Functionalisation of Saturated Hydrocarbons. Part 1. Some Reactions of a Ferrous Chloride–Chloramine-T Complex with Hydrocarbons

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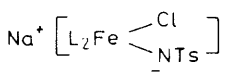
The reactions of several hydrocarbon substrates with a ferrous chloride–chloramine-T complex, generated *in situ*, have been studied. Tosylamination of adamantane and chlorination of mesitylene proceed in good yield while naphthalene gives *N,N'*-bis(toluene-*p*-sulphonyl)-1,4-naphthoquinone di-imine. A variety of olefinic substrates undergo both *cis*- and *trans*-addition to the double bond as well as allylic functionalisation.

The introduction of a functional group into the unactivated C–H bond of a hydrocarbon *in vitro* normally requires the use of a powerful electrophilic or radical reagent. Such a process, however, is often difficult to control and leads to products of over-oxidation. Nevertheless, a variety of useful methods for hydroxylation [1] and halogenation [2] have been developed. By way of contrast, these transformations are smoothly accomplished in nature by using molecular oxygen and an iron-based enzymatic system such as cytochrome P-450.[3] A higher-valent iron oxenoid intermediate has often been proposed as the active species in such reactions.[4]

We conceived that oxidation of a ferrous complex with inexpensive chloramine-T [5] (sodium *N*-chlorotoluene-*p*-sulphonamide) would lead, *via* oxidative addition, to an intermediate of type (1), and that subsequent elimination of chloride anion could give rise to the organo-iron nitrenoid (2) which is the isoelectronic tosylimino-analogue of the putative oxenoid. The elegant work of Sharpless [6] on the aza analogues of osmium tetraoxide lends some support to this speculation. Complexes of type (2) would therefore be of interest not only as possible mechanistic probes for the mechanism of microbiological hydroxylation, but also as reagents for direct amination of the C–H bond. The latter reaction is a relatively rare process.[7,8] In the first instance, we chose to investigate the chemistry of the simple complex formed by reaction of chloramine-T with ferrous chloride (L = Cl) † and to attempt functionalisation of the spherically symmetrical hydrocarbon, adamantane (3).



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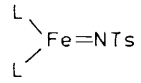

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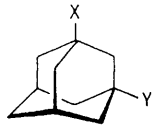
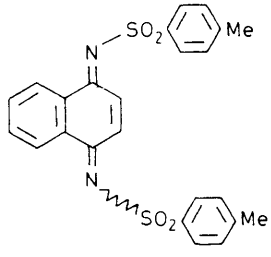


(3) X = Y = H
(4) X = H, Y = *p*—NHSO$_2$C$_6$H$_4$Me
(5) X = Y = *p*—NHSO$_2$C$_6$H$_4$Me
(6) X = Y = Cl



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Treatment of anhydrous chloramine-T with rigorously dry ferrous chloride in dichloromethane gives rise to the formation of a dark blood-red complex. In the presence of adamantane, careful aliquot monitoring of the reaction by analytical g.l.c. indicated the disappearance of the hydrocarbon after two hours. Work-up of the reaction after this time by treatment with aqueous base led to a poor mass balance of adamantanoid products and isolation of *N*-(adamantyl)toluene-*p*-sulphonamide (4) in only 16% yield. However, identical work-up after a three-day period gave encouraging yields of the mono-substituted derivative (4) (43%) and the bis-derivative (5) (24%). These results suggested that breakdown of the penultimate complex was slow and inefficient. A variety of chemical trapping reagents were therefore added in order to test the possibility of triggering a more facile decomposition. The results obtained (Table) indicate that a useful degree of control over formation of the monofunctionalised product can be achieved. Moreover, the consistent formation of the sulphonamide derivative indicates that breakdown of the complex involves rupture of an iron–nitrogen bond.

Further experimentation revealed that direct column chromatography of the crude reaction mixture after only a two-hour period gave the sulphonamide (4) in good yield (63%). Addition of pyridine, oxygen, or water at time zero leads to complete inhibition of the reaction. Anhydrous ferric chloride may also be used but tends to give a more complex reaction mixture.

We have also attempted to generate the nitrenoid complex by thermolysis of toluene-*p*-sulphonyl azide in the presence of ferrous chloride and adamantane at 40 °C for 6.8 days. The isolation of sulphonamide (4) (8.6%) and toluene-*p*-sulphonyl amide (22%) clearly indicate that such a process is inefficient. The reaction of *N,N*-dichlorotoluene-*p*-sulphonamide with zinc has previously been considered to give a nitrenoid species capable of hydrocarbon functionalisation in very low yield.[9]

A valuable mechanistic clue was provided by analytical g.l.c. analysis of the early stages of the reaction which revealed the formation of 1-chloroadamantane (9%) after 1 h 40 min. 2-Chloroadamantane is also consistently detected as a minor

† The representations (1) and (2) (L = Cl) for the ferrous chloride–chloramine-T complex are simplifications, since all chlorine atom bridges have been omitted. It is also conceivable that a non-stoicheiometric iron cluster complex can result from this reaction.

Table. Reaction of adamantane with ferrous chloride–chloramine-T complex followed by addition of a trapping reagent

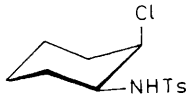
Reagent	Time: Before addition of trap	Time: After addition of trap	Products (% Yield): (3)	(4)	(5)	Other
None	1 h 40 min		17	16		1-Chloro [a] 8.8 2-Chloro [a] 0.1
Oxygen (Excess)	1 h 40 min	5 days		26.5	12.5	
	2 h 35 min	24 h		29	9	
SO_2Cl_2 (2 mmol)	1 h 35 min	25 min		41		
H_2S (Excess)	1 h 50 min	25 min		43		
SO_2 (Excess)	1 h 45 min	5 min	3	39		
I_2 (2 mmol)	1 h 35 min	20 min	12.6	42		1-Iodo [b] 5
Br_2 (2 mmol)	1 h 15 min	7 min		50		
N_2O_4 (Excess)	2 h	5 min				Adamantan-1-ol 33 2-Chloro [a] 10.6

[a] Yield determined by g.l.c. [b] By comparison with an authentic sample (J. A. Miller and M. J. Nunn, *J. Chem. Soc., Perkin Trans. 1*, 1976, 416).

product in these reactions. These observations led us to believe that the complex functions in the first instance as a powerful chlorinating agent and that subsequent displacement by the nitrogen nucleophile occurs. Support for this hypothesis was obtained by use of 1-chloroadamantane as substrate, reaction with the complex giving 1,3-dichloroadamantane (6) (19%) and the sulphonamide (4) (49%). A second experiment in the presence of gaseous hydrogen chloride gave an improved yield of compound (4) (74%). A series of blank experiments served to establish that neither ferrous nor ferric chloride effected halogenation in the absence of chloramine-T and that replacement of chloramine-T by toluene-*p*-sulphonamide or its sodium salt did not lead to *N*-(1-adamantyl)toluene-*p*-sulphonamide from either the parent hydrocarbon or 1-chloroadamantane.

