Reactions of Steroid Allylic Systems: Solvolyses of Cholest-4-en-3β- and 3α-yl Trifluoroacetates

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The title compounds give in unimolecular solvolyses different mixtures of 3-substituted-Δ^4- and 5-substituted-Δ^3-products probably *via* two distinct allylic carbonium ions. Bimolecular substitution and configurational inversion occur when the title compounds are treated with sodium azide-hexamethylphosphoramide.

3-HYDROXY-Δ^4-STEROIDS represent typical $\alpha\gamma$-trialkyl allylic systems and their esters with electron-attracting acyl groups should undergo ready uncatalysed unimolecular solvolyses with alkyl–oxygen cleavage.[1]

An attempted preparation of cholest-4-en-3β-yl tosylate was shown to yield directly a mixture of solvolytic products.[2]

Hydrolysis of 3β-dichloroacetoxy-Δ^4-derivatives in the pregnane series has been reported to afford the 3α-hydroxy-analogues in low yield.[3]

Following our recent paper on the substitution and elimination reactions of tertiary trifluoroacetates,[4] the cholest-4-en-3β-yl trifluoroacetate (1a) and its 3α-epimer (1b) have been prepared from the corresponding alcohols (1c) and (1d) and their behaviour under a variety of solvolysing conditions has been examined.

Methanolyses of (1a) and (1b) in the presence of sodium acetate, followed by alumina chromatography gave a little hydrocarbon fraction,† 5α-methoxycholest-3-ene (2a), 5β-methoxycholest-3-ene (2b),[5] 3α-methoxycholest-4-ene (1f),[5,6] 3β-methoxycholest-4-ene (1e),[7] and starting alcohols [(1c) and (1d) respectively].

Both (2a) and (2b) were converted into the saturated analogues (3a) and (3b) by hydrogenation over Adams catalyst in ethanol solution. Compounds (3a) and (3b) were oxidised with ruthenium tetraoxide in carbon tetrachloride [8] and the crude formates obtained were hydrolysed to give the known 5α-hydroxycholestane (3c) [9] and 5β-hydroxycholestane (3d) [10] respectively.

Solvolyses of (1a) and (1b) in aqueous acetone in the presence of sodium hydrogencarbonate as described by Shoppee *et al.*[11] yielded (in order of elution by alumina chromatography) hydrocarbons, 5α-hydroxycholest-3-ene (2c),[9] a mixture of 5β-hydroxycholest-3-ene (2d) [10]

† Hydrocarbon fractions obtained in low yield in all the solvolyses were shown by n.m.r. to contain cholesta-3,5-diene as the major component but were not further examined.

[1] H. L. Goering and R. R. Josephson, *J. Amer. Chem. Soc.*, 1962, **84**, 2779, and references therein.
[2] S. B. Laing and P. J. Sykes, *J. Chem. Soc.*, (*C*), 1968, 421.
[3] Ger. Offen. 2 155 137 (*Chem. Abs.*, 1972, **77**, 62,242d).
[4] G. Ortar and A. Romeo, *J. Org. Chem.*, 1976, **41**, 4036.
[5] J. Pusset and R. Beugelmans, *Tetrahedron Letters*, 1967, **34**, 3249.
[6] C. W. Shoppee, B. D. Agashe, and G. H. R. Summers, *J. Chem. Soc.*, 1957, 3107.
[7] C. R. Narayanan and K. N. Iyer, *J. Org. Chem.*, 1965, **30**, 1734.
[8] C. Just and V. di Tullio, *Canad. J. Chem.*, 1964, **42**, 2153.
[9] E. Glotter, S. Greenfield, and D. Lavie, *Tetrahedron Letters*, 1967, 5261; E. Glotter, S. Greenfield, and D. Lavie, *J. Chem. Soc.* (*C*), 1968, 1646.
[10] P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, 1961, **26**, 3615.
[11] (*a*) W. G. Young, R. E. Ireland, T. I. Wrigley, C. W. Shoppee, B. D. Agashe, and G. H. R. Summers, *J. Amer. Chem. Soc.*, 1959, **81**, 1452; (*b*) C. W. Shoppee, J. K. Hummer, R. E. Lack, P. Ram, and S. K. Roy, *Tetrahedron*, 1966, suppl. 7, 315.

