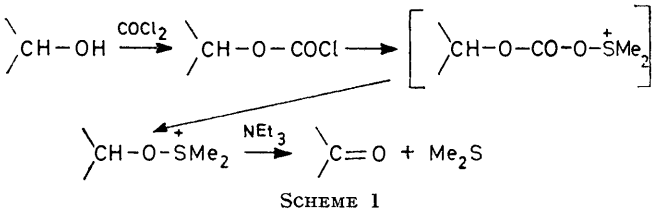
Improved Methods for the Oxidation of Primary and Secondary Alcohols

By **Derek H. R. Barton** * and **Craig P. Forbes,** Department of Chemistry, Imperial College, London SW7 2AY

The two-stage procedure for the oxidation of secondary alcohol chloroformates by treatment with dimethyl sulphoxide and then with triethylamine has been much improved by the addition of an acid scavenger, conveniently 1,2-epoxypropane, in the first stage of the sequence.

In agreement with mechanistic considerations, treatment of cholestanol, or of its nitrite, with nitrosyl cations in the presence of hexamethyldisiloxane as acid scavenger gave an excellent yield of cholestanone.

SOME years ago we described [1] a new procedure for the oxidation of alcohols (Scheme 1). The alcohol was converted into its chloroformate and the latter treated with dimethyl sulphoxide. After loss of carbon dioxide the intermediate alkoxydimethylsulphonium salt was treated with triethylamine [2] to give the carbonyl compound and dimethyl sulphide. This procedure gave



SCHEME 1

good yields in the oxidation of primary alcohols to aldehydes, as further confirmed by a recent application.[3] The method has the advantage that the reagents are cheap and that all operations are carried out at room temperature or lower under near neutral conditions. Large-scale operations would be no problem.

The mechanism by which the alkoxydimethylsulphonium salt eliminates dimethyl sulphide has subsequently been clarified by isotope labelling experiments.[4] It is known that first the triethylamine abstracts a proton from one of the methyl groups bonded to positive sulphur and then an intramolecular hydride transfer takes place.

In our original work [1] we found that a secondary alcohol [cholestanol (I)] was oxidised to the ketone (II) in poor yield (20%). We have now discovered that the yields of ketone can be improved remarkably by the addition of a non-basic acid scavenger, suitably 1,2-epoxypropane, in the first stage of the reaction.

When the oxidation of cholestanol (I) was attempted in dry tetrahydrofuran in the usual way,[1] no cholestanone (II) was formed. The product was a mixture of unchanged alcohol (I) and 3β,3′β-methylenedioxydicholestane (III).[5] The structure of this acetal was confirmed

[1] D. H. R. Barton, B. J. Garner, and R. H. Wightman, *J. Chem. Soc.*, 1964, 1855.

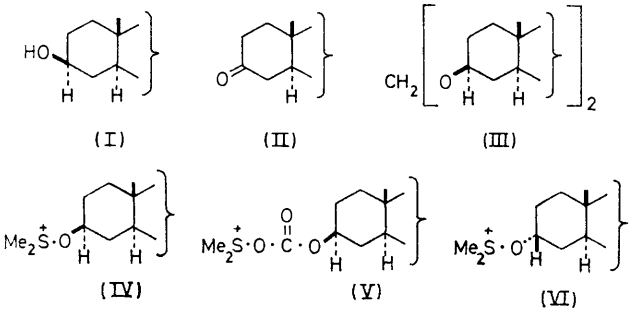
[2] N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, and W. M. Weaver, *J. Amer. Chem. Soc.*, 1957, **79**, 6562; N. Kornblum, W. J. Jones, and G. J. Anderson, *ibid.*, 1959, **81**, 4113.

[3] N. Finch, J. J. Fitt, and I. H. S. Hsu, *J. Org. Chem.*, 1975, **40**, 206.

[4] K. Torssell, *Tetrahedron Letters*, 1966, 4445.

