Some Anomalous Products from the Attempted Halogenation of Unsaturated Alcohols by the Complex from Dimethyl Sulphide and *N*-Halogenosuccinimide

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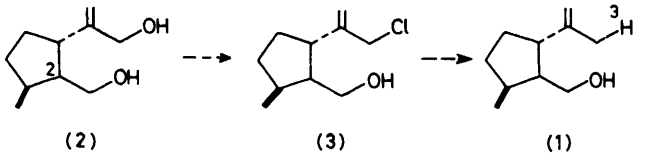
Intramolecular participation of carbon–carbon double bonds and hydroxy-groups can occur when alcohols are treated with complexes derived from dimethyl sulphide and *N*-halogenosuccinimides. Neighbouring group participation is more common in the reactions in which *N*-bromosuccinimide rather than *N*-chlorosuccinimide is employed; the results suggest caution when the alcohol to halide conversion is attempted in certain polyfunctional molecules.

DURING our studies on biosynthesis,[1] it was necessary to prepare the alcohol (1), labelled with ^3H in an allylic position. This aim seemed to be achievable with the transformations shown in Scheme 1, using the procedure

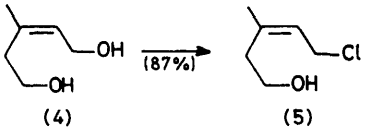


(2) (3) (1)

SCHEME 1

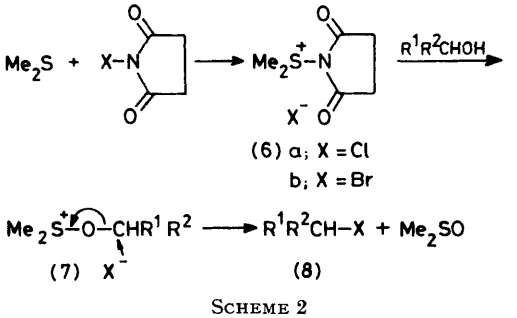
recently discovered by Corey *et al.*,[2] for the selective and mild conversion of allylic alcohols into halides; sulphoxonium derivatives have been described as intermediates.

When treated with *N*-chlorosuccinimide and dimethyl sulphide, the diol (4), which is structurally similar to



(4) (5)

compound (2), does indeed afford [2] the monochloride (5) in very good yields. However, when compound (2) was treated similarly, formation of cyclic products occurred. The results reported in this paper help to rationalize this anomalous behaviour and to show the limits of applicability of this reagent in the conversion of alcohols into halides. Apart from the difficulty of rationalizing the course of all the reactions by a common mechanism, caution is advised when other functions (*e.g.*, hydroxy-groups or olefinic double bonds) in the molecule are suitably placed for a neighbouring group participation.



(6) a; X = Cl
b; X = Br

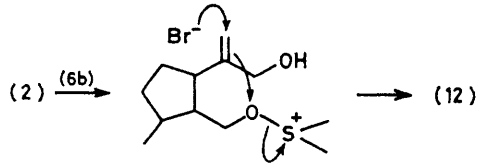
(7) (8)

SCHEME 2

The mechanism previously suggested [2] for the substitution is shown in Scheme 2. In the case of allylic substrates the sulphoxonium derivative (7) is unstable and is rapidly transformed into the corresponding halide (8).

By treating dolichodiol [3] (2) with the complex (6a) from *N*-chlorosuccinimide and dimethyl sulphide, a mixture of products was obtained (see Table 1); surprisingly, the most abundant does not contain halogen and shows physicochemical characteristics concordant with structure (9). Small quantities of the expected monohalide (10) have been found in the reaction mixture, together with the cyclic ether (11). Even if the formation of (9) may seem to be a common etherification through the intramolecular addition of a hydroxy group to a double bond, the stability of (2) under various chemical conditions leads us to suppose that a route *via* a sulphoxonium derivative is more probable.†

