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OZONOLYTIC CLEAVAGE OF CYCLOALKENES TO TERMINALLY DIFFERENTIATED PRODUCTS

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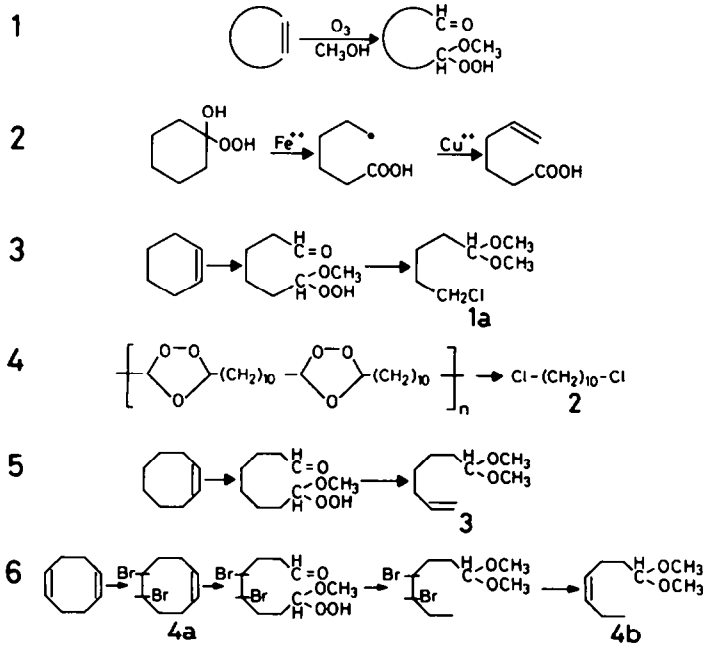
Abstract—A method is described by which alkoxy hydroperoxides, obtained by ozonising cycloalkenes in alcohol solution, can be converted into terminally differentiated products by the action of metal salts. Cyclohexene and cycloheptene were converted to 1,1-dimethoxy-5-chloropentane and 1,1-dimethoxy-6-chlorohexane respectively in 47% yield, using ferric chloride. With ferrous sulphate as reactant salt, cyclooctene was converted into 1,1-dimethoxy-6-heptene. A synthesis of (Z)-4-heptenal from (Z,Z)-1,5-cyclooctadiene is also described. Fragmentation, causing the loss of one carbon atom, is a characteristic of these transformations. Other variations employed the salts as oxidants and reductants simultaneously.

Criegee[1] has described the ozonolysis of alkenes in alcohol solution whereby alkoxy hydroperoxides are formed. When applied to cycloalkenes this reaction affords products, the carbon chains of which have an aldehyde group and an alkoxy hydroperoxide group at the ends (reaction 1 of the scheme). In a recent publication on the ozonolytic cleavage of cycloalkenes to terminally differentiated products. Schreiber *et al.*[2] showed how, by simple modifications of the workup, these hydroperoxides could give rise to a variety of products with differentiated terminal functionalities. For unsubstituted and symmetrically substituted cycloalkenes, there is no problem of possible isomer formation. In planning the synthesis of certain aldehydes, our reasoning was similar to that of Schreiber *et al.*, but for the chemical modification of the alkoxy hydroperoxide group we chose a different course, based on cleavage of the terminal carbon–carbon bond bearing the alkoxy hydroperoxy group.

DISCUSSION

From the literature it is known that the oxidation and reduction of free radicals by metal chlorides and bromides results in the formation of the corresponding substituted products. For example, ethyl chloride was obtained from ethyl radical and cupric chloride.[3] More interestingly, when cyclohexanone peroxide was treated with a mixture of ferrous and cupric sulphates, 5-hexenoic acid was the principal product formed in a ring fragmentation reaction (reaction 2 of the scheme).

We considered that the alkoxy hydroperoxides described by Criegee could also be used for this



carbon–carbon bond fragmentation reaction. We confirmed this by ozonizing cyclohexene in methanol and treating the reaction product with ferric chloride hexahydrate. Chain fragmentation and substitution by chloride was accompanied by acetal formation at the aldehyde group. The final product was 1,1-dimethoxy-5-chloropentane **1a**, isolated in 47% yield (reaction 3 of the scheme). Cycloheptene reacted in the same way to 1,1-dimethoxy-6-chlorohexane **1b** in the same yield.