TABLE 1

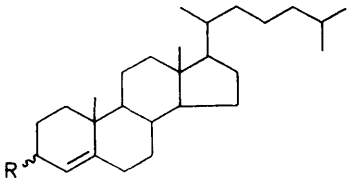
Solvolyses of (1a) and (1b)

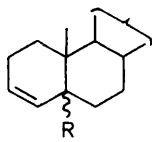
Reaction medium	MeOH + AcONa			Me_2CO–H_2O (9 : 1) + $NaHCO_3$			AcOH + AcONa			HMPA + NaN_3		
Reactant		(1a) %	(1b) %		(1a) %	(1b) %		(1a) %	(1b) %		(1a) %	(1b) %
Products isolated and yields [a]	Olef.	2	2	Olef.	5.5	3.5	Olef.	5.5	4.5	Olef.	1	1
	(2a)	3	14	(2c)	6	20	(1g)	26.5	10.5	(1i)		97
	(2b)	23	2	(2d)	21	Traces	(1h)	68	85	(1j)	97	
	(1f)	38	68	(1d)	48.5	70				Gums	2	2
	(1e)	22	7.5	(1c)	19	6						
	(1c)	12										
	(1d)		4.5									

[a] Yield calculated from weights of chromatographic fractions.

and 3α-hydroxycholest-4-ene (1d),[12] which could be resolved, and then characterised, after selective acetylation at C-3, and 3β-hydroxycholest-4-ene (1c).[12]

Finally buffered acetolyses of (1a) and (1b) afforded mixtures of cholest-4-en-3β-yl acetate (1g) and its 3α-epimer (1h) which were more easily resolved as the hydroxy-derivatives. Both acetoxy-derivatives, when





(1) a; R = β-$OCOCF_3$ h; R = α-OAc

b; R = α-$OCOCF_3$ i; R = β-N_3

c; R = β-OH j; R = α-N_3

d; R = α-OH k; R = β-NHAc

e; R = β-OMe l; R = α-NHAc

f; R = α-OMe m; R = β-Cl

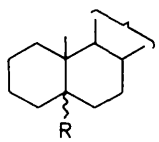
g; R = β-OAc n; R = α-Cl

(2) a; R = α-OMe

b; R = β-OMe

c; R = α-OH

d; R = β-OH



(3) a; R = α-OMe

b; R = β-OMe

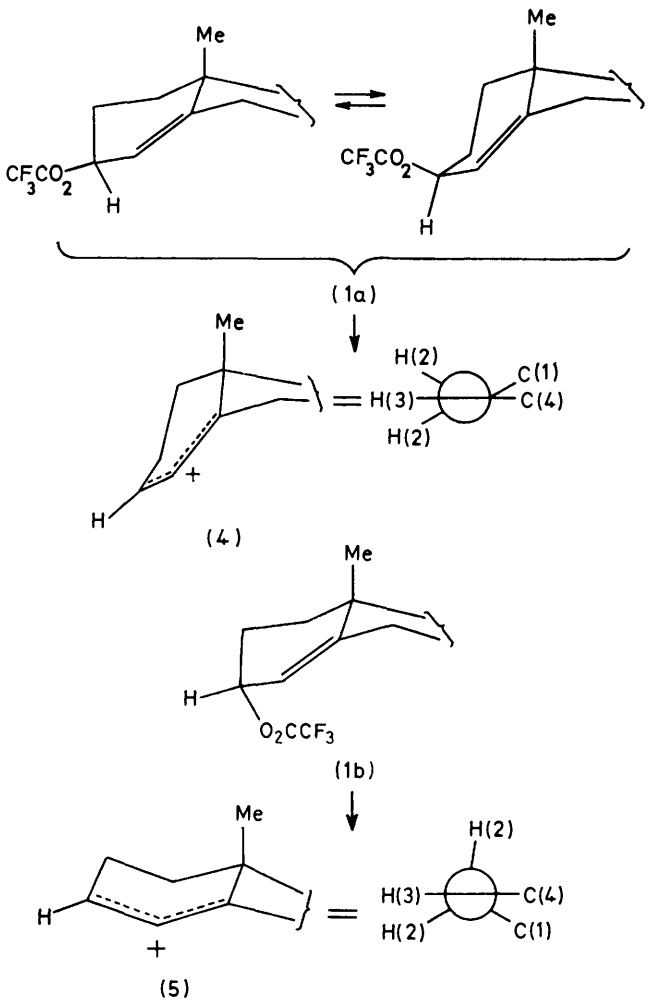
c; R = α-OH

d; R = β-OH

subjected to the same conditions as used for acetolyses of (1a) and (1b), were unchanged.