Corey and his co-workers observed [2] that the reagent from methyl sulphide and *N*-bromosuccinimide is somewhat more effective in halogenation than that from *N*-chlorosuccinimide; we therefore treated the substrate (2) with the complex (6b). From the reaction mixture a bromo-derivative (homogeneous on t.l.c.) was recovered (Table 1) in high yields; its spectral characteristics do not agree with those of the expected monobromide. The olefinic double bond has been saturated and the chemical and spectral properties indicate the bicyclic



SCHEME 3

structure (12). The mechanism suggested in Scheme 3 accounts for the formation of (12) and is supported by the relatively high nucleophilic power of the bromide ion and the favourable steric arrangement of the

† The formation of (9) may be tentatively explained by supposing an internal elimination process [4] assisted by a neighbouring hydroxy group; as Dreiding models show, the overall process may be concerted.

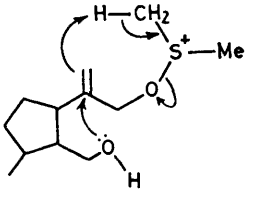
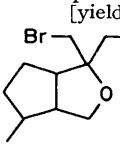
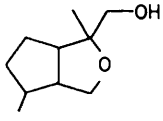
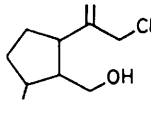
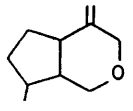
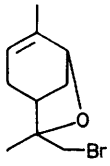
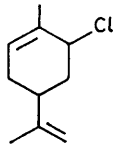
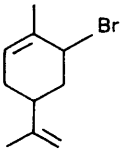
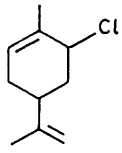
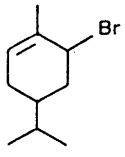
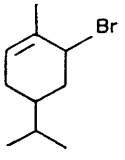
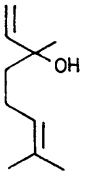
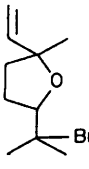
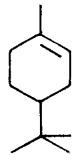
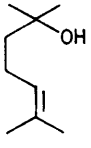
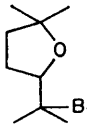
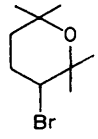
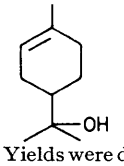
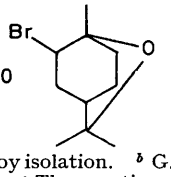


TABLE 1

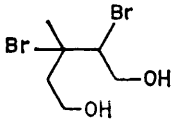
The reaction of multifunctional alcohols with the reagent formed from dimethyl sulphide and *N*-bromo- or *N*-chloro-succinimide

Alcohol	NBS–Me_2S (6b) *t*/h	*T*/°C	products [yield, %] [a]	NClS–Me_2S (6a) *t*/h	*T*/°C	products [yield, %] [a]
(2)	2	−10	 (12) [85]	7	0	 (9) [49] +  (10) [13] +  (11) [6]
cis-(14)	1.5	−10	 (15) [89]	4	−10	 (16a) [90]
trans-(17)	3	0	 (18) [46]	3	0	 (16b) [86]
cis-(19a)	3	0	 (20a) [63]			
trans-(19b)	3	0	 (20b) [74]			
 (21)	3	0	 (22) [75] [b]	40	20	 (23) [51]
 (24)	4	−10	 +  (25) [43] (26) [17]			c
 (27)	48	20	 (28) [34]			c

[a] Yields were determined by isolation. [b] G.c.–m.s. and n.m.r. show that small amounts of the isomeric tetrahydropyran bromo-derivative may be present. [c] The reaction at 20 °C is extremely slow.

substrate; besides, it seems that the structure of the hydroxy group does not strikingly influence the rate of formation of the sulphoxonium derivative, but only the rate of its decomposition.[2]

