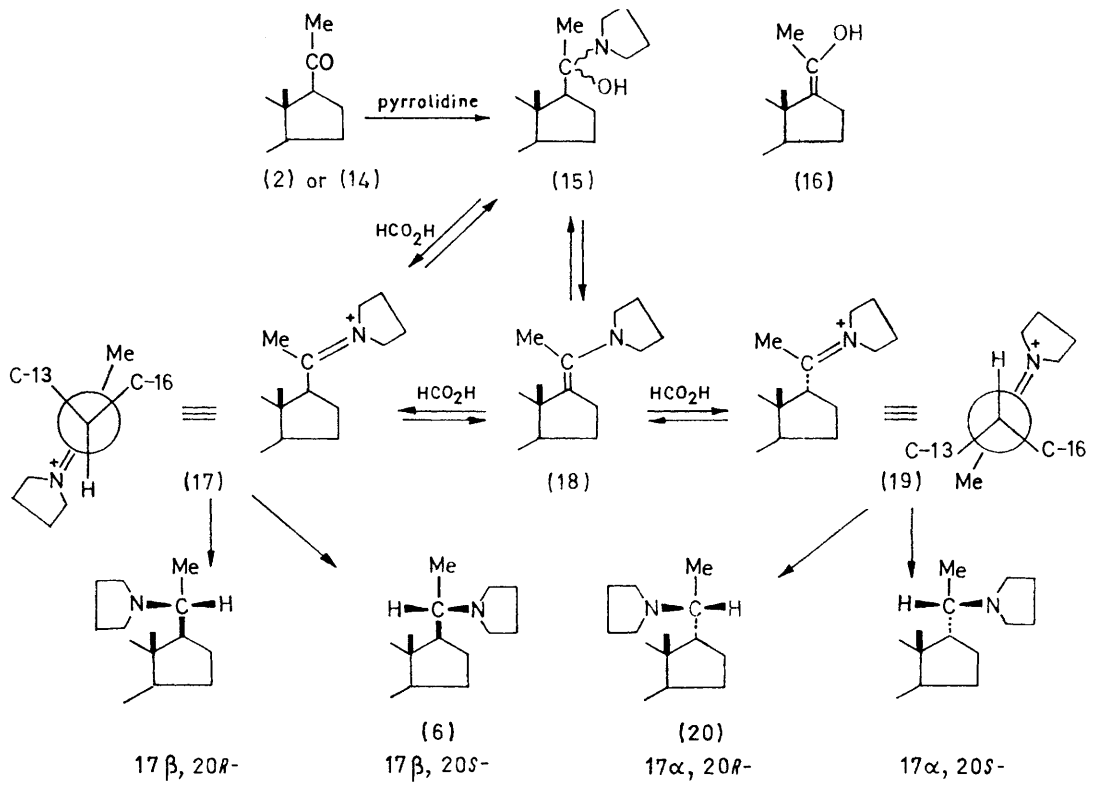


TABLE 2

N.m.r. data [a]