The behaviour of aromatic substrates in this reaction also substantiated an initial halogenation sequence. Thus, mesitylene with the complex gave 1-chloro-2,4,6-trimethylbenzene in 86% yield. Interestingly, the use of a ferrous bromide–chloramine-T complex led, at a slower rate, to almost exclusive formation of the corresponding bromo-mesitylene derivative, indicating that the complex does not function merely as an activated *N*-halogeno-amine derivative in a classical electrophilic aromatic substitution. In an analogous manner, reaction of naphthalene with the ferrous chloride–chloramine-T complex gave 1-chloronaphthalene (21%) together with a small amount (4%) of a yellow crystalline derivative which contained two tosylamino-residues per naphthalene unit. Use of an excess of the reagent completely suppressed the formation of 1-chloronaphthalene and led to an increased yield (29%) of the minor product. The structure of this substance was confirmed to be the bis(toluene-*p*-sulphonyl)-1,4-naphthoquinone di-imine (7) by direct comparison with an authentic sample prepared by reduction of 1-amino-4-nitronaphthalene, tosylation, and lead tetra-acetate oxidation.[10] Since 1-chloronaphthalene itself is a poor substrate for this reaction and does not lead to formation of the quinone derivative, it seems reasonable to postulate that reaction proceeds *via* addition of the elements of chlorine or chloramine-T to the naphthalene ' double bond '.

Consequently, we have also studied the reactions of the complex with a variety of olefinic substrates. Thus, cyclohexene gave the products of both *cis* (8) and *trans* (9) addition



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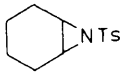

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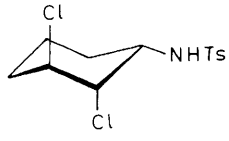

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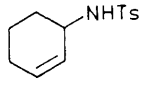
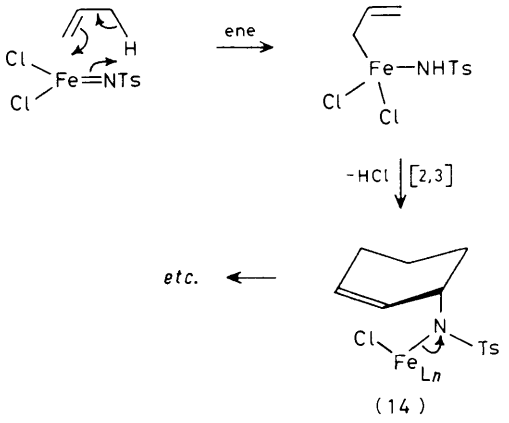


(12)

(13)

to the double bond in purified yields of 12 and 18% respectively. These two products were easily distinguished by 400 MHz n.m.r. spectra and by the facile conversion of the *trans*-derivative (9) into the known aziridine [11] (10) on treatment with an alcoholic solution of sodium hydroxide. The *cis*-isomer was recovered unchanged under otherwise identical reaction conditions. A third product of considerable mechanistic interest was also isolated from this reaction. Analytical and mass spectral data suggested that the cyclohexane ring contained two chlorine atoms and one tosylamino-residue, and the 400 MHz n.m.r. spectrum indicated the stereochemistry shown in structure (11) as the sole dichloro-isomer. In a separate experiment, chlorination of the allylic tosylamide [12] (12) with chlorine in carbon tetrachloride gave equal parts of structure (11) and the alternative isomeric product of *trans*-addition to the double bond (13). It is therefore possible that the formation of (11) involves intramolecular chlorination of a penultimate complex (14), with exclusive delivery of chlorine from the same side as the tosylamino-residue. This complex in turn can formally be derived from the organoiron nitrenoid and the olefin by an ene reaction and subsequent rearrangement (Scheme) or, more probably, by allylic hydrogen atom abstraction in a radical process.



Scheme

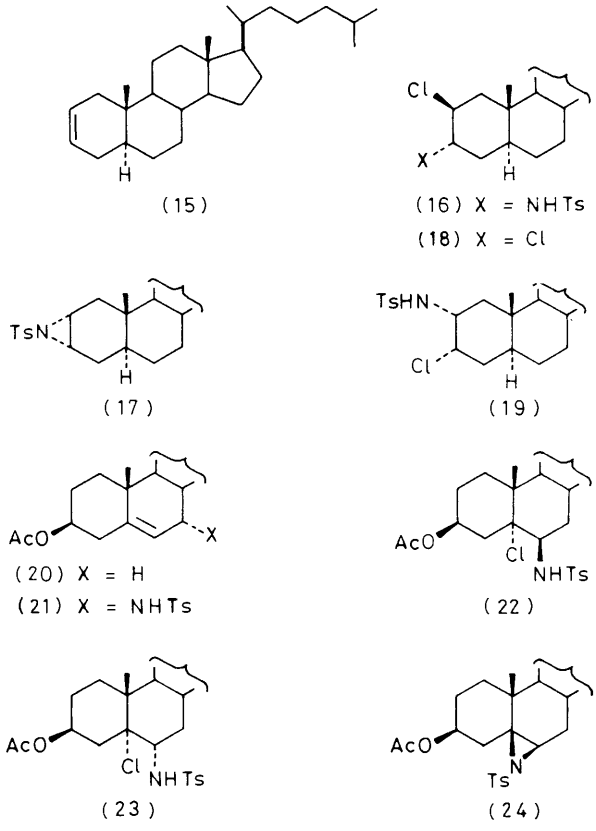
In order to investigate the regio- and stereo-chemical consequences of the reaction cholest-2-ene (15) was selected as substrate. In this instance, the major product of addition to the double bond (43%) was the 2β-chloro-3α-(toluene-*p*-sulphonamido)-derivative (16). The *trans*-relationship of the two substituents was established by cyclisation to the aziridine (17) and the position of the tosylamino-substituent was determined by tri-n-butylstannane reduction and comparison of the product with a sample of 3α-(toluene-*p*-sulphonamido)-cholestane prepared from 3α-azidocholestane [13] by lithium aluminium hydride reduction followed by tosylation. We have also identified several minor reaction products including the *trans*-2β,3α-dichlorocholestane [14] (18) (13%) and an inseparable mixture of the aziridine (17) (7%) and a compound (7%) whose differential 400 MHz n.m.r. spectrum and mass spectrum are consistent with the structure (19).

