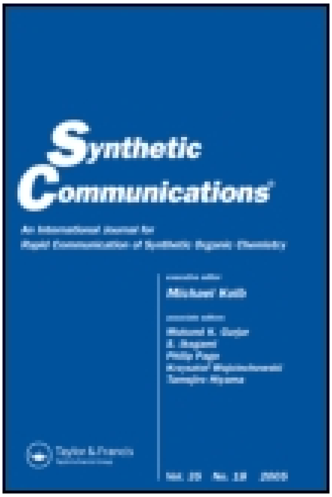

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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To cite this article: Mohammad Mushfiq , Thresiamma Manuel & Rakhshanda Rehman (2004) Synthesis of Steroidal Oxazolidine Thiones in the Cholestane Series, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:21, 3989-3996, DOI: 10.1081/SCC-200034819

To link to this article: http://dx.doi.org/10.1081/SCC-200034819

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 21, pp. 3989–3996, 2004

Synthesis of Steroidal Oxazolidine Thiones in the Cholestane Series

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ABSTRACT

Steroidal α-epoxides (I, III, and VIII) on reaction with 4-fluorophenylisothiocyanate give the corresponding oxazolidine thiones (II, V, VI, VII, and XI) along with other products (IV and IX). Characterization of the compounds is based on spectral properties and elemental analysis.

Key Words: Epoxides; Isothiocyanates; Steroidal oxazolidine thiones.

Epoxides are well recognized, useful intermediates for organic synthesis.[1–4] Reported useful biological activities[5–9] with nitrogen and sulphur containing heterocycles generated interest for the synthesis of simple oxazolidine-2′-thiones by the reaction of epoxides with isothiocyanates.[10]

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DOI: 10.1081/SCC-200034819
0039-7911 (Print); 1532-2432 (Online)

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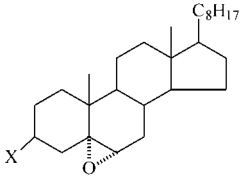
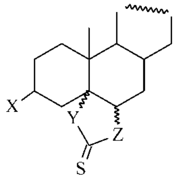
Such epoxides in the steroidal substrates have also been prepared and used for obtaining other derivatives,[11,12] and our continued interest in the field of steroids prompted us to try such reactions in order to obtain steroidal oxazolidine derivatives. In the content for the present studies, easily accessible epoxides 5,6α epoxy-5α-cholestane (I)[13] and its 3β-acetoxy and 3β hydroxy analogues (III)[14] and (VIII)[15] were subjected to the reaction with easily available and previously studied p-fluorophenyl isothiocyanate in DMF with LiBr as the catalyst. We report the formation and characterization of corresponding oxazolidine thiones (II, V, VI, VII, and XI) along with other products.

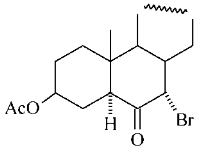
The characterization is based on elemental analysis in each new compound formed (Table 1) and spectral properties including IR and ^{1}HNMR (Table 2).



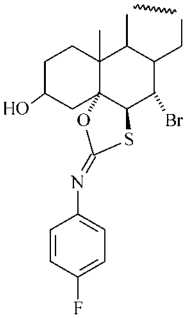
	X
(I)	H
(III)	OAc
(VIII)	OH



	X	Y	Z	
(II)	H,	O	NC_6H_4F,	5α, 6α
(V)	OAc,	NH,	O,	5α, 6α
(VI)	OAc,	O,	NC_6H_4F	5α, 6α
(VII)	OAc,	NC_6H_4F,	O,	5β, 6α
(X)	OH,	O,	NC_6H_4F,	5α, 6α
(XI)	OH,	NC_6H_4F,	O,	5β, 6α
(Va)	OAc,	NH,	O,	5β, 6α
(Vb)	OAc,	NH,	O,	5β, 6β
(Vc)	OAc,	NH,	O,	5α, 6β
(Vd)	OAc,	O,	NH,	5α, 6α
(Ve)	OAc,	O,	NH,	5β, 6α
(Vf)	OAc,	O,	NH,	5β, 6β
(Ve)	OAc,	O,	NH,	5α, 6β



