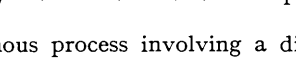
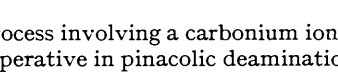
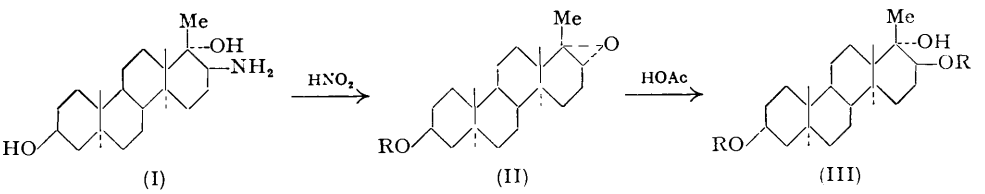
380. *Steroids and Walden Inversion. Part X.* The Reconversion* D-*Homosteroids into Steroids.*

By R. J. W. Cremlyn, D. L. Garmaise, and C. W. Shoppee.

On the basis of stereoelectronic considerations the smooth conversion of 17α-amino-17*a*β-hydroxy-17*a*-methyl-D-homoandrost-5-en-3β-ol (IX) by deamination into 17-*iso*pregnenolone has been achieved. The 17*a*-epimeride (VII) of (IX) by deamination gives 17-*iso*pregnenolone accompanied by relatively much of the 17α : 17*a*α-epoxide (X). These results suggest that a synchronous process involving a diazonium ion :  rather than a process involving a carbonium ion :  may be operative in pinacolic deamination in cyclic systems.

Deamination with nitrous acid of the dihydroxy-amine (I) was found by Ruzicka and Meldahl (*Helv. Chim. Acta*, 1941, **24**, 1321) to give an epoxide (II ; R = H). The structure of this epoxide was proved by acetolysis of its acetate (II ; R = Ac) by Ruzicka and Meldahl to a triol diacetate (III ; R = Ac) hydrolysed by alkali to a triol (III ; R = H) which was obtained by Ruzicka, Gätzi, and Reichstein (*Helv. Chim. Acta*, 1939, **22**, 676) and by Stavely (*J. Amer. Chem. Soc.*, 1941, **63**, 3127) ; the structure of the triol was first correctly given by Shoppee and Prins (*Helv. Chim. Acta*, 1943, **26**, 201).



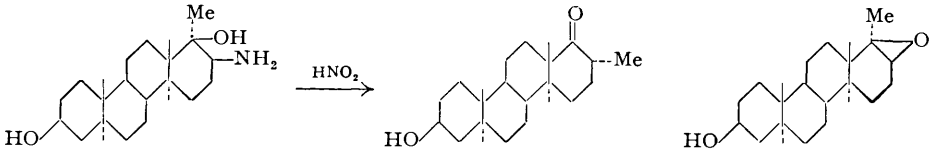
(I) (II) (III)

During a study of methods for the conversion of D-homosteroids into steroids, the 17*a*-epimeric dihydroxy-amine (IV) was found by Prins and Shoppee (*J.*, 1946, 494) to give a substance isomeric with (II ; R = H), which they regarded as the 17β : 17*a*β-epoxide (VI) because it appeared in the non-ketonic fraction on Girard separation, but this substance has since been shown by Klyne (*Nature*, 1950, **166**, 559) to be identical with the 3β-hydroxy-17*a*-ketone (V) (≡ " uranolone ") of Marker and Rohrmann (*J. Amer. Chem. Soc.*, 1938, **60**, 2719).

