

Factors in the Formation of Isomerically and Optically Pure Alkyl Halides. Part X.¹ Reactions of Saturated Aliphatic Alcohols with Thionyl Chloride

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Whereas primary alcohols such as butan-1-ol and 3-methylbutan-1-ol are converted into the corresponding chlorides without rearrangement on heating with thionyl chloride, varying degrees of alkyl rearrangement are observed for those which are branched at the 2-position (2-methylpropyl, 0.3; 2-methylbutyl, 22; 2,2-dimethylpropyl, 98%). Straight-chain secondary alcohols afford 2—10% of the isomeric s-alkyl chlorides whilst 3-methylbutan-2-ol gives mainly the tertiary halide. The presence of pyridinium chloride (0.01—0.1 mol. equiv.) reduces the extent of rearrangement but does not eliminate it. In pyridine, 2,2-dimethylpropyl chlorosulphite gives isomerically pure 1-chloro-2,2-dimethylpropane, although the yield is poor. Reactions of alcohols with thionyl chloride in either dimethylformamide or hexamethylphosphoric triamide give isomerically pure products from all types of alcohol except the branched 3-methylbutan-2-ol. In dimethylformamide, an alkoxyformamidinium intermediate is involved.

THIONYL CHLORIDE is commonly used, either alone² or in the presence of a tertiary base,³ for the replacement of a hydroxy-group by halogen. A primary or secondary

¹ Part IX, H. R. Hudson, A. R. Qureshi, and D. Ragoonanan, *J.C.S. Perkin I*, 1972, 1595.

alcohol normally affords an intermediate chlorosulphite, which loses sulphur dioxide on heating ($\text{ROSOCI} \longrightarrow$

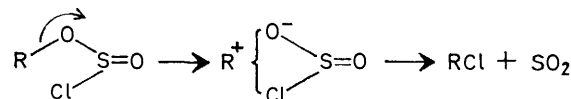
² R. H. Clark and H. R. L. Streight, *Trans. Roy. Soc. Canada*, 1929, **23**, 77.

³ G. Darzens, *Compt. rend.*, 1911, **152**, 1314, 1601.

$\text{RCl} + \text{SO}_2$);^{4,5} however, such esters have not been isolated from tertiary alcohols or from those having aryl substituents at the 1-position.⁶ Whereas the thermal decomposition of the analogous alkyl chlorosulphates is frequently accompanied by high percentages of rearrangement in the alkyl group,⁷ n-butyl chlorosulphate affords 1-chlorobutane as a pure isomer.⁸ Rearrangement has been observed in the attempted preparations of 1-chloro-2,2-dimethylpropane^{9,10} and 2-chloro-3-methylbutane¹¹ by the use of thionyl chloride, but no other studies of rearrangement in alcohol-thionyl chloride systems have been reported.

Results of the analysis by g.l.c.¹² of the products obtained from a representative range of alcohols are shown in Tables 1—3. Table 1 refers to reaction in the

the alkyl chlorosulphate decompositions.⁷ It is likely that an ion-pair mechanism accounts for the rearrangement products obtained (Scheme 1).¹⁴ However, the



SCHEME 1

preponderant inversion of configuration which accompanies the decomposition of (+)-1-methylheptyl chlorosulphate in the absence of solvent^{8,15} indicates that the unrearranged isomers are formed largely by end-on attack of chloride ion on the alkyl group (Scheme 2 or 3). Preponderant retention of configuration is observed only

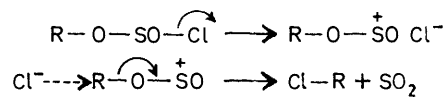
TABLE 1
Alcohol-thionyl chloride interactions in the absence of added base or solvent