[5] J. E. Herz, J. Lucero, Y. Santoyo, and E. S. Waight, *Canad. J. Chem.*, 1971, **49**, 2418.

by n.m.r. spectroscopy, elemental analysis, and its ready hydrolysis to cholestanol. Its formation was favoured if the reaction was carried out in dichloromethane in the presence of dissolved hydrogen chloride or phosgene. However, in the presence of a proton scavenger like



(I) (II) (III)

(IV) (V) (VI)

1,2-epoxypropane, 1-chloro-2,3-epoxypropane, or epoxyethylbenzene, the oxidation proceeded smoothly to produce a reasonable yield of the desired ketone. Four steroidal chloroformates were oxidised in this way by using epoxypropane. The results are given in the Table. The low yield of 11-oxoprogesterone may indicate that even our modified procedure is not applicable to the formation of hindered ketones.

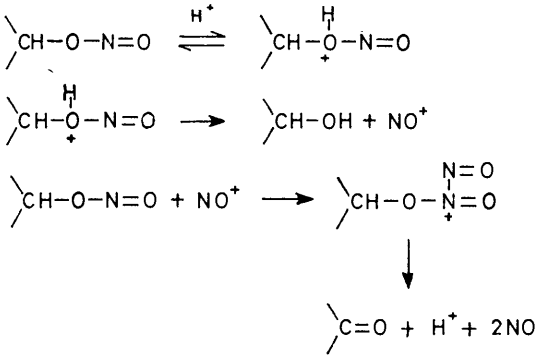
Oxidation of steroidal chloroformates by dimethyl sulphoxide

Chloroformate of	Product	Yield (%)
Cholestanol	Cholestanone	80
Cholesterol	Cholest-4-enone	71
Pregnenolone	Progesterone	73
11α-Hydroxyprogesterone	11-Oxoprogesterone	24

The other products of the oxidation were the alcohol from which the chloroformate was derived and a low yield of a sulphur-containing steroid, probably the methylthiomethyl ether. The initial oxidation products from cholesterol and pregnenolone chloroformates were the βγ-unsaturated ketones. Isomerisation to the conjugated ketones by oxalic acid and ethanol was carried out with scrupulous exclusion of oxygen prior to work-up. In one case, concentration and crystallisation of the crude product from cholesterol chloroformate afforded cholest-5-en-3-one in 47% yield, but generally the product mixtures contained too much alcohol for purification by crystallisation and the oxidation products were isolated by column or preparative thin-layer chromatography.

Despite variation of solvent, relative concentrations of reactants, reaction times, and the absence or presence of moisture, some alcohol was always re-formed. This alcohol formation does not appear to be occurring in the final step of the reaction because the decomposition of the intermediate alkoxydimethylsulphonium salt (IV) was found to proceed in high yield without any alcohol formation. Furthermore, the presence of alcohol in the reaction mixtures was shown by t.l.c. in all cases prior to addition of triethylamine. It seems that alcohol formation is occurring primarily in the rearrangement of the intermediate (V).

The salt (IV) formed a crystalline precipitate which could be isolated in analytically pure state by filtration in a sealed system. It was unstable in air and melted with decomposition over the range 90—120 °C. Reduction with sodium borohydride in bis-(2-methoxyethyl) ether gave 3β-cholestanol, with no detectable 3α-cholestanol. This excludes the possibility that the intermediate (V) suffers an S_N2 inversion by dimethyl sulphoxide to give the salt (VI) prior to elimination. Such a mechanism could have explained the loss of carbon dioxide from the intermediate (V) and the poor yield in the formation of 11-oxoprogesterone.



SCHEME 2

In a previous paper[6] we proposed a mechanism (Scheme 2) for the acid-catalysed decomposition of nitrites. If this mechanism is correct, treatment of an alcohol or nitrite with a source of nitrosyl cations in the presence of a proton scavenger should favour the formation of a ketonic product. This was found to be the case. Treatment of cholestanol with nitrosyl tetrafluoroborate in methylene chloride–acetonitrile in the presence of hexamethyldisiloxane as scavanger produced a nearly quantitative yield of cholestanone. Benzyl alcohol was similarly oxidised to benzaldehyde in 90% yield. This is an interesting result because the chloroformate method of oxidation of benzyl alcohol gave only benzyl chloride. The formation of ketone by nitrosation of nitrite supports our Scheme 2.