Since a classical ionic mechanism involving electrophilic chlorination from the less-hindered α-face followed by attack of a nitrogen nucleophile would give the 3α-chloro-2β-(*N*-toluene-*p*-sulphonylimine) derivative we have tested the possibility that (16) is formed *via* the 2β,3β-chloronium ion derived from the *trans*-dihalide (18). However, use of this latter compound as substrate with the ferrous chloride–chloramine-T complex led only to recovery of the starting material.

The reaction of cholesteryl acetate (20) with the reagent gave the 7α-tosylamino-derivative (21) as the major product (22%), thus providing support for the previously proposed allylic functionalisation in the cyclohexene series. The structure and stereochemistry of (21) was confirmed by independent synthesis.[15] Once again, the products of direct *cis*- and *trans*-addition [(22) and (23)] to the double bond were isolated. The *trans*-stereochemistry of (23) was indicated by its smooth cyclisation to the aziridine (24), whose identity was established by comparison with an authentic sample [16] prepared from cholesterol by successive addition of chlorine azide, lithium aluminium hydride reduction, selective tosylation, and finally acetylation. The 6β-configuration of the tosylamino-residue is supported by 400 MHz n.m.r. spectra.

Finally, it is important to note that throughout this investigation the substrate under study was present at the outset of the reaction. Efforts to generate the complex and then to study its behaviour led to entirely different results from those described above. Clearly, the reactive species has a relatively short lifetime.

From the mechanistic standpoint, several of the above reactions may have some parallel in the chemistry of chromyl chloride,[17] particularly in terms of mechanistic variety and complexity of reaction mixtures. We are clearly dealing with reactions which involve several competing mechanisms.



Experimental

M.p.s were determined with a Köfler hot-stage apparatus. ^{1}H N.m.r. spectra were recorded on a Varian T-60 instrument using [^{2}H]chloroform as solvent and tetramethylsilane as internal standard unless otherwise stated. 400 MHz N.m.r. spectra and decoupling experiments were performed on a Brücker instrument. I.r. spectra were recorded on a Perkin-Elmer 257 instrument. Optical rotations were measured on a Perkin-Elmer 141 polarimeter for solutions in chloroform unless stated to the contrary. Mass spectra were recorded on an AEI MS 9 instrument. U.v. spectra were measured on a Jobin Yvon Duospac 203 spectrophotometer. Analytical g.l.c. employed a Girdel Series 330 gas chromatograph with a 140-cm 5% SE 30 column. Adamantane derivatives were detected with a temperature programme of 80—120 °C at 2 °C min^{-1}, while naphthalene and mesitylene required a programme of 90—120 °C at 2 °C min^{-1} for optimum resolution. Dry dichloromethane was passed through an alumina column immediately before use. Anhydrous chloramine-T [12] (sodium *N*-chlorotoluene-*p*-sulphonamide) (**CAUTION**) was prepared by careful thermal dehydration *in vacuo* of the hydrate. Anhydrous ferrous chloride was prepared by a literature method.[18]

Reaction of Adamantane with Ferrous Chloride–Chloramine-T.—(a) Method A. Work-up by base extraction. To a mixture of anhydrous ferrous chloride (0.523 g, 4.3 mmol), anhydrous chloramine-T (0.915 g, 4 mmol), and adamantane (0.141 g, 1.04 mmol) under nitrogen was added dry dichloromethane (20 ml) and the reaction mixture was vigorously stirred at room temperature for 69.5 h. Removal of solvent under reduced pressure gave a viscous residue which was treated with an aqueous solution of sodium hydroxide (5%; 20 ml) with continued stirring. The reaction mixture was then filtered and the aqueous filtrate successively extracted with pentane and

then dichloromethane. The residue from filtration was dissolved in 1M-sulphuric acid (20 ml) and thoroughly extracted with dichloromethane. The organic phases were washed with water, dried (Na_2SO_4) and the solvent removed. Purification by chromatography on silica gel gave *N*-(1-adamantyl)-toluene-*p*-sulphonamide (4) (136.4 mg, 43%), m.p. 168.5—169.5 °C (from ethanol) (lit.,[19] 166 °C), whose spectroscopic properties (i.r., n.m.r., and *m/e*) were identical with those of an authentic sample prepared by tosylation of 1-aminoadamantane; and 1,3-*bis*(*toluene*-p-*sulphonamido*)*adamantane* (5) (118.3 mg, 24%), m.p. 195—196 °C (from hexane–dichloromethane), $\nu_{max.}$ ($CHCl_3$) 3 350, 3 250 (NH), 1 600 (aromatic), 1 310, and 1 140 cm^{-1} (S=O); δ 7.62 and 7.13 (4 H, AB quartet, J_{AB} 8 Hz, aromatic), 5.0 (2 H, s, NH), 2.36 (6 H, s, Me), and 1.83—1.2 (14 H, m); *m/e* 474 (M^+) (Found: C, 60.45; H, 6.35; N, 5.85; O, 13.45; S, 13.45. $C_{24}H_{30}N_2O_4S_2$ requires C, 60.73; H, 6.35; N, 5.90; O, 13.48; S, 13.51%).

