Steroids and Walden Inversion. Part XXIII. The Production of 3α-Substituted Δ⁵-Steroids in Replacement Reactions of 3β-Substituted Δ⁵-Steroids.*

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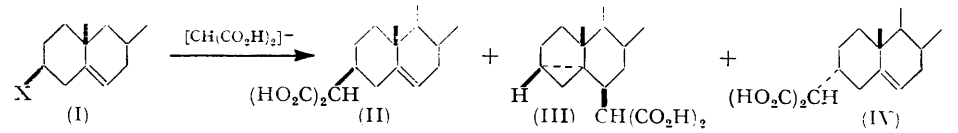
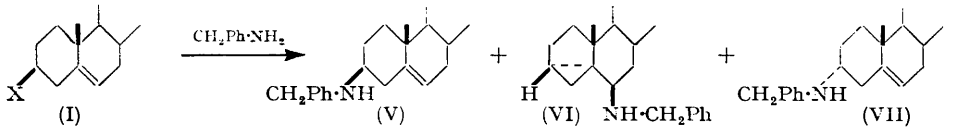
It has been generally thought that replacement reactions at $C_{(3)}$ in 3β-substituted Δ⁵-steroids proceed by a unimolecular heterolysis with complete retention of configuration at $C_{(3)}$ owing to participation of the π-electrons of the 5 : 6-double bond. This view is correct for weak nucleophilic reagents, *e.g.*, OAc^-, but requires modification for more powerful nucleophilic reagents. Six examples are given, with appropriate experimental proof, to show that in media of low dielectric constant and with nucleophiles of sufficient power, the unimolecular heterolysis may be accompanied, or largely superseded, by a bimolecular substitution with inversion of configuration at $C_{(3)}$ in which the π-electrons of the 5 : 6-double bond do not participate.

In 1951, two of us observed that a replacement reaction at $C_{(3)}$ in a 3β-substituted Δ⁵-steroid could lead to a 3α-substituted Δ⁵-steroid; thus the reaction of cholesteryl toluene-*p*-sulphonate (I; X = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$) with malonate ion in toluene at 110° gives three isomeric products: 3β-cholesterylmalonic acid (II), 3 : 5-*cyclo*cholestan-6β-ylmalonic acid (III), and 3α-cholesterylmalonic acid (IV) (Shoppee and Stephenson, *J.*, 1954, 2230; cf. Kaiser and Svarz, *J. Amer. Chem. Soc.*, 1945, **67**, 1309; 1947, **69**, 846; 1949, **71**, 517).



A second case was reported in 1952. Julian *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 1831 : ref. *a*) found that cholesteryl toluene-*p*-sulphonate with benzylamine at 180° gave *N*-benzyl-3β-cholesterylamine (V) and *N*-benzyl-3 : 5-*cyclo*cholestan-6β-ylamine (VI). Vavasour *et al.* (*Canad. J. Chem.*, 1952, **30**, 933 : ref. *b*) by similar treatment of cholesteryl chloride (I; X = Cl) isolated three isomeric amines: two of these products, (V) and (VI), were identical with those obtained by Julian *et al.*; the third was correctly regarded as *N*-benzyl-3α-cholesterylamine (VII).

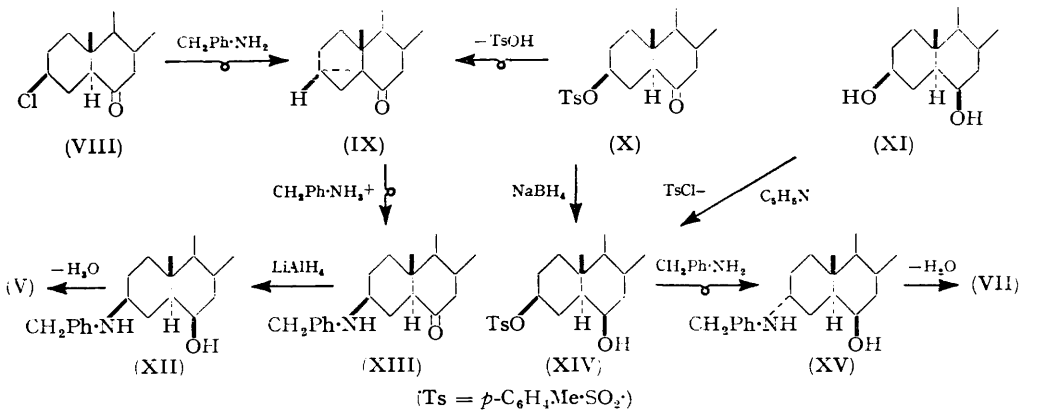


(Figures in square brackets are $[\alpha]_D$. Superscripts refer to references so marked in the text.)

We have confirmed the Canadian work and we have now (ref. *c*) proved the structures of the amines (V) and (VII) by the following partial syntheses. 3β-Chlorocholestan-6-one (VIII) with benzylamine at 180° gives initially 3 : 5-*cyclo*cholestan-6-one (IX); this is cleaved in benzylamine by the benzylammonium cation $[NH_3{\cdot}CH_2Ph]^+$, which functions as an acid, like $[NH_4]^+$ in liquid ammonia (cf. Shoppee and Summers, *J.*, 1952, 1787,

* Part XXII, preceding paper.

3365), to yield *N*-benzyl-6-oxocholestan-3β-ylamine (XIII). This by reduction with lithium aluminium hydride affords *N*-benzyl-6β-hydroxycholestan-3β-ylamine (XII), smoothly dehydrated by phosphorus oxychloride–pyridine at 15° [5α-H(axial)/6β-OH(axial) : *trans*] to give *N*-benzyl-3β-cholesterylamine (V).