An examination of the proportions of the products resulting from our experiments (Table 1) reveals that they markedly depend on the starting trifluoroacetate.

Since there is little doubt but that the above substitutions involve a carbonium-ion process,[1] we would account for the different ratios arising from (1a) and (1b) by the intermediacy of the two conformationally distinct allylic carbonium ions (4) and (5), according to



SCHEME

the picture developed by Overton,[13] for the hydrogenolysis of 3-hydroxycholest-4-enes, based on Goering's suggestions [1] (see Scheme).*

Nevertheless our results seem to indicate a preference of the 3α- over the 3β-attack even in the case of the

* The Newman projections for the carbonium ions (4) and (5) are viewed along the C(3)–C(2) bond.

[12] W. G. Dauben, P. Laug, and G. H. Berezin, *J. Org. Chem.*, 1966, **31**, 3869.

[13] I. M. Cunningham and K. H. Overton, *J.C.S. Perkin I*, 1974, 2458.

carbonium ion (4) derived from the 3β-trifluoroacetate (1a).

Noteworthy is the complete inversion in the ratios between the 5-substituted-Δ^3-products which is probably due to the *quasi-trans*-conformation of rings A and B in (5) (attack at the C-5 position from the α-side vastly preferred over β-attack) and to the *quasi-cis*-conformation in (4) (and consequent attack at the C-5 position from the β-side preferred over α-attack).

The absence of 5-acetoxy-derivatives in the buffered acetolyses of (1a) and (1b) is not unexpected since the tertiary allylic acetates are known to be easily rearranged in acetic acid,[14] although we cannot rule out that, for steric hindrance reasons, they are not formed.

At this point a re-examination of some reported [11] substitution reactions of 3β-chlorocholest-4-ene (1m) and its 3α-epimer (1n) became necessary, owing to the considerable differences with our product patterns [*e.g.* formation of identical mixtures (*ca.* 1 : 1) of (1c) and (1d) by hydrolysis of either (1m) and (1n) and absence of products arising from stereochemical partition at C-5].

By repeating solvolyses of (1m) and (1n) in aqueous acetone and in buffered acetic acid as described by Shoppee [11] we have, in fact, obtained product distributions which are, except for minor variations (*e.g.* more olefins), consistent with those found for allylic trifluoroacetates and widely differing from those previously reported (see Table 2).

TABLE 2

Solvolyses of (1m) and (1n)

Reaction medium	Me_2CO–H_2O (9 : 1) + $NaHCO_3$			AcOH + AcONa		
Reactant		(1m) %	(1n) %		(1m) %	(1n) %
	Olefin	16	5	Olefin	18	17
Product	(2c)	6	19	(1g)	17	13
isolated	(2d)	16	Traces	(1h)	65	70
and yields [a]	(1d)	48.5	70			
	(1c)	12.5	5			

[a] Yields calculated from weights of chromatographic fractions.

The intermediacy of a single allylic carbonium ion which should exhibit no preference for either 3β- or 3α-attack, the absence of any allylic rearrangement, and the incursion of an S_N2 displacement with acetate ion no longer seem valid.

An S_N2 mechanism has been observed in the solvolyses of (1a) and (1b) in hexamethylphosphoramide (HMPA) in the presence of sodium azide where (1j) [15] and (1i) respectively were formed, in 97% yield.

Compound (1i) has never been isolated before. Ponsold and Preibsch [16] reported that the solvolysis of 3β-chlorocholest-4-ene (1m) in dimethyl sulphoxide in the presence of sodium azide afforded a mixture of (1i) and (1j) which were directly converted into the corresponding acetamido-derivatives (1k) and (1l).

The configurational assignment for (1i) was fully supported by its n.m.r. spectrum and was confirmed by conversion of the compound into (1k).[11b]

It would not be unfair in this connection to point out that, analogously to the 7-substituted-Δ^5-series,[17] 3β- and 3α-substituted-Δ^4-derivatives are reliably distinguished by n.m.r. spectra on the basis of the chemical shift of the 10-Me and, better, of both the position and pattern of 4-H olefinic protons. The n.m.r. method can also be used for analysis of mixtures (Table 3).

