Steroids. Part IX. The Catalytic Hydrogenation of 3α-Substituted Δ⁵-Steroids.*

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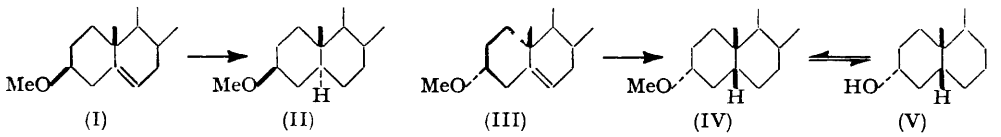
The influence of a 3α-substituent on the stereochemical course of catalytic hydrogenation of a steroid 5 : 6-double bond has been examined, and found to lead to the preferential, and sometimes apparently exclusive, formation of coprostane derivatives. The effect of the following 3α-orientated substituents has been examined : OH, OMe, OAc, Cl, Br, NHMe, NHAc, and NMe_2; the results suggest that the bulkier the axial 3α-substituent, the larger is the proportion of coprostane derivative formed.

Catalytic hydrogenation of 3β-substituted Δ⁵-steroids yields mainly saturated steroids of the A/B-*trans*-series; thus, cholest-5-ene affords cholestane (Mauthner, *Monatsh.*, 1906, **27**, 421), whilst cholesterol gives cholestan-3β-ol (Willstätter and Mayer, *Ber.*, 1908, **41**, 2199), cholesteryl chloride gives 3β-chlorocholestane (Mauthner, *Monatsh.*, 1909, **30**, 635; Windaus and Hossfeld, *Z. physiol. Chem.*, 1925, **145**, 177; Ruzicka, Goldberg, and Wirz, *Helv. Chim. Acta*, 1935, **18**, 998; Shoppee, *J.*, 1946, 1147), cholesteryl bromide gives 3β-bromocholestane (Roberts, Shoppee, and Stephenson, *J.*, 1954, 2705), and 3β-dimethylaminocholest-5-ene gives 3β-dimethylaminocholestane (Haworth and Dodgson, *J.*, 1952, 67; Haworth, McKenna, and Powell, *J.*, 1953, 1110; Šorm, Labler, and Cerny, *Chem. Listy*, 1953, **47**, 418). These products are probably accompanied by small quantities of the saturated steroids of the 5-epimeric A/B-*cis*-series; thus Reichstein, Lardon, and Wenner (*Helv. Chim. Acta*, 1941, **24**, 955; 1944, **27**, 24) by hydrogenation of dehydro-*epi*androsterone acetate with platinum–acetic acid obtained *iso*androsterone acetate accompanied by 10—15% of 3β-acetoxy-5β-androstan-17-one [= 3β-acetoxy*ætio*cholan-17-one]. Until recently, the hydrogenation of 3β-substituted Δ⁵-steroids has been subject to some difficulty in regard to completion of reduction; Hershberg, Oliveto, Rubin, Staeudle, and Kuhlen (*J. Amer. Chem. Soc.*, 1951, **73**, 1144) found, however, that the hydrogenation was catalysed by traces of strong acids. The catalytic effect is determined by the strength of the acid; thus, weak acids with $pK > 3$, *e.g.*, acetic acid and benzoic acid, were ineffective, whilst strong acids with $pK < 3$, *e.g.*, perchloric acid, sulphuric acid, hydrogen bromide, and hydrogen chloride, were efficient catalysts. Cholesterol by hydrogenation with platinum–ethyl acetate in the presence of traces of perchloric acid rapidly gave 90% of cholestan-3β-ol, which was accompanied by 3·5% of coprostan-3β-ol.

* Part VIII, *J.*, 1954, 3422.

There appears to be little information in the literature relating to the hydrogenation of 3α-substituted Δ^5-steroids, and we have made a study of the catalytic reduction of various 3α-substituted cholest-5-enes. Whereas hydrogenation of cholesteryl methyl ether (I) with platinum–acetic acid gave 3β-methoxycholestane (II) (Wagner-Jauregg and Werner, *Z. physiol. Chem.*, 1932, **213**, 119), hydrogenation of *epi*cholesteryl methyl ether (III) with



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

platinum–methanol in the presence of a trace of hydrogen bromide gave 3α-methoxycoprostane (IV) as the sole product. The 3α-ether was shown by mixed m. p. and the infrared spectrum to be identical with a specimen prepared by methylation of coprostan-3α-ol (V) with potassium and methyl iodide in benzene, and was demethylated to coprostan-3α-ol (V) (Lewis and Shoppee, following paper).