| ROH | | Temp. (°C) | Time (h) | RCl obtained ^a | |
|---|---------------------|---------------|-------------|---------------------------|--|
| R | g | | | Mol. equiv. | Composition (%) |
| $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2$ | 14.8 | 100 | 10 | 0.68 | Bu ⁿ (100) |
| $\text{Me}_2\text{CH-CH}_2$ | 14.8 | 100 | 10 | 0.62 | Bu ⁱ (99.7), Bu ^s (0.3) |
| $\text{Me}_2\text{CH-CH}_2\text{-CH}_2$ | (26.3) | 100 | 10 | 0.68 ^c | Pe ⁱ (100) |
| EtMeCH-CH_2 | (14.5) ^b | 100 | 11 | 0.75 ^c | Pe ^{pa} (78), Pe ² (1), Pe ³ (11), Pe ^t (10) |
| $\text{Me}_3\text{C-CH}_2$ ^d | (16.6) ^b | 100 | 60 | 0.09 ^c | Pe ^{neo} (2), Pe ^t (98) |
| Pr^nMeCH | 8.8 | 100 | 2 | 0.51 | Pe ² (98), Pe ³ (2) |
| Et_2CH | 10.0 | 100 | 1.5 | 0.45 | Pe ² (10), Pe ³ (90) ^e |
| Pr^iMeCH | 10.0 | 50 | 1.5 | 0.40 | Pe st (5), Pe ^t (95) |
| Pr^iMeCH | 10.0 | 20 | 24 | 0.56 | Pe st (5), Pe ^t (95) |
| $n\text{-C}_6\text{H}_{13}\text{MeCH}$ | 20.0 | 70—80 | 14 | 0.46 | Oc ² (98), Oc ³ (2) ^f |
| Et_2MeC | 10.0 | 20 | 2 | 0.74 | Pe ^t (100) |

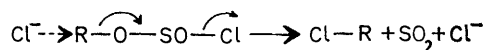
^a Yield of distilled product based on alcohol taken. Peⁱ = $\text{Me}_2\text{CH-CH}_2$; Pe^{pa} (prim. active) = EtMeCH-CH_2 ; Pe^{neo} = $\text{Me}_3\text{C-CH}_2$; Pe^t = Et_2MeC ; Pe² = Pr^iMeCH ; Pe³ = Et_2CH ; Pest (sec. iso) = Pr^iMeCH ; Oc² = $\text{Me-CH}_2\text{-CHMe}$; Oc³ = $\text{Me-CH}_2\text{-CH}_2\text{-CHMe}$. ^b Weight of ROSOCl, isolated by distillation before decomposition. ^c Yield based on ROSOCl taken. ^d Ref. 10. ^e After 4 h at 20 °C the product (0.03 mol. equiv.) contained Pe² (14) and Pe³ (86). ^f Product of earlier experiment reanalysed.⁸

absence of added base or solvent and shows that there is considerably less tendency for primary alkyl groups to rearrange than in the analogous chloroformate systems.⁷ n-Butyl and 3-methylbutyl chlorosulphate yielded isomerically pure products although rearrangement was observed to an increasing extent with increase in the degree of substitution at the 2-position. Straight-chain secondary alcohols, such as pentan-2-ol, pentan-3-ol, and octan-2-ol, which were previously thought to give isomerically pure alkyl chlorides by reaction with thionyl chloride,^{8,13} yielded products which were shown by improved g.l.c. techniques¹² to contain 2—10% of other secondary isomers. The branched-chain secondary alcohol 3-methylbutan-2-ol gave mainly (but not entirely¹¹) t-pentyl chloride, whilst t-pentyl alcohol reacted without rearrangement, as expected. The products were not isomerised after formation and rearrangement patterns were similar to those reported for

as a result of decomposition in dioxan,⁵ or in the case of aryl-substituted alkyl groups which afford relatively stable carbocation intermediates.¹⁴



SCHEME 2



SCHEME 3

Results obtained by reaction in the presence of pyridinium chloride (either added as such,¹⁶ or formed as by-product in the alcohol-thionyl chloride-pyridine system³) appear in Table 2. Rearrangement products were still formed under these conditions, although the

⁴ W. Gerrard, *J. Chem. Soc.*, 1940, 218; W. Gerrard, G. Machell, and P. Tolcher, *Research Correspondence*, 1955, 8, S7.

⁵ E. S. Lewis and C. E. Boozer, *J. Amer. Chem. Soc.*, 1952, 74, 308; 1953, 75, 3182.

⁶ P. Carré and D. Libermann, *Bull. Soc. chim. France*, 1933, 53, 1050.

⁷ P. W. Clinch and H. R. Hudson, *J. Chem. Soc. (B)*, 1971, 747.

⁸ W. Gerrard and H. R. Hudson, *J. Chem. Soc.*, 1963, 1059.

⁹ W. Gerrard and P. Tolcher, *J. Chem. Soc.*, 1954, 3640.

¹⁰ H. R. Hudson, *J. Chem. Soc. (B)*, 1968, 664.