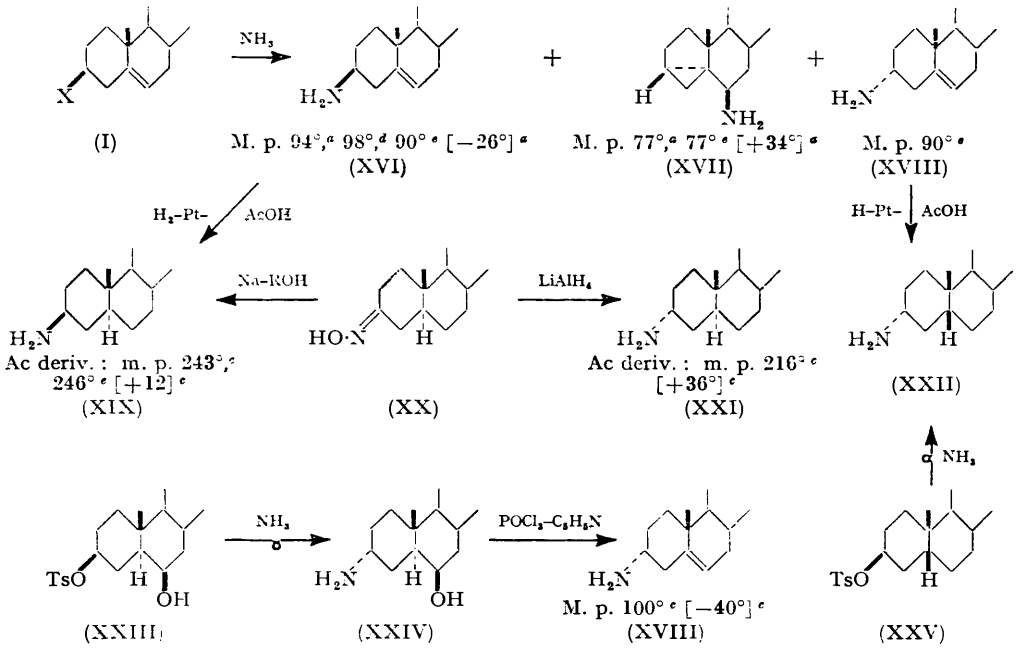


6-Oxocholestan-3β-yl toluene-*p*-sulphonate (X) (Dodgson and Riegel, *J. Org. Chem.*, 1948, **13**, 424) on reduction with sodium borohydride gives 6β-hydroxycholestan-3β-yl toluene-*p*-sulphonate (XIV), previously prepared from cholestane-3β : 6β-diol (XI) by partial esterification (Reich and Lardon, *Helv. Chim. Acta*, 1946, **29**, 671). The 3β-toluene-*p*-sulphonate (XIV) with benzylamine at 180° furnishes, with inversion of configuration, *N*-benzyl-6β-hydroxycholestan-3α-ylamine (XV), smoothly dehydrated by phosphorus oxychloride–pyridine at 15° [5α-H(axial)/6β-OH(axial) : *trans*] to *N*-benzyl-3α-cholesterylamine (VII).

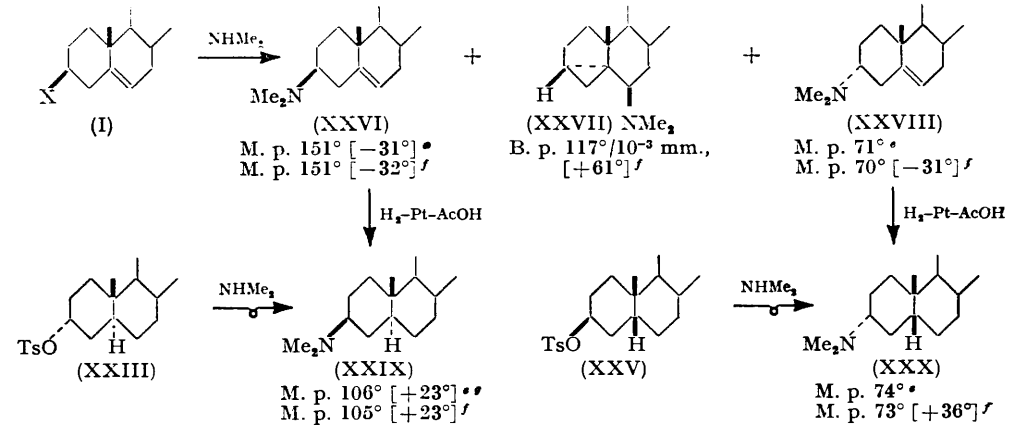
A third case was reported in 1953. The reaction of cholesteryl chloride (I; X = Cl) with ammonia in the presence of ammonium iodide was examined by Windaus and Adamla (*Ber.*, 1911, **44**, 3051 : ref. *d*), who isolated 3β-cholesterylamine (XVI). Julian *et al.* (*loc. cit.* : ref. *a*) later examined the reaction of cholesteryl toluene-*p*-sulphonate (I; X = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$) with liquid ammonia, and isolated 3β-cholesterylamine (XVI) and 3 : 5-*cyclo*cholestan-6β-ylamine (XVII), which were also obtained from *N*-benzyl-3β-cholesterylamine (V) and *N*-benzyl-3 : 5-*cyclo*cholestan-6β-ylamine (VI) respectively by conversion with hypochlorous acid into the chloramines, dehydrochlorination, and hydrolytic fission of the resulting benzylidene compounds. More recently, Haworth, McKenna, and Powell (*J.*, 1953, 1110 : ref. *e*) re-investigated the reaction of cholesteryl toluene-*p*-sulphonate with liquid ammonia, and isolated three isomeric bases. Two of these, (XVI) and (XVII), are identical with the compounds isolated by Julian *et al.*; the third, which was to be examined later, is 3α-cholesterylamine (XVIII) because we (ref. *c*) have obtained it from *N*-benzyl-3α-cholesterylamine (VII) by degradation *via* the chloramine and the related benzylidene compound. Vavasour *et al.* (*loc. cit.*) performed this transformation but converted their degradation product into the acetyl derivative, m. p. 189°, which may be identical with the acetyl derivative, m. p. 190°, of a minor product obtained by reduction of cholest-4-en-3-one oxime with sodium and ethanol by Windaus and Adamla (*loc. cit.*). We (ref. *c*) have also obtained the base (XVIII) from 6β-hydroxycholestan-3β-yl toluene-*p*-sulphonate (XXIII) by ammonolysis, whereby 6β-hydroxycholestan-3α-ylamine (XXIV) is produced with inversion of configuration; by dehydration with phosphorus oxychloride in pyridine this affords 3α-cholesterylamine (XVIII).

Hydrogenation of 3β-cholesterylamine (XVI) gives cholestan-3β-ylamine (XIX), previously obtained by Dodgson and Haworth (*J.*, 1952, 67) by reduction of cholestan-3-one oxime (XX); they also isolated a minor product [acetate, m. p. 216°, possibly identical with the acetate, m. p. 216°, of the major product of the reduction with sodium–ethanol of cholest-4-en-3-one oxime (Windaus and Adamla, *loc. cit.*)], which is cholestan-3α-ylamine

(XXI) since we have obtained it from the oxime (XX) by reduction with lithium aluminium hydride. It is of interest here that hydrogenation of 3α-cholesterylamine (XVIII) gives mainly coprostan-3α-ylamine (XVII) (cf. Lewis and Shoppee, *Chem. and Ind.*, 1953, 897, 933), also obtainable by ammonolysis of coprostan-3β-yl toluene-*p*-sulphonate (XXV) (Richards, Shoppee, and Summers, unpublished work).



