Epoxidation with Pyridine–Trifluoroacetic Anhydride–Molecular Oxygen and Its Mechanistic Aspects

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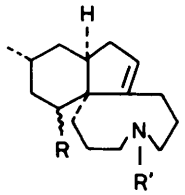
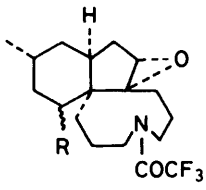
Epoxidation of cholesteryl acetate (**3**) with pyridine–trifluoroacetic anhydride–molecular oxygen afforded bis(trifluoroacetate) (**4**), β-epoxide (**5**), α-epoxide (**6**), hydroxy trifluoroacetates A (**7**) and B (**9**), and enone (**8**). An oxidation mechanism proceeding *via* the hydroperoxide intermediate (**A**) is presented.

In connection with our synthetic study on the Lycopodium alkaloid lycophlegmarine,[1] we have already reported that acylation of the alkene (**1**) with trifluoroacetic anhydride (TFAA) in pyridine overnight at room temperature gave the corresponding epoxide (**2**) stereoselectively and this unusual epoxidation was accelerated in an oxygen atmosphere.[2] Then, we applied the method (pyridine–TFAA–O_2) to cholesteryl acetate (**3**), and briefly described the results and the mechanistic aspects of the reaction.[3] The details of the oxidation reactions are the subject of this paper. Oxidation of compound (**3**) with pyridine–TFAA–O_2 in dry benzene for 4 days at room temperature or with pyridine–TFAA–O_2 for 4 h at 35 °C gave bis(trifluoroacetate) (**4**), β-epoxide (**5**), α-epoxide (**6**), hydroxy trifluoroacetate A (**7**), enone (**8**), and hydroxy trifluoroacetate B (**9**). The compounds (**5**),[4] (**6**),[4] and (**8**)[5] were identified by comparison with authentic samples prepared according to the literature method. Bis(trifluoroacetate) (**4**) was very labile and easily hydrolysed with 5% aqueous sodium hydrogen carbonate in methanol to produce hydroxy trifluoroacetate B (**9**), indicating that the stereochemistry of the two oxygen functions newly introduced in (**4**) and (**9**) is the same. As it can be presumed that compounds (**4**), (**7**), and (**9**) were formed *via* epoxides (**5**) and/or (**6**), reactions of epoxides with TFAA–pyridine were investigated. Thus, treatment of β-epoxide (**5**) with pyridine–TFAA for 1 h, followed by hydrolysis with 5% $NaHCO_3$ in methanol, afforded compound (**9**). Its ^1H n.m.r. spectrum showed the signals due to a proton geminal to a newly introduced hydroxy group at δ 4.62 (1 H, m, $w_{\frac{1}{2}}$ 8 Hz), suggesting that the hydroxy group is axial. Then, oxidation of compound (**9**) with Jones' reagent, followed by chromatography on alumina, gave the known hydroxy ketone (**10**).[6] Therefore, the structures of the bis(trifluoroacetate) and hydroxy trifluoroacetate B were confirmed as (**4**) and (**9**), respectively. On the other hand, the α-epoxide (**6**), when treated with pyridine–TFAA for 4 h and successively with 5% $NaHCO_3$ in methanol, afforded the hydroxy trifluoroacetate A (**7**) along with the starting material (**6**). The ^1H n.m.r. spectrum of compound (**7**) showed signals due to a proton geminal to the hydroxy group at δ 4.80 (1 H, m, $w_{\frac{1}{2}}$ 10 Hz), suggesting that the hydroxy group is axial. Therefore, the structure of the hydroxy trifluoroacetate A was confirmed as (**7**). These results indicate that the above oxidation of alkene (**3**) initially produced the epoxides (**5**) and (**6**), and that their subsequent diaxial cleavages afforded compounds (**4**) and (**9**), and (**7**), respectively, although the epoxide (**5**) was more reactive. It is interesting to note that epoxidation by the present method produced the β-epoxide (**5**) preferentially [(**5**):(**6**) = 11:1] in comparison with epoxidation by *m*-chloroperbenzoic acid [(**5**):(**6**) = 3:7].[4]