Further experimentation showed that hydrogenation of *epi*cholesteryl methyl ether with platinum in methanol or ethyl acetate gave 3α-methoxycoprostane provided that reduction was promoted by traces of perchloric acid or sulphuric acid; with platinum in ethyl acetate–acetic acid, or in ethanol in the presence of potassium hydroxide (Wilds, Johnson, and Sutton, *J. Amer. Chem. Soc.*, 1950, **72**, 5524; Yashin, Rosenkranz, and Djerassi, *ibid.*, 1951, **73**, 4654), or in methanol–piperidine (Mancera, Ringold, Djerassi, and Sondheimer, *ibid.*, 1953, **75**, 1286), reduction did not occur.

We have also found that *epi*cholesteryl acetate by hydrogenation with platinum–methanol–hydrogen bromide gives as the sole crystalline product 3α-acetoxycoprostane, converted by alkaline hydrolysis into coprostan-3α-ol. The hydrogenation of *epi*cholesterol using platinum in ether at 3 atm. has been reported by Marker, Oakwood, and Crooks (*ibid.*, 1936, **58**, 481) to give a quantitative yield of cholestan-3α-ol, and more recently Fieser (*ibid.*, 1953, **75**, 4377) confirmed his isolation of *epi*cholesterol, produced from cholesterol by oxidation with sodium dichromate in benzene–acetic acid *via* an intermediate cyclic 3α : 5α-chromate, by hydrogenation with platinum–ethyl acetate–perchloric acid in 35% yield to cholestan-3α-ol. Examination of the hydrogenation of *epi*cholesterol with platinum in methanol or ethyl acetate in the presence of various promoters showed that the product in all cases was a mixture of coprostan-3α-ol, m. p. 114—115°, and cholestan-3α-ol, m. p. 186°. Table 1 shows the proportions of these compounds formed, expressed as a percentage of the total product. The compounds constituting the small proportion of other products were eluted from columns of aluminum oxide with pentane; they probably consist, from hydrogenations in methanol, of cholestane, coprostane, 3α-methoxycholestane, and 3α-methoxycoprostane, and, from hydrogenations in ethyl acetate, of cholestane, coprostane, 3α-acetoxycholestane, and 3α-acetoxycoprostane.

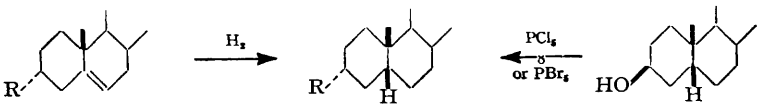
TABLE 1

Promoter	Cholestan-3α-ol (%)	Copro-stan-3α-ol (%)	Other products (%)	Promoter	Cholestan-3α-ol (%)	Copro-stan-3α-ol (%)	Other products (%)
In methanol.				*In ethyl acetate.*			
Hydrogen bromide	41	55	4·4	Hydrogen bromide	40	51	9·3
Perchloric acid ...	46	49	6·5	Perchloric acid ...	40	51	8·8
Sulphuric acid ...	37	48	15·5	Sulphuric acid ...	39	50	11·2
Hydrogen iodide...	No reduction		—	Acetic acid	No reduction		—
Acetic acid	No reduction		—				

These results recall the remarkable influence of 11-hydroxyl groups on the stereochemical course of hydrogenation of 3-keto-Δ^4-steroids; whereas the presence of an 11β-hydroxyl group leads to 99% yields of 3-ketones of the A/B-*trans*-series (Shoppee and Reichstein, *Helv. Chim. Acta*, 1941, **24**, 352; Pataki, Rosenkranz, and Djerassi, *J. Biol. Chem.*, 1952, **195**, 791), the presence of an 11α-hydroxyl group leads to high yields of 3-ketone(s) of the A/B-*cis*-series (Mancera, Ringold, Djerassi, Rosenkranz, and Sondheimer, *J. Amer. Chem.*

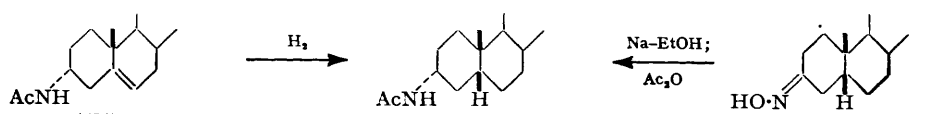
Soc., 1953, **75**, 1286) and can also modify the normal course of reduction of a Δ^{14}-linkage to yield C/D-*trans*-steroids by furnishing up to 50% of the epimeric C/D-*cis*-compound (Kuno Meyer, *Helv. Chim. Acta*, 1949, **32**, 1599).