The above mechanism is not restricted to simple alkoxy hydroperoxides. Cyclododecene, ozonised in light petroleum solution, afforded a polymeric ozonide (see Ref. 4 for a discussion on polymeric ozonides) which also suffered carbon–carbon bond fragmentation and substitution when treated with ferric chloride hexahydrate (reaction 4 of the scheme). The isolated amount of 1,10-dichlorodecane **2** was, however, low (10%).

When the methoxy hydroperoxide, obtained by ozonolysing cyclooctene in methanol, was treated with a mixture of ferrous and cupric salts, the reactions were analogous to those given under 2 of the scheme; 1,1-dimethoxy-6-heptene **3** was formed (reaction 5 of the scheme) and isolated in yields of 22–34%. Some free aldehyde was still present, and a dimerisation product, 1,1,14,14-tetramethoxytetradecane was formed in significant amounts from the intermediate radical. We assume that the one-carbon fragment was eliminated as methyl formate.

Another variant of the radical fragmentation reaction was used to synthesise (Z)-4-heptenal from (*Z,Z*)-1,5-cyclooctadiene. First a selective bromination of the latter with a bromine-dioxane complex[5] afforded (1E)-5,6-dibromo-1-cyclooctene **4a** (yield 63%) as a crystalline compound. (A dibromo derivative of 1,5-cyclooctadiene was described by Willstätter and Veraguth[6] in 1905, but no structure was given.) Then ozonolysis in methanol and treatment with ferric nitrate afforded a crude product which was immediately debrominated with activated zinc in methanol (*cf* Ref. 7); see reaction 6 of the scheme. The dimethyl acetal of (Z)-4-heptenal **4b** was isolated 96% pure in 11% yield. Although its content in the crude final product was about 25%, separation proved difficult.

EXPERIMENTAL

Starting materials. Cyclohexene (ex BASF) purity 99%; cycloheptene, cyclooctene and cyclododecene (ex Aldrich) 82–85% by GLC (rest unidentified); cyclooctene (ex Fluka) 95%; (Z,Z)-1,5-cyclooctadiene (ex Aldrich), n_D^{20} 1.4934, 95% by GLC; $FeSO_4 \cdot 7H_2O$, $FeCl_3 \cdot 6H_2O$, $Fe(NO_3)_3 \cdot 9H_2O$ and $Cu(OAc)_2 \cdot H_2O$ were analytical grade (ex Noury-Baker); methanol was analytical grade (ex Merck); Br_2–dioxane complex was prepared according to Ref. 5 and activated Zn according to Ref. 7, using HCl and $CuSO_4$.

Combustion analyses. These were carried out by Mr. A. Bernhart, Microanalytical Laboratory, Max Planck Institute for Coal Research, Mülheim, Germany.

GLC analysis. The GLC analyses were carried out on a silicone elastomer SE 30 or on PEGA 5% (support Diatoport S 80–100) at suitable temperatures.

NMR, IR and mass spectroscopy. The proton magnetic-resonance spectra were run in CCl_4 solutions at 30° on a Varian HA-100 spectrometer; δ-values are quoted in ppm downfield from internal TMS and are accurate to within ±0.01 ppm. The coupling constants are accurate to within ±0.2 Hz. IR spectra were recorded with an Infrascan and an Infracord spectrophotometer as films. The mass spectra were recorded with an A.E.I. MS 12 spectrometer.