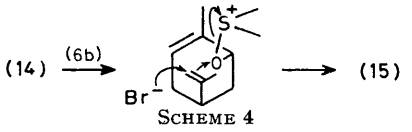
To test whether the anomalous course of the reaction may be caused by the particular chemical structure of dolichodiol (2), we investigated the behaviour with the reagent (6b) of the diol (4), previously treated by Corey *et al.*[2] with (6a). When the reaction was carried out under the same conditions described for geraniol,[2] the bromo-derivative analogous to (5) was recovered in very small amounts (*ca.* 5%); the most abundant (51%) conversion product was the crystalline dibromodiol (13).*



(13)

The complexity of this type of reaction on multifunctional molecules prompted us to investigate the behaviour of substrates for which one would expect participation by other neighbouring groups, *e.g.*, γ–δ double bonds. Even in the cases we shall discuss below, some difference in the degree and type of participation is noted in the use of the complexes from dimethyl sulphide and *N*-chloro- or *N*-bromo-succinimide; this seems to be due to the different nucleophilic power of bromide and chloride ions.

When using (6b) it was observed (Table 1) that in the case of cyclic products in which the double bond γ–δ was in a sterically favourable position with respect to the hydroxy group [as for *cis*-carveol [6] (14)] or in the case of acyclic products [as for linalool (21)], bromoethers are formed, as also occurs with dolichodiol. This involves nucleophilic attack of bromine on the double bond and subsequent interaction of this with the hydroxy function; accordingly, DMSO is absent from the reaction products. Structure (15) was assigned on the basis of spectral characteristics and chemical behaviour; reaction with magnesium turnings afforded quantitatively *cis*-carveol, according to the behaviour [7] of carbanions α to an ether group. Similarly, linalool (21) leads to the bromoether (22).



SCHEME 4

The bromoether (22) has been obtained previously [8] by treating linalool with *N*-bromosuccinimide in CCl_4 *via* normal cleavage of a cyclic bromonium ion by a hydroxy group. However, the formation of (15) from *cis*-carveol (14) and complex (6b) cannot be caused by attack of Br^+ (or of an equivalent oxidative group), owing to the following considerations: (*a*) the reagent (6b) appears to be stable [9] under the reaction conditions; (*b*) the course of the reaction does not change when a large excess (*ca.* 8-fold) of dimethyl sulphide is used or when the time allowed for formation of the complex (6a) or (6b) is greatly increased; and (*c*) both *trans*-carveol (17),[6,†] for which the formation of a cyclic ether is impossible, and *cis*- (19a) or *trans*-carvotanacetol (19b) [6] react with (6b) by simple substitution to form (18) and (20a or b), respectively.

The use of the chlorinated complex (6a) induces a different reaction course. With *cis*-carveol (14) the corresponding allylic chloride (16a) was obtained. On the other hand, with linalool we obtained the derivative (23), by means of intramolecular cyclization promoted by removal of the sulphoxonium groups from the tertiary position. The reaction may be thought of as analogous to the cyclization of linalool by solvolysis [10] of its phosphate ester to give rise to α-terpineol.

As both *cis*-carveol (14) and linalool (21), when treated with *N*-chlorosuccinimide in the absence of dimethyl sulphide, give rise to chloroethers analogous to (15) and (22) respectively, clearly the products we obtained by using (6a) must be formed through a mechanism substantially different from that described in ref. 8.

Neighbouring group participation of a double bond also occurs in the case of non-allylic alcohols (Table 1). In effect, whereas the reagent (6a) has practically no effect on the unsaturated alcohol (24), use of the complex (6b) affords rapidly the cyclic bromoethers (25) and (26) in good yields. By means of the same reagent, α-terpineol (27) affords the bromoether (28) (Table 1).

EXPERIMENTAL

N-Halogenosuccinimides were obtained from Carlo Erba and used without purification. Dimethyl sulphide (Schuchardt) was distilled before use. Methylene chloride was distilled from phosphorus pentaoxide. The alcohols (21) and (27) were commercial products, (14), (17), and (19a, b) were obtained [6] from carvone, (2) (mixture of two epimers at C-2) from iridodial,[3] and (25) from methylheptenone and methylmagnesium iodide. Mass spectra were recorded using g.l.c. or direct insertion; n.m.r. spectra were obtained using Me_4Si as internal standard. Physical data for new compounds are shown in Table 2.