The dihydroxy-amines (I) and (IV) were each obtained by catalytic hydrogenation, with platinum and acetic acid, of the oximes of the corresponding dihydroxy-ketones. Examples of the reduction of oximes may be found in the recent work of McNiven and Read (*J.*, 1952, 153) on the isomeric menthylamines. It is clear from the behaviour of the menthylammonium hydroxides on decomposition that the amines produced by reduction of the oximes with sodium and ethanol have equatorial amino-groups, whilst those produced by catalytic hydrogenation have polar amino-groups. It therefore is

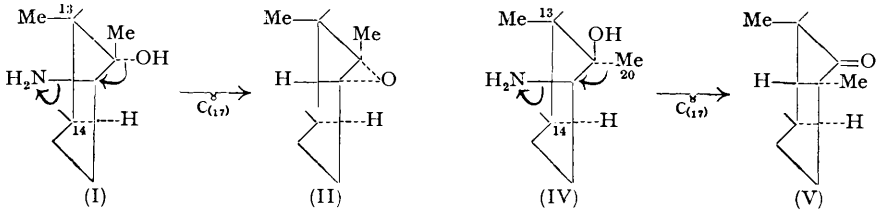
* Part IX, *J.*, 1953, 241 ; Part XI, *J.*, 1953, 1709.

highly probable that the amino-groups in the D-homohydroxy-amines are polar (*i.e.*, 17β) as in (I) and (IV).



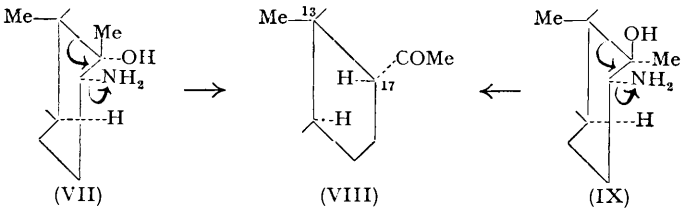
(IV) (V) (VI)

The rearrangement (I ⟶ II) may now be represented as follows (cf. Klyne and Shoppee, *Chem. and Ind.*, 1952, 470). The polar hydroxyl group (17*a*α) and the polar amino-group (17β) afford a transition state with four coplanar centres [O, $C_{(17a)}$, $C_{(17)}$, N] leading with inversion at $C_{(17)}$ to the 17α : 17*a*α-epoxide (II). Similarly, the rearrangement (IV ⟶ V) may be represented by interaction of the polar methyl group [17*a*α] and the polar amino-group [17β] to furnish a transition state with four coplanar centres [$C_{(20)}$, $C_{(17a)}$, $C_{(17)}$, N] leading with inversion at $C_{(17)}$ to the 17α-methyl ketone (V).



(I) (II) (IV) (V)

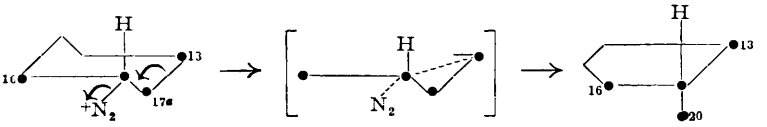
These stereo-electronic considerations suggest that 17-epimeric dihydroxy-17α-amines (VII, IX; NH_2 equitorial) should undergo deamination with rearrangement accompanied by ring-decrease to give 17α-pregnan-20-ones (VIII). In either case a transition state involving the four coplanar centres [$C_{(13)}$, $C_{(17a)}$, $C_{(17)}$, N] should lead with retention of configuration * at $C_{(17)}$ to the ketone [" 17-*iso*pregnenolone "] (VIII).†



(VII) (VIII) (IX)

The 17*a*-epimeric dihydroxy-17α-amines (VII, IX) were prepared by reduction of the oximes of the corresponding 17-ketones with sodium and propanol; they were carefully purified and appeared homogeneous. Deamination of (IX) gave, as sole crystalline product

* As a consequence of the formation of a linear transition state, there is a *formal* inversion of configuration at $C_{(17)}$ in the transformation of both (VII) and (IX) into the ketone (VIII); there is, however, no *actual* inversion of configuration at $C_{(17)}$ because the hydrogen atom attached to $C_{(17)}$ does not cross the plane of ring D :