1,1-Dimethoxy-5-chloropentane (**1a**) *and 1,1-dimethoxy-6-chlorohexane* (**1b**). To cyclohexene (**a**) (56.7 g, 0.69 mol) or cycloheptene (**b**) (47 g, 0.49 mol) in methanol (1 l) at −30°, an O_3–O_2 mixture was passed from a Stage K.G. ozonizer. About 0.1 mol O_3/h was passed through till a 20% excess of O_3 had been reached. The mixture was heated at 40° for 15 min and cooled. The solvent was evaporated at 20°/2.0 kPa; residue 133 g (**a**); 104, 4 g (**b**). The residue was added gradually in 16 min to a boiling solution of 326 g (1.2 mole) $FeCl_3 \cdot 6H_2O$ in 1.21 methanol (**a**) or in 7 min to 270 g (1.0 mole) $FeCl_3 \cdot 6H_2O$ in 1.0 l methanol (**b**). The rate of addition was such that the solution remained at the boil without additional heating. When all had been added and spontaneous boiling stopped, the reaction mixture again was heated and boiled for 15 min. Immediately after cooling to room temp, the reaction mixture was extracted with light petroleum (b.p. 40–60°) and (for **a** only) after dilution with water extracted with 800 ml CH_2Cl_2. The total extract was dried with sodium sulphate. After distilling off the solvents, we obtained 54 g **1a** (46.6% yield), b.p. 85–88°/1.6 kPa. IR: 1008, 1068, 1132 and 1160 cm^{-1} (acetal); 1735 cm^{-1} (slight carbonyl impurity). NMR: δ4.38 [tr, J = 5.0, 1H, $-CH(O-)_2$], 3.4 (complex, 2H, $-CH_2Cl$), about 1.5 [complex, 6H, $-(CH_2)_3-$], 3.19 [s, 6H, $(-OCH_3)_2$]. Compound **1a** was further characterised by conversion to the 2.4-DNP of 5-chloropentanal, m.p. 106–108° (lit[8] m.p. 106–108°), which was also obtained from authentic 1,1-diethoxy-5-chloropentane.[9] The yield of **1b** was 40 g (47% yield), b.p. 96–105°/2.4 kPa. Mild acid hydrolysis with formic acid afforded 6-chlorohexanal, b.p. 70–73°/47 Pa (lit[10] b.p. 35°/1.3 Pa).

1,10-Dichlorodecane (**2**). Cyclododecene (24.9 g, 0.15 mol) in light petroleum (1 l, 1 b.p. 40–60°) was quantitatively converted into 22 g polyozonide at room temp by the action of O_3-containing O_2. The polyozonide (a solid insoluble in solvents such as methanol, ethanol, butanol, acetone, ethyl acetate and chlorinated hydrocarbons) was added in 5 min to a boiling solution of $FeCl_3 \cdot 6H_2O$ (131 g, 0.485 mol) in ethanol (485 ml), whereby a suspension was formed. After *ca* 30 min, the mixture had become homogeneous and after another 15 min peroxide could not be detected any more. After cooling, the reaction mixture was extracted with light petroleum (3 × 250 ml). Drying and evaporation of the extract gave 28 g residue. Gaschromatographically, 17% **2** was detected, using authentic 1,10-dichlorodecane as model substance. Distillation of the residue and purification by column chromatography gave 3.1 g, b.p. 148–150°/1.3 kPa (lit[11] b.p. 151°/2.1 kPa), gaschromatographic purity 95%, yield Calc on polyozonide 9.5%. IR: $-CH_2-CH_2Cl$, 650(S) and 750(m) cm^{-1}; $-CH_2Cl$, 1280(m–S) and 1310(m–S) cm^{-1}.

1,1-Dimethoxy-6-heptene (**3**). Through a solution of cyclooctene (50 g, 0.45 mol) in methanol (500 ml) at −30°, an O_3-O_2 stream was led (0.1 mol O_3/h). After 4 h, the ozonolysis was completed (no starting material was detected by TLC). The solution was warmed to and kept at *ca* 20° for 48 h (this operation is necessary for the methanolysis of the polycondensate peroxide–formed during the ozonolysis at low temp—to a monomeric peroxide which gives better yields of the desired title compound in the radical reaction which followed). The solution of the monomeric peroxide was then quickly added with stirring to a fresh, cooled (*ca* 10°) solution of $Cu(OCOCH_3)_2 \cdot H_2O$ (100 g, 0.510 mol) and $FeSO_4 \cdot 7H_2O$ (140 g, 0.504 mol) in methanol (800 ml). The reaction was instantaneous and exothermic (the temp rose to *ca* 35°). After 30 min, the solvent was evaporated (35°, 2.1 kPa) to about 1/10 of its original volume. The residue, a suspension of inorganic material in a viscous dark-red oil, was extracted with ether (3 × 300 ml), evaporated off and extracted again with light petroleum (6 × 300 ml); evaporation of the solvent gave 88.0 g light green oil (this double-extraction method is necessary for the isolation, without the

use of water, of the reaction products as acetals). Distillation gave **3** (23.2 g, 34% yield), b.p. 50°/0.7 kPa, n_D^{20} 1.4238 (Found: C, 68.4; H, 11.4; O, 20.2. $C_9H_{18}O_2$ requires: C, 68.35; H, 11.41; O, 20.23). MS: M^+ 158. IR (film): 2830, 1130, 1081, 1057 and 957 cm^{-1} (acetal); 3075, 1644, 1420, 996 and 912 (vinyl group). NMR: δ5.74 (tr of d, J = 10.3, J = 17.1, J = 6.6, 1H, –C=CH–), 4.79–5.07 (complex, 2H, $=CH_2$), 4.24 [tr, 1H, $-CH(O-)_2$], 3.19 [s, 6H, $(-OCH_3)_2$], 1.88–2.21 (complex, 2H, $-C=C-CH_2-C-$), 1.16–1.69 [complex, 6H, $-(CH_2)_3-$].