Compound	17β,20*S*			17β,20*R*			17α,20ξ		
	18-H_3	19-H_3	21-H_3	18-H_3	19-H_3	21-H_3	18-H_3	19-H_3	21-H_3
20-Aminopregn-5-en-3β-ol (present work)	0·70	1·03	1·12 (*J* 6·5)	0·76	1·02	1·02 (*J* 6·5)			
Ref. 7	0·68	1·01	1·12 (*J* 6·5)	0·75	1·02	1·02 (*J* 6·5)			
Ref. 8	0·68	1·02	1·13 (*J* 6)	0·76	1·03	1·02 (*J* 6·5)			
Ref. 15	0·68		1·10 (*J* 6·5)	0·75		1·03 (*J* 6·5)			
20-Pyrrolidin-1-ylpregn-5-en-3β-ol From (1)	0·68	1·00	0·95 (*J* 6)	0·69	1·01	0·84 (*J* 6·5)			
Leuckart products (6) and (7)	0·69	1·01	0·94 (*J* 6—7)				0·81	1·00	0·96 (*J* 6·5)
20-Dimethylaminopregn-5-en-3-ol Ref. 7	0·68	1·02	0·89 (*J* 6·5)	0·69	1·02 [b]	0·78 (*J* 6·5)			
20-Amino-5α-pregnan-3β-ol Ref. 7	0·65	0·80	1·10 (*J* 6·2)	0·72	0·80	1·00 (*J* 6·2)			
Ref. 15	0·65		1·10 (*J* 6·5)	0·72		1·00 (*J* 6·0)			
20-Pyrrolidin-1-yl-5α-pregnan-3β-ol Leuckart products (10) and (11)	0·65	0·80	0·94 (*J* 6·5)				0·78 (or 0·79)	0·79 (or 0·78)	0·93 (*J* 6·5)
20-Dimethylamino-5α-pregnan-3β-ol Ref. 7	0·66	0·81	0·87 (*J* 6·5)	0·65	0·80	0·75 (*J* 6·2)			

[a] δ Values in p.p.m. from tetramethylsilane; *J* in Hz. [b] Given as 0·12, presumably in error.

[15] C. H. Robinson and P. Hofer, *Chem. and Ind.*, 1966, 377.

respectively. For 20-oxopregnanes a downfield shift is characteristic of 17α-pregnanes compared with their 17β-epimers.[14]

Molecular rotation differences for the saturated and unsaturated alcohols and ketones are reasonably consistent (Table 3).

The saturated ketones (9) and (12) were formed from the alcohols (10) and (11), respectively, by chromic acid oxidation. For the unsaturated ketones (5) and (8), Oppenauer oxidation of the alcohols (6) and (7) was employed.

EXPERIMENTAL

$[\alpha]_D$ Values were determined for solutions in chloroform. The formic acid used was 98—100% pure. Except where stated otherwise, chromatography was carried out on Florisil. N.m.r. spectra were measured for solutions in deuteriochloroform.

The amino-alcohols frequently crystallised as hydrates or solvates, and good analyses were sometimes obtained only after prolonged drying *in vacuo*. The m.p.s of the pyrrolidine derivatives fell when the compounds were exposed to air.

(20S)-20-*Amino-* (1) *and* (20R)-20-*Amino-pregn-5-en-3β-ol* (3).—3β-Hydroxypregn-5-en-20-one oxime (5 g) was reduced with sodium (20 g) in n-propanol (250 ml) and the product was chromatographed on silica gel (Merck 7734) as described in ref. 7. Crystallisation of the early fractions from methanol gave (20*R*)-20-aminopregn-5-en-3β-ol (800 mg), m.p. 213—216°, $[\alpha]_D$ −73·8° (lit.,[7] m.p. 218·6—219·2°, $[\alpha]_D$ −76·2°; lit.,[9] m.p. 220°, $[\alpha]_D$ −75°). Later fractions afforded (20*S*)-20-aminopregn-5-en-3β-ol (900 mg), m.p. 173—176°, $[\alpha]_D$ −62·9° (lit.,[7] m.p. 171—173°, $[\alpha]_D$ −65·6°; lit.,[8] m.p. 177°, $[\alpha]_D$ −62°).

(20S)-20-*Amino-5α-pregnan-3β-ol* (13).—A mixture of 3β-hydroxypregn-5-en-20-one oxime (5·0 g) and platinum oxide (0·7 g) in acetic acid (120 ml) was hydrogenated at room temperature. The filtered solution was evaporated *in vacuo* and the residue was made basic. The crude amine was chromatographed in benzene giving the 20*S*-amine, m.p. 169—172°, $[\alpha]_D$ +12° (lit.,[7] m.p. 173—175°, $[\alpha]_D$ +13·6°).