Reaction with N-Halogenosuccinimide and Dimethyl Sulphide in Methylene Chloride.—The general procedure was essentially that described by Corey *et al.*[2] To a cold (0 °C) solution of *N*-chlorosuccinimide (1.1 mmol) [or *N*-bromosuccinimide (1.5 mmol)] in anhydrous methylene chloride (10 ml) under nitrogen was added dropwise with stirring dimethyl sulphide (1.2 or 1.8 mmol, respectively). The mixture was cooled to −20 °C and substrate (1 mmol) in methylene chloride (1 ml) was added dropwise over 5 min.

* The formation of vicinal dichlorides has been observed in the reaction of unsaturated alcohols (*e.g.* cyclohex-2-enol) with dimethyl sulphoxide–chlorine.[5]

† A strong influence of geometrical factors may be noted also in acyclic derivatives. Whereas geraniol affords cleanly the corresponding allylic bromide with complex (6b), as already described by Corey *et al.*,[2] the *cis*-isomer, nerol, reacts markedly slower and the allylic bromide is accompanied by a variety of by-products.

The mixture was then warmed and stirred; temperatures and reaction times are shown in Table 1. After dilution with pentane (30 ml), the mixture was poured into ice–water (15 ml). The organic phase was washed with cold brine, filtered through a small quantity of silica gel (deactivated) and concentrated. Products were isolated and purified by preparative t.l.c. (silica gel) and/or preparative g.l.c. (3% EAS or 3% SE 30 on Chromosorb W, 30—60 mesh). The reactions and isolation procedures were monitored by t.l.c. and g.l.c. (on-column injection).

Acetylation of (9), (12), and (13) was accomplished using acetic anhydride–pyridine at room temperature; usual work-up allowed isolation of the products.

Reaction with N-Halogenosuccinimide in Carbon Tetrachloride.—The procedure was identical with that reported in ref. 8 for *N*-bromosuccinimide. The reaction of *cis*-carveol (14) with *N*-chlorosuccinimide is described as a representative example. *cis*-Carveol (450 mg, 3 mmol) and *N*-chlorosuccinimide (410 mg, 3.1 mmol) in CCl_4 (15 ml) were allowed to react at 38—40° for 48 h. Petroleum ether (20 ml) was then added and the precipitate filtered and washed with a little petroleum ether. After addition of sodium acetate (10 mg), the filtrate was concentrated under vacuum. Chromatography (silica gel; petroleum ether–diethyl ether gradient) and distillation yielded the chloro-derivative analogous to (15) (385 mg, 70%), b.p. 76—78° at 0.01 mmHg; *m/e* 186 (*M*) and 137 (*M* − CH_2Cl); δ (CCl_4) 1.28 (3 H, s, MeC), 1.69 (3 H, br s, Me C=C), 3.43 (2 H, d, *J* 3.8 Hz, CH_2Cl), 3.93 (1 H, dd, *J* 1.2 and 4.0 Hz, HCO), and 5.18 (1 H, br s, CH=C).