A 3α-substituent is thus able to influence the stereochemical course of hydrogenation of a 5 : 6-double bond. Because ring A is a chair form in cholest-5-enes (Elks and Shoppee, *J.*, 1953, 241), a 3α-substituent possesses the axial conformation (Evans and Shoppee, *J.*, 1953, 540), and is therefore able to compel preferential adsorption of the β-face, rather than the normally more accessible α-face, of the steroid molecule on to the surface of the catalyst, with subsequent transfer of hydrogen leading to a coprostane derivative. The above results suggest that the bulkier the 3α-substituent, the larger the proportion of the coprostane derivative formed; we therefore examined the hydrogenation of *epi*cholesteryl chloride (VI; R = Cl), *epi*cholesteryl bromide (VI; R = Br), 3α-acetamidocholest-5-ene (IX), and 3α-dimethylaminocholest-5-ene (XII).



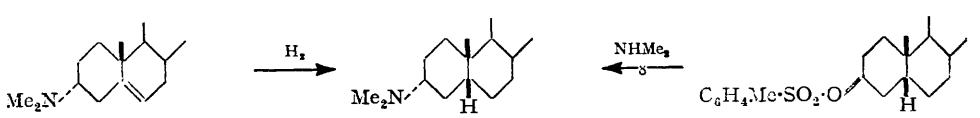
(VI) (VII) (VIII)

Hydrogenation of *epi*cholesteryl chloride (VI; R = Cl) with platinum–ethyl acetate–perchloric acid gave, as the sole product, 3α-chlorocoprostane (VII; R = Cl), which was identical with the compound previously obtained from coprostan-3β-ol (VIII) by treatment with phosphorus pentachloride (Bridgewater and Shoppee, *J.*, 1953, 1709). Similarly, hydrogenation of *epi*cholesteryl bromide (VI; R = Br) under similar conditions yielded coprostane accompanied by 3α-bromocoprostane, m. p. 80—82°, $[\alpha]_D$ +33° (VII; R = Br), which gave no depression by admixture with the product, m. p. 80°, $[\alpha]_D$ +27·5°, previously prepared in poor yield from coprostan-3β-ol (VIII) by reaction with phosphorus pentabromide (Bridgewater and Shoppee, *loc. cit.*).



(IX) (X) (XI)

Similar stereochemical behaviour is observed when 3α-substituents of the form OR are replaced by those of the form NHR or NR_2. Dr. G. H. R. Summers has found that hydrogenation of 3α-acetamidocholest-5-ene (IX) with platinum–acetic acid–ether yields 3α-acetamidocoprostane (X), identical with the principal product (after acetylation) of the reduction of coprostan-3-one oxime (XI) with sodium–ethanol (Evans, Shoppee, and Summers, *Chem. and Ind.*, 1954, 1535). We have likewise found (Pierce, Richards, Shoppee, Stephenson, and Summers, *J.*, 1955, 694) that 3α-dimethylaminocholest-5-ene (XII) by hydrogenation with platinum–acetic acid affords 3α-dimethylaminocoprostane (XIII); this reaction has also been observed by Haworth, McKenna, and Powell (*J.*, 1953, 1110), and by Šorm, Labler, and Czerny (*Chem. Listy*, 1953, **47**, 48) who lately have correctly interpreted their original experiments which included the preparation of the tertiary base (XIII) from 3β-toluene-*p*-sulphonyloxycoprostane (XIV) by solvolysis with dimethylamine, in a more recent paper (*Chem. Listy*, 1954, **48**, 1058).



(XII) (XIII) (XIV)

Analogous observations have recently been recorded in the hydrogenation with platinum–acetic acid of 3α-*N*-methylaminopregna-5 : 20-diene and of 3α-dimethylaninopregn-5-ene (as XII), which both furnish (after methylation in the former case)

3α-*NN*-dimethylaminopregnane (as XIII) (Haworth, McKenna, and Powell, *loc. cit.*; Pierce *et al.*, *loc. cit.*). A conspectus of the foregoing results is provided by Table 2, which shows the approximate proportions of saturated steroids of the A/B-*cis*- and the A/B-*trans*-series formed by catalytic hydrogenation of various 3α-substituted Δ^5-steroids.