(IV)



(IX)

The epoxide (I), when allowed to react with 4-fluorophenylisothiocynate, on usual workup and column chromatography afforded a pure solid with m.p. 131° (II) along with unresolved mixture, which could not be pursued further. The compound m.p. 131° showed ir bands at 1520–1500 cm^{-1} characteristic of oxazolidine ring[10] along with peaks at 1570, 830 cm^{-1} for the aromatic ring. This clearly indicated the incorporation of the reagent. On the basis of

Table 1. Reaction of epoxides(I), (III), and VIII with p-fluorophenylisothiocyanate.

Starting compound	Product	Solvent system	Crystallized from	Yield %	M.P. °C/oil
I	II unresolved mixture	4 : 1	MeOH	26.86	131
		1 : 1	—	30.00	oil
III	IV	20 : 2	MeOH	10.63	143
	V	20 : 6	MeOH	21.64	194
	VI + VII	20 : 7	—	19.34	oil
VIII	IX	10 : 2	MeOH	16.66	184
	X + XI	10 : 3	—	25.36	oil

the mechanism reported,[10] it was formulated as 5α-cholestano [5,6α:5′4′]-3′(p-flourophenyl) oxazolidine-2′-thione(II). The n.m.r spectrum supported the structure proposed by a broad signal at δ 6.7 for four aromatic protons. Another signal at δ 3.3 as a multiplet can be ascribed to C6-H, and the half-band width (7 Hz) clearly suggests it to be axial β-oriented, thus rendering nitrogen as α-oriented.

Under similar conditions, epoxides (III) provided three fractions A, B, and C on chromatographic separation. Fraction A obtained as pure compound on crystallization has been identified as 3β-acetoxy-7α-bromo-5α-cholestane-6-one (IV).[16] Fraction B also obtained as pure crystalline substance showed the presence of N, S, and O on elemental analysis. The ir spectrum of this compound indicated presence of NH (3475 cm^{-1}), CH_3COO (1730, 1255, 1020 cm^{-1}), and oxazolidine ring (1520–1500 cm^{-1})[10] but it did not show any band in the aromatic proton region. On the basis of these studies, many isomeric structures can be drawn, such as V, and Va-g in agreement with elemental analysis and ir spectrum. The structure V is preferred on account of the n.m.r spectrum of this compound, which accounts for all the signals in a better way. The singlet at δ 8.0 is ascribed to N-H[17] and the multiplet δ 5.1 with $w\,1/2 = 20\,\text{Hz}$ is ascribed to C3α axial proton, suggesting that junction A/B is trans. The important signal at δ 4.72 as broadened singlet for one proton can be accounted for by considering it to the C6β-H, thus rendering oxygen as α-oriented. Hence, this compound is characterized as 3β-acetoxy-5α-cholestano [5, 6α: 4′,5′] oxazolidine-2′-thione (V).

The third fraction obtained as oil showed the presence of two components of very close R_f and could not be separated. Elemental analysis corresponds to composition $C_{36}H_{53}O_3NSF$. The i.r. spectrum showed bands at 1725, 1720 (C=O), 1625 (aromatic ring), 1520–1500 (oxazolidine ring), and 1240,

Table 2. Analytical and spectral data of the compounds.