TABLE 2

Physical data of new products

Product [a]	$\nu_{max.}$/cm^{-1}	B.p./°C (mmHg)	M.p./°C	δ [b] (60 MHz)	M.s.
(9)	(film) 3 420 1 050	106—108 (0.5)		(CCl_4) 0.99 (3 H, d, *J* 6.2 Hz, MeC), 1.14 (3 H, s, MeCO), 3.20 (2 H, ABq, *J* 11.5 Hz, CH_2OH), and 3.3—4.0 (2 H, m, CH_2O)	139 (*M* − CH_2OH)
Ac-(9)	(film) 1 737 1 240	120—122 (0.5)		($CDCl_3$) 1.0 (3 H, d, *J* 6.0 Hz, MeCH), 1.23 (3 H, s, CH_3CO), 2.05 (3 H, s, MeC=O), 3.80 (2 H, ABq, *J* 10.8 Hz, CH_2OAc), and 3.3—4.0 (2 H, m, CH_2O)	139 (*M* − CH_2OAc)
(10)	(film) 3 370	92—94 (0.05)		($CDCl_3$) 0.96 (3 H, d, *J* 6.3 Hz, MeC), 3.2—3.8 (2 H, m, CH_2O), 4.09 (2 H, br s, CH_2Cl), and 4.9—5.4 (2 H, m, CH_2=C)	188 (*M*)
(11)		78—80 (0.5)		(CCl_4) 1.0 (3 H, d, *J* 6.2 Hz, MeC), 3.23—3.98 (2 H, m, CH_2O), 4.0 (2 H, br s, CH_2O), and 4.85 (2 H, br s, CH_2=C)	152 (*M*)
(12)	(film) 3 400	99—102 (0.01)		(CCl_4) 1.03 (3 H, d, *J* 5.5 Hz, MeC) and 3.1—4.3 (6 H, CH_2X)	217 (*M* − CH_2OH) 155 (*M* − CH_2Br)
Ac-(12)	(film) 1 737 1 240	93—95 (0.01)		($CDCl_3$) 1.04 (3 H, d, *J* 6 Hz, MeC), 2.14 (3 H, s, MeC=O), 3.2—4.2 (4 H, CH_2O and CH_2Br), and 4.25 (2 H, ABq, *J* 12 Hz, CH_2OAc)	217 (*M* − CH_2OAc) 197 (*M* − CH_2Br)
(13)	(nujol) 3 350		60 (Pr^i_2O)	[$CDCl_3$ + $(CD_3)_2CO$, 1 : 1] 1.94 (3 H, s, MeCBr), 2.24 (2 H, t, *J* 6.6 Hz, CH_2C), and 3.6—4.5 (5 H, CHX)	195 (*M* − Br) 177 (*M* − Br − H_2O) 97 (*M* − Br − H_2O − HBr)
Ac-(13)	(film) 1 740 1 240	90—92 (0.005)		($CDCl_3$) 1.95 (3 H, s, MeCBr), 2.04 and 2.11 (3 H each, 2 s, MeC=O), 2.30 (2 H, t, *J* 7 Hz, CH_2C), and 4.1—4.9 (5 H, CHX)	279 (*M* − Br) 219 (*M* − Br − AcOH) 159 (*M* − Br − 2AcOH)
(15)		65—67 (0.005)		(CCl_4) 1.36 (3 H, s, MeCO), 1.71 (3 H, d, *J* 2 Hz, MeC=), 3.41 (2 H, d, *J* 2 Hz, CH_2Br), 4.02 (1 H, dd, *J* 1.2 and 4.5 Hz, CHO), and 5.25 (1 H, br s, CH=C)	230 (*M*) 215 (*M* − CH_3) 137 (*M* − CH_2Br)
(16a)		62—63 (0.01)		(CCl_4) 1.83 (6 H, br s, MeC=C), 4.42 (1 H, br t, CHCl), 4.78 (2 H, br s, CH_2=C), and 5.62 (1 H, br t, CH=C)	170 (*M*) 134 (*M* − HCl)
(16b)		62—64 (0.01)		(CCl_4) 1.81 and 1.84 (3 H each, br s, MeC=C), 4.41 (1 H, br t, CHCl), 4.78 (2 H, br s, CH_2=C), and 5.64 (1 H, br t, CH=C)	170 (*M*) 134 (*M* − HCl)
(18)		94—95 (0.01)		(CCl_4) 1.82 (3 H, s, MeC=C), 2.08 (3 H, s, MeC=C), 4.16 1 H, m, CHBr), 4.78 (1 H, m, CH=C), and 4.88 (2 H, br s, CH_2=C)	214 (*M*) 134 (*M* − HBr)
(20a)		97—99 (0.01)		($CDCl_3$) 0.90 (6 H, d, *J* 5.7 Hz, MeC), 2.03 (3 H, s, MeC=C), 3.59 (1 H, m, CHBr), and 4.80 (1 H, br t, CH=C)	216 (*M*) 136 (*M* − HBr)
(20b)		97—99 (0.01)		(CCl_4) 0.98 (6 H, d, *J* 5.6 Hz, MeC), 2.05 (3 H, s, MeC=C), 4.13 (1 H, m, CHBr), and 4.73 (1 H, t, *J* 4.5 Hz, CH=C)	216 (*M*) 136 (*M* − HBr)
(22)		70—73 (0.01)		(CCl_4) 1.25 (3 H, br s, MeCO), 1.72 (6 H, Me_2CBr), 4.02 (1 H, m, CHO), and 4.8—6.4 (3 H, ABC m, CH_2=CH)	217 (*M* − CH_3) 111 [*M* − $(CH_3)_2CBr$]
(23)		58—60 (0.1)		(CCl_4) 1.56 (6 H, Me_2C—Cl), 1.66 (3 H, MeC=C), and 5.35 (1 H, br s, CH=C)	172 (*M*) 136 (*M* − HCl) 121 (*M* − HCl − CH_3)
(25)		67—68 (1)		(CCl_4) 1.19 and 1.24 (3 H each, s, MeCO), 1.65, 1.69 (3 H each, s, MeCBr), and 3.85 (1 H, t, *J* 6.5 Hz, CHO)	219 (*M* − 1) 205 (*M* − CH_3) 140 (*M* − HBr)
(26)		80—83 (2)		(CCl_4) 1.13, 1.27, and 1.38 (12 H, MeCO), and 3.86 (1 H, q, *J* 6 and 9 Hz, CHBr)	205 (*M* − CH_3)
(28)		71—73 (0.5)		(CCl_4) 1.13 (6 H, s, MeCO), 1.19 (3 H, s, MeCO), and 3.83 (1 H, m, CHBr)	232 (*M*) 217 (*M* − CH_3) 152 (*M* − HBr)