A fourth case was also reported in 1953. Haworth, McKenna, and Powell (*loc. cit.*) by treatment of cholesteryl toluene-*p*-sulphonate (I; X = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$) with dimethylamine isolated *N*-benzyl-3β-cholesterylamine (XXVI), previously obtained from cholesteryl chloride (I; X = Cl) by Dodgson and Haworth (*loc. cit.*), and an isomeric base later (personal communication) identified as *NN*-dimethyl-3α-cholesterylamine (XXVIII). Sorm, Labler, and Czerny (*Chem. Listy*, 1953, **47**, **418**) have also investigated the reaction and have isolated three isomeric bases; two of these products, (XXVI) and (XXVIII), are identical with those of Haworth *et al.*, whilst the the third is *NN*-dimethyl-3 : 5-*cyclo*-cholestan-6β-ylamine (XXVII).



[*e* = Haworth *et al.*; *f* = Sorm *et al.*; *g* = Haworth and Dodgson (*locc. cit.*).]

For some reason, possibly because of unfamiliarity with the S_N2 orientation rule (Ingold, " Structure and Mechanism in Organic Chemistry, George Bell and Sons, London, 1953, p. 377), Sorm *et al.* preferred not to assign configuration at $C_{(3)}$ * to the unsaturated products (XXVI) and (XXVIII), although by partial syntheses of their reduction products they were in a position to do so. Thus hydrogenation of the base (XXVI) gave *NN*-dimethylcholestan-3β-ylamine (XXIX), corresponding to the hydrogenation product obtained by Haworth and his collaborators and also obtained by Haworth and Dodgson by methylation of cholestan-3β-ylamine (XIX), which Sorm *et al.* prepared by solvolysis with dimethylamine of *epi*cholestanyl toluene-*p*-sulphonate (XXIII). Hydrogenation of the base (XXVIII) gave, as also recorded by Haworth *et al.*, *NN*-dimethylcoprostan-3α-ylamine (XXX), which constitutes a further example of the influence of a 3α-substituent on the steric course of hydrogenation of a 5 : 6-double bond (Lewis and Shoppee, *locc. cit.*) since its structure has been established by Sorm *et al.* by solvolysis of coprostanyl toluene-*p*-sulphonate (XXV) with dimethylamine. Sorm *et al.* further strengthened their position by partial syntheses of the remaining stereoisomeric saturated bases *NN*-dimethylcholestan-3α-ylamine (cf. Haworth, McKenna, and Powell, *loc. cit.*) and *NN*-dimethylcoprostan-3β-ylamine from cholestanyl and *epi*coprostanyl toluene-*p*-sulphonate respectively by solvolysis with dimethylamine.

Haworth, McKenna, and Powell, by treatment of pregna-5 : 20-dien-3β-yl toluene-*p*-sulphonate (XXXI) with monomethylamine, also obtained two isomeric secondary bases; one is *N*-methylpregna-5 : 20-dien-3β-ylamine (XXXII), which was identified by methylation and hydrogenation to *NN*-dimethyl*allo*pregnan-3β-ylamine (XXXV), prepared by reduction of *allo*pregnan-3-one oxime (XXXIV) with sodium and amyl alcohol and then methylation; the other is *N*-methylpregna-5 : 20-dien-3α-ylamine (XXXIII), although Haworth *et al.* suggested that it might be *N*-methyl-3 : 5-*cyclo*pregn-20-en-6ξ-ylamine because it was stable to oxidation with potassium iodate in 2N-sulphuric acid, and on account of its conversion by successive methylation and hydrogenation into a tertiary base, $C_{23}H_{41}N$, m. p. 79° (XXXVI), of unknown structure, which was different from *NN*-dimethyl*allo*pregnan-3β- (XXXV) and -3α-ylamine (XXXIX).†

Haworth, McKenna, and Powell made the notable observation that solvolysis of pregn-5-en-3β-yl toluene-*p*-sulphonate (XXXVII) with dimethylamine furnished only a *single* product, m. p. 130°, which gave a negative iodate reaction and by hydrogenation afforded the base (XXXVI); they suggested that this product must have a structure analogous to that of the base (XXXIII).‡ We have proved the structure of the product, m. p. 130°, to be *NN*-dimethylpregn-5-en-3α-ylamine (XXXVIII), so that here substitution (XXXVII ⟶ XXXVIII) proceeds with substantially complete inversion of configuration.

Kishner–Wolff reduction of pregnenolone (XL) gave pregn-5-en-3β-ol (XLI), which by

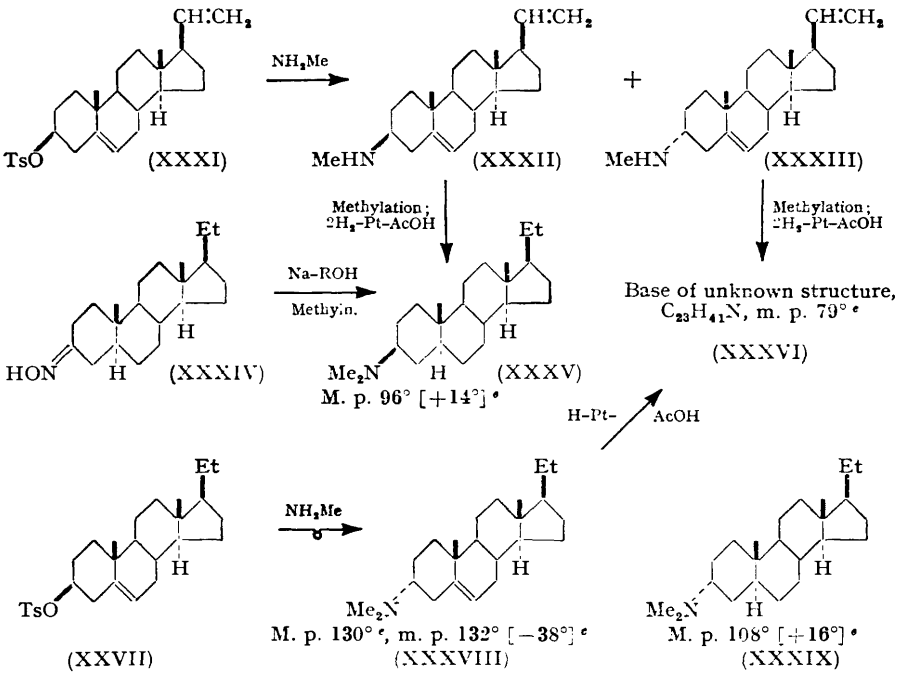
* Sorm *et al.* state (*loc. cit.*, p. 420, last paragraph) : " We no not ascribe to any of the 3-dimethylamino-steroid derivatives, prepared by us, a definite configuration of the dimethylamino-group at $C_{(3)}$, because neither in the case of these bases, nor in that of the 3-amino-steroid derivatives that have been described earlier, has there been so far any definite proof concerning configuration." Accordingly they use the symbol ξ throughout their paper.