¹¹ C. C. Lee and A. J. Finlayson, *Canad. J. Chem.*, 1961, 39, 260.

¹² B. A. Chaudri, H. R. Hudson, and W. S. Murphy, *J. Chromatog.*, 1967, 29, 218; D. R. Hepburn and H. R. Hudson, *ibid.*, 1975, 103, 166.

¹³ F. C. Whitmore and F. A. Karnatz, *J. Amer. Chem. Soc.*, 1938, 60, 2536; J. Cason and J. S. Correia, *J. Org. Chem.*, 1961, 26, 3645.

¹⁴ W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott, *J. Chem. Soc.*, 1937, 1252, and references therein; D. J. Cram, *J. Amer. Chem. Soc.*, 1953, 75, 332.

¹⁵ A. J. H. Houssa, J. Kenyon, and H. Phillips, *J. Chem. Soc.*, 1929, 1700.

¹⁶ K. V. H. French and W. Gerrard, *J. Chem. Soc.*, 1949, 3326.

percentages were less than in the absence of the hydrochloride. Similarly, the net inversion observed in the thermal decomposition of (+)-1-methylheptyl chloro-sulphite is increased when pyridinium chloride is present; but not to 100%.⁸ The function of the pyridinium chloride is thought to be to increase the concentration of chloride ions and hence to promote S_N2 attack as shown (Scheme 3).¹⁷ However, it seems likely that the

because of the concurrent formation of alkylpyridinium chloride.¹⁸

Dimethylformamide (DMF) and hexamethylphosphoric triamide (HMPT) are solvents which favour the S_N2 mechanism in displacement reactions and both have been used in conjunction with thionyl chloride for the replacement of a hydroxy-group by halogen.¹⁹⁻²² No comment on the isomeric purity of the alkyl chlorides

TABLE 2
Alcohol-thionyl chloride interactions in the presence of pyridinium chloride

| ROH | | C ₅ H ₅ NHCl ^a (mol. equiv.) | Temp. (°C) | Time (h) | RCl obtained ^b | |
|---|---------------------|--|---------------|-------------|---------------------------|---|
| R | g | | | | Mol. equiv. | Composition (%) |
| Me ₂ CH·CH ₂ ·CH ₂ | (30.0) ^c | 0.5 | 100 | 8 | 0.75 ^d | Pe ^t (100) |
| | 10.0 | 1.0 | 100 | 4.5 | 0.87 | Pe ^t (100) |
| EtMeCH·CH ₂ | 10.0 | 1.0 | 100 | 5 | 0.93 | Pe ^{na} (91), Pe ^s (9) |
| | 10.0 | 0.01 | 100 | 5 | 0.90 | Pe ^{na} (90), Pe ^s (9), Pe ^t (1) |
| Me ₂ CCH ₂ | 14.8 | 1.0 | 100 | 100 | 0.38 | Pe ^{neo} (56), Pe ^t (44) |
| Pr ⁿ MeCH | 10.0 | 1.0 | 100 | 1 | 0.67 | Pe ^s (99), Pe ^t (1) |
| Et ₂ CH | 10.0 | 1.0 | 100 | 1 | 0.61 | Pe ^s (0.5), Pe ^s (99.5) |
| | 10.0 | 0.01 | 100 | 1.5 | 0.48 | Pe ^s (11), Pe ^s (89) |
| Pr ⁱ MeCH | 10.0 | 1.0 | 100 | 5 | 0.69 | Pe st (18), Pe ^t (82) |
| | 10.0 | 0.01 | 100 | 1.5 | 0.74 | Pe st (9), Pe ^t (91) |
| n-C ₆ H ₁₃ MeCH | 20.1 | (Trace) ^e | 80 | 6 | 0.48 | Oc ^s (99), Oc ^s (1) ^f |

^a Either formed *in situ* from the ROH-SOCl₂-pyridine interaction (if 1.0 mol. equiv. specified) or added as such. ^b See footnote a to Table 1. ^c Weight of ROSOCl, isolated by distillation before decomposition. ^d Yield based on ROSOCl taken. ^e Residual hydrochloride from sulphite preparation (see ref. 8). ^f Product of earlier experiment reanalysed.