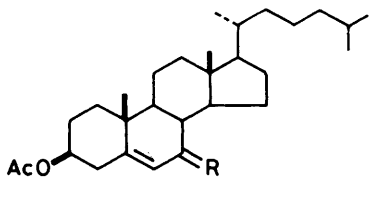
In order to investigate the mechanism (active species) of this reaction, the effects of substituents on the pyridine ring and of other aromatic bases in the epoxidations of compounds (**1c**)



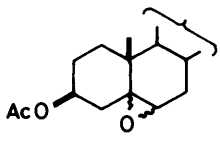
(**1a**) R = β-OH, R' = H
(**1b**) R = α-OH, R' = H
(**1c**) R = β-$OCOCF_3$, R' = $COCF_3$



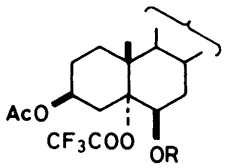
(**2a**) R = β-$OCOCF_3$
(**2b**) R = α-$OCOCF_3$



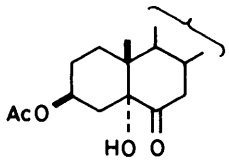
(**3**) $R = H_2$
(**8**) R = O



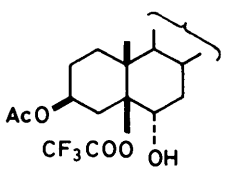
(**5**) β - epoxide
(**6**) α - epoxide



(**4**) R = $COCF_3$
(**9**) R = H



(**10**)



(**7**)

Table 1. The results of oxidation of cholesteryl acetate (**3**)

Base	Yields (%) of oxidation products (3)	(4)	(5)	(6)	(7)	(8)	(9)	Reaction time (days)
Pyridine[a]		59.6	3.7	1.7	2.0	4.7	14.6	4
Pyrazine	86							10
Pyrimidine	84.2	0.6					1.2	11
Pyridazine	62.5		1.2	trace	3.2		6.8	7
2-Picoline[b]	95							5
3-Picoline	90.2					0.8	7.3	5
4-Picoline	95							5

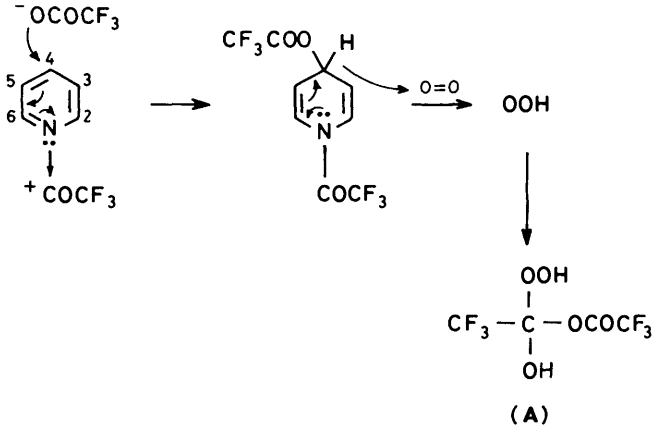
[a] Oxidation in pyridine for 4 h at 35 °C also gave a similar result. [b] Picolines are methylpyridines.

Table 2. Results of epoxidation of alkene (**1c**) to oxirane (**2a**)

Base[a]	Yield (%) of (**2a**)	Base	Yield (%) of (**2a**)
Pyridine	58% (3 h)	2,6-Lutidine	*b*
2-Picoline	*b*	3,5-Lutidine	*b*
3-Picoline	67% (120 h)	Quinoline	*b*
4-Picoline	*b*	2,4,6-Collidine	*b*
2,4-Lutidine	*b*		

[a] Picolines are methylpyridines, lutidines are dimethylpyridines, and collidines are trimethylpyridines. [b] The starting material (**1c**) was recovered in 75—83% yield.