(20S)-20-*Pyrrolidin-1-ylpregn-5-en-3β-ol* (6).—A mixture of (20*S*)-20-aminopregn-5-en-3β-ol (400 mg), 1,4-dibromobutane (330 mg) and potassium carbonate (500 mg) in ethanol (10 ml) was stirred and heated under reflux for 22 h, then diluted with water (20 ml) and extracted with methylene chloride. The product obtained by evaporation of the extract was chromatographed on silica (Merck 7734; 2·5 g) prepared in benzene saturated with aqueous ammonia.[7] Elution with benzene and benzene–ether gave successively the pyrrolidine (265 mg), m.p. 155—160°, and unchanged primary amine (135 mg). Recrystallisation from methanol and from methanol–acetone gave (20S)-20-*pyrrolidin-1-ylpregn-5-en-3β-ol*, m.p. 168—170°, $[\alpha]_D$ −44·0° (Found: C, 80·5; H, 11·1; N, 3·6. $C_{25}H_{41}NO$ requires C, 80·8; H, 11·1; N, 3·8%). The *hydrochloride* had m.p. >300° (decomp.) (Found: C, 73·6; H, 10·8; Cl, 8·7; N, 3·4. $C_{25}H_{41}NO,HCl$ requires C, 73·6; H, 10·4; Cl, 8·7; N, 3·4%).

(20R)-20-*Pyrrolidin-1-ylpregn-5-en-3β-ol* (4).*—(20*R*)-20-Aminopregn-5-en-3β-ol (400 mg), similarly treated with 1,4-dibromobutane, afforded the tertiary amine (160 mg) and unchanged primary amine (240 mg). After recrystallisation from methanol and from acetone, (20R)-20-*pyrrolidin-1-ylpregn-5-en-3β-ol* had m.p. 196—198°, $[\alpha]_D$ −83·3° (Found: C, 80·9; H, 11·2; N, 3·6. $C_{25}H_{41}NO$ requires C, 80·8; H, 11·1; N, 3·8%).

TABLE 3

Molecular rotations (M_D/°)[a]

Series	5-en-3β-ol (A)	4-en-3-one (B)	5α-an-3β-ol (C)	5α-an-3-one (D)	ΔM_D (B) − (A)	(D) − (C)	(A) − (C)	(B) − (D)
(20*S*)-20-Aminopregnane	−208 [b]		44 [b]				−251	
(20*S*)-20-Methylaminopregnane	−109 [b]		80 [b]				−189	
(20*S*)-20-Dimethylaminopregnane	−176 [b]		83 [b]				−259	
(20*S*)-20-Pyrrolidin-1-ylpregnane	−164	320	−10	−40	484	−30	−154	360
20ξ-Pyrrolidin-1-yl-17α-pregnane	−315	89	−154	−114	404	40	−161	203
17α-Pyrrolidin-1-ylandrostane	−255 [c]	192 [c]	−78 [c]	31 [c]	447	109	−177	161
17β-Pyrrolidin-1-ylandrostane	−201 [d]	333 [d]	47 [d]	121 [d]	534	74	−154	212

[a] Values to nearest integer. [b] Ref. 7. [c] Ref. 6. [d] Ref. 5.

Leuckart Reaction with Pregnenolone.—A mixture of 3β-hydroxypregn-5-en-20-one (20 g), pyrrolidine (26 ml), and formic acid (20 ml) was heated in a sealed tube for 20 h at 170 ± 10°. The mixture was poured into dilute aqueous methanesulphonic acid, the solution was clarified by filtration, and the filtrate was basified with aqueous sodium hydroxide. The solid product was collected, dried, and chromatographed in benzene. Elution with benzene gave a colourless solid which afforded 20ξ-*pyrrolidin-1-yl-17α-pregn-5-en-3β-ol* (7) (42%), m.p. 172—175° (from acetone), $[\alpha]_D$ −84·6° (Found: C, 79·1; H, 11·0; N, 3·8; loss on drying at 100°, 2·6. $C_{25}H_{41}NO,0{\cdot}5H_2O$ requires C, 78·9; H, 11·1; N, 3·7; H_2O, 2·4%). The *hydrochloride* had m.p. >300° (decomp.) (Found: C, 73·1; H, 11·0; Cl, 8·9; N, 3·5. $C_{25}H_{41}NO,HCl$ requires C, 73·6; H, 10·4; Cl, 8·7; N, 3·4%).