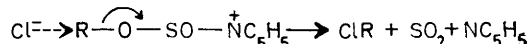
TABLE 3
Alcohol-thionyl chloride interactions in the presence of DMF or HMPT

| ROH | | Solvent | | Temp. (°C) | Time (h) | RCl obtained ^a | |
|---|-----|---------|-----------------|---------------|-------------|---------------------------|--|
| R | g | | cm ³ | | | Mol. equiv. | Composition (%) |
| CH ₂ ·CH ₂ ·CH ₂ ·CH ₂ ·CH ₂ | 3.7 | HMPT | 20 ^b | 20 | 3 | 0.57 | Bu ⁿ (100) |
| | 8.8 | DMF | 40 | 150 | 2 | 0.46 | Pe ^{neo} (100) ^c |
| Me ₃ C·CH ₂ | 4.4 | HMPT | 30 | 100 | 8 | 0.31 | Pe ^{neo} (100) |
| Pr ⁿ MeCH | 4.4 | HMPT | 20 | 20 | 3 | 0.65 | Pe ^s (100) ^d |
| | 8.8 | DMF | 40 | 100 | 0.5 | 0.73 | Pe ^s (100) |
| Et ₂ CH | 4.4 | HMPT | 20 | 20 | 3 | 0.61 | Pe ^s (100) ^d |
| | 8.8 | DMF | 40 | 100 | 1 | 0.56 | Pe st (48), Pe ^t (52) |
| Pr ⁱ MeCH | 4.4 | HMPT | 20 | 20 | 3 | 0.16 | Pe st (90), Pe ^t (10) ^e |
| | 4.4 | DMF | 15 | 100 | 0.5 | 0.63 | Oc ^s (100) ^f |
| n-C ₆ H ₁₃ MeCH ^f | 4.3 | DMF | 20 | 20 | 4 | 0.72 | Oc ^s (100) ^h |
| | 4.3 | HMPT | 20 | 20 | 4 | 0.72 | Oc ^s (100) ^h |

^a See footnote a to Table 1. ^b 2-Chloro-octane (2.2 g), α_D²⁰ +23.85° (l = 1) added. Recovered after reaction: 1.5 g, b.p. 60° at 15 mmHg, n_D²⁰ 1.4261, α_D²⁰ +23.80° (l = 1). ^c After 7 h at 100°C the product (3.2 g) contained (g.l.c.) 1-chloro-2,2-dimethylpropane (1.72 g), τ 9.06 and 6.73, and 2,2-dimethylpropyl formate (1.46 g), τ 9.02, 6.16, and 1.96. ^d Similar results were obtained after heating under reflux (1 h). ^e After 1 h under reflux the product (0.28 mol. equiv.) contained Pest (92) and Pe^t (8). ^f α_D²⁰ -7.34° (l = 1). ^g B.p. 58-60° at 15 mmHg, n_D²⁰ 1.4261, α_D²⁰ +23.85° (l = 1); α_D²⁰ +26.06° (l = 1) (optical purity 82.5%); calc. for ROH: α_D²⁰ -8.02° (l = 1). ^h B.p. 60-62° at 15 mmHg, n_D²⁰ 1.4266, α_D²⁰ +27.87° (l = 1). Redistillation gave 2.0 g, b.p. 59-60° at 13 mmHg, n_D²⁰ 1.4261, α_D²⁰ +28.52° (l = 1); α_D²⁰ +31.16° (l = 1) (optical purity 98.6%); calc. for ROH: α_D²⁰ -8.02° (l = 1).

ionic mode of decomposition will also be encouraged under these conditions by an increase in the ionic strength of the medium.

Isomerically pure 1-chloro-2,2-dimethylpropane was obtained when purified 2,2-dimethylpropyl chloro-sulphite was decomposed in pyridine. The result is similar to that observed with 2,2-dimethylpropyl chloro-formate⁷ and is consistent with the exclusive operation of an S_N2 mechanism in the dealkylation of the intermediate complex:



Yields of alkyl chloride by this route are in general low,

¹⁷ E. S. Lewis and G. M. Coppinger, *J. Amer. Chem. Soc.*, 1954, **76**, 796.

¹⁸ W. Gerrard, *J. Chem. Soc.*, 1936, 688.

produced by these methods was made, although in HMPT it was reported that allylic groups rearranged and that a 25% loss in optical purity occurred in the 1-methylheptyl system.²² The isomeric purity of the products which we obtained by each procedure from a range of saturated alcohols (Table 3) indicates that both methods should be generally applicable to the preparations of straight-chain secondary alkyl chlorides and primary alkyl chlorides of all types. From 3-

¹⁹ H. H. Bosshard, R. Mory, M. Schmid, and Hch. Zollinger, *Helv. Chim. Acta*, 1959, **42**, 1653.