Compd.	Molecular formula	Analysis (calc.) found (%) C	H	N	I.R. (KBr) ν_{max} cm^{-1}	^{1}H-n.m.r (100 MHz)
II	$C_{34}H_{50}ONSF$	75.58 (75.69)	9.24 (9.27)	2.55 (2.59)	1570 (phenyl), 1520–1500 (oxazolidine ring), 830 (p-substituted benzene).	6.7 (4H, brm, aromatic), 3.3(1H, m, C6-βH, W1/2 = 7 Hz), 1.28, 0.93, 0.83, 0.7 (4 × Me).
IV	$C_{29}H_{47}O_3Br$	66.54 (66.66)	8.95 (9.09)	—	1732, 1712 (C=O), 1240, 1032 (C-O), 780 (C-Br).	4.62 (1H, m, C3-αH, W1/2 = 16 Hz), 4.18 (1H, d, C7-βH, J = 7 Hz), 2.0 (3H, s, O-CO-CH_3), 0.95, 0.87, 0.80, 0.75 4 × Me).
V	$C_{30}H_{49}O_3NS$	71.53 (71.57)	9.60 (9.74)	2.74 (2.78)	3475 (NH), 1730 (C=O), 1520–1500 (oxazolidine ring), 1255, 1020 (C-O).	8.0 (1H, s, NH), 5.1(1H, m, C3-αH W1/2 = 20 Hz), 4.72 (1H, brs, C6-βH), 1.94 (3H, s, O-CO-CH_3), 1.07, 0.81, 0.74, 0.6 (4 × Me).
VI + VII	$C_{36}H_{52}O_3NSF$	72.33 (72.36)	8.67 (8.71)	2.30 (2.34)	1725 (C=O), 1625 (aromatic C=C), 1520–1500 (oxazolidine ring) 1240, 1205, 1020 (C-O), 835 (p-substituted benzene).	6.95 (4H, m, aromatic protons), 5.55 (1/2 H, m, C3-αH, W1/2 = 7 Hz, e), 5.12 (1/2 H, m, C3-αH W1/2 = 20 Hz, a), 4.12 (1/2 H, m, C6-βH, W1/2 = 19 Hz, a), 3.5 (1/2 H, m, C6-βH, W1/2 = 18 Hz, a), 2.02 (3H, s, CH_3COO), 1.01, 0.85, 0.77, 0.65 (4 × Me).

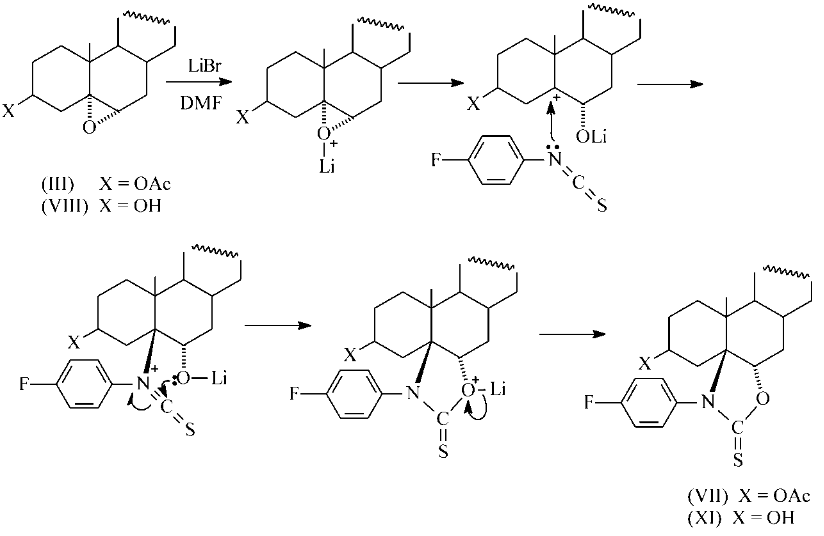
IX	$C_{34}H_{50}O_2NSF$	73.40 (73.51)	8.90 (9.00)	2.35 (2.52)	3275 (OH), 1507–1525 (ring and aromatic C=C), 1170 (ring), 1020 (C-O), 835 (p-substituted benzene)	6.94 (4H, m, aromatic protons), 5.52 (1H, m, C3-αH, W1/2 = 20 Hz, a), 2.87 (1H, d, C6-αH, J = 4Hz), 1.02, 0.83, 0.75, 0.55 (4 × Me).
X + XI	$C_{34}H_{50}O_2NSF$	73.45 (73.51)	8.95 (9.00)	2.50 (2.52)	3375 (OH), 1612 (aromatic C=C), 1520–1500 (oxazolidine ring), 1015 (C-O), 830 (p-substituted benzene).	8.04 (1H, s, OH), 6.87 (4H, m, aromatic protons), 5.74 (1/2H, m, C3-αH, W1/2 = 20 Hz, a), 4.77 (1/2 H, m, C-3-αH, W1/2 = 6.5 Hz, e), 4.12 (1/2H, brs, C6-βH W1/2 = 11 Hz), 3.26 (1/2H, brs, C6-βH, W1/2 = 10 Hz), 0.97, 0.85, 0.80, 0.65 (4 × Me).

