

THE STEREOCHEMISTRY OF REDUCTIVE DEHALOGENATION

THE REDUCTION OF 1,2,3,4,7,7-HEXACHLORO-5-*ENDO*-ACETOXY-BICYCLO[2.2.1]-2-HEPTENE*

K. L. WILLIAMSON, Y. FANG LI HSU and E. I. YOUNG†

Contribution from the Department of Chemistry,
Mount Holyoke College, South Hadley, Massachusetts 01075

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Abstract—The stereochemistry of reductive dehalogenation has been examined employing three representative reducing agents—zinc and acetic acid, chromous acetate, and catalytic hydrogenation over Pd-C. Chromous acetate and zinc and acetic