In another experiment starting from cyclooctene (150 g) **3** (41.9 g) was isolated and the residue (147 g) fractionally distilled to give methyl 8,8-dimethoxyoctanoate **3a** (39.8 g), b.p. 115°/53 Pa, n_D^{20} 1.4300 [IR: 2840, 1190, 1125, 1070 and 1060 cm^{-1} (acetal); 1740 cm^{-1} (ester –CO)] (lit[12] b.p. 80°/7 Pa) and 1,1,14,14-tetramethoxytetradecane **3b** 39.8 g), b.p. 155°/7 Pa, n_D^{20} 1.4395 [IR: 2840, 1196, 1132, 1081, 1060 and 966 cm^{-1} (acetal)]. These compounds were further characterized by the formation of crystalline 2,4-DNPs: from **3**, m.p. 91–92° (lit[13] m.p. 95–96°), from **3a**, m.p. 76–78° (lit[14] m.p. 76–78°) and from **3b**, m.p. 105–109° (bis-DNP).

(1*E*)-5,6,*Dibromo*-1-*cyclooctene* (**4a**). Bromine/dioxane complex[5] (190 g, 0.965 mol) in absolute ether (1 l, freshly prepared) was added in 30 min to 1,5-cyclooctadiene (190 g, 1.76 mol) in absolute ether (1 l), under nitrogen with stirring and external cooling (ice water) to maintain an internal temp of about 15–20°. The solvent was then evaporated at 2.7 kPa/25° and excess cyclooctadiene was distilled off under high vacuum. Fractionation of the residue by distillation gave unchanged cyclooctadiene (108 g) and **4a** (146 g), b.p. 80–102°/7 Pa. After 24 h in the refrigerator a liquid supernatant (14 g) was decanted from the crystallized fraction, (132 g, 63% yield), GLC purity 95%. Recrystallization from ethanol gave **4a**, m.p. 33–35° (Found: C, 36.0; H, 4.6; Br, 59.7. $C_8H_{12}Br_2$ requires C, 35.85; H, 4.51; Br, 59.64). MS: M^+ 266 (^{79}Br). The compound remained stable for several weeks at 0°. After one week at room temp, the bromide content had decreased by 1.2%. IR (KBr) indicated that the halogen atoms are trans to each other, i.e. axial–axial or equatorial–equatorial; δCH 1181–978–835 cm^{-1} (eq–eq), 1145–1008–885 cm^{-1} (ax–ax); νC–Br 678 cm^{-1} (eq–eq), 670 cm^{-1} (ax–ax); νC=C 1658 cm^{-1}; γ=CH 965 cm^{-1} (trans). NMR: δ5.6 (2H, alkene), 4.6 (2H, –CHBr), 2.0–3.0 (8H, complex).

(4*Z*)-1,1-*Dimethoxy*-4-*heptene* (**4b**). **4a** (100 g, 0.354 mol) in methanol (900 ml) was ozonized completely at 10–20°, concentrated *in vacuo* (2.1 kPa/25°) to *ca* 300 ml and then added with stirring to $Fe(NO_3)_3 \cdot 9H_2O$ (450 g) in methanol (1.5 l) at 65°. The mixture was refluxed for 15 min, cooled and extracted with 1.5 l light petroleum (b.p. 40–60°). After drying and distilling off the solvent, 79 g product (portion A) remained. The methanolic solution was evaporated and the residue shaken with water and ether; the ether extract gave 37.9 g product (portion B) on evaporation. The portions A and B were separately debrominated. While stirring, portion A (79 g) in methanol (50 ml) was added dropwise in 40 min to a suspension of activated Zn (192 g prepared from 250 g Zn[7]) in methanol (150 ml) at 65°; stirring and heating were continued under reflux for a further 20 min; the mixture was cooled and extracted with light petroleum (*ca* 300 ml) yielding 28.5 g product. After treatment with Zn (100 g) and extraction, fraction B (37.9 g) gave 14.9 product. Each of these products contained free heptenal besides **4b** (25% yield, from GLC analyses, based on dibromocyclooctene). Fractional distillation of the combined cruder fractions gave **4b** (7.0 g, 11% yield), b.p. 76–82°/3.1 kPa; n_D^{20} 1.4270 (Found: C, 68.3; H, 11.4; 0, 20.4; OCH_3, 37.6. $C_9H_{18}O_2$ requires: C, 68.41; H, 11.48; 0, 20.25; OCH_3, 39.28). MS: M^+158. IR: 1065, 1130, 1195, 2840 cm^{-1} (acetal); 700–720, 1660, 3010 cm^{-1} (cis alkene, –CH=CH–), 797 cm^{-1} [$CH_3(-CH_2)$]. NMR: δ5.32 (complex, 2H, –CH=CH–); 4.28 [tr, J = 5.8, 1H, $-CH(O-)_2$]; 3.21 [s, 6H, $(-OCH_3)_2$]; 2.03 (complex, 4H, $-CH_2-C=C-CH_2-$); 1.56 (complex, 2H, $-CH_2-C-O-$); 0.95 (tr, J = 7.9, 3H, $-CH_3$).