1205, and 1020 cm^{-1} (C-O). Two carbonyl peaks also support it to be a mixture and suggest that one is for equatorial acetate (A/B trans) (VI) and the other is for axially oriented acetate (A/B cis) (VII). This is further supported by the n.m.r. spectrum displaying two multiplets δ 5.12 and 5.55 each integrating for 1/2 proton with W 1/2 = 20 & 7 Hz, respectively.

Another pair of signals as multiplet for 1/2 proton each is observed at δ 3.5 (W 1/2 = 18 Hz) and 4.12 (W 1/2 = 19 Hz), both being β-oriented can be accounted for by considering it to be C6 proton when C6 is attached to nitrogen as in (VI) and when C6 is attached to oxygen[17] as in (VII), respectively. Other signals (Table 2) are observed as usual and hence this fraction can best be characterized as a mixture of 3β-acetoxy-5α-cholestano [5, 6α: 5′, 4′]-3′-(p-fluorophenyl) oxazolidine-2′-thione (VI) and 3β-acetoxy-5β-cholestano [5,6α: 4′,5′]-3′-[p-fluorophenyl) oxazolidine-2′-thione (VII).

Epoxide (VIII) under similar conditions gave two fractions, which on the basis of the similar studies as described with (III), are characterized as compound (IX) and a mixture of (X) and (XI), respectively (see Table 2).

The mechanism proposed[10] can account for the formation of (II), (V), (VI), (IX), and (X) but the products (VII) and (XI) need special mention for their formation. It is suggested that (Sch. 1) C5 being a tertiary carbon favors the formation of carbocation followed by nucleophilic attack by nitrogen in SN^1 type rather than SN^2 type as suggested earlier.[10] This could also be considered as a concerted process of attack of nitrogen to C5 and the attack



Scheme 1.

of oxygen to carbon of isothiocyanate moiety, but with this one would expect α-attack on C5 more favorable. Hence, the stepwise mechanism is preferred in this case for formation of product with ring junction A/B cis.

EXPERIMENTAL

Melting points determined on a Kofler block are uncorrected, i.r. spectra were determined in KBr/CCl_4 with a 408-Shimadzu spectrophotometer, and n.m.r spectra were run in $CDCl_3$ on a Varian FT 8 A instrument with TMS as internal standard. T.l.c. plates were coated with silica gel and spots were developed in iodine chamber.

Reaction of steroidal epoxide with p-flurophenylisothiocyanate: General Procedure — A solution of the epoxide (1 g, 2.59 mmol) in dimethyl formamide (20 mL) was mixed with an equimolar quantity of p-flurophenyl isothiocyanate and catalytic amount of lithium bromide at room temperature. The reaction mixture was then refluxed under anhydrous conditions and the progress of the reaction was monitored by t.l.c. After completion of the reaction the mixture was poured into water and extracted with ether. The ethereal extract was washed with water, sodium bicarbonate (5%), and water, and then dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oily residue (ca. 0.95 g), which was chromatographed over a column of silica gel (25 g). Elution with light petroleum (b.p. 60–80°C): diethyl ether gave the products as shown in Table 1. Analytical and spectral data of the products are given in Table 2.

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Received in India May 7, 2004