TABLE 3

N.m.r. data [δ values (90 MHz)] for 3β- and 3α-Δ^4-derivatives

Compds.	13-Me (s)	10-Me (s)	3-H (m)	4-H	Other signals
(1a)	0.67	1.07	5.43	5.25	
(1b)	0.67	0.99	5.32	5.47	
(1c)	0.67	1.02	4.13	5.25	
(1d)	0.67	0.95	4.08	5.47	
(1e)	0.67	1.02	3.73	5.33	3.34(s,–OMe)
(1f)	0.67	0.97	3.57	5.47	3.33(s,–OMe)
(1g)	0.67	1.03	5.22 [a]	5.22 [a]	2.01(s,–OCOMe)
(1h)	0.67	0.98	5.13	5.42	2.00(s,–OCOMe)
(1i)	0.67	1.03	3.80	5.25	
(1j)	0.67	0.98	3.77	5.38	
(1k)	0.67	1.02	4.40	5.13	1.95(s,–NHCO*Me*), 5.35(m,–N*H*)
(1l)	0.67	0.98	4.35	5.28	1.95(s,–NHCO*Me*), 5.53(m,–N*H*)
(1m)	0.67	1.05	4.53	5.38	
(1n)	0.67	0.98	4.62	5.49	

[a] Overlapping signals.

The 10-Me resonance of the 3β-series occurs at slightly lower field (0.04—0.07 p.p.m.) than the corresponding resonance of the 3α-series.

The 4-H signal appears for 3α-substituted compounds as an apparent doublet (J 4.5 Hz) and is *ca.* 0.1—0.2 p.p.m. downfield from the corresponding signal of the 3β-analogues (which is a broad singlet with a peak width at half height of 4.5 Hz).

In conclusion, solvolyses of the 3-substituted-Δ^4-series confirm the importance of stereoelectronic preferences in the relatively mobile ring A and allow a refinement of the simple carbonium-ion mechanism quoted in classic steroid literature.[18]

EXPERIMENTAL

M.p.s were measured on a Kofler hot-stage apparatus. Optical rotations were taken at 20 °C with a Schmidt–Haensch polarimeter for solutions in chloroform in a 1 dm cell. I.r. spectra (KBr discs) were recorded on a Perkin-Elmer 521 spectrophotometer. ^1H N.m.r. spectra were measured for solutions in deuteriochloroform (tetramethylsilane as internal standard) with a Varian EM-390 spectrometer. Column chromatography was carried out on Woelm neutral alumina (Brockmann grade III, unless otherwise specified) and preparative layer chromatography (p.l.c.) on Merck HF_{254} silica gel (layers 0.5 mm thick). Hexamethylphosphoramide was distilled *in vacuo* over calcium hydride; methanol was dried by treatment with magnesium. Light petroleum refers to the fraction b.p. 40—60 °C.

Cholest-4-en-3β-yl Trifluoroacetate (1a).—A solution of

[14] R. H. De Wolf and W. G. Young, *Chem. Rev.*, 1956, **56**, 753.
[15] H. Loibner and E. Zbiral, *Helv. Chim. Acta*, 1976, **59**, 2100.
[16] K. Ponsold and W. Preibsch, *J. prakt. Chem.*, 1964, **23**, 173.
[17] P. Morand and A. Van Tongerloo, *Steroids*, 1973, **21**, 65.
[18] D. N. Kirk and M. P. Hartshorn, ' Steroid Reaction Mechanisms ', Elsevier, Amsterdam, 1968, p. 381.

3β-hydroxycholest-4-ene (1c) (1.16 g, 3 mmol) in pyridine (5 ml) was treated with trifluoroacetic anhydride (2.1 ml, 1.5 mmol) at 0 °C for 15 min. Cold N-hydrochloric acid (35 ml) was then added and the mixture extracted with ether. The ether layers were washed to neutrality with cold water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue (1.33 g) was dissolved in acetone by gentle warming and crystallised after 12 h at 0 °C to give needles of cholest-4-en-3β-yl trifluoroacetate (1a), m.p. 88 °C,* $[\alpha]_D$ +9° (*c* 1.0), $\nu_{max.}$ 1 770 cm^{-1} (CF_3CO_2) (Found: C, 72.4; H, 9.5; F, 11.6. $C_{29}H_{45}F_3O_2$ requires C, 72.2; H, 9.4; F, 11.8%).†