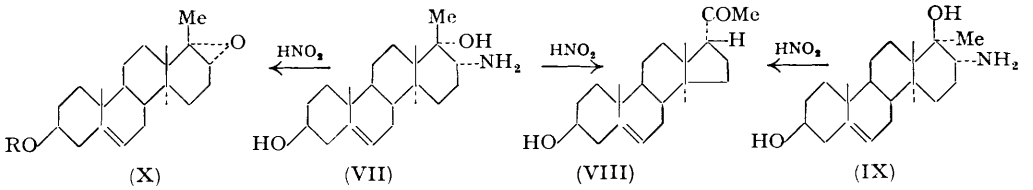


Linear transition state

(D-Homosteroid $C_{(17a)}$ becomes steroid $C_{(20)}$.)

† Since this paper was written our attention has been directed to the work of McCasland (*J. Amer. Chem. Soc.*, 1951, **73**, 2293) on the deamination of the *cis*- and *trans*-2-hydroxy*cyclo*hexylamines which each exist as a non-resolvable mixture of two antimeric equatorial-polar conformations. In our case all four conformations correspond to individual substances.

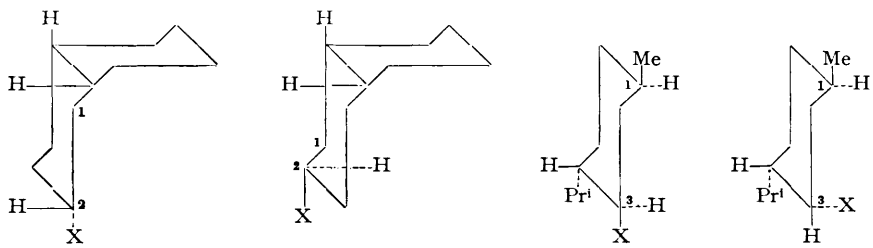
and in good yield, 17-*iso*pregnenolone (VIII), m. p. 172—173°, $[\alpha]_D$ −138° {Butenandt and Fleischer (*Ber.*, 1937, **70**, 96) give m. p. 172°, $[\alpha]_D$ −140°}, characterised as the acetate, m. p. 171°.



(X) (VII) (VIII) (IX)

By contrast, deamination of (VII) led to a mixture separated by use of Girard's reagent T into a relatively small quantity of 17-*iso*pregnenolone (VIII) and a relatively large amount of the 17α : 17aα-epoxide (X; R = H); the latter, as the acetate, by hydrogenation gave a product, m. p. 161°, which appeared to correspond with the epoxide (II; R = Ac).

It has been shown by Ingold, Hughes, *et al.* (*Nature*, 1950, **166**, 178) on the basis of configurational studies that, for simple aliphatic primary amines, the last steps of deamination must have the form of a S_N1 process involving a carbonium-ion intermediate : $R{\cdot}NH_2 \longrightarrow R{\cdot}\overset{+}{N}{\equiv}N \longrightarrow \overset{+}{R}$. It appears that in cyclic systems molecular geometry may confer importance upon the earlier diazonium-ion intermediate. Thus the epimeric *cis*-2-decalylamines (XI, XII; X = NH_2, equatorial in both epimers *) undergo deamination to give the epimeric *cis*-2-decalols (XI, XII; X = OH) with almost complete retention of configuration (Dauben and Hoerger, *J. Amer. Chem. Soc.*, 1951, **73**, 1504); these observations seem to exclude a carbonium-ion intermediate. On the other hand, whilst (−)-



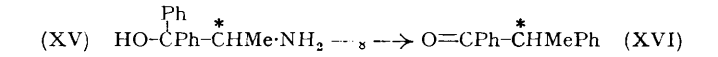
(XI) (XII) (XIII) (XIV)

menthylamine (XIII; X = NH_2, equatorial) is deaminated to (−)-menthol (XIII; X = OH) with retention of configuration and so presumably without intervention of a carbonium ion, (+)-*neo*menthylamine (XIV; X = NH_2, polar) gives (+)-*p*-menth-3-ene (elimination) (cf. Birch, *Ann. Reports*, 1950, **47**, 192), accompanied by *p*-menthan-4-ol (rearrangement), products which suggest the formation of a carbonium ion.