TABLE 2.

3α-Substituent	OH	OMe	OAc	Cl	Br	NHMe	NHAc	NMe_2
A/B-*cis*-Steroid (%)	~50	>90	>90	>90	~40 *	~100	>90	~100
A/B-*trans*-Steroid (%)	~40	None isolated						

* Together with *ca.* 60% of coprostane.

EXPERIMENTAL.

For general details see *J.*, 1955, 694. Specific rotations were determined in $CHCl_3$; infra-red absorption spectra were measured in CS_2 on a Perkin-Elmer double-beam instrument.

3α-*Methoxycoprostane from* 3α-*Methoxycholest-5-ene.*—Cholest-5-en-3α-ol, m. p. 141°, prepared according to the directions of Plattner *et al.* (*Helv. Chim. Acta*, 1944, **27**, 1872; 1947, **30**, 1454; 1948, **31**, 1455), was methylated as described by Wallis and Ford (*J. Amer. Chem Soc.*, 1937, **59**, 1415); the product, purified by elution with pentane from aluminium oxide and by crystallisation from acetone, formed plates, m. p. 88°, $[\alpha]_D$ −46°.

(*a*) 3α-Methoxycholest-5-ene (189 mg.), dissolved in methanol (50 c.c.) containing 48% hydrobromic acid (4 drops), was shaken with platinum oxide (35 mg.) in an atmosphere of hydrogen until absorption ceased. The usual working up gave an oil (176 mg.), which by crystallisation from acetone gave 3α-*methoxycoprostane*, m. p. 87—88°, $[\alpha]_D$ +36° (*c*, 1·0) [Found: (after drying at 45°/0·01 mm. for 4 hr.): C, 83·3; H, 12·5. $C_{28}H_{50}O$ requires C, 83·5; H, 12·5%], whose infra-red absorption spectrum will be discussed by Dr. J. E. Page in a forthcoming paper. In another experiment, 3α-methoxycholest-5-ene (500 mg.) yielded 3α-methoxycoprostane (470 mg.), m. p. 88° after crystallisation from acetone.

(*b*) Similar experiments were made as follows:

3α-Methoxycholest-5-ene (III) (mg.)	PtO_2,H_2O (mg.)	Solvent	Promoter	3α-Methoxycoprostane (IV) m. p.	mg.
100	75	MeOH, 15 c.c.	60% $HClO_4$, 4 drops	86—88°	91
75	35	MeOH, 15 c.c.	10N-H_2SO_4, 3 drops	87—88	70
120	72	EtOAc, 15 c.c.	48% HBr, 4 drops	87—88	115
62	73	EtOAc, 10 c.c.	60% $HClO_4$, 4 drops	86—88	57
90	85	EtOAc, 12 c.c.	10N-H_2SO_4, 4 drops	87—88	85

The specimens of 3α-methoxycoprostane were crystallised from acetone and gave no depressions by admixture with authentic 3α-methoxycoprostane, m. p. 88°, $[\alpha]_D$ +32° (see Lewis and Shoppee, following paper), whilst the infra-red adsorption spectra were identical.

(*c*) 3α-Methoxycholest-5-ene (350 mg.), in ethanol (50 c.c.) containing finely powdered potassium hydroxide (80 mg.) shaken with platinum oxide (97 mg.) in hydrogen, failed to absorb hydrogen. The product was unchanged starting material, m. p. 86—88°, depressed on admixture with 3α-methoxycoprostane to 50°. A repetition gave the same result.

(*d*) 3α-Methoxycholest-5-ene (100 mg.), in methanol (10 c.c.) containing piperidine (2 c.c.) shaken with platinum oxide (30 mg.) in hydrogen, failed to absorb hydrogen and furnished unaltered starting material, m. p. and mixed m. p. 87—88°.

(*e*) 3α-Methoxycholest-5-ene (85 mg.), in ethyl acetate (15 c.c.) containing acetic acid (15 drops) shaken with platinum oxide (47 mg.), failed to take up hydrogen and gave starting material, m. p. and mixed m. p. 87—88°.

