THE RITTER REACTION OF THE ISOMERIC 3β-ACETOXY-5,6-EPOXY-CHOLESTANES

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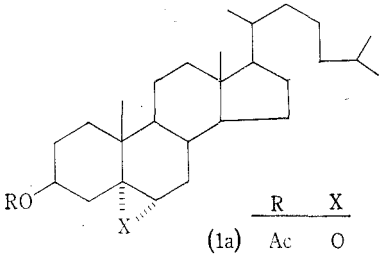
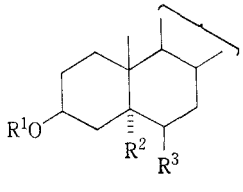
Many investigations[1] of the opening of steroidal epoxides with boron trifluoride etherate have been performed in inert solvents. Continuation of a study of synthetic aspects of the Ritter reaction[2,3] has led to an examination of the boron trifluoride promoted opening of the title epoxides in acetonitrile.

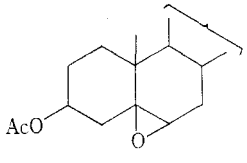
Treatment of a solution of 3β-acetoxy-5,6α-epoxy-5α-cholestane (1a) in acetonitrile with boron trifluoride etherate gave the hydroxy amide (2a) in 85% yield. The formation of this product results from a Ritter reaction at C6 following the expected *trans* diaxial opening of the epoxide ring. In contrast to the reaction of the α-epoxide (1a) with boron trifluoride in benzene,[4,5] no fluorohydrin formation or rearrangements were observed.



	R	X
(1a)	Ac	O
(1b)	H	NH
(1c)	H	NAc
(1d)	Ac	NAc



	R^1	R^2	R^3
(2a)	Ac	OH	NHAc
(2b)	Ac	NHAc	OH
(2c)	Ac	NHAc	Ac
(2d)	Ac	NHAc	OMs



(3)

Under the same conditions, 3β-acetoxy-5,6β-epoxy-5β-cholestane (3) gave a complex mixture, whose infrared spectrum showed that some amide was indeed formed, together with ketonic material. However, when the boron trifluoride etherate was replaced by boron trifluoride gas the desired Ritter reaction did take place, with the exclusion of complicating features, to give the expected hydroxy amide (2b) in

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[1] Kirk, D. N., and Hartshorn, M. P., "Steroid Reaction Mechanisms." Ch. 8. (Elsevier: Amsterdam 1968.)

[2] Ducker, J. W., *Chemy Ind.*, 1968, 1276.

[3] Ducker, J. W., and Gunter, M. J., *Aust. J. Chem.*, 1968, **21**, 2809.

[4] Henbest, H. B., and Wrigley, T. I., *J. chem. Soc.*, 1957, 4765.

[5] Blunt, J. W., Hartshorn, M. P., and Kirk, D. N., *Tetrahedron*, 1966, **22**, 3195.

90% yield. ApSimon and King[6] have also reported obtaining a different result using boron trifluoride gas in place of boron trifluoride etherate in cleavage of epoxides.

Acetylation of (2b) gave the triacetate (2c): the identity of this product, and of (2a), were confirmed by comparison with authentic samples. The published routes[7,8] to these authentic samples were lengthy and inefficient; thus this new reaction offers a useful improvement in the synthesis of these steroidal amides.

trans-β-Hydroxy amides may be transformed via their derived sulphonyl esters to aziridines, on treatment with base.[9] Application of this reaction to the mesylate (2d) gave the aziridine (1c). The structure of (1c) followed from its infrared spectrum, and from hydrolysis and acetylation to the known compounds (1b) and (1d).[7]

Experimental

Melting points were determined on a Kofler apparatus and are uncorrected. Infrared spectra were determined as Nujol mulls between sodium chloride plates using a Unicam SP200 instrument. N.m.r. were recorded at 29° in deuterochloroform (unless otherwise stated) using a Varian HA-60-IL spectrometer; all chemical shifts are referred to tetramethylsilane. Optical rotations are at 20° in chloroform. Light petroleum was the fraction b.p. 50–70°.

Ritter Reaction of the α-Epoxide (1a)

Boron trifluoride etherate (1 ml) was added dropwise over 5 min to a stirred suspension of 3β-acetoxy-5,6α-epoxy-5α-cholestane (1a) (1 g) in acetonitrile (10 ml). The resulting solution was stirred at room temperature for 2 hr, then diluted with water until crystallization was complete. The crystals were filtered off, washed with water, and recrystallized from acetonitrile to give 6β-acetylamino-5α-cholestane-3β,5-diol 3-acetate (2a) (860 mg, 85%) as needles, m.p. 193–195°, $[\alpha]_D$ −40° (*c*, 1·0) (lit.[8] m.p. 195–196°, $[\alpha]_D$ −12°), ν_{max} 3550 (OH), 3450 (NH), 1725 (OAc), 1660 (amide I), and 1525 cm^{-1} (amide II). The n.m.r. spectrum shows: δ 0·68 (3H singlet, C 18 methyl), 1·10 (3H singlet, C 19 methyl), and 1·97 (6H singlet, *N*-acetyl and *O*-acetyl).

The product was identical (i.r. spectrum and mixed melting point) with an authentic sample.[8]

Ritter Reaction of the β-Epoxide (3)

(A) Under the conditions described in the previous experiment 3β-acetoxy-5,6β-epoxy-5β-cholestane (3) (750 mg) gave an oil (740 mg) which resisted crystallization. ν_{max} (film) 3470 (broad, OH and NH), 1730 (OAc), 1710 (ketone), 1662 (amide I), and 1525 cm^{-1} (amide II).