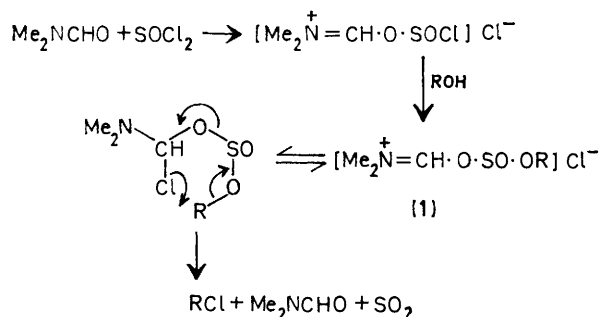
²⁰ G. Ferré and A. L. Palomo, *Anales de Quim.*, 1969, **55**, 163; *Tetrahedron Letters*, 1969, 2161.

²¹ R. F. Dods and J. S. Roth, *Tetrahedron Letters*, 1969, 165; R. C. De Selms, C. J. Fox, and R. C. Riordan, *ibid.*, 1970, 781.

²² J. F. Normant, J. P. Foulon, and H. Deshayes, *Compt. rend.*, 1969, **269C**, 1325; J. F. Normant and H. Deshayes, *Bull. Soc. chim. France*, 1972, 2854.

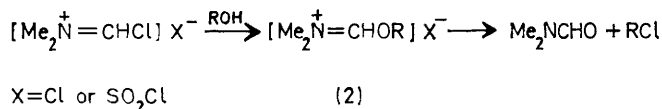
methylbutan-2-ol the purest product (*ca.* 10% rearranged) was obtained in HMPT at room temperature, although the yield was low. In DMF, about 50% rearrangement occurred.

The use of the DMF-SOCl₂ complex for the replacement of a hydroxy-group by halogen was first introduced for the preparation of acyl chlorides¹⁹ but was later extended to alkyl chloride preparations.²⁰ It has been proposed that an intermediate (1) is formed and that this decomposes by way of a cyclic transition state (Scheme 4).²⁰ Spectroscopic studies on Vilsmeier re-



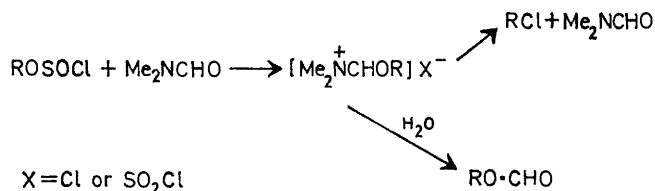
SCHEME 4

agents have, however, shown that the DMF-SOCl₂ complex has the structure [Me₂N⁺=CHCl][OSOCl]⁻ (although sulphur dioxide is readily lost on heating),²³ and it follows that alkyl chloride formation would be expected to occur by a path analogous to that previously demonstrated for reactions of alcohols with chloromethylenedimethylammonium chloride (Scheme 5).²⁴



SCHEME 5

Formation of the alkoxyformamidinium intermediate (2) was confirmed by the identification of alkyl formate (R = Me₃C·CH₂) in the products obtained by hydrolysis of the mixture before alkyl chloride formation was complete. Similar results were obtained by addition of the preformed chlorosulphite to DMF (Scheme 6).



SCHEME 6

Furthermore, we obtained optically active 2-chloro-

²³ M. L. Filleux-Blanchard, M. T. Quemeneur, and G. J. Martin, *Chem. Comm.*, 1968, 836; G. J. Martin and S. Poignant, *J.C.S. Perkin II*, 1972, 1964.

²⁴ D. R. Hepburn and H. R. Hudson, *Chem. and Ind.*, 1974, 664.