We also examined the alkylation of nitrites as a comparable source of carbonyl compounds. Treatment of cholestanyl nitrite with triethyloxonium tetrafluoroborate gave cholestanone (50%).

EXPERIMENTAL

M.p.s were carried out on a Kofler hot-stage apparatus. Optical rotations were measured for solutions in chloroform. I.r. spectra were obtained on a Unicam SP 200 spectrophotometer. N.m.r. spectra (solutions in $CDCl_3$) were obtained on a Varian T60 spectrometer. Qualitative and preparative t.l.c. was carried out on silica gel (G254)

[6] D. H. R. Barton, G. C. Ramsey, and D. Wege, *J. Chem. Soc.* (*C*), 1967, 1915.

developed with 20% ethyl acetate in light petroleum or benzene. Column chromatography was carried out with grade III alumina eluted with increasing proportions of methylene chloride in light petroleum. All solvents were purified by standard procedures. Light petroleum refers to the fraction of b.p. 60—80°. All chloroformates were prepared as in our previous publication.[1]

Oxidation of Cholestan-3β-yl Chloroformate.—(i) Cholestan-3β-yl chloroformate (2.15 g, 5 mmol) in dry tetrahydrofuran (10 ml) was treated with dimethyl sulphoxide (1.56 g, 20 mmol) and stirred at room temperature for 20 h. Triethylamine (0.8 g, 8 mmol) was added and the mixture was stirred for 30 min, diluted with methylene chloride, washed with water, and dried (Na_2SO_4). T.l.c. indicated the presence of a mixture of cholestanol and a compound of higher R_F values. No ketone was formed.

(ii) The reaction was repeated in methylene chloride (10 ml) containing dissolved hydrogen chloride (1 mmol). After work-up t.l.c. indicated the presence of the same two compounds but a greater amount of the high R_F component. P.l.c. produced 3β,3′β-methylenedioxycholestane (III) (1.1 g), m.p. 203—206° (from acetone) (lit.,[5] 206—207°), δ ($CDCl_3$) 3.6 (2 H, s), and 4.9 (2 H, s) (Found: C, 83.55; H, 12.0. Calc. for $C_{55}H_{96}O_2$: C, 83.7; H, 12.25%).

(iii) The reaction was repeated in tetrahydrofuran in the presence of 1,2-epoxypropane (480 mg, 8.3 mmol). T.l.c. indicated the presence of cholestanol and cholestanone (by comparison with authentic samples). A minor high R_F sulphur-containing steroid (palladium chloride spray reagent) was also present but none of the acetal (III). Column chromatography gave pure cholestan-3-one (1.55 g, 4 mmol), m.p. 130—132°, mixed m.p. 130—132°, $[\alpha]_D$ +44.5° (*c* 1.86).

(iv) Cholestan-3β-yl chloroformate (670 mg, 1.5 mmol) in methylene chloride (4 ml) was treated with 1,2-epoxypropane (140 mg, 2.5 mmol) and dimethyl sulphoxide (1 ml) and the solution was left at room temperature for 20 h. The crystals of *cholestan-3β-yloxydimethylsulphonium chloride* (V) were filtered off in a Craig tube, washed five times with small volumes of dry ether and dried under vacuum for 4 h; m.p. 90—120° (decomp.) (Found: C, 71.6; H, 10.85; Cl, 7.0; S, 6.3. $C_{29}H_{53}ClOS$ requires C, 71.75; H, 11.0; Cl, 7.3; S, 6.6%).

The reaction was repeated and without removing the salt the suspension was cooled to 0 °C, treated with sodium borohydride (250 mg, 6.6 mmol) in bis-(2-methoxyethyl) ether (5 ml), and left for 3 h to warm to room temperature. It was diluted with 0.5N-hydrochloric acid and extracted with ether. The organic phase was washed, dried, and concentrated to leave a crystalline solid. T.l.c. showed the presence of only cholestan-3β-ol. No cholestan-3α-ol was present (comparison with an authentic specimen).