and (**3**) were examined. The results are summarised in Tables 1 and 2. As can be seen from the Tables, epoxidation is apparently influenced by the pattern of substitution on the pyridine ring and pyridine itself is the most effective base for epoxidation. Since neither substrate (**1c**) nor (**3**) was oxidised with either TFAA–O_2 or pyridine–O_2, then pyridine, TFAA, and O_2 must all be essential for this epoxidation and O_2 works as an indirect oxidant. Furthermore, oxidation of alkene (**3**) with TFAA–O_2 in pyridine for 4 h at 35 °C and successive hydrolysis with 5% aqueous $NaHCO_3$ gave the hydroxy trifluoroacetate B (**9**) in 66.3% yield, whereas oxidation of compound (**3**) in [$^2H_5$]pyridine under the same conditions gave compound (**9**) in only 20.6% yield along with recovery of some of the starting material (**3**). Oxidation for 24 h, giving complete consumption of alkene (**3**), gave compound (**9**) in 62.9% yield; an isotope effect was apparently observed. This result indicates that the hydrogen(s) on the pyridine nucleus directly participates in the epoxidation. From these observations, we present the mechanism shown in the Scheme as one possible mechanism, involving the hydroperoxide intermediate (**A**)[7] generated from TFAA



Scheme.

and the hydroperoxide anion formed by reduction of O_2 *via* a process similar to NADH reduction. The mechanism mentioned above seems to be essentially different from that of the autoxidation.[8] Isolation of 4-hydroxypyridine supports this mechanism including the intermediary 1,4-dihydropyridine derivative as a reductant. The formation of 4,4′-bipyridine also would be initiated by reductive dimerisation of pyridine by the above reductant.*

Experimental

M.p.s were taken on a Yanagimoto micro-melting-point apparatus and are uncorrected. I.r. spectra were obtained on a Shimadzu IR-400 spectrometer and ^1H n.m.r. spectra on a JEOL FX 200 spectrometer. The n.m.r. data are reported relative to internal tetramethylsilane. Mass spectra were taken on a JEOL JMS 01SG-2 instrument by direct insertion at 70 eV. In general, the extract was dried over anhydrous potassium carbonate, filtered, and the filtrate was evaporated to dryness. Column chromatography was carried out with Silica gel 60 (E. Merck, 70—230 mesh) or Aluminiumoxid 90 (E. Merck, activity II—III), and preparative t.l.c. was run on 20 × 20 cm plates coated with 0.25 mm layer of Merck silica gel GF_{254} or PF_{254}. 4,4′-Bipyridine and 4-hydroxypyridine were purchased from Wako Pure Chemical Industries, Ltd (Japan).

General Procedures for Oxidation of Cholesteryl Acetate (**3**) *with Pyridine–TFAA–O_2.*—A mixture of cholesteryl acetate (**3**) (200 mg, 0.47 mmol) and TFAA (1 ml) in base (2 g) and dry benzene (2 ml) was stirred at room temperature for the period indicated in Table 1 under oxygen. The reaction mixture was evaporated to dryness under reduced pressure. The residue was diluted with water and extracted with ether. The residue was chromatographed on silica gel (20 g) and elution with hexane gave cholest-5-en-3β-yl acetate (**3**). Successive elution with hexane gave 5α-*cholestane*-3β,5,6β-*triol* 3-*acetate* 5,6-*bis*(*trifluoroacetate*) (**4**), $\nu_{max.}$($CHCl_3$) 1 790 and 1 730 cm^{-1} (CO); δ_H($CDCl_3$) 0.69 (3 H, s, C-Me), 0.85 (6 H, d, *J* 6.5 Hz, 2 × CH*Me*), 0.91 (3 H, d, *J* 6.6 Hz, CH*Me*), 1.24 (3 H, s, CMe), 4.71 (1 H, m, $w_{\frac{1}{2}}$ 30 Hz, C*H*OAc), and 5.91 (1 H, m, $w_{\frac{1}{2}}$ 8 Hz, C*H*OCOCF$_3$) (Found: M^+, 654.3338. $C_{33}H_{48}F_6O_6$ requires *M*, 654.3354).

Elution with 10% AcOEt in hexane afforded a mixture of the epoxides (**5**) and (**6**). The mixture was separated by preparative t.l.c. ($CHCl_3$). The less polar zone afforded 5β,6β-epoxycholestan-3β-yl acetate (**5**) as needles, m.p. 108—110 °C (from MeOH) (lit.,[4] 106—108 °C) and the more polar zone, 5α,6α-epoxycholestan-3β-yl acetate (**6**) as needles, m.p. 96—99 °C (from MeOH) (lit.,[4] 98—100 °C). The epoxides (**5**) and (**6**) were identified by comparison with corresponding authentic samples prepared according to the literature method,[4] by ^1H n.m.r. and i.r. spectral comparisons, and by mixed m.p. determination.