²⁵ H. M. R. Hoffmann, *J. Chem. Soc.*, 1964, 1249; H. R. Hudson, *Synthesis*, 1969, 1, 112.

octane with over 80% net inversion of configuration²⁵ by the DMF-thionyl chloride method, whereas reaction as in Scheme 4 would proceed with retention of configuration at carbon. The loss in optical purity which is observed is probably due to gradual racemisation of the product under the conditions of reaction.²⁴

There is no evidence that thionyl chloride and HMPT give rise to a quasiphosphonium intermediate of the type [(Me₂N)₃P⁺Cl]Cl⁻,²² analogous to the intermediate obtained from DMF.²⁶ We have confirmed this observation but have also found that tetramethylphosphorodiamidic chloride is formed slowly at room temperature.²⁷ This appears to require attack by the nitrogen atom of HMPT at sulphur²⁸ but is slow and does not interfere with the more rapid formation and decomposition of the alkyl chlorosulphite. The HMPT possibly assists decomposition of the chlorosulphite by acting as a base (*cf.* pyridine),¹⁸ in addition to providing a favourable medium for S_N2 reaction. It is not clear whether the nitrogen or the oxygen of HMPT is involved as a base in this process, although the above result with thionyl chloride suggests that it is probably the nitrogen.

Contrary to the report that 25% loss in optical purity occurs in the reaction of octan-2-ol with thionyl chloride in HMPT²² we observed virtually complete inversion of configuration. It was also shown that no racemisation of the product occurs under the reaction conditions.

EXPERIMENTAL

Alcohols were obtained and analysed as described.⁷ Thionyl chloride (Hopkin and Williams 'Purified') was used as supplied. Pyridine was dried over sodium hydroxide pellets; DMF and HMPT were dried over molecular sieves.

Product Analysis.—Distilled products were identified by b.p., refractive index, chlorine analysis, and g.l.c.¹² The lower limit for the detection of one alkyl chloride amongst its isomers was <0.1%. Optical rotations were measured in a thermostatted 0.1 dm cell on a Perkin-Elmer 141 photoelectric polarimeter.

General Methods.—(a) *Reactions in the absence of solvent.* The alcohol, either alone or mixed with pyridine (1.0 mol. equiv.), was added dropwise to thionyl chloride (1.1 mol. equiv.) at 0–10 °C. Where specified, pyridinium chloride was added. The mixture was then heated under reflux for a given period (Tables 1 and 2). Volatile products were removed at 20 °C and 0.1 mmHg, trapped (–80 °C), washed, dried (K₂CO₃), and distilled.

(b) *Reactions in solvents.* Thionyl chloride (1.1 mol. equiv.), followed by the alcohol (1.0 mol. equiv.), was added dropwise to DMF or HMPT at 0–10 °C (Table 3). After reaction as specified, an excess of water was added. The upper layer was then washed, dried (K₂CO₃), and distilled.

Reactions of 2,2-Dimethylpropyl Chlorosulphite.—(a) *With pyridine.* The chlorosulphite (15.0 g) was added to pyridine (13.9 g, 2.0 mol. equiv.) at 0 °C and the mixture was heated under reflux (100 °C for 50 h). Products were isolated under reduced pressure and treated as above to

²⁶ M. Fieser and L. F. Fieser, 'Reagents for Organic Synthesis,' vol. 3, Wiley, New York, 1972, p. 153.

²⁷ H. R. Hudson, A. J. Koplick, and J. Sapsford, unpublished work.

²⁸ H. Normant, *Angew. Chem. Internat. Edn.*, 1967, 6, 1046.

yield isomerically pure 1-chloro-2,2-dimethylpropane (2.7 g, 0.29 mol. equiv.).

(b) *With DMF.* Similarly, the chlorosulphite (86.8 g) and DMF (95.0 g, 2.55 mol. equiv.) was heated at 100 °C (62 h) to give a product (27.2 g), b.p. 83—90°, which contained (g.l.c.) pentyl chlorides (20.5 g, 0.38 mol. equiv.) (Pe^{neo}, 99.3; Pe^t, 0.7%) and 2,2-dimethylpropyl formate (6.5 g, 0.11 mol. equiv.) [separated by preparative g.l.c. on 30% silicone oil SE30 at 74 °C and identified by n_D^{20} 1.3931; τ 9.03 (9 H, s, Me₃C), 6.15 (2 H, s, CH₂), and 1.96 (1 H, s, CHO)].

Product Stability.—3-Chloropentane (1.1 g) and thionyl chloride (1.5 g) were kept together for 18 h and then heated (100 °C; 1 h). No isomerisation was detected.

We thank the University of London Central Research Fund for a grant (to H. R. H.) for the purchase of a Perkin-Elmer F11 Chromatograph and the Royal Society for a grant (to G. R. de S.) for the purchase of equipment and materials at North Paddington School.

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