Haworth, McKenna, and Powell (*loc. cit.*) described various Hofmann degradations. The 3β-(equatorial)-configuration of the substituent group in the related primary (XIX), secondary, and tertiary (XXVI) bases can be deduced from the resistance to Hofmann degradation of the quaternary hydroxide derived from the tertiary base (XXIX) as compared with the relatively ready decomposition of *NNN*-trimethylcholestan-3α-ylammonium hydroxide (3α-substituent : axial). The discovery by Lewis and Shoppee (*locc. cit.*) that hydrogenation of 3α-substituted cholest-5-enes leads predominantly to coprostane derivatives enables a parallel deduction to be made of the 3α(equatorial)-configuration of the substituent group in the related secondary and tertiary (XXVIII) bases, since the quaternary hydroxide derived from the tertiary base (XXX) resisted Hofmann degradation.

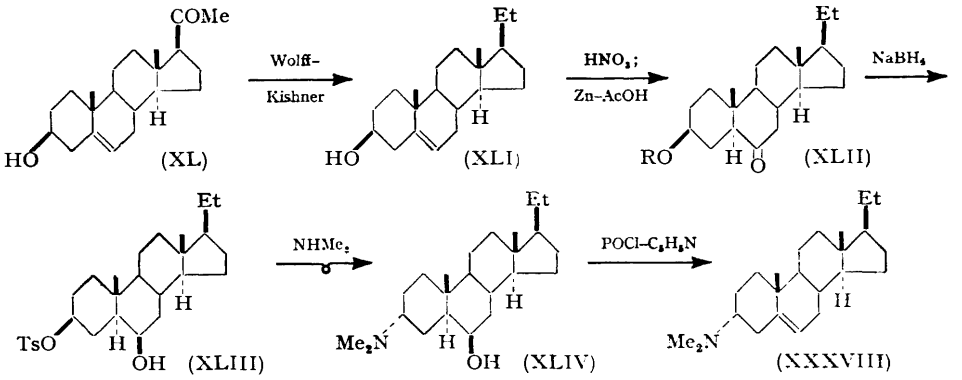
† 3 : 5-*cyclo*Cholestan-6β-ylamine is stable to acidic iodate (Haworth, McKenna, and Powell, *loc. cit.*, p. 1111), but we find that this is also the case for 3α-amino-Δ^5-steroids in contrast to 3β-amino-Δ^5-steroids, which are readily oxidised.

‡ During a personal discussion at Ashburne Hall, Manchester, on March 31st, 1954, Dr. McKenna informed the senior author that the Sheffield University group had modified their earlier view as to the 3 : 5-*cyclo*-structure of this base and that it was now regarded as the 3α-amine (XXXIII). A copy of the MS. of this paper was sent on August 17th, 1954, to Professor R. D. Haworth; in a letter of September 8th, 1954, Professor Haworth and Dr. McKenna informed us that further work, which will be communicated shortly, has shown that the bases, previously regarded as 3 : 5-*cyclo*pregnanes, are in fact the 3α-substituted pregn-5-enes (XXXIII) and (XXXVIII) respectively.

successive nitration and reduction with zinc–acetic acid yielded 6-oxo*allo*pregnan-3β-ol (XLII; R = H); the toluene-*p*-sulphonate of this, on reduction with sodium borohydride, furnished 6β-hydroxy-3β-toluene-*p*-sulphonyloxy*allo*pregnane (XLIII), which by solvolysis

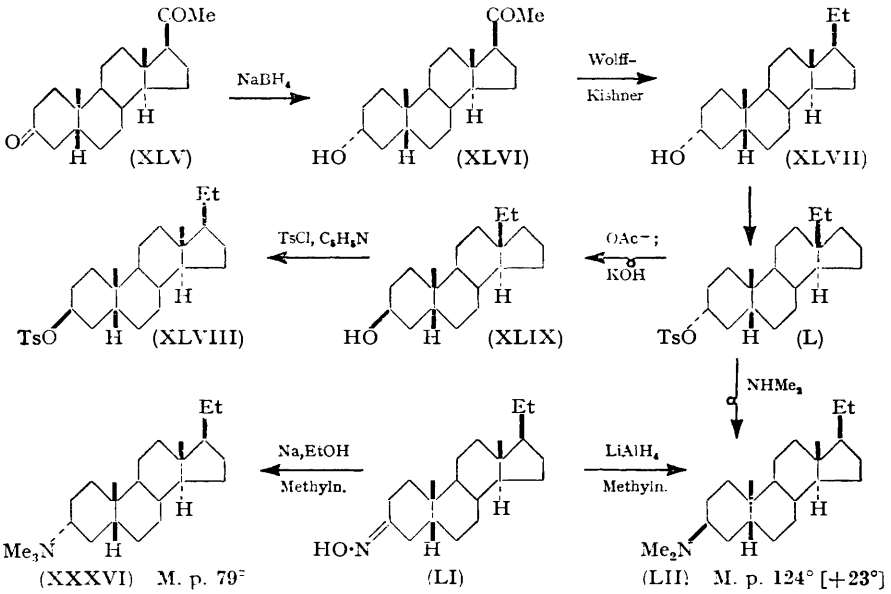


with dimethylamine furnished with inversion of configuration 6β-hydroxy-*NN*-dimethyl*allo*-pregnan-3α-ylamine (XLIV), smoothly dehydrated by phosphorus oxychloride–pyridine at 20° to *NN*-dimethylpregn-5-en-3α-ylamine (XXXVIII).



In an attempt to ascertain the structure of the base (XXXVI), we have prepared *NN*-dimethylpregnan-3α- and -3β-ylamine by the following methods. Pregnane-3 : 20-dione (XLV) was converted by differential reduction with sodium borohydride into 3α-hydroxypregnan-20-one (XLVI) (Mancera, Ringold, Djerassi, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1953, **75**, 1286), which by Wolff–Kishner reduction gave pregnan-3α-ol (XLVII). This alcohol was converted into the toluene-*p*-sulphonate (L), a portion of which by solvolysis with dimethylamine gave with inversion of configuration *NN*-dimethylpregnan-3β-ylamine (LII). We have also obtained this base, m. p. 124°, from pregnan-3-one oxime (LI) by reduction with lithium aluminium hydride and methylation of the

primary base; when the oxime (LI) was reduced, however, with sodium–ethanol and the resulting primary base methylated,* we obtained the base, m. p. 79°, (XXXVI), which is therefore *NN*-dimethylpregnan-3α-ylamine. The hydrogenations (XXXIII ⟶ XXXVI) and (XXXVIII ⟶ XXXVI) thus afford further examples of the influence of a 3α-substituent on the stereochemical course of reduction of a 5 : 6-double bond (Lewis and Shoppee, *locc. cit.*).