(B) Boron trifluoride gas was passed into a stirred ice-cooled suspension of 3β-acetoxy-5,6β-epoxy-5β-cholestane (3) (1·0 g) in acetonitrile (10 ml) until all the solid dissolved (*c.* 1 min). The mixture was stirred at room temperature for 15 min, then diluted with water; the product was isolated with ether. Recrystallization from aqueous methanol gave *5-acetylamino-5α-cholestane-3β,6β-diol 3-acetate* (2b) (1·01 g, 90%) as needles, m.p. 119–121°, $[\alpha]_D$ +6·2° (*c*, 0·8) (Found: C, 73·8; H, 10·6; N, 2·7. $C_{31}H_{53}NO_4$ requires C, 73·9; H, 10·6; N, 2·8%). ν_{max} 3550 (OH), 3460 (NH), 1715 (OAc), 1657 (amide I), and 1520 cm^{-1} (amide II). The n.m.r. spectrum shows: δ 0·68 (3H singlet, C 18 methyl), 1·33 (3H singlet, C 19 methyl), 1·93 and 1·95 (3H singlets, *O*-acetyl and *N*-acetyl).

Acetylation of (2b)

A solution of 5-acetylamino-5α-cholestane-3β,6β-diol 3-acetate (2b) (1·0 g) in pyridine (5 ml) and acetic anhydride (5 ml) was heated at 100° for 2 hr. The mixture was poured into water and the

[6] ApSimon, J. W., and King, R. R., *Chem. Commun.*, 1967, 1214.
[7] Snatzke, G., and Veithen, A., *Liebigs Ann.*, 1967, **703**, 159.
[8] Drefahl, G., and Ponsold, K., *Chem. Ber.*, 1958, **91**, 271.
[9] Baker, B. R., and Hullar, T. L., *J. org. Chem.*, 1965, **30**, 4049.

product isolated with ether. Recrystallization from aqueous methanol gave 5-acetylamino-5α-cholestane-3β,6β-diol 3,6-diacetate (2c) (1·07 g, 100%) as needles, m.p. 221–223°, $[\alpha]_D$ −20·7° (*c*, 1·0) (lit.[7] m.p. 222·5–223·5°, $[\alpha]_D$ −20·7°), ν_{max} 3460 (NH), 1730 (OAc), 1660 (amide I), and 1525 cm^{-1} (amide II). The n.m.r. spectrum (deuteropyridine) shows: δ 0·63 (3H singlet, C 18 methyl), 1·33 (3H singlet, C 19 methyl), 1·88, 1·92, and 2·08 (3H singlets, *O*-acetyl and *N*-acetyl).

The product was identical (i.r. spectrum and mixed melting point) with an authentic sample.[7]

5-Acetylamino-5α-cholestane-3β,6β-diol 3-Acetate 6-Mesylate (*2d*)

Redistilled methanesulphonyl chloride (1·5 ml) was added dropwise over 5 min to a stirred ice-cooled solution of 5-acetylamino-5α-cholestane-3β,6β-diol 3-acetate (2b) (2·0 g) in dry pyridine (20 ml). The mixture was kept at 10° for 48 hr, then diluted with water; the product was isolated with ether. Recrystallization from acetone–light petroleum gave *5-acetylamino-5α-cholestane-3β,6β-diol 3-acetate 6-mesylate* (2d) (1·6 g, 75%) as plates, m.p. 136–138°, $[\alpha]_D$ +28·5° (*c*, 0·98) (Found: C, 66·0; H, 9·5; N, 2·5; S, 5·7. $C_{32}H_{55}NO_6S$ requires C, 66·1; H, 9·5; N, 2·4; S, 5·5%). ν_{max} 3390 (NH), 1730 (OAc), 1662 (amide I), 1525 (amide II), and 1178 cm^{-1} (mesylate).

1′-Acetyl-3β-hydroxy-1′,3′-dihydro-5α-cholestano[*5,6*-b]*azirine* (*1c*)

The mesylate (2d) (1·15 g) was boiled under reflux for 80 min with a solution of sodium (0·45 g) in ethanol (20 ml). The solution was cooled, diluted with water, and the product isolated with ether. Recrystallization from aqueous ethanol gave *1′-acetyl-3β-hydroxy-1′,3′-dihydro-5α-cholestano*[*5,6*-b]*azirine* (1c) (0·3 g, 32%), m.p. 161–163° and 181–184° (Found: C, 78·3; H, 11·1; N, 3·2. $C_{29}H_{49}NO_2$ requires C, 78·5; H, 11·1; N, 3·2%). ν_{max} 3450 (OH) and 1656 cm^{-1} (tertiary amide).

Acetylation of (*1c*)

A solution of (1c) (100 mg) in pyridine (1 ml) and acetic anhydride (1 ml) was heated at 100° for 1 hr. The mixture was cooled and poured into water. The product was filtered off and washed with water. Recrystallization from aqueous methanol gave 3β-acetoxy-1′-acetyl-1′,3′-dihydro-5α-cholestano[5,6-*b*]azirine (1d) (100 mg, 98%), m.p. 158–159° (lit.[7] 160°), ν_{max} 1705 (OAc) and 1670 cm^{-1} (tertiary amide).

The product was identical (i.r. spectrum and mixed melting point) with an authentic sample.[7]

Hydrolysis of (*1c*)

A solution of (1c) (80 mg) in ethanolic sodium hydroxide (0·2M, 25 ml) was boiled under reflux for 6 hr. Concentration to 10 ml and cooling gave crystals which were purified from aqueous ethanol to yield 3β-hydroxy-1′,3′-dihydro-5α-cholestano[5,6-*b*]azirine (1b) (50 mg, 63%) as needles, m.p. 210–213° (lit.[7] 214°), ν_{max} 3400 (NH) and 3310 cm^{-1} (OH).

The product was identical (i.r. spectrum and mixed melting point) with an authentic sample.[7]