Elution with CH_2Cl_2 gave a mixture of the hydroxy trifluoroacetates A and B (**7**) and (**9**), and the enone (**8**). The mixture was separated by preparative t.l.c. [hexane–AcOEt (9:1)]. The highest zone gave 5β-*cholestane*-3β,5,6α-*triol* 3-*acetate* 5-*trifluoroacetate* (**7**), $\nu_{max.}$($CHCl_3$) 3 400br (OH), 1 780 and 1 720 cm^{-1} (CO); δ_H($CDCl_3$) 0.67 (3 H, s, CMe), 0.86 (6 H, d, *J* 6.6 Hz, 2 × CH*Me*), 0.91 (3 H, d, *J* 6.4 Hz, CH*Me*), 1.15 (3 H, s, CMe), 2.03 (3 H, s, OCOMe), 4.80 (1 H, m, $w_{\frac{1}{2}}$ 10 Hz, C*H*OH), and 5.10 (1 H, m, $w_{\frac{1}{2}}$ 30 Hz, C*H*OAc) (Found: M^+, 558.3528. $C_{31}H_{49}F_3O_5$ requires *M*, 558.3532). The middle zone afforded 7-oxocholest-5-en-3β-yl acetate (**8**) as needles, m.p. 162—164 °C

* It is well known that the reductive dimerisation of pyridine in acetic anhydride, followed by aerial oxidation, gives 4,4′-bipyridine (see, for example, A. T. Nielsen, D. W. Moore, G. M. Muha, and K. H. Berry, *J. Org. Chem.*, 1964, **29**, 2175).

(from pentane) (lit.,[5] 161—163 °C). The i.r. and ^{1}H n.m.r. spectra were identical with those of an authentic sample prepared by Dauben's method.[5] The lowest zone afforded 5α-*cholestane*-3β,5,6β-*triol* 3-*acetate* 5-*trifluoroacetate* (**9**) as prisms (from pentane), m.p. 139—142 °C; $\nu_{max.}$($CHCl_3$) 3 400 (OH), 1 770 and 1 725 cm^{-1} (CO); δ_H($CDCl_3$) 0.69 (3 H, s, CMe), 0.86 (3 H, d, *J* 6.6 Hz, CH*Me*), 0.87 (3 H, d, *J* 6.6 Hz, CH*Me*), 0.91 (3 H, d, *J* 6.4 Hz, CH*Me*), 1.26 (3 H, s, CMe), 2.02 (3 H, s, COMe), 4.62 (1 H, m, $w_{\frac{1}{2}}$ 8 Hz, C*H*OH), and 4.71 (1 H, m, $w_{\frac{1}{2}}$ 30 Hz, C*H*OAc) (Found: M^+, 558.3502. $C_{31}H_{49}F_3O_5$ requires *M* 558.3532).

Reaction of β-*Epoxide* (**5**) *with TFAA in Pyridine*.—To an ice-cooled solution of β-epoxide (**5**) (12 mg, 0.027 mmol) in pyridine (2 ml) was added TFAA (1 ml). The mixture was stirred for 1 h at room temperature under argon, and then concentrated to dryness under reduced pressure. A mixture of the residue in MeOH (2 ml) and 5% aqueous $NaHCO_3$ (0.5 ml) was stirred for 30 min at room temperature, diluted with water, and extracted with ether. Work-up of the extract gave a residue, which was recrystallised from pentane to afford compound (**9**) (11 mg, 73%), m.p. 139—141 °C.

Reaction of α-*Epoxide* (**6**) *with TFAA in Pyridine*.—To an ice-cooled solution of α-epoxide (**6**) (30 mg, 0.068 mmol) in pyridine (2 ml) was added TFAA (1 ml). The mixture was stirred for 4 h at room temperature under argon and was then worked up in the same way as described for the reaction of (**5**) with TFAA. The residue was separated by preparative t.l.c. [hexane–AcOEt (9:1)]. The less polar zone gave the starting material (**6**) (18 mg, 60% recovery), and the more polar zone gave hydroxy trifluoroacetate A (**7**) (7 mg, 18.5%).