(*b*) *Method* B. *Work-up by column chromatography.* Dry dichloromethane (10 ml) was added to a vigorously stirred mixture of adamantane (70.4 mg, 0.52 mmol), anhydrous ferrous chloride (249 mg, 2 mmol) and anhydrous chloramine-T (464 mg, 2.04 mmol) under nitrogen at room temperature. After 2.75 h, pentane (10 ml) was added and the reaction mixture was directly chromatographed on a medium-pressure silica-gel column using dichloromethane–pentane (1 : 1) as eluant. G.l.c. analysis of the eluant using naphthalene as a calibrated internal standard gave unchanged adamantane (27.8%) and 2-chloroadamantane [20] (4.3%), the latter being identified by g.l.c. comparison with an authentic sample. Subsequent elution of the column with dichloromethane gave *N*-(1-adamantyl)toluene-*p*-sulphonamide (4) (99.2 mg, 62.8%), identical with the above sample. Under otherwise identical conditions, no reaction was observed in the absence of chloramine-T after 7 days. Replacement of chloramine-T by the sodium salt of toluene-*p*-sulphonamide (387 mg, 2 mmol) likewise led to recovery of adamantane after 25 h. The above reaction is also completely inhibited by the addition of pyridine (206 mg, 2.6 mmol).

Reaction of Adamantane with Ferric Chloride–Chloramine-T.—To a mixture of adamantane (72.5 mg, 0.53 mmol), anhydrous ferric chloride (276 mg, 1.7 mmol), and anhydrous chloramine-T (271 mg, 2.5 mmol) under nitrogen was added dry dichloromethane (10 ml) and the resultant reaction mixture was vigorously stirred at room temperature for 6 days. Removal of solvent and work-up as described above (method A) gave 2-chloroadamantane (10% identified by g.l.c. comparison with an authentic sample using napththalene as a calibrated internal standard), *N*-(1-adamantyl)toluene-*p*-sulphonamide (4) (16 mg, 10%), and the disulphonamide (5) (70.6 mg, 28%), identical with the previously described samples. In the absence of chloramine-T, minor amounts of 1-chloroadamantane [21] (2%) and 2-chloroadamantane (0.2%) may be detected by g.l.c. analysis after 6 days. Replacement of the nitrogen atmosphere by oxygen, or addition of water (5% by volume), leads to complete inhibition of the reaction.

Reaction of Adamantane with Toluene-p-*sulphonyl Azide in the Presence of Ferrous Chloride.*—A stirred mixture of anhydrous ferrous chloride (263 mg, 2.06 mmol) and toluene-*p*-sulphonyl azide (406 mg, 2.06 mmol) in dry dichloromethane (10 ml) was heated to reflux under nitrogen. After 1.5 h, adamantane (67.2 mg, 0.49 mmol) was added and heating and stirring were continued for a further 6—8 days. Addition of pentane (10 ml) and chromatography on silica gel as above yielded adamantane (60.6 mg, 90.2%), *N*-(1-adamantyl)-toluene-*p*-sulphonamide (4) (13 mg, 8.6%) and toluene-*p*-sulphonamide (78 mg, 22%), identical with an authentic sample (m.p. and mixed m.p. 138 °C).

Attempted Cleavage of an Intermediate Complex by Trapping Experiments. General Procedure.—Dry dichloromethane (10 ml) was added to a mixture of adamantane (0.5 mmol), anhydrous ferrous chloride (2.0 mmol), and anhydrous chloramine-T (2 mmol) and the reaction mixture was vigorously stirred under nitrogen at room temperature. Aliquot monitoring by g.l.c. indicated the complete disappearance of adamantane after *ca.* 2 h. The trapping reagent (2 mmol) (or, in the case of gases, an excess) was then added and the reaction was allowed to continue for the indicated time. Work-up involving base extraction (method A) gave the results indicated in the Table.

Reaction of 1-*Chloroadamantane with Ferrous Chloride and Chloramine-T.*—To a mixture of 1-chloroadamantane [21] (85.8 mg, 0.5 mmol), anhydrous ferrous chloride (256 mg, 2 mmol), and chloramine-T (464 mg, 1.04 mmol) was added dry dichloromethane (10 ml) and the reaction mixture was vigorously stirred under nitrogen for 3.1 h. Addition of pentane and column chromatography (method B) gave 1,3-dichloroadamantane (6) (19 mg, 18%), identified by mass spectral and g.l.c. comparison with an authentic sample prepared by reaction of adamantane with aluminium trichloride in the presence of paraformaldehyde.[22] Further elution of the column gave *N*-(1-adamantyl)toluene-*p*-sulphonamide (4), identical with the above samples (77.3 mg, 49.5%). Repetition of the above experiment but with a solution of dichloromethane containing 0.37 mmol of dry hydrogen chloride gave, after 4 h and chromatographic work-up, 1,3-dichloroadamantane (6) (8%) and *N*-(1-adamantyl)toluene-*p*-sulphonamide (4) (74%).

Reaction of 1-(*Toluene*-p-*sulphonamido*)*adamantane with Ferrous Chloride–Chloramine-T.*—Dry dichloromethane (10 ml) was added to a mixture of *N*-(1-adamantyl)toluene-*p*-sulphonamide (152 mg, 0.5 mmol), anhydrous ferrous chloride (247 mg, 2.0 mmol), and chloramine-T (454 mg, 2.0 mmol) and the reaction mixture was vigorously stirred under nitrogen for 2.7 days. Work-up by base extraction (method A) gave unchanged *N*-(1-adamantyl)toluene-*p*-sulphonamide (4) (46 mg, 30%) and 1,3-bis(toluene-*p*-sulphonamido)adamantane (5) (93 mg, 39%), identical with the above sample.

Reaction of Mesitylene with Ferrous Chloride–Chloramine-T.—To a mixture of mesitylene (60 mg, 0.5 mmol), anhydrous ferrous chloride (263 mg, 2.07 mmol), and chloramine-T (461 mg, 2.05 mmol) was added dry dichloromethane (10 ml) and the reaction mixture was stirred at room temperature under nitrogen for 5.9 days. Addition of pentane and chromatographic work-up (method B) gave mesitylene (4.3%) and 1-chloro-2,4,6-trimethylbenzene (86%, by g.l.c. using α-tetralone as a calibrated internal standard) which was identified by spectral (n.m.r., *m/e*) and chromatographic (g.l.c.) comparison with an authentic sample.