3α-*Acetoxycoprostane from* 3α-*Acetoxycholest-5-ene.*—(*a*) 3α-Acetoxycholest-5-ene (60 mg.) was hydrogenated with platinum oxide (163 mg.) in methanol (10 c.c.) containing 48% hydrobromic acid (3 drops); the product crystallised only with difficulty from ethanol, had m. p. 81°, and was purified by elution with benzene–pentane (1 : 9) from aluminium oxide, to give 3α-acetoxycoprostane, m. p. and mixed m. p. 82—83°, $[\alpha]_D$ +52° (*c*, 0·4), after crystallisation from ethanol.

(*b*) 3α-Acetoxycholest-5-ene (52 mg.) was hydrogenated with platinum oxide (94 mg.) in methanol (15 c.c.) containing 60% perchloric acid (5 drops). Similar purification gave 3α-acetoxycoprostane, m. p. and mixed m. p. 83°, $[\alpha]_D$ +44° (*c*, 0·4).

(*c*) 3α-Acetoxycholest-5-ene (54 mg.) was hydrogenated with platinum oxide (55 mg.) in ethyl

acetate (10 c.c.) containing 60% perchloric acid (4 drops) to give after similar purification 3α-acetoxycoprostane (47 mg.), m. p. and mixed m. p. 81—83°.

(*d*) 3α-Acetoxycholest-5-ene (47 mg.) was hydrogenated with platinum oxide (40 mg.) in ethyl acetate (10 c.c.) containing 10N-sulphuric acid (5 drops); similar purification gave 3α-acetoxycoprostane (42 mg.), m. p. and mixed m. p. 80—82°.

The specimens of 3α-acetoxycoprostane (150 mg.) were hydrolysed with hot 5% methanolic potassium hydroxide to give, after the usual working up, a solid, m. p. 110—112°, after crystallisation from methanol; recrystallisation afforded coprostan-3α-ol, m. p. and mixed m. p. 113—114°, $[\alpha]_D$ +29° (*c*, 0·44).

Coprostan-3α-ol and Cholestan-3α-ol from Cholest-5-en-3α-ol.—(*a*) Cholest-5-en-3α-ol (50 mg.) was hydrogenated with platinum oxide (76 mg.) in methanol (15 c.c.) containing 48% hydrobromic acid (4 drops). After filtration from the catalyst, the solution was kept over anhydrous potassium carbonate for 0·5 hr., refiltered, and evaporated in a vacuum. The residual oil (48 mg.) was chromatographed on aluminium oxide (4 g.). Elution with pentane (3 × 5 c.c.) gave a little oil (2 mg.), but use of benzene–pentane (1 : 3; 4 × 4 c.c.) gave cholestan-3α-ol (19 mg.), m. p. and mixed m. p. 183—185°, $[\alpha]_D$ +34°, after recrystallisation from acetone, characterised as the acetate, m. p. 94—95°, $[\alpha]_D$ +33° (*c*, 1·1). Further elution with benzene–pentane (1 : 3; 8 × 5 c.c.) gave an oil (25 mg.) which crystallised from acetone to yield coprostan-3α-ol, m. p. and mixed m. p. 110—112°, $[\alpha]_D$ +29° (*c*, 0·44), characterised as the acetate, m. p. 87—88°, $[\alpha]_D$ +43° (*c*, 0·4).

(*b*) Similar experiments were made as follow:

Cholest-5-en-3α-ol (mg.)	PtO_2,H_2O (mg.)	Solvent	Promoter	Coprostan-3α-ol m. p.	mg.	Cholestan-3α-ol m. p.	mg.
67	104	MeOH, 15 c.c.	60% $HClO_4$, 4 drops	109—111°	24	182—185°	22
45	69	MeOH, 12 c.c.	10N-H_2SO_4, 4 drops	111—112 *	25	182—183 *	19
50	72	EtOAc, 15 c.c.	48% HBr, 4 drops	109—110	22	183—184	17
54	70	EtOAc, 15 c.c.	60% $HClO_4$, 3 drops	111—112	29	184	23
40	50	EtOAc, 12 c.c.	10N-H_2SO_4, 3 drops	110—111	15	182—183	12

* Elution with pentane gave 8 mg. of uncrystallisable material.

(*c*) Cholest-5-en-3α-ol (66 mg.) was shaken with platinum oxide (107 mg.) and methanol (15 c.c.) containing 57% hydriodic acid (3 drops) in hydrogen for 1·5 hr.; no reduction took place and cholest-5-en-3α-ol, m. p. and mixed m. p. 140—141°, was recovered unchanged.