Ingold and Shoppee (*J.*, 1928, 365) originally classified pinacolic deamination of α-hydroxy-amines and Wagner rearrangements with elimination reactions; it is now known that the Wagner rearrangement is a form of unimolecular nucleophilic substitution or elimination [S_N1, $E1$] involving the carbonium ions $R{-}C_\alpha{-}C_\beta^+$ and $^+C_\alpha{-}C_\beta{-}R$ or their synartetic hybrid (Hughes, Ingold, *et al.*, *Nature*, 1951, **168**, 65). Whilst Ingold (*Ann. Reports*, 1928, **25**, 133) emphasised the importance of a carbonium-ion intermediate : $\bar{O}{-}C_\alpha R{-}C_\beta{-}\overset{+}{N}{\equiv}N \longrightarrow \bar{O}{-}\overset{R\rightarrow}{C_\alpha}{-}\overset{+}{C_\beta} \longrightarrow \bar{O}{-}\overset{+}{C_\alpha}{-}C_\beta R$, Shoppee (*Proc. Leeds Phil. Soc.*, 1928, **1**, 301) suggested the operation of a synchronous process involving a diazonium ion : $\bar{O}{-}\overset{R\rightarrow}{C_\alpha}{-}C_\beta{-}\overset{+}{N}{\equiv}N \longrightarrow \bar{O}{-}\overset{+}{C_\alpha}{-}C_\beta R$. Only the latter mechanism appears able to account for the preservation of optical activity, with inversion of configuration, in the pinacolic

* *cis*-Decalin exists in two equivalent conformations inter-convertible by transformation of all equatorial into polar bonds and *vice versa* (Hassel, *Research*, 1950, **3**, 504).

deamination of (−)-2-amino-1 : 1-diphenylpropanol (XV) to (+)-methyldeoxybenzoin (XVI) (McKenzie, Roger, and Wills, *J.*, 1926, 779).



If a carbonium ion is of major importance in pinacolic deamination then (I; α-OH, polar/β-NH_2, polar; *trans*) and (VII; α-OH, polar/α-NH_2, equatorial; *cis*) should yield the same main product(s), and the 17α : 17*a*α-epoxide (X) is formed from both (I) and (VII), the 17*a*-oxygen atom being geometrically favourably placed to maintain configuration in an intermediate carbonium ion. Similarly (IV; β-OH, equatorial/β-NH_2, polar; *cis*) and (IX; β-OH, equatorial/α-NH_2, equatorial: *trans*) should yield some common product(s). But now the oxygen atom is geometrically unfavourably placed for intervention and the methyl group has no electrons available to participate in maintaining configuration in a carbonium ion. Not only is no common product formed but each α-hydroxy-amine gives the product appropriate to the geometry of a precursor diazonium ion. This result suggests that in pinacolic deamination in polycyclic systems the diazonium ion is of major importance.

Experimental

For general details see *J.*, 1953, 1709. $[\alpha]_D$ are in $CHCl_3$ unless otherwise stated.

3β : 17aβ-*Dihydroxy*-17a-*methyl*-D-*homoandrost*-5-*en*-17-*one*.—3β : 17β-Dihydroxy-17α-ethynylandrost-5-ene was hydrated by Stavely's method (*J. Amer. Chem. Soc.*, 1941, **63**, 3217) to 3β : 17β-dihydroxy-17α-pregn-5-en-20-one, double m. p. 140° and 180°, $[\alpha]_D^{19}$ −61° ± 2° (cf. Shoppee and Prins, *Helv. Chim. Acta*, 1943, **26**, 201), which was rearranged on a column of aluminium oxide in moist benzene to the D-homoketone, m. p. 188°, $[\alpha]_D^{19}$ −108° ± 1° (*c*, 2·12) (Shoppee and Prins, *J.*, 1946, 494, record m. p. 188—190°, $[\alpha]_D^{18}$ −105° ± 5°). The oxime had m. p. 282° (lit., m. p. 283°).