Reaction of Mesitylene with Ferrous Bromide–Chloramine-T.—Repetition of the above experiment but with the use of ferrous bromide (441 mg, 2.04 mol) and a reaction time of 7.9 days gave, after work-up (method B), mesitylene (3.2%), chloromesitylene (0.3%), and 1-bromomesitylene (51%), which was identified by spectral (n.m.r., mass spec.) and g.l.c. comparison with an authentic sample.[23]

Reaction of Naphthalene with Ferrous Chloride–Chloramine-T.—To a stirred mixture of naphthalene (67 mg, 0.52

mmol), ferrous chloride (262 mg, 2.06 mmol), and chloramine-T (462 mg, 2.03 mmol) under nitrogen was added dichloromethane (10 ml) and the reaction mixture was vigorously stirred for 46 h. Addition of pentane (10 ml) and column chromatography (method B) gave unchanged naphthalene (2.9% by g.l.c., using adamantane as calibrated internal standard) and 1-chloronaphthalene (21%), identified by g.l.c. comparison with an authentic sample. Further elution of the column gave a more polar yellow crystalline product which was identified as *N,N'*-bis(toluene-*p*-sulphonyl)-1,4-naphthoquinone di-imine (7) (10.7 mg, 4.4%), m.p. 230—233 °C, mixed m.p. 229—232 °C. All spectroscopic and chromatographic properties of this substance were identical with those of an authentic sample prepared by reduction of 1-amino-4-nitronaphthalene, tosylation, and lead tetra-acetate oxidation.[10]

Repetition of the above experiment using an excess of the complex [ferrous chloride (1.02 g, 8.05 mmol)], chloramine-T (1.82 g, 8.0 mmol) in dichloromethane (17 ml) for 2.75 h gave, from naphthalene (71.6 mg, 0.56 mmol), after chromatographic purification, unchanged naphthalene (29%) and the above bis(tosyl)quinone di-imine (7) (75 mg, 29%), identical in all respects with the samples prepared above. The use of 1-chloronaphthalene in this reaction did not lead to formation of the bis(tosyl)quinone di-imine.

Reaction of Cyclohexene with Ferrous Chloride–Chloramine-T.—To a mixture of anhydrous ferrous chloride (535 mg, 4.2 mmol), chloramine-T (921 mg, 4.05 mmol), and purified cyclohexene (82 mg, 0.101 ml, 1 mmol) under nitrogen was added dichloromethane (15 ml) and the reaction mixture was vigorously stirred at room temperature for 7.9 days. Addition of pentane (15 ml) and initial column chromatography (method B) was followed by careful purification by preparative t.l.c. using multiple development with a system of diethyl ether–pentane (1 : 3) to give the following products: N-(trans-2-*chlorocyclohexyl*)*toluene*-p-*sulphonamide* (9) (53 mg, 18%), m.p. 101—102 °C (from ethyl acetate–hexane); $\nu_{max.}$ ($CHCl_3$) 3 650, 3 350 (NH), 1 600 (aromatic), 1 325, and 1 150 cm^{-1} (S=O); δ (400 MHz) 7.78 and 7.31 (4 H, AB quartet, J_{AB} 8.3 Hz, aromatic), 4.88 (1 H, d, *J* 5.3 Hz exch. with CD_3OD, NH), 3.68 (1 H, m, $w_{\frac{1}{2}}$ 27 Hz, 2-H axial), 3.07 (1 H, m, $w_{\frac{1}{2}}$ 25 Hz, 1-H axial), 2.43 (3 H, s, Me), 1.21 (2 H, m, ring H), 1.65 (4 H, m, ring H), and 1.3 (2 H, m, ring H); *m/e* 287, 289 (M^+) (Found: C, 54.45; H, 6.25; Cl, 12.5; N, 4.7; S, 11.35. $C_{13}H_{18}ClNO_2S$ requires C, 54.25; H, 6.30; Cl, 12.32; N, 4.87; S, 11.14%); N-(cis-2-*chlorocyclohexyl*)*toluene*-p-*sulphonamide* (8) (33.6 mg, 12%), m.p. 113—114 °C (from ethyl acetate–hexane), $\nu_{max.}$ ($CHCl_3$) 3 650, 3 350 (NH), 1 600 (aromatic), and 1 325, 1 150 cm^{-1} (S=O); δ (400 MHz) 7.76 and 7.30 (4 H, AB quartet, J_{AB} 8.3 Hz, aromatic), 4.82 (1 H, d, *J* 9 Hz, exch. with CD_3OD, NH), 4.16 (1 H, m, $w_{\frac{1}{2}}$ 8 Hz, 2-H equatorial), 3.42 (1 H, m, $w_{\frac{1}{2}}$ 29 Hz, 1-H axial), 2.42 (3 H, s, Me), 1.97 (1 H, m, ring H), 1.61 (5 H, m, ring H), 1.41 (1 H, m, ring H), and 1.24 (1 H, m, ring H); *m/e* 287, 289 (M^+) (Found: C, 54.4; H, 6.05; Cl, 12.55; N, 4.7; S, 11.05. $C_{13}H_{18}NClO_2S$ requires C, 54.25; H, 6.30; Cl, 12.32; N, 4.87; S, 11.14%); N-(trans-3,cis-2-*dichlorocyclohexyl*)*toluene*-p-*sulphonamide* (11) (13 mg, 4%), m.p. 114—115 °C (from ethyl acetate–hexane), $\nu_{max.}$ ($CHCl_3$) 3 550, 3 360 (NH), 1 600 (aromatic), 1 335, and 1 155 cm^{-1} (S=O); δ(400 MHz) 7.75 and 7.32 (4 H, AB quartet, J_{AB} 8 Hz, aromatic), 4.78 (1 H, d, *J* 10 Hz, exch. with CD_3OD, NH), 4.34 (1 H, m, $w_{\frac{1}{2}}$ 9 Hz), 4.01 (2 H, m), 2.44 (3 H, s, Me), 2.10 (1 H, m, ring H), and 1.26 (1 H, m, ring H); δ (400 MHz; C_6D_6) 8.095 and 6.953 (4 H, AB quartet, J_{AB} 8 Hz, aromatic), 4.84 (1 H, d, *J* 10 Hz, NH), 4.28 (1 H, m, $w_{\frac{1}{2}}$ 26 Hz, 1-H axial), 4.19 (1 H, m, $w_{\frac{1}{2}}$ 8.5 Hz, 2-H equatorial), 3.92 (1 H, m, $w_{\frac{1}{2}}$ 9 Hz, 3-H equatorial), 2.04 (3 H, s, Me), and 1.87—1.12 (complex, ring hydrogens); *m/e* 321, 323, 325 (M^+) (Found: C, 48.25; H, 5.25; Cl, 22.3; N, 4.15; S, 10.1. $C_{13}H_{17}NCl_2O_2S$ requires C, 48.45; H, 5.32; Cl, 22.00; N, 4.35; S, 9.95%).