The residue of the toluene-*p*-sulphonate (L) was subjected to successive acetolysis and alkaline hydrolysis to yield a mixture of pregn-2- and pregn-3-enes accompanied by pregnan-3β-ol (XLIX); this alcohol was converted into the toluene-*p*-sulphonate (XLVIII), which was heated with dimethylamine. Unexpectedly, the product was a base, $C_{23}H_{41}N$, m. p. 142°, for which we are unable to suggest a structure. It is clearly different from the isomeric bases (XXXVI) and (LII); it may be a polymorphic form of the base (XXXVI), although we have so far been unable to convert this into the compound, m. p. 142°.

Configurational studies (Shoppee, *J.*, 1946, 1138) and kinetic investigations (Winstein and Adams, *J. Amer. Chem. Soc.*, 1948, **70**, 838; Hafez, Halsey, and Wallis, *Science*, 1949, **110**, 475; Pearson, King, and Langer, *J. Amer. Chem. Soc.*, 1951, **73**, 4149; Davies, Meecham, and Shoppee, *J.*, 1955, 679) have led to the view that replacement reactions at $C_{(3)}$ in 3β-substituted Δ^5-steroids occur through a unimolecular heterolysis, giving rise to a carbonium ion, whose configuration (sp^3-hybridisation with a vacant orbital) is preserved by interaction with the π-electrons of the 5 : 6-double bond and which (with appropriate rehybridisation) can react in three ways: (*a*) by union with an external anion and with retention of configuration at $C_{(3)}$, (*b*) by rearrangement with inversion at $C_{(3)}$ to give a 6β-substituted 3 : 5-*cyclo*steroid, and (*c*) by internal depolarisation with ejection of a proton to give a 3 : 5-diene. It now appears that in 3β-substituted Δ^5-steroids, under appropriate conditions, *e.g.*, in media of low dielectric constant, and with nucleophiles of sufficient power, the unimolecular heterolysis leading to the sequelæ (*a*), (*b*), or (*c*) may be accompanied, or even largely superseded, by a bimolecular substitution † with inversion of configuration at $C_{(3)}$ in which the π-electrons of the 5 : 6-double bond do not participate.

This S_N2 process provides a new method for the preparation of 3α-substituted Δ^5-steroids

* Professor R. D. Haworth and Dr. McKenna inform us that they have also obtained the base of m. p. 79° by this proceedure.

† S_N2 replacement in homoallylic systems has recently been envisaged as a competing reaction path by Winstein and Simonetta (*J. Amer. Chem. Soc.*, 1954, **76**, 21; formula XV) but without stereochemical implications.

from their 3β-analogues, which is particularly useful when the entering group is a strong nucleophile, such as an organic base which acts also as the medium for the reaction (3β-substituent *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$, Hal; resulting 3α-substituent = NH_2, NHR, NR_2). Whilst 3α-substituted A/B-*trans* saturated and Δ^5-steroids are accessible from their 3β-analogues by epimerisation, the yields are relatively poor both for covalently unsaturated groups (*e.g.*, CO_2Me, CO_2H, $CO{\cdot}NH_2$, COMe, CN) and for co-ordinatively unsaturated groups (*e.g.*, OH), because the position of equilibrium is controlled by molecular geometry whereby the percentage of the 3β(equatorial)-epimeride largely exceeds that of the 3α(axial)-epimeride; the situation is of course reversed in saturated steroids of the A/B-*cis*-series.

Experimental

For general experimental directions see preceding paper. $[\alpha]_D$ are measured in $CHCl_3$.

N-Benzylcholest-5-en-3α-ylamine (VII).—(i) Cholesteryl chloride (29 g.) was refluxed with benzylamine (60 c.c.) for 2 hr., the mixture cooled and diluted with ether (500 c.c.), and the precipitated benzylamine hydrochloride removed. Removal of the ether and addition of dilute hydrochloric acid furnished the water-insoluble hydrochlorides of the epimeric *N*-benzylcholest-5-en-3-ylamines and of *N*-benzyl-3 : 5-*cyclo*cholestan-6β-ylamine. Washing with water and ether removed the ether-soluble hydrochloride of the 3 : 5-*cyclo*-base, and the residue was basified with dilute aqueous ammonia. Ether-extraction furnished an oil (9·7 g.) which was chromatographed on a column of aluminium oxide (250 g.) prepared in pentane. Elution with pentane (200 c.c.) furnished a solid (650 mg.), m. p. 60—68°, whilst use of benzene–pentane (1 : 19; 4 × 200 c.c.) furnished an oil (1·8 g.). Elution with benzene–pentane (1 : 1; 8 × 100 c.c.) gave a solid (4·06 g.), which was recrystallised from acetone to furnish *N*-benzylcholest-5-en-3α-ylamine (3·2 g.), m. p. 88—90°, $[\alpha]_D$ −10° (*c*, 1·4) (Vavasour *et al.*, *Canad. J. Res.*, 1952, **30**, 933, report m. p. 90—91°, $[\alpha]_D$ −9°).

(ii) 6β-Hydroxycholestan-3β-yl toluene-*p*-sulphonate (Shoppee and Stephenson, *J.*, 1954, 2230) (550 mg.) was refluxed with benzylamine (5 c.c.) for 2 hr. Dilution with water, acidification with hydrochloric acid, and ether-washing of the insoluble hydrcchloride gave, after basification and isolation of the product in the usual manner, *N*-benzyl-6β-hydroxycholestan-3α-ylamine (280 mg.) as an oil, which failed to crystallise. The oil was dissolved in pyridine (5 c.c.), and phosphorus oxychloride (0·3 c.c.) added at 15°. After 1 hr. the solution was diluted with water, made alkaline with 2N-potassium hydroxide, and extracted with ether. Drying and removal of solvents gave a product, which was filtered through a column of aluminium oxide in benzene–pentane (1 : 1), and crystallised from ethanol to furnish *N*-benzylcholest-5-en-3α-ylamine, m. p. 88—90°, identical with material obtained in the previous preparation.

N-Benzyl-6-oxocholestan-3β-ylamine (XIII).—(i) 3β-Chlorocholestan-6-one (5 g.) was refluxed with benzylamine (25 c.c.) for 2 hr. Dilution with ether and removal of the precipitated benzylamine hydrochloride furnished a filtrate, which after removal of ether and dilution with water gave a solid; this was recrystallised from ethanol to yield *N-benzyl-6-oxocholestan-3β-ylamine* (2·4 g.), m. p. 158°, $[\alpha]_D$ −9° (*c*, 1·6) [Found (after sublimation at 160°/0·005 mm.) : C, 82·7; H, 10·8. $C_{34}H_{53}ON$ requires C, 83·0; H, 10·7%].