(*d*) Cholest-5-en-3α-ol (51 mg.) was shaken with platinum oxide (59 mg.) and methanol (15 c.c.) containing acetic acid (3 c.c.) in hydrogen; no absorption occurred and the starting material was recovered, having m. p. 140° after crystallisation from methanol.

(*e*) Cholest-5-en-3α-ol (55 mg.) was shaken with platinum oxide (51 mg.) and ethyl acetate (15 c.c.) containing acetic acid (3 c.c.) in hydrogen; no absorption occurred and the starting material was recovered, having m. p. 140—141° after crystallisation from methanol.

3α-Chlorocoprostane from 3α-Chlorocholest-5-ene.—3α-Chlorocholest-5-ene (m. p. 107°; 101 mg.) (Shoppee and Summers, *J.*, 1952, 1790) was hydrogenated with platinum oxide (120 mg.) in ethyl acetate (15 c.c.) containing 60% perchloric acid (4 drops). After 1 hr., the usual working up yielded an oil (98 mg.), which failed to crystallise. Chromatography on a column of aluminium oxide (5 g.) prepared in pentane gave by elution with pentane (5 c.c.) an oil (20 mg.); further elution with pentane (4 × 5 c.c.) afforded 3α-chlorocoprostane (79 mg.), m. p. 73°, $[\alpha]_D$ +33° (*c*, 0·5), after crystallisation from acetone. The specimen gave no colour with tetranitromethane–chloroform, and no m. p. depression on admixture with 3α-chlorocoprostane prepared from coprostan-3β-ol by treatment with phosphorus pentachloride (Bridgewater and Shoppee, *J.*, 1953, 1709).

3α-Bromocoprostane from 3α-Bromocholest-5-ene.—3α-Bromocholest-5-ene (m. p. 105°; 190 mg.) was hydrogenated under the conditions employed for the chloro-derivative; the reduction required 4 hr., and furnished an oil (189 mg.) giving a yellow colour with tetranitromethane–chloroform. The oil was shaken with a 2% solution of chromium trioxide in acetic acid at 60° for 0·75 hr., and the solution poured into water and extracted with ether. The neutral fraction yielded an oil (135 mg.), which gave no colour with tetranitromethane–chloroform but failed to crystallise. Chromatography on a column of specially activated aluminium oxide [10 g.; activity I—II on the scale of Brockmann and Schodder (*Ber.*, 1941, **74**, 73)], prepared in pentane, gave by elution with pentane (6 × 5 c.c.) an oil (81 mg.), which by crystallisation from acetone afforded coprostane, m. p. and mixed m. p. 66—70°; further elution with pentane (4 × 5 c.c.) gave an oil (47 mg.), which by crystallisation from acetone yielded pure *3α-bromocoprostane*, m. p. 80—82°, $[\alpha]_D$ +33° (*c*, 0·63) [Found (after drying at 50°/0·01 mm. for 3 hr.):

Br, 17·6. $C_{27}H_{47}Br$ requires Br, 17·7%], giving no colour with tetranitromethane–chloroform and no m. p. depression with a specimen, m. p. 80°, $[\alpha]_D$ +27·5°, previously thought to be impure because of poor analyses, prepared from coprostan-3β-ol by treatment with phosphorus pentabromide (Bridgewater and Shoppee, *loc. cit.*). M. p. depressions were observed with 3α-bromocholestane, m. p. 103° (Roberts, Shoppee, and Stephenson, *J.*, 1954, 2705) and with 3β-bromocoprostane, m. p. 113° (Bridgwater and Shoppee, *loc. cit.*).

3α-Acetamidocoprostane from 3α-Acetamidocholest-5-ene [by G. H. R. SUMMERS].—3α-Acetamidocholest-5-ene (m. p. 186—189°; 20 mg.) was hydrogenated with platinum oxide (10 mg.) in acetic acid–ether (1 : 1, 10 c.c.) containing 60% perchloric acid (1 drop). The uptake of hydrogen was complete after 0·5 hr. The product, an oil, was isolated in the usual way, and chromatographed on aluminium oxide (1·5 g.). Elution with pentane yielded an oil, whilst use of pentane–benzene (1 : 1) gave a solid, m. p. 210—214°, which after sublimation at 200—210°/0·02 mm. and crystallisation from acetone yielded 3α-acetamidocoprostane as plates, m. p. 214—217°, undepressed on admixture with authentic specimen but depressed to 190—120° by 3α-acetamidocholestane, m. p. 189° (Pierce *et al.*, *J.*, 1955, 694).

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