Hydrolysis of the Bis(*trifluoroacetate*) (**4**) *to the Hydroxy Trifluoroacetate B* (**9**).—A mixture of the bis(trifluoroacetate) (**4**) (45 mg, 0.069 mmol) in MeOH (2 ml) and 5% aqueous $NaHCO_3$ solution (0.5 ml) was stirred for 30 min at room temperature. The mixture was diluted with water and extracted with $CHCl_3$. The residue was recrystallised from pentane to afford (**9**) (32 mg, 83.3%), m.p. 139—142 °C.

Conversion of the Hydroxy Trifluoroacetate B (**9**) *into the Hydroxy Ketone* (**10**).—To a solution of hydroxy trifluoroacetate (**9**) (30 mg, 0.054 mmol) in acetone (3 ml) were added five drops of Jones' reagent and the solution was ice-cooled and stirred for 1 h. Excess of the reagent was decomposed with Pr^{i}OH. The mixture was diluted with water and extracted with ether. Work-up gave a residue, which was dissolved in $CHCl_3$ and chromatographed on alumina (2 g). Elution with $CHCl_3$ afforded 6-oxo-5a-cholestane-3β,5-diol 3-acetate (**10**) as prisms (20 mg, 81%), m.p. 230—233 °C (lit.,[6] 233—235 °C). The i.r. and ^{1}H n.m.r. spectra were identical with those of an authentic sample prepared according to the literature method.[6]

General Procedure for Epoxidation of N,O-*Bis*(*trifluoroacetate*) (**1c**).—To an ice-cooled solution of compound (**1c**) (15 mg, 0.032 mmol) in base (3 ml) was added TFAA (2 ml) and the mixture was stirred for 24 h at room temperature under oxygen; it was then diluted with water and extracted with ether. The residue obtained on work-up of the extract was purified by preparative t.l.c. ($CHCl_3$) to give the starting material (**1c**) and/or the epoxide (**2a**), m.p. 150—152 °C (lit.,[2] 151—152 °C).

Oxidation of Cholesteryl Acetate (**3**) *with TFAA–*O_2 *in Pyridine or* [$^2H_5$]*Pyridine*.—To an ice-cooled solution of compound (**3**) (42.9 mg, 0.1 mmol) in pyridine (2 ml) or [$^2H_5$]-pyridine (2 ml) was added TFAA (1 ml), and the mixture was stirred at 35 °C for a designated period (4 h or 24 h) under oxygen. The mixture was worked up in the same way as described for reaction of compound (**5**) with TFAA. The residue obtained on work-up of the extract was separated by preparative t.l.c. [hexane–AcOEt (9:1)] to give the starting material (**3**) and/or hydroxy trifluoroacetate **B** (**9**), m.p. 139—141 °C.

Isolation of 4-*Hydroxypyridine and* 4,4′-*Bipyridine*.—A solution of pyridine (2 ml) and TFAA (1 ml) was stirred for 3 days at room temperature under oxygen. The mixture was concentrated to dryness under reduced pressure. The residue was diluted with water and extracted with butan-1-ol. The extract was evaporated to dryness and the residue, dissolved in $CHCl_3$, was chromatographed on silica gel (10 g). Elution with 10% MeOH in $CHCl_3$ gave 4,4′-bipyridine (44.4 mg, 2.3% based on starting pyridine) as plates, m.p. 110—112 °C (from ether) (lit.,[9] 114 °C). The i.r. and ^{1}H n.m.r. spectra were identical with those of a commercially available sample.

Elution with 30—50% MeOH in $CHCl_3$ gave 4-hydroxypyridine (4.4 mg, 0.18% based on starting pyridine), which was methylated to afford *N*-methyl-γ-pyridone, m.p. 188—190 °C (picrate) (yellow prisms from methanol) (lit.,[10] m.p. 188 °C). The i.r. and ^{1}H n.m.r. spectra of these compounds were identical with those of an available sample and an authentic sample prepared by methylation of 4-hydroxypyridine, respectively.

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