The structural assignments for the above three compounds were confirmed by double irradiation experiments and by the chemical reactions and synthesis outlined below. No reaction was observed between cyclohexene and chloramine-T in the absence of ferrous chloride.

N-(*Toluene*-p-*sulphonyl*)-1,2-*iminocyclohexane* (10).—*trans*-2-Chloro-1-(toluene-*p*-sulphonylamino)cyclohexane (13 mg, 0.045 mmol) in chloroform (1.5 ml) was vigorously stirred with aqueous sodium hydroxide (5%; 0.5 ml) at room temperature overnight. Chloroform (10 ml) was added and the organic phase was washed with cold sodium hydroxide solution (5%) and then with water and dried (Na_2SO_4). Removal of solvent and recrystallisation from pentane gave the title compound (10 mg, 88%), m.p. 59.5—60.5 °C (lit.,[11] 60—61 °C) whose spectroscopic properties were identical with those of an authentic sample. Under identical reaction conditions, the corresponding *cis*-isomer (8) was recovered (75%) unchanged from the reaction mixture.

Chlorination of N-*Cyclohex*-2-*enyltoluene*-p-*sulphonamide.*—To a solution of *N*-cyclohex-2-enyltoluene-*p*-sulphonamide (12) (158 mg, 0.63 mmol), prepared by a known method,[12] in carbon tetrachloride (5 ml) was added a solution of chlorine in carbon tetrachloride until the chlorine colouration persisted [89 mg of chlorine (1.26 mmol in 1.08 ml)]. Ethanol (15 ml) and sodium iodide (189 mg, 1.26 mmol) were added and the reaction was stirred at room temperature for 18 h. The mixture was poured into water and thoroughly extracted with dichloromethane. The organic phase was successively washed with water, sodium thiosulphate solution (5%), water, brine and dried ($MgSO_4$). Removal of solvent and careful purification by multiple development preparative t.l.c. using diethyl ether–pentane (1 : 1) gave N-(trans-3,cis-2-*dichlorocyclohexyl*)-*toluene*-p-*sulphonamide* (11) (65 mg, 32%), identical in all respects with that obtained from the reaction of cyclohexene with the ferrous chloride–chloramine-T complex, and N-(cis-3,trans-2-*dichlorocyclohexyl*)*toluene*-p-*sulphonamide* (13) (48 mg, 24%) m.p. 136—137 °C (from ethyl acetate–hexane), $\nu_{max.}$ ($CHCl_3$) 3 550, 3 350 (NH), 1 600 (aromatic), 1 330 and 1 155 cm^{-1} (S=O); δ 7.78 and 7.32 (4 H, AB quartet, J_{AB} 8 Hz, aromatic), 5.16 (1 H, d, *J* 8 Hz, exch with CD_3OD, NH), 3.70 (2 H, m, 2-H and 3-H), 3.25 (1 H, m, $w_{\frac{1}{2}}$ 22 Hz, 1-H, axial), 2.45 (3 H, s, Me), 2.22 (1 H, m, ring-H), and 1.9—1.18 (5 H, m, ring H); *m/e* 321, 323, 325 (M^+). High resolution mass measurement, M^+ (321) = 321.0351. $C_{13}H_{17}{}^{35}Cl_2N^{32}SO_2$ requires 321.0357.

Reaction of Cholest-2-*ene with Ferrous Chloride–Chloramine-T.*—To a mixture of ferrous chloride (524 mg, 4.1 mmol), chloramine-T (937 mg, 4.1 mmol), and cholest-2-ene (15) (373 mg, 1.01 mol) under nitrogen was added dichloromethane (20 ml) and the reaction mixture was stirred vigorously for 5.75 h. Addition of pentane (20 ml) followed by column chromatography (method B) and further purification by preparative t.l.c. gave the following compounds: 2β,3α-dichlorocholestane (18) (57.7 mg, 13%), m.p. and mixed m.p. 109—110 °C (lit.,[14] m.p. 108—112 °C), identical in its spectral (i.r., n.m.r., and *m/e*) and chromatographic properties with a sample prepared by chlorination of cholest-2-ene; 2β-*chloro*-3α-(*toluene*-p-*sulphonamido*)*cholestane* (16) (249 mg, 43%), m.p. 260—262 °C (from ethyl acetate), $[\alpha]_D^{20}$ +31.5 (*c*, 0.338), δ (400 MHz) 7.77 and 7.33 (4 H, AB quartet, J_{AB} 7.3 Hz, aromatic), 4.85 (1 H, d, *J* 7 Hz, exch with CD_3OD, NH), 4.27 (1 H, m, $w_{\frac{1}{2}}$ 10 Hz, 2-H, equatorial), 3.54 (1 H, m, $w_{\frac{1}{2}}$ 14 Hz,

3-H equatorial), 2.45 (3 H, s, Me), 1.017 (3 H, s, C-19, Me), and 0.63 (3 H, s, C-18, Me); *m/e* 575, 577 (M^+) (Found: C, 70.8; H, 9.3; Cl, 6.45; N, 2.7; S, 5.65. $C_{34}H_{54}ClNO_2S$ requires C, 70.86; H, 9.44; Cl, 6.15; N, 2.43; S, 5.56%). The spectral and chromatographic properties of a further fraction (14%) of the reaction mixture indicate it to be composed of equal parts of N-(*toluene*-p-*sulphonyl*)-2α,3α-*iminocholestane* (17) and 3α-*chloro*-2α-(*toluene*-p-*sulphonamido*)*cholestane* (19). The identity of the aziridine (17) was established by independent synthesis (*vide infra*) and the structure (19) is supported by the following differential n.m.r. spectrum of the mixture and by mass spectral studies: compound (19), δ (400 MHz), 7.73 and 7.29 (4 H, AB quartet, J_{AB} 8 Hz, aromatic), 4.73 (1 H, d, *J* 10 Hz, NH), 4.14 (1 H, m, $w_{\frac{1}{2}}$ 7.2 Hz, 3-H), 3.58 (1 H, m, $w_{\frac{1}{2}}$ 27.5 Hz, 2-H axial), 2.45 (3 H, s, Me), 0.74 (3 H, s, 19-Me), 0.62 (3 H, s, 18-Me); *m/e* 575, 577 (M^+). High resolution mass measurement M^+ (575) = 575.3558. $C_{34}H_{54}{}^{35}ClNO_2{}^{32}S$ requires 575.3564. Repetition of the above experiment using 2β,3α-dichlorocholestane as substrate led to the recovery of unchanged starting material.