Further elution, with chloroform, yielded a second product, which crystallised from methanol to give (20*S*)-20-pyrrolidin-1-ylpregn-5-en-3β-ol (6) (23%), m.p. 164—167°, $[\alpha]_D$ −41·3°; m.p. unaltered by admixture with an authentic sample (see before) but depressed by the 17α-isomer (7).

20ξ-*Pyrrolidin-1-yl-17α-pregn-4-en-3-one* (8).—To a solution of 20ξ-pyrrolidin-1-yl-17α-pregn-5-en-3β-ol (7) (2 g) in dry toluene (150 ml) and cyclohexanone (15 ml) (from which water had been removed azeotropically) was added aluminium isopropoxide (1·2 g) in toluene (120 ml), and the

* First prepared by Dr. D. Warburton.

mixture was refluxed for 2 h. Toluene was continuously distilled out of the mixture and dry solvent (*ca.* 500 ml) was added to maintain the volume. The solution was concentrated to low bulk *in vacuo*, the residue was diluted with aqueous sodium hydroxide, and the product was extracted with chloroform (3 × 50 ml). The washed and dried extracts were evaporated to dryness and the residue was crystallised from acetone to yield the *ketone* (45%), m.p. 130—132°, $[\alpha]_D$ +24·1°, $\lambda_{max.}$ (EtOH) 241 nm (ε 18,700), $\nu_{max.}$ (KBr) 1680 cm^{-1} (Found: C, 80·8; H, 10·3; N, 3·8. $C_{25}H_{39}NO$ requires C, 81·2; H, 10·6; N, 3·8%).

(20S)-20-*Pyrrolidin*-1-*ylpregn*-4-*en*-3-*one* (5), similarly prepared, had m.p. 165—166°, $[\alpha]_D$ +86·6°, $\lambda_{max.}$ (EtOH) 240 nm (ε 17,650), $\nu_{max.}$ (KBr) 1680 cm^{-1} (Found: C, 81·1; H, 10·4; N, 3·6. $C_{25}H_{39}NO$ requires C, 81·2; H, 10·6; N, 3·8%).

20ξ-*Pyrrolidin*-1-*yl*-5α,17α-*pregnan*-3β-*ol* (11; R = H).—A mixture of 20ξ-pyrrolidin-1-yl-17α-pregn-5-en-3β-ol (7) (2·5 g) and platinum oxide (0·4 g) in glacial acetic acid (30 ml) was hydrogenated at room temperature. The catalyst was filtered off and the filtrate evaporated to dryness *in vacuo*. Dilute sodium hydroxide solution was added to the residue and the solid product was collected and crystallised from acetone to yield the *amine* (2·0 g, 80%), m.p. 161—163°, $[\alpha]_D$ −41·3° (Found: N, 3·8. $C_{25}H_{43}NO$ requires N, 3·75%). The *hydrochloride* had m.p. 287—289° (Found: C, 73·2; H, 10·7; Cl, 8·5; N, 3·4. $C_{25}H_{43}NO$,HCl requires C, 73·2; H, 10·8; Cl, 8·65; N, 3·4%). The *tosylate* (11; R = *p*-$MeC_6H_4{\cdot}SO_2$) had m.p. 118—121° (Found: N, 2·9; S, 5·5. $C_{32}H_{49}NO_3S$ requires N, 2·65; S, 6·1%).