17α-*Amino*-3β : 17aβ-*dihydroxy*-17a-*methyl*-D-*homoandrost*-5-*ene* (IX).—The ketoxime (m. p. 282°; 200 mg.) in propanol (20 c.c.; freshly distilled over sodium) was heated with sodium (1 g.) for 2 hr. The cooled solution was neutralised with glacial acetic acid, and solvent removed under reduced pressure; the residue was dissolved in water, the solution made slightly alkaline with 2N-sodium hydroxide, and the precipitated amine collected. This was dissolved in methanol (10 c.c.) and a few drops of concentrated hydrochloric acid were added; the crystalline hydrochloride was filtered off and dissolved in methanol (20 c.c.), and the solution made alkaline with methanolic potassium hydroxide. After partial removal of methanol, water was added dropwise to the hot solution; cooling gave the *amine* (IX) (122 mg.), m. p. 259—261°, $[\alpha]_D^{25}$ −106° ± 4° (*c*, 0·43 in dioxan), after recrystallisation from methanol [Found (after drying at 110°/0·01 mm. for 1 hr.): C, 75·6; H, 10·5; N, 4·6. $C_{21}H_{35}O_2N$ requires C, 75·6; H, 10·6; N, 4·2%].

Deamination of (IX) *to* 3β-*Hydroxy*-17α-*pregn*-5-*en*-20-*one* (VIII).—The amine (95 mg.) was dissolved in 50% acetic acid (2 c.c.), and a solution of sodium nitrite (100 mg.) in 50% acetic acid (2 c.c.) gradually added with stirring; a crystalline precipitate was formed and after 18 hr. the suspension was extracted with ether. Ether-insoluble material (20 mg.) was removed by filtration and the ethereal extract washed with ice-cold sodium hydrogen carbonate solution, ice-cold N-hydrochloric acid, and water, dried, and evaporated. The crystalline residue, m. p. 160—170°, recrystallised from acetone–hexane, gave 3β-hydroxy-17α-pregn-5-en-20-one (35 mg.), m. p. 171—172°, $[\alpha]_D^{18}$ −144° (*c*, 3·3); a mixture with an authentic sample, m. p. 173—174°, prepared by the method of Butenandt and Fleischer (*loc. cit.*) had m. p. 172—174°. The product after sublimation at 140°/0·01 mm. had m. p. 172—173°, $[\alpha]_D^{18}$ −138° ± 2° (*c*, 2·2) (Found: C, 79·05; H, 10·1. Calc. for $C_{21}H_{32}O_2$: C, 79·65; H, 10·2%), and was characterised as the acetate, m. p. 171° [Found (after drying at 90°/0·02 mm.): C, 77·3; H, 9·45. Calc. for $C_{23}H_{34}O_3$: C, 77·0; H, 9·55%].

3β : 17a*α*-*Dihydroxy*-17a-*methyl*-D-*homoandrost*-5-*en*-17-*one*.—3β : 17β-Dihydroxy-17α-ethynylandrost-5-ene was converted into the diacetate, m. p. 169° (cf. Ruzicka and Hofmann, *Helv. Chim. Acta*, 1937, **20**, 1280), which was hydrated with mercuric oxide–acetic acid–acetic anhydride in presence of boron trifluoride by the procedure of Ruzicka and Meldahl (*ibid.*, 1938, **21**, 1760) to give a 93% yield of 3β : 17β-diacetoxy-17α-pregn-5-en-20-one, m. p. 190°. This ketone (3·3 g.) was rearranged by hot 4% methanolic potassium hydroxide to the D-homoketone (2·6 g.), m. p. 303—305°, which was converted into the oxime, m. p. 280—283°, by treatment in