3α-(N-*Toluene*-p-*sulphonamido*)*cholestane*.—(*a*) To a solution of 3α-aminocholestane [13] (110 mg, 0.28 mmol) in dry tetrahydrofuran (4 ml) was added sodium hydride (7 mg, 0.29 mmol) followed by toluene-*p*-sulphonyl chloride (67.5 mg, 0.35 mmol) and the mixture was stirred under nitrogen at room temperature until the reaction was complete (t.l.c.). The reaction mixture was then acidified by addition of dilute hydrochloric acid (1.2 M) and the tetrahydrofuran was evaporated under reduced pressure. The aqueous phase was thoroughly extracted with dichloromethane and the combined organic extracts washed with water and brine and dried ($MgSO_4$). Removal of solvent gave the title derivative (151 mg, 99%), m.p. 186—187 °C (from ethanol–ethyl acetate), $[\alpha]_D{}^{20}$ +18° (*c*, 0.26); δ 7.78 and 7.30 (4 H, AB quartet, J_{AB} 8 Hz, aromatic), 4.88 (1 H, d, *J* 7 Hz, exch with CD_3OD, NH), 3.5 (1 H, m, $w_{\frac{1}{2}}$ 14 Hz, 3-H equatorial), 2.42 (3 H, s, Me), 0.9 (3 H, s, 19-Me), 0.62 (3 H, s, 18-Me); *m/e* 541 (M^+) (Found: C, 75.2; H, 10.2; N, 2.75; S, 6.2. $C_{34}H_{55}NO_2S$ requires C, 75.36; H, 10.23; N, 2.58; S, 5.92%).

(*b*) *Tri-n-butyltin hydride reduction of* 2β-*chloro*-3α-(*toluene*-p-*sulphonamido*)*cholestane* (16). 2β-Chloro-3α-(toluene-*p*-sulphonamido)cholestane (16) (66 mg, 0.11 mmol) in benzene (2 ml) containing azobis(isobutyronitrile) (4 mg, 0.02 mmol) was added dropwise to a refluxing solution of tri-n-butyltin hydride (114.4 mg, 0.29 mmol) in benzene (1 ml) under nitrogen and heating was continued for 6 h (t.l.c.). Removal of solvent and preparative t.l.c. gave 3α-(toluene-*p*-sulphonamido)cholestane (50 mg, 80%) whose physical, spectral, and chromatographic properties were in every way identical with the sample prepared above.

N-(*Toluene*-p-*sulphonyl*)-2α,3α-*iminocholestane* (17).—A solution of 2β-chloro-3α-(toluene-*p*-sulphonamido)cholestane (16) (54.5 mg, 0.094 mmol) in chloroform (2 ml) was vigorously stirred with aqueous sodium hydroxide (5%, 0.5 ml) at room temperature overnight. Chloroform (10 ml) was added and the organic phase was washed with cold aqueous sodium hydroxide (5%), water, brine and dried ($MgSO_4$). Removal of solvent and recrystallisation from ethanol gave the *title aziridine* (17) (37 mg, 70%), m.p. 163—165 °C, $[\alpha]_D{}^{20}$ +36° (*c*, 0.653); δ (400 MHz) 7.80 and 7.33 (4 H, AB quartet, J_{AB} 8.2 Hz, aromatic), 3.01 (1 H, m, $w_{\frac{1}{2}}$ 13 Hz, 2-H or 3-H), 2.93 (1 H, m, $w_{\frac{1}{2}}$ 17 Hz, 2-H or 3-H), 2.43 (3 H, s, Me), 0.70 (3 H, s, 19-Me), and 0.61 (3 H, s, 18-Me); *m/e* 539 (M^+) (Found: C, 75.45; H, 9.8; N, 2.75; S, 5.75. $C_{34}H_{53}NSO_2$ requires C, 75.64; H, 9.90; N, 2.59; S, 5.94%).