(20S)-20-*Pyrrolidin*-1-*yl*-5α-*pregnan*-3β-*ol* (10; R = H).—(*a*) The 20*S*-amine, similarly prepared by hydrogenation of (20*S*)-20-pyrrolidin-1-ylpregn-5-en-3β-ol (6), had m.p. 159—161°, $[\alpha]_D$ −2·6° (Found: N, 3·8. $C_{25}H_{43}NO$ requires N, 3·8%). The *hydrochloride* had m.p. >300° (decomp.) (Found: C, 73·1; H, 10·6; Cl, 8·7. $C_{25}H_{43}NO$,HCl requires C, 73·2; H, 10·8; Cl, 8·65%). The *tosylate* (10; R = *p*-$MeC_6H_4{\cdot}SO_2$) had m.p. 120—122°, $[\alpha]_D$ −21·3° (Found: C, 73·2; H, 9·6; S, 6·1. $C_{32}H_{49}NO_3S$ requires C, 72·8; H, 9·4; S, 6·1%).

(*b*) 1,4-Dibromobutane (0·8 g) was added to a stirred suspension of (20*S*)-20-amino-5α-pregnan-3β-ol (13) (0·8 g) and sodium carbonate (0·7 g) in ethanol (50 ml), and the mixture was heated under reflux for 16 h, then poured into water. The product was extracted into chloroform, isolated, and crystallised from acetone to give the pyrrolidine, m.p. 160—161°.

Leuckart Reaction with Pregnanolone.—A mixture of 3β-hydroxy-5α-pregnan-20-one (8·7 g), pyrrolidine (25 ml), and formic acid (10 ml) was heated in a sealed tube for 20 h at 170 ± 10°. After the usual work-up and acid–base extraction, the product was dissolved in benzene and chromatographed. Elution with benzene afforded 20ξ-pyrrolidin-1-yl-5α,17α-pregnan-3β-ol (11; R = H) (3·5 g, 33%), m.p. 162—164°, $[\alpha]_D$ −41·2° (Found: C, 80·5; H, 12·0; N, 3·8. Calc. for $C_{25}H_{45}NO$: C, 80·4; H, 11·6; N, 3·8%), identical (mixed m.p.) with a sample prepared as before. Further elution, with chloroform, gave the 20*S*-amine (10; R = H) (2 g, 18%), m.p. 158—160°, $[\alpha]_D$ −2·6° (Found: C, 80·3; H, 11·7; N, 3·75%), identical (mixed m.p.) with a specimen prepared as before.

20ξ-*Pyrrolidin*-1-*yl*-5α,17α-*pregnan*-3-*one* (12).—A solution of chromium trioxide (1 g) in acetic acid (10 ml) and water (2 ml) was added slowly to a solution of 20ξ-pyrrolidin-1-yl-5α,17α-pregnan-3β-ol (3·5 g) in acetic acid (80 ml), and the mixture was kept at room temperature for 16 h. The suspension was diluted with aqueous sodium hydroxide and extracted with ether (4 × 75 ml). The washed and dried extracts were evaporated to dryness and the residue was crystallised from ethanol to yield the *amino-ketone* (1·2 g, 30%), m.p. 167—169°, $[\alpha]_D$ −30·7°, $\nu_{max.}$ (KBr) 1717 cm^{-1} (Found: C, 80·7; H, 11·2; N, 3·7. $C_{25}H_{41}NO$ requires C, 80·8; H, 11·1; N, 3·8%).

(20S)-20-*Pyrrolidin*-1-*yl*-5α-*pregnan*-3-*one* (9), m.p. 137—139°, $[\alpha]_D$ −10·9° (Found: C, 78·7; H, 11·1; N, 3·8; loss on drying, 2·0. $C_{25}H_{41}NO,0{\cdot}5H_2O$ requires C, 78·9; H, 11·1; N, 3·7; H_2O, 2·4%), was similarly prepared.

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