dioxan under reflux with a filtered solution of hydroxylamine acetate in methanol. The following m. p.s have been recorded : 243—244° (Ruzicka and Meldahl, *Helv. Chim. Acta*, 1938, **21**, 1760), 239° (Ruzicka, Goldberg, and Hunziker, *ibid.*, 1939, **22**, 707), 245—246° (Stavely, *J. Amer. Chem. Soc.*, 1939, **61**, 79), 263—265° (Ruzicka and Meldahl, *Helv. Chim. Acta*, 1941, **24**, 1321), 269—272° and 266—274° (Hirschmann and Hirschmann, *J. Biol. Chem.*, 1947, **167**, 7).

17α-*Amino*-3β : 17aα-*dihydroxy*-17a-*methyl*-D-*homoandrost*-5-*ene* (VII).—The ketoxime (m. p. 280—283°; 700 mg.) in propanol (80 c.c.; freshly distilled over sodium) was heated with sodium (3 g.) for 2 hr. The cooled solution was neutralised with acetic acid, then evaporated in a vacuum, and water added; the precipitate was filtered off, dried, and crystallised from methanol as plates (155 mg.), m. p. 198—200°. The mother-liquors by concentration and neutralisation with concentrated hydrochloric acid gave the crystalline amine hydrochloride, which was dried and converted into the free base (155 mg.), m. p. 196—198°. After recrystallisation from methanol, the ***amine*** had m. p. 200—201°, $[\alpha]_D^{23}$ −59° ± 2° (*c*, 1·25 in dioxan) [Found (after drying at 110°/0·01 mm. for 4 hr.) : C, 75·9; H, 10·8. $C_{21}H_{35}O_2N$ requires C, 75·6; H, 10·6%]. It was unchanged by sodium in boiling propanol during 5 hr. A second preparation gave a product, m. p. 200—201°.

Deamination of (VII) *to* 3β-*Hydroxy*-17α-*pregn*-5-*en*-20-*one* (VIII) *and* 17α : 17aα-*Epoxy*-3β-*hydroxy*-17a-*methyl*-D-*homoandrost*-5-*ene* (X).—The amine (310 mg.), dissolved in 50% acetic acid (6·5 c.c.), was treated with a solution of sodium nitrite (335 mg.) in 50% acetic acid (6·5 c.c.) and set aside for 18 hr. The product was dissolved in methanol (6 c.c.), to which acetic acid (0·5 c.c.) and Girard's reagent T (465 mg.; freshly washed with methanol and rapidly dried) were added. The mixture was refluxed for 20 min., cooled to 0°, and poured into ice-water (100 c.c.) containing 2N-sodium hydroxide (4·9 c.c.), and at once extracted with ether to yield non-ketonic material (202 mg.). The aqueous solution was made just acid to Congo-red with 2N-hydrochloric acid, kept for 0·5 hr., partially evaporated under reduced pressure to remove methanol, and extracted with ether **to give ketonic material (35 mg.).** Finally the aqueous phase was acidified with 10% of its volume of concentrated hydrochloric acid, kept for 0·5 hr., and again extracted with ether to yield further ketonic material (7 mg.).

The ketonic fraction (42 mg.) was chromatographed on neutralised aluminium oxide (1·4 g.) prepared in pentane; elution with ether–benzene (6 × 8 c.c.; 1 : 8, 1 : 5, and 1 : 3, each twice) gave a solid (15 mg.), which after sublimation at 110°/0·01 mm. and crystallisation from acetone–pentane yielded 3β-hydroxy-17α-pregn-5-en-20-one (VIII) (8 mg.), m. p. 170—172°, $[\alpha]_D^{18}$ −134° ± 3° (*c*, 0·70) [Found (after drying at 80°/0·01 mm. for 4 hr.) : C, 79·15; H, 10·35%], mixed m. p. 171—173° with a genuine specimen.