[a] All isolated products gave satisfactory elemental analyses (C,H), the results of which are available in Supplementary Publication No. SUP 22395 (3 pp.). See Notice to Authors No. 7 in *J.C.S. Perkin I*, 1978, Index issue. [b] Downfield from internal Me_4Si. [c] The product has i.r., n.m.r., and mass spectra superimposable on those of a sample obtained by addition of HCl to limonene (ref. 11).

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REFERENCES

[1] U. M. Pagnoni, A. Pinetti, and R. Trave, *Phytochemistry*, in press.
[2] E. J. Corey, C. U. Kim, and M. Takeda, *Tetrahedron Letters*, 1972, 4339.
[3] U. M. Pagnoni, A. Pinetti, R. Trave, and L. Garanti, *Austral. J. Chem.*, 1976, **29**, 1375.
[4] C. R. Johnson and W. G. Phillips, *J. Amer. Chem. Soc.*, 1969, **91**, 682.
[5] E. J. Corey and C. U. Kim, *Tetrahedron Letters*, 1973, 919.
[6] R. Grandi, U. M. Pagnoni, R. Trave, and L. Garanti, *Tetrahedron*, 1974, **30**, 4037.
[7] H. O. House and R. S. Ro, *J. Amer. Chem. Soc.*, 1958, **80**, 182.
[8] E. Demole and P. Enggist, *Helv. Chim. Acta*, 1971, **54**, 456.
[9] E. Vilsmaier and W. Sprugel, *Annalen.*, 1971, **747**, 151.
[10] W. Rittersdorf and F. Cramer, *Tetrahedron*, 1968, **24**, 43.
[11] O. Wallach and E. Kremers, *Annalen*, 1892, **270**, 189.