(ii) 3 : 5-*cyclo*Cholestan-6-one (1 g.) and benzylamine hydrochloride (250 mg.) were refluxed with benzylamine (10 c.c.) for 2 hr. Dilution with water and acidification with hydrochloric acid furnished a precipitate which was removed, dissolved in ethanol, and basified by addition of N-ethanolic potassium hydroxide. Dilution with water, followed by ether-extraction, gave, after removal of solvent and crystallisation from ethanol, *N*-benzyl-6-oxocholestan-3β-ylamine, m. p. 158°, identical with the material obtained in the previous preparation. Refluxing of 3 : 5-*cyclo*cholestan-6-one with benzylamine in the absence of benzylamine hydrochloride resulted in quantitative recovery of the starting material.

N-Benzyl-6β-hydroxycholestan-3β-ylamine (XII).—*N*-Benzyl-6-oxocholestan-3β-ylamine (2 g.) in ether (50 c.c.) was treated at 15° with a solution of lithium aluminium hydride (2 g.) in ether (50 c.c.) for 30 min. Excess of lithium aluminium hydride was decomposed by the addition of water; 50% aqueous potassium hydroxide (50 c.c.) was added and the product extracted with ether. Drying and removal of solvent furnished *N-benzyl-6β-hydroxycholestan-3β-ylamine* (1·5 g.), which, crystallised from ether–acetone, had m. p. 178°, $[\alpha]_D$ +7° (*c*, 2·2) [Found (after sublimation at 200°/0·005 mm.) : C, 83·0; H, 11·1; N, 2·5. $C_{34}H_{55}ON$ requires C, 82·7; H, 11·2; N, 2·8%].

N-Benzylcholest-5-en-3β-ylamine (V).—*N*-Benzyl-6β-hydroxycholestan-3β-ylamine (1 g.) was treated in pyridine with phosphorus oxychloride (2 c.c.) at 10°. After 2 hr. at 15° water was

added, and the precipitated solid removed, dissolved in ether, and washed with 2N-potassium hydroxide. Drying and removal of solvent furnished *N*-benzylcholest-5-en-3β-ylamine (760 mg.), m. p. 116—117°, $[\alpha]_D$ −24° (*c*, 1·1), after crystallisation from ethanol (Julian *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 1834, report m. p. 116°).

Cholest-5-en-3α-ylamine (XVIII).—(i) 6β-Hydroxycholestan-3β-yl toluene-*p*-sulphonate (850 mg.) and liquid ammonia (50 c.c.) were heated in a stainless-steel autoclave at 100° for 18 hr., then cooled to 15°. Excess of ammonia was allowed to evaporate, and the brown solid product (810 mg.) collected; an ether–chloroform solution of the product was washed with water, dried, and evaporated to give a gel which was purified by chromatography on aluminium oxide (7 g.). Elution with acetone (200 c.c.) yielded a solid, which by crystallisation from acetone gave *6β-hydroxycholestan-3α-ylamine* as needles, double m. p. 114—115° and 160—162°, $[\alpha]_D$ +19° (*c*, 1·04) [Found (after drying at 60°/0·01 mm. for 3 hr.): C, 80·2; H, 12·3. $C_{27}H_{49}ON$ requires C, 80·3; H, 12·2%]. Further elution with acetone–methanol and methanol gave material difficult to crystallise because it tended to form a gel; all the fractions were united (450 mg.) and treated in pyridine with phosphorus oxychloride (5 drops) at 0°. The dark solution was allowed to attain room temperature, left for 0·25 hr., and poured into ice-cold 2N-hydrochloric acid; the hydrochloride was filtered off, washed with 2N-hydrochloric acid and with water, dried (porous porcelain), and basified with potassium hydroxide, and the resultant oil was extracted with ether. The product (220 mg.) was chromatographed on aluminium oxide (5 g.); elution with benzene–ether (1 : 1), ether, ether–acetone (1 : 1), and acetone gave fractions which failed to crystallise, and whose solutions tended to discolour. The fractions were therefore combined and acetylated with acetic anhydride at 100° to give a solid, which after several recrystallisations from acetone–pentane yielded needles, m. p. 180—186°. Sublimation at 120—130°/0·02 mm. gave 3α-acetamidocholest-5-ene, m. p. 187—189°, $[\alpha]_D$ −30° (*c*, 0·89) (Found: C, 81·2; H, 11·7. Calc. for $C_{29}H_{49}ON$: C, 81·4; H, 11·55%).

(ii) *N*-Benzylcholest-5-en-3α-ylamine, prepared according to the procedure of Vavasour *et al.* (*loc. cit.*), was degraded by hypochlorous acid to the chloramine, dehydrochlorination to afford the benzylidene compound with sodium ethoxide, and acid hydrolysis according to the directions of Vavasour *et al.* The base did not crystallise, and was acetylated by treatment with acetic anhydride at 100°; the resultant solid by recrystallisation from acetone–pentane and sublimation at 120—130°/0·02 mm. gave 3α-acetamidocholest-5-ene, m. p. and mixed m. p. 189°; Vavasour *et al.* record m. p. 189°.

The amide by hydrolysis with 2N-hydrochloric acid under nitrogen and appropriate working up gave *cholest-5-en-3α-ylamine*, m. p. 90° after crystallisation from pentane, raised to 100° on sublimation at 120°/0·02 mm., $[\alpha]_D$ −40° (*c*, 0·89) (Found: C, 84·0; H, 12·4. $C_{27}H_{47}N$ requires C, 84·1; H, 12·3%). The base, with acetic anhydride, regenerated the acetyl derivative, m. p. 189° after crystallisation from acetone–pentane, and by methylation with formaldehyde–formic acid gave after chromatography of the reaction product, *NN*-dimethylcholest-5-en-3α-ylamine (XXVIII), m. p. 70°, $[\alpha]_D$ −29° (*c*, 0·5) after crystallisation from acetone–pentane (cf. refs. *e* and *f*, pp. 695, 696).

Pregn-5-en-3β-ol (m. p. 134°) was prepared from 3β-hydroxypregn-5-en-20-one in 88% yield by Huang-Minlon's method (*J. Amer. Chem. Soc.*, 1949, **71**, 3301) and acetylated to furnish 3β-acetoxypregn-5-ene, m. p. 149—150°, $[\alpha]_D$ −60° (*c*, 2·3).

6-Nitropregn-5-en-3β-yl Acetate.—Nitration in ether with fuming nitric acid according to Anagnostopoulos and Fieser's method (*J. Amer. Chem. Soc.*, 1954, **76**, 532) gave mainly unchanged starting material. Pregn-5-en-3β-yl acetate (850 mg.) was therefore dissolved in glacial acetic acid (50 c.c.), and fuming nitric acid (8 c.c.) added with external cooling. After 30 min., water was added, and the precipitated solid washed, dried, and crystallised from methanol to furnish the *6-nitro-compound* as needles, m. p. 136°, $[\alpha]_D$ −91° (*c*, 1·4) [Found (after drying at 60°/0·005 mm. for 12 hr.): C, 70·9; H, 9·2. $C_{23}H_{35}O_4N$ requires C, 70·9; H, 9·1%].