Cholest-4-en-3α-yl Trifluoroacetate (1b).—This was prepared in the same manner as above from 3α-hydroxycholest-4-ene (1d) and crystallised from acetone by cooling at −15 °C, m.p. 74 °C,* $[\alpha]_D$ +184° (*c* 1.0), $\nu_{max.}$ 1 770 cm^{-1} (CF_3CO_2) (Found: C, 72.3; H, 9.5; F, 11.6. $C_{29}H_{45}F_3O_2$ requires C, 72.2; H, 9.4; F, 11.8%).†

Solvolyses of (1a) *and* (1b) *in Methanol in the Presence of Sodium Acetate.*—A stirred solution of (1a) [or (1b)] (3 mmol) and sodium acetate (6 mmol) in dry methanol (36 ml) was heated at 60 °C for 20 min. Methanol was then evaporated off *in vacuo* and the product isolated with ether. The ethereal solution was washed twice with water and then dried (Na_2SO_4). The residue was chromatographed on alumina (250 g). Elution with light petroleum gave: olefins; 5α-*methoxycholest-3-ene* (2a), m.p. 93—94 °C (from acetone), $[\alpha]_D$ −16° (*c* 1.0), δ 0.65 (3 H, s, 13-Me), 0.87 (3 H, s, 10-Me), 3.10 (3 H, s, 5α-OMe), 5.47 and 5.82 (2 H, m, 4- and 3-H) (Found: C, 83.95; H, 12.05. $C_{28}H_{48}O$ requires C, 83.95; H, 12.1%); 5β-*methoxycholest-3-ene* (2b),[5] m.p. 68—69 °C (from acetone), $[\alpha]_D$ +88° (*c* 1.0), δ 0.65 (3 H, s, 13-Me), 0.92 (3 H, s, 10-Me), 3.20 (3 H, s, 5β-OMe), 5.48 and 5.91 (2 H, m, 4- and 3-H) (Found: C, 83.8; H, 12.15. $C_{28}H_{48}O$ requires C, 83.95; H, 12.1%). Elution with hexane gave: 3α-*methoxycholest-4-ene* (1f),[5,6] m.p. 43—44 °C (from acetone), $[\alpha]_D$ +112° (*c* 1.0) (Found: C, 83.9; H, 12.1. $C_{28}H_{48}O$ requires C, 83.95; H, 12.1%).‡ Elution with hexane–benzene (9 : 1) gave 3β-methoxycholest-4-ene (1e), m.p. 75—75.5 °C (from acetone), $[\alpha]_D$ +32° (*c* 1.0) identical with an authentic sample.[7] Elution with benzene–ethyl acetate (9 : 1) gave finally predominantly (1c) [or (1d) starting from (1b)].

Hydrogenation of (2a) with platinum oxide in ethanol at room temperature with uptake of one equivalent of hydrogen yielded 5α-*methoxycholestane* (3a), m.p. 86.5—87.5 °C (from acetone), $[\alpha]_D$ +26° (*c* 1.0), δ 0.63 (3 H, s, 13-Me), 0.94 (3 H, s, 10-Me), and 3.04 (3 H, s, 5α-OMe) (Found: C, 83.6; H, 12.6. $C_{28}H_{50}O$ requires C, 83.5; H, 12.5%).

The ether (3a) (80 mg) in carbon tetrachloride (13 ml) was oxidised with ruthenium tetraoxide (198 mg) (molar ratio 1 : 6), according to the procedure of Berkowitz and Rylander.[19] The reaction product (83 mg) was directly saponified with 5% methanolic potassium hydroxide to give, after p.l.c. [elution with benzene–ether (95 : 5)], 5α-hydroxycholestane (3c) (55 mg), m.p. 77—78 °C (from methanol), identical with an authentic sample.[9]

In the same manner (2b) was hydrogenated to give 5β-*methoxycholestane* (3b), m.p. 59—60 °C (from acetone), $[\alpha]_D$ +27° (*c* 1.0), δ 0.63 (3 H, s, 13-Me), 0.87 (3 H, s, 10-Me), and 3.11 (3 H, s, 5β-OMe) (Found: C, 83.4; H, 12.4. $C_{28}H_{50}O$ requires C, 83.5; H, 12.5%). Compound (3b) was oxidised with ruthenium tetraoxide as described above and the crude formate hydrolysed to give 5β-hydroxycholestane (3d), m.p. 79—81 °C (from methanol), identical with an authentic sample.[10]