The non-ketonic fraction was chromatographed on neutral aluminium oxide (6 g.) prepared in pentane. Elution with ether–benzene (1 : 3; 4 × 100 c.c.) yielded a crystalline solid (173 mg.), which by recrystallisation from acetone–pentane gave 17α : 17aα-*epoxy*-3β-*hydroxy*-17a-*methyl*-D-*homoandrost*-5-*ene* (X; R = H), m. p. 196—198°, $[\alpha]_D^{18}$ −114° ± 2° (*c*, 1·40). A good analysis could not be obtained [Found (after drying at 110°/0·01 mm. for 3 hr.) : C, 78·7; H, 10·6. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%], which recalls the experience of Ruzicka and Meldahl (*Helv. Chim. Acta*, 1941, **24**, 1326) with the saturated analogue (II; R = H). The epoxide showed selective absorption at 208 mμ (ε = 2123) (CR_2·CHR-group), but not in the 290-mμ region (C=O group absent). The *acetate* (X; R = Ac), prepared by using acetic anhydride–pyridine at 18° for 48 hr., after several crystallisations from acetone–pentane formed plates, m. p. 186—187°, $[\alpha]_D^{18}$ −116° ± 1° (*c*, 2·20), which contained 1 mol. of water [Found (after drying at 80°/0·01 mm. for 4 hr.) : C, 73·8; H, 9·45. $C_{23}H_{34}O_3,H_2O$ requires C, 73·5; H, 9·6%]; the infra-red spectrum of a Nujol mull exhibited strong bands at 1734 and 1232 cm.$^{-1}$ (acetate group), and bands at 1672, 838, 812, and 800 cm.$^{-1}$ (CR·CH group); a weak band at 1305 cm.$^{-1}$ and a strong band at 902 cm.$^{-1}$ are consistent with one epoxide grouping, whilst the hydroxyl band at 3450 cm.$^{-1}$ was too weak to account for more than one hydroxyl group and may have been due to the molecule of water. The epoxide acetate (22 mg.) was hydrogenated with platinum oxide (42 mg.) in acetic acid (2 c.c.) at 20° for 1 hr.; absorption had then ceased; the product was chromatographed on aluminium oxide (1·5 g.) prepared in pentane. Elution with pentane (6-c.c. eluates) gave 11 fractions, of which nos. 2—10 were crystalline and were recrystallised from ether–pentane : fraction 2 (5 mg.), cubes, m. p. 186°, positive tetranitromethane test, consisted of unreduced starting material; fractions 3, 4, and 5 were united (10 mg.) to give needles m. p. 164°; fractions 6 and 7 were united (2 mg.) to give needles, m. p. ~160°; fractions 8, 9, and 10 were united (5 mg.) to give clusters of needles, m. p. 161°; fractions 3—10 gave negative tetranitromethane tests; all the fractions appeared to consist of 3β-acetoxy-17α : 17aα-epoxy-D-homoandrostane (II; R = Ac) [Found (after sublimation of fractions 3, 4,

and 5 at 120—140°/0·02 mm.) : C, 77·1; H, 10·5. Calc. for $C_{23}H_{36}O_3$: C, 76·65; H, 10·1%], for which Ruzicka and Meldahl (*Helv. Chim. Acta*, 1941, **24**, 1321) record m. p. 160°.

Similar results were obtained in an independent experiment : the amine (VII) (370 mg.) gave 17-*iso*pregnenolone (VIII) (5 mg.), m. p. 168—172°, $[\alpha]_D^{20}$ −133° ± 5° (*c*, 0·43) and the epoxide acetate (X; R = Ac) (170 mg.), m. p. 183—185° [Found (after drying at 20°/0·05 mm. for 18 hr.) : C, 74·15; H, 9·4%].

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