6-Oxoallopregnane-3β-yl Acetate (XLII; R = Ac).—6-Nitropregn-5-en-3β-yl acetate (2 g.) was dissolved in 90% acetic acid (50 c.c.); zinc dust (5 g.) was added during 30 min. to the refluxing mixture. After a total reflux period of 3 hr. the solution was decanted, the zinc dust was extracted with hot acetic acid, and the combined extracts were cooled and diluted with water to furnish a solid, which after washing and drying crystallised from methanol to furnish *6-oxoallopregnan-3β-yl acetate* (1·24 g.), m. p. 173—174°, $[\alpha]_D$ −24·5° (*c*, 1·2) [Found (after sublimation at 160°/0·005 mm.): C, 76·2; H, 10·0. $C_{23}H_{36}O_3$ requires C, 76·6; H, 10·1%].

6-Oxoallopregnan-3β-ol (XLII; R = H).—The foregoing acetate (1·2 g.) was refluxed with N-methanolic potassium hydroxide for 1 hr., the solution diluted with water, and the product extracted with ether to yield, after washing, drying, and removal of solvent and crystallisation

from methanol, 6-*oxo*allo*pregnan*-3β-*ol* (1·05 g.) as plates, m. p. 165°, $[\alpha]_D$ −13° (*c*, 1·1) [Found (after sublimation at 140°/0·005 mm.): C, 78·9; H, 11·1. $C_{21}H_{34}O_2$ requires C, 79·2; H, 10·8%].

6-*Oxo*allo*pregnan*-3β-*yl Toluene*-p-*sulphonate* (XLII; R = *p*-$C_6H_4Me{\cdot}SO_2$).—6-Oxo*allo*-pregnan-3β-ol (750 mg.) (dried by azeotropic distillation with benzene) was treated in pyridine (4 c.c.) at 25° with toluene-*p*-sulphonyl chloride (750 mg.) for 8 hr. Dilution with water gave, after the usual washing and drying, 6-*oxo*allo*pregnan*-3β-*yl toluene*-p-*sulphonate* (505 mg.), m. p. 157—158°, $[\alpha]_D$ −9° (*c*, 1·1), after 3 crystallisations from ether [Found (after drying at 60°/0·005 mm. for 12 hr.; C, 71·1; H, 8·6. $C_{28}H_{40}O_4S$ requires C, 71·2; H, 8·5%].

6β-*Hydroxy*allo*pregnan*-3β-*yl Toluene*-p-*sulphonate* (XLIII).—6-Oxo*allo*pregnan-3β-yl toluene-*p*-sulphonate (500 mg.), dissolved in dioxan (10 c.c.) and methanol (20 c.c.), was treated with a solution of sodium borohydride (50 mg.) in water (0·1 c.c.) and methanol (2 c.c.) at 15° for 2 hr. Dilution with water, filtration, washing, and drying gave 6β-*hydroxy*allo*pregnan*-3β-*yl toluene*-p-*sulphonate* (460 mg.) which, crystallised from ether–pentane, had double m. p. 143° and 151°, $[\alpha]_D$ −11·5° (*c*, 1·4) [Found (after drying at 60°/0·005 mm. for 12 hr.): C, 70·6; H, 8·9. $C_{28}H_{42}O_4S$ requires C, 70·9; H, 8·9%].

6β-*Hydroxy*-NN-*dimethyl*allo*pregnan*-3α-*ylamine* (XLIV).—6β-Hydroxy*allo*pregnan-3β-yl toluene-*p*-sulphonate (XLIII) (400 mg.) was heated in a sealed tube at 110° with dimethylamine (10 c.c. of 33% w/w solution) for 5 hr. Evaporation, dilution with ether and N-hydrochloric acid, and addition of potassium hydroxide to the aqueous hydrochloride solution precipitated the base, which was extracted with ether from its strongly alkaline suspension, and then dried. The ether was removed (washing of the ether-extracts to neutrality results in loss of slightly water-soluble base). Crystallisation from 70% methanol gave 6β-*hydroxy*-NN-*dimethyl*allo-*pregnan*-3α-*ylamine* as plates, m. p. 142—150°, raised after sublimation to 145—152°, $[\alpha]_D$ +14° (*c*, 0·8) (yield, 136 mg.) [Found (after sublimation at 140°/0·005 mm.): C, 79·4; H, 11·7. $C_{23}H_{41}ON$ requires C, 79·5; H, 11·9%].

NN-*Dimethylpregn*-5-*en*-3α-*ylamine* (XXXVIII).—6β-Hydroxy-*NN*-dimethyl*allo*pregnan-3α-ylamine (90 mg.) in pyridine (0·5 c.c.) was treated with phosphorus oxychloride (0·2 c.c.) at 15° for 2·5 hr. Dilution with water furnished a precipitate which was filtered off and dissolved in N-ethanolic potassium hydroxide (5 c.c.). Dilution with water furnished a solid, which by recrystallisation from acetone furnished *NN*-dimethylpregn-5-en-3α-ylamine, m. p. 131—132° (after sublimation, m. p. 135°), giving no depression on admixture with a specimen, m. p. 130°, kindly supplied by Professor R. D. Haworth, $[\alpha]_D$ −37·5° (*c*, 1·1) [Found (after sublimation at 150°/0·005 mm.): C, 83·8; H, 11·6. $C_{23}H_{39}N$ requires C, 83·8; H, 11·9%].

Pregnan-3α-*ol*.—3α-Hydroxypregnan-20-one (1·5 g.) (Mancera, Ringold, Djerassi, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1953, **75**, 1286) was refluxed in diethylene glycol (50 c.c.) with sodium hydroxide (2·5 g.) and hydrazine (0·75 c.c.) for 30 min.; the reflux temperature was allowed to rise to 200° and refluxing continued for 2 hr. Dilution with water gave a solid which was dried and chromatographed on aluminium oxide (45 g.). Benzene–pentane (1 : 9 and 1 : 4; each 150 c.c.) gave an oil (20 mg.) whilst use of benzene–pentane (3 : 7; 1 × 150 c.c. and 2 : 3; 2 × 150 c.c.) gave a solid (1·24 g.), which after several crystallisations from methanol furnished pregnan-3α-ol, m. p. 144—146° (Marker and Lawson, *J. Amer. Chem. Soc.*, 1938, **60**, 2938, report m. p. 148°). Further elution with benzene gave oils.