(*Z*)-4-*Heptenal*[8,16] (**4c**). **4b** (96% by GLC; 2 g, 12.7 mmol) in 20 ml acetone/20 ml water/0.4 g oxalic acid was hydrolysed at 45–50° while stirring under argon for 2.5 h[15]. The acetone was distilled off and the residue extracted with light petroleum. The extract was dried (Na_2SO_4) and evaporated (2.1 kPa/25°). Chromatography of the residue on silica gel with light petroleum/ether (95/5 v/v) as eluent gave **4c** (0.95 g, 67% yield), GLC purity 99%; n_D^{20} 1.4343 (Found: C, 74.3; H, 10.4; O, 15.4. $C_7H_{12}O$ requires: C, 75.06; H, 10.80; O, 14.3). MS: M^+112. IR: 700–710 cm^{-1} (δ –CH=CH–), 3000 cm^{-1} (cis –CH=CH–), 1655 cm^{-1} (–C=C–), 1725 cm^{-1} (aldehyde –CO), 2710 cm^{-1} (–CHO). NMR: δ9.63 (tr, J = 1.3, 1H, –CHO); 5.33 (complex, 2H, –CH=CH–), 2.37 and 2.04 (complex, 6H, $-CH_2-C=C-CH_2-CH_2-$); 0.94 (tr, J = 7.9, 3H, $-CH_3$).

REFERENCES

[1] R. Criegee, *Ann.* **583**, 1 (1953).
[2] S. L. Schreiber, R. E. Claus and J. Reagan, *Tetrahedron Letters* 3867 (1982).
[3] H. E. De La Mare, J. K. Kochi and F. F. Rust, *J. Am. Chem. Soc.* **85**, 1437 (1963).
[4] R. W. Murray and Jang-Szu Su, *J. Org. Chem.* **48**, 817 (1983).
[5] J. D. Billimoria and N. F. Maclagan, *J. Chem. Soc.* 3257 (1954).
[6] R. Willstätter and H. Veraguth, *Chem. Ber.* **38**, 1981 (1905).
[7] J. W. McCutcheon, *Org. Synth. Coll.* **3**, 526 and 531 (1955).
[8] A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen and R. C. Portnoy, *J. Org. Chem.* **38**, 36 (1973).
[9] J. P. Ward and D. A. van Dorp, *Rec. Trav. Chim. Pays-Bas*, **88**, 177 (1969).
[10] J. F. Le Borgne, *J. Organometal. Chem.* **122**, 123 (1976).
[11] F. Erbe, T. Grewer and K. Wehage, *Angew. Chem.* **74**, 988 (1962).
[12] R. O. Adlof, W. E. Neff, E. A. Emken and E. H. Pryde, *J. Am. Oil Chemists' Soc.* **54**, 414 (1977).
[13] N. A. Le Bel, M. E. Post and J. J. Whang, *J. Am. Chem. Soc.* **86**, 3759 (1964); see p. 3764.
[14] H. Rapoport and E. J. Volcheck, *J. Am. Chem. Soc.* **78**, 2451 (1956); see p. 2453.
[15] M. Winter, *Helv. Chim. Acta* **56**, 1792 (1963).
[16] H. Stetter and H. Kuhlmann, *Synthesis*, 379 (1975).