Reaction of Cholesteryl Acetate with Ferrous Chloride–Chloramine-T.—Ferrous chloride (133 mg, 1.05 mmol), chloramine-T (229 mg, 1 mmol), and cholesteryl acetate (20) (107 mg, 0.25 mmol) were thoroughly mixed under nitrogen. To this was added dry dichloromethane (5 ml) and vigorous stirring was continued at room temperature for 4 h. Addition of pentane (5 ml) followed by column chromatography (method B) gave a crude product which was purified by multiple development preparative t.l.c. using benzene–acetone (99.1 : 0.9) as eluant to give the following products: 3β-*acetoxy*-5α-*chloro*-6β-(*toluene*-p-*sulphonamido*)*cholestane* (22) (23 mg, 14.5%), m.p. 195—197 °C (change of form 168—171 °C) (from ethyl acetate–ethanol mixtures), $[\alpha]_D{}^{20}$ −17.7 (*c*, 0.323), $\nu_{max.}$ ($CHCl_3$) 3 350 (NH), 1 720 (C=O), 1 600 (aromatic), 1 330 and 1 155 cm^{-1} (S=O); δ (400 MHz) 7.73 and 7.33 (4 H, AB quartet, *J* 8 Hz, aromatic), 5.27 (1 H, m, $w_{\frac{1}{2}}$ 24 Hz, 3-H, axial), 4.53 (1 H, d, *J* 10 Hz, exch. with CD_3OD, NH), 3.51 (1 H, m, $w_{\frac{1}{2}}$ 18 Hz, 6-H, equatorial), 2.44 (3 H, s, Me), 2.01 (3 H, s, OCOMe), 1.19 (3 H, s, 19-Me), and 0.63 (3 H, s, 18-Me); *m/e* 633, 635 (M^+). High resolution mass measurement M^+ (633) = 633.3515. $C_{36}H_{56}{}^{35}ClO_4{}^{32}S$ requires 633.3619: 3β-*acetoxy*-5α-*chloro*-6α-*toluene*-p-*sulphonamidocholestane* (23) (22.2 mg, 14%), m.p. 180—182 °C (from ethyl acetate–hexane mixtures), $[\alpha]_D{}^{20}$ +6.7 (*c*, 0.262), $\nu_{max.}$ ($CHCl_3$) 3 350 (NH), 1 720 (C=O), 1 600 (aromatic), 1 330 and 1 150 cm^{-1} (S=O); δ (400 MHz) 7.73 and 7.30 (4 H, AB quartet, J_{AB} 8 Hz, aromatic), 5.15 (1 H, m, $w_{\frac{1}{2}}$ 25 Hz, 3-H, axial), 4.57 (1 H, d, *J* 10 Hz, exch. with CD_3OD, NH), 3.53 (1 H, m, $w_{\frac{1}{2}}$ 28 Hz, 6-H, axial), 2.425 (3 H, s, Me), 1.99 (3 H, s, OCOMe), 1.07 (3 H, s, 19-Me), and 0.60 (3 H, s, 18-Me); *m/e* 633, 635 (M^+) (Found: C, 68.35; H, 9.05; N, 2.05; S, 5.25. $C_{36}H_{56}ClNO_4S$ requires C, 68.16; H, 8.90; N, 2.21; S, 5.06%); 3β-*acetoxy*-7α-(*toluene*-p-*sulphonamido*)*cholest*-5-*ene* (21) (33.6 mg, 22%), m.p. 160—162 °C (from ethanol), $[\alpha]_D{}^{20}$ −176° (*c*, 0.56), $\nu_{max.}$ ($CHCl_3$) 3 350 (NH), 1 720 (C=O), 1 600 (aromatic), 1 330 and 1 150 cm^{-1} (S=O); δ (400 MHz) 7.78 and 7.32 (4 H, AB quartet, *J* 10 Hz, aromatic), 4.99 (1 H, m, $w_{\frac{1}{2}}$ 9 Hz, 6-H), 4.47 (1 H, m, $w_{\frac{1}{2}}$ 26 Hz, 3-H, axial), 4.26 (1 H, d, *J* 10 Hz, exch with CD_3OD, NH), 3.58 (1 H, m, $w_{\frac{1}{2}}$ 20 Hz, 7-H equatorial), 2.425 (3 H, s, Me), 2.02 (3 H, s, OCOMe), 0.95 (3 H, s, 19-Me), and 0.62 (3 H, s, 18-Me); *m/e* 597 (M^+) (Found: C, 72.5; H, 9.35; N, 2.6; S, 5.35. $C_{36}H_{55}NO_4S$ requires C, 72.37; H, 9.27; N, 2.34; S, 5.36%).

The above structural assignments were confirmed by double irradiation experiments and by the following reactions and syntheses.

Syntheses of 3β-*Acetoxy*-N-(*toluene*-p-*sulphonyl*)-5β,6β-*iminocholestane* (24).—(*a*) *N*′,*N*″-Tetramethyl-*N*-t-butylguanidine [24] (8.4 mg, 0.049 mmol) was added to a solution of 5α-chloro-6β-(toluene-*p*-sulphonamido)cholestane (22) (17 mg, 0.026 mmol) in toluene (1 ml) and the mixture was heated at 100 °C until the reaction was complete (t.l.c.). Removal of toluene and preparative t.l.c. gave the *title derivative* (14.6 mg, 94%), m.p. 148—150 °C (from hexane), $[\alpha]_D{}^{20}$ −11.6° (*c*, 0.88), $\nu_{max.}$ ($CHCl_3$) 1 720 (C=O), 1 600 (aromatic), 1 360 and 1 150 cm^{-1} (S=O); δ 7.80 and 7.28 (4 H, AB quartet, J_{AB} 8 Hz, aromatic), 4.93 (1 H, m, $w_{\frac{1}{2}}$ 20 Hz, 3-H, axial), 3.15 (1 H, m, $w_{\frac{1}{2}}$ 5 Hz, 6-H), 2.43 (3 H, s, Me), 2.02 (3 H, s, OCOMe), 1.05 (3 H, s, 19-Me), and 0.58 (3 H, s, 18-Me) (Found: C, 72.3; H, 9.35; N, 2.5; S, 5.35. $C_{36}H_{55}NSO_4$ requires C, 72.32; H, 9.27; N, 2.34; S, 5.36%).

(*b*) A sample of 5β,6β-iminocholestan-3β-ol was prepared by addition of chlorine azide to cholesterol followed by lithium aluminium hydride reduction.[16] The above aziridine (156 mg, 0.39 mmol) was dissolved in the minimum volume of pyridine, and toluene-*p*-sulphonyl chloride (81.8 mg, 0.43 mmol) and 4-dimethylaminopyridine (3.2 mg) were added. The

mixture was stirred at room temperature until the reaction was complete (t.l.c.). Acetic anhydride (1 ml, 10 mmol) was then added and stirring was continued until no further evolution was observed by t.l.c. The mixture was then diluted with water and thoroughly extracted with dichloromethane. The organic phase was washed successively with water, dilute hydrochloric acid (1M), water, and brine and dried ($MgSO_4$). Removal of solvent and column chromatography on silica gel gave the title aziridine (116 mg, 50%) whose physical, spectral, and chromatographic properties were identical in all respects with that prepared above.

3β-*Acetoxy*-7α-(*toluene*-p-*sulphonamido*)*cholest*-5-*ene* (21). —7α-Aminocholest-5-en-3β-ol [15] (80.7 mg, 0.2 mmol) was dissolved in the minimum volume of pyridine, and toluene-*p*-sulphonyl chloride (41.6 mg, 0.218 mmol) and 4-dimethylaminopyridine (3.8 mg) were added. The mixture was stirred at room temperature until the reaction was complete (t.l.c.). Acetic anhydride (0.114 ml, 1.2 mmlo) was then added and stirring continued until no further evolution was observed by t.l.c. The reaction mixture was diluted with water and thoroughly extracted with dichloromethane. The combined organic extracts were washed with water, dilute hydrochloric acid (1M), water, and brine, and dried ($MgSO_4$). Removal of solvent and preparative t.l.c. gave the title derivative (21) (73.4 mg, 61%) which was identical in all respects (i.r., n.m.r., t.l.c., m.p., and $[\alpha]_D$) with that obtained from the reaction of cholesteryl acetate with the ferrous chloride–chloramine-T complex (*vide supra*).

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