Oxidation of Cholesterol Chloroformate.—(i) Cholesterol chloroformate (10 g, 22.3 mmol) in tetrahydrofuran (60 ml) was treated with 1,2-epoxypropane (2.5 g, 44 mmol) and dimethyl sulphoxide (16 g, 200 mmol) and the mixture was stirred under nitrogen for 20 h. Triethylamine (3 g, 30 mmol) was added and stirring was continued for 30 min. The mixture was concentrated to 20 ml, treated with ethanol (25 ml) and oxalic acid (2.0 g) and refluxed under nitrogen for 2 h. The solution was diluted with water and extracted with methylene chloride, and the organic phase was dried and concentrated to a solid. Chromatography gave pure cholest-4-en-3-one (6.0 g, 15.6 mmol).

(ii) The reaction was repeated with cholesteryl chloroformate (4.52 g, 10 mmol). The solution was concentrated to dryness without work-up. The residue in ether (30 ml) was treated with methanol (15 ml), concentrated to half its volume, and cooled, to give cholest-5-en-3-one (180 mg, 4.7 mmol), m.p. 119—124° (from ethanol), $[\alpha]_D$ −4.4° (*c* 1.96).

Oxidation of Pregnenolone Chloroformate.—The oxidation was carried out with pregnenolone chloroformate (6.3 g, 16.7 mmol) exactly as for cholesterol chloroformate. After isomerisation and work-up, chromatography gave progesterone (3.76 g, 12.4 mmol), m.p. 129—132° (from ethanol), $[\alpha]_D$ +216° (*c* 2.4). An authentic sample crystallised in the same way had the same m.p. and $[\alpha]_D$ +214° (*c* 1.08).

Oxidation of 11α-Hydroxyprogesterone Chloroformate.—The oxidation was carried out with 11α-hydroxyprogesterone chloroformate (490 mg, 1.25 mmol) exactly as for cholestan-3β-yl chloroformate. After work-up and concentration, p.l.c. gave 11-oxoprogesterone (100 mg, 0.32 mmol), identical with an authentic specimen.

Oxidations with Nitrosyl Tetrafluoroborate.—Cholestan-3β-ol (883 mg, 1.5 mmol) in acetonitrile (12 ml) and methylene chloride (3 ml) was treated with hexamethyldisiloxane (2.9 g, 18 mmol) and nitrosyl tetrafluoroborate (1.10 g, 9.0 mmol) and stirred at 0 °C for 2 h. The solution was washed with aqueous 5% sodium disulphite and water, dried, and concentrated to a crystalline solid (540 mg). Crystallisation from acetone gave pure cholestan-3-one, m.p. 128—130°, $[\alpha]_D$ +44° (*c* 1.8).

(ii) Benzyl alcohol (326 mg, 3.0 mmol) in methylene chloride (15 ml) was treated with hexamethyldisiloxane (900 mg, 5.6 mmol) and nitrosyl tetrafluoroborate (670 m, 5.5 mmol). The suspension was stirred for 15 min at room temperature, worked up as above, and added to methanolic 2,4-dinitrophenylhydrazine. The precipitated benzaldehyde 2,4-dinitrophenylhydrazone (820 mg, 2.7 mmol), crystallised from benzene–ethanol, was identical with an authentic specimen.

Alkylation of Cholestan-3β-yl Nitrite.—Cholestan-3β-yl nitrite (417 mg, 1 mmol) in methylene chloride (5 ml) was treated with triethyloxonium tetrafluoroborate (569 mg, 3 mmol) and stirred under nitrogen at room temperature for 50 min. The solution was washed with water, dried, and concentrated to leave a solid. Column chromatography gave cholestan-3-one (187 mg, 0.5 mmol).

We thank the Schering-Plough Corporation for financial support and for gifts of chemicals.

[5/494 *Received*, 13*th March*, 1975]