Solvolyses of (1a) *and* (1b) *in Aqueous Acetone in the Presence of Sodium Hydrogencarbonate.*—Compound (1a) [or (1b)] (2 mmol) and sodium hydrogencarbonate (10 mmol) in acetone–water (9 : 1) (20 ml) were stirred at 55 °C for 30 min. Solvent was then evaporated off *in vacuo* and water was added to the mixture. The product was extracted with ether, and the extract washed with water to neutrality and dried (Na_2SO_4). The residue was chromatographed on alumina (40 g). Elution with hexane–benzene (1 : 1) gave: hydrocarbons; 5α-hydroxycholest-3-ene (2c), m.p. 75—76 °C (from methanol), identical with an authentic sample;[9] a mixture of 5β-hydroxycholest-3-ene (2d)[10] and 3α-hydroxycholest-4-ene (1d)[12] which could be resolved (and then characterised) by p.l.c. (elution with benzene) after selective acetylation (acetic anhydride–pyridine at room temperature) at C-3.

Elution with benzene finally afforded 3β-hydroxycholest-4-ene (1c).[12]

Buffered Acetolyses of (1a) *and* (1b).—Compound (1a) [or (1b)] (1 mmol) and sodium acetate (2 mmol) in acetic acid (12 ml) were stirred at room temperature for 2 h. The solution was poured into water, and the products were isolated with ether. The residue was chromatographed on alumina (grade II, 20 g). Elution with light petroleum gave olefins. Elution with light petroleum–ether (1 : 1) afforded mixtures of cholest-4-en-3β-yl acetate (1g) and its 3α-epimer (1h) which were analysed by n.m.r. spectra. This material was furthermore refluxed with 5% methanolic potassium hydroxide for 30 min to give the corresponding alcohols (1c) and (1d), which were readily resolved by chromatography on alumina in the same manner as reported above.

Solvolysis of (1a) *in Hexamethylphosphoramide in the Presence of Sodium Azide.*—Compound (1a) (1 mmol) and sodium azide (5 mmol) in 10 ml of dry hexamethylphosphoramide were stirred at 60 °C for 1 h. The solution was poured into water and extracted with ether. The extract was washed with water to neutrality and dried (Na_2SO_4). The residue was chromatographed on alumina (80 g). Elution with light petroleum gave olefin traces, followed by 3α-azidocholest-4-ene (1j),[15] m.p. 64—65 °C (from acetone–methanol), $[\alpha]_D$ +284° (*c* 1.0). Elution with ethyl acetate gave a gum which was not characterised.

Solvolysis of (1b) as above gave 3β-*azidocholest-4-ene* (1i), m.p. 43—44 °C (from acetone–methanol), $[\alpha]_D$ +1° (*c* 2.0) (Found: C, 78.75; H, 11.05; N, 10.2. $C_{27}H_{45}N_3$ requires C, 78.75; H, 11.0; N, 10.2%).

The two azides exhibit the same R_F values on t.l.c. (light petroleum as eluant); examination by n.m.r. of the mother-liquors from their crystallisation did not reveal the presence of the corresponding epimer.

Compound (1i) (0.2 g, 0.48 mmol) in dry ether (10 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (92 mg, 2.4 mmol) in dry ether (10 ml). The mixture was stirred at room temperature for 15 h and the crude

* Instantaneous m.p. determination (stage preheated at increasing temperatures).

† (1a) and (1b) can be stored unchanged for several days in the dark in the refrigerator; in the air they decompose with time turning violet.

‡ The product obtained by Shoppee [6] and provisionally termed 3α-methoxycholest-4-ene might have been in fact a molecular compound of (1e) and (1f).

[19] L. M. Berkowitz and P. N. Rylander, *J. Amer. Chem. Soc.*, 1958, **80**, 6682.

amino-derivative (0.19 g) isolated in the usual way [4] was directly acetylated (acetic anhydride–pyridine) to give 3β-acetamidocholest-4-ene (1k) (0.21 g),[11b] m.p. 215—220 °C (from ethyl acetate), $[\alpha]_D$ +9° (*c* 1.0).

In the same manner (1j) was converted into the 3α-acetamidocholest-4-ene (1l),[11b] m.p. 198—200 °C (from methanol), $[\alpha]_D$ +129° (*c* 1.0).

[7/547 *Received* 28*th March*, 1977]