Pregnan-3α-*yl Toluene*-p-*sulphonate*.—Pregnan-3α-ol (950 mg.) was dissolved in pyridine (5 c.c.), with toluene-*p*-sulphonyl chloride (1 g.) added. After 20 hr. at 20°, water was added, and the precipitated solid *ester* filtered off, washed, dried, and crystallised from acetone; it had m. p. 132—134° $[\alpha]_D$ +43° (*c*, 1·1) (yield 990 mg.) [Found (after drying at 60°/0·005 mm. for 3 hr.): C, 73·3; H, 9·2. $C_{28}H_{42}O_3S$ requires C, 73·3; H, 9·2%].

Pregnan-3β-*ol*.—The foregoing ester (500 mg.) was heated at 100° for 3 hr. in acetic acid (15 c.c.) with fused potassium acetate (5 g.). Dilution with water and isolation of the product in the usual manner afforded an oil which was refluxed in N-methanolic potassium hydroxide (10 c.c.) for 1 hr., then diluted with water, and the product was extracted with ether. Drying and removal of solvent gave an oil which was chromatographed on a column of aluminium oxide (12 g.). Pentane (100 c.c.) gave a solid (125 mg.) which even after several crystallisations melted over the range 54—78° and had $[\alpha]_D$ +18° (*c*, 2·3) [Found (after sublimation at 120°/0·005 mm.): C, 88·4; H, 12·2. Calc. for $C_{21}H_{34}$: C, 88·0; H, 12·0%]; hydrogenation of the mixture of Δ^2- and Δ^3-pregnene (20 mg.) in ethyl acetate (5 c.c.) in the presence of platinum oxide (10 mg.) gave pregnane, m. p. 78—80°, identical with an authentic specimen kindly supplied by Professor Reichstein. Use of ether as eluant then gave a solid (193 mg.) which after two crystallisations from methanol gave pregnan-3β-ol, m. p. 141—144°, giving a depression of m. p. on admixture with pregnan-3α-ol (Marker and Lawson, *loc. cit.*, report m. p. 144°).

*Pregnan-3β-yl Toluene-*p*-sulphonate.*—Pregnan-3β-ol (120 mg.) in pyridine (1 c.c.) was treated with toluene-*p*-sulphonyl chloride (150 mg.) at 20°. After 12 hr. water was added, and the precipitated solid filtered off, washed and dried to furnish the 3β-*toluene*-p-*sulphonate*, m. p. 98—101°, $[\alpha]_D$ +23° (*c*, 1·0) (yield 105 mg.) [Found (after drying at 60°/0·005 mm. for 3 hr.): C, 73·5; H, 9·8. $C_{28}H_{42}O_3S$ requires C, 73·3; H, 9·2%].

NN-*Dimethylpregnan-3β-ylamine.*—(*a*) The foregoing ester (300 mg.) was heated in a sealed tube at 110° for 5 hr. with dimethylamine (7 c.c.; 33% w/w). Evaporation of the excess of dimethylamine, dilution with ether, and precipitation of the hydrochloride gave a solid which was dissolved in N-methanolic potassium hydroxide and diluted with water. The base was extracted with ether. Drying and removal of solvent gave NN-*dimethylpregnan-3β-ylamine*, m. p. 124°, $[\alpha]_D$ +23° (*c*, 0·85) after recrystallisation from acetone [Found (after sublimation at 130°/0·01 mm.): C, 83·6; H, 12·2; N, 4·3. $C_{23}H_{41}N$ requires C, 83·3; H, 12·5; N, 4·2%].

(*b*) *Pregnan-3-one oxime* (350 mg.), m. p. 165—167°, $[\alpha]_D$ +66° (*c*, 0·97) [Found (material dried at 100°/0·02 mm. for 2 hr.): C, 79·8; H, 11·0. $C_{21}H_{35}ON$ requires C, 79·5; H, 11·1%], was reduced in ethereal solution with lithium aluminium hydride during 3 hr. Pregnan-3β-ylamine was isolated in the usual way as an oil, which, after distillation at 120—140°/0·02 mm., crystallised from ether in needles, m. p. 78° after softening from 65°; 3β-*acetamidopregnane*, prepared in the usual manner, crystallised from acetone in plates, m. p. 213° [Found (after sublimation at 230°/0·02 mm.): C, 79·6; H, 11·3. $C_{23}H_{39}ON$ requires C, 79·9; H, 11·3%]. Methylation of the base with formaldehyde–formic acid gave *NN*-dimethylpregnan-3β-ylamine, m. p. 124° after sublimation at 140—150°/0·01 mm., and recrystallisation from acetone, identical with a specimen prepared by method (*a*).

NN-*Dimethylpregnan-3α-ylamine.*—Pregnan-3-one oxime (250 mg.) was treated with sodium in boiling ethanol. The product was isolated as an oil, which by sublimation at 120—140°/0·02 mm. gave crystalline material, m. p. 125—140° (polymorphic form ?); this by recrystallisation from ether gave pregnan-3α-ylamine as tiny prisms, m. p. 158—161°, $[\alpha]_D$ +43° (*c*, 1·0) [Found (after sublimation at 140°/0·02 mm.): C, 83·3; H, 12·0. $C_{21}H_{37}N$ requires C, 83·1; H, 12·3%]. 3α-*Acetamidopregnane*, prepared in the usual way, crystallised from acetone as plates, m. p. 220°, $[\alpha]_D$ +46° (*c*, 1·1) [Found (after sublimation at 200°/0·02 mm.): C, 79·4; H, 11·4. $C_{23}H_{39}ON$ requires C, 79·9; H, 11·3%]. The base was methylated with formaldehyde–formic acid to yield an oil, which was obtained crystalline from acetone with some difficulty, and was chromatographed on a column of aluminium oxide. Elution by repeated washing with pentane gave an oil, which was sublimed at 110—130°/0·02 mm., and the sublimate crystallised with difficulty from acetone to yield *NN*-dimethylpregnan-3α-ylamine, m. p. 75—77°, after softening from 70°.

*Action of Dimethylamine on Pregnan-3β-yl Toluene-*p*-Sulphonate.*—The toluene-*p*-sulphonate (80 mg.) was treated at 110° with 33% (w/w) dimethylamine (2·5 c.c.) for 3 hr. The product was extracted with ether, washed with N-potassium hydroxide, and dried, and the solvent then removed. Chromatography of the product on aluminium oxide (2 g.), with pentane (15 c.c.) as eluant, gave an oil (5 mg.) whilst benzene (15 c.c.) furnished a solid (33 mg.) which after two crystallisations from acetone gave a base, $C_{23}H_{41}N$, m. p. 142—144° [Found (after sublimation at 140°/0·005 mm.): C, 83·1; H, 12·0%]. There was insufficient material to permit determination of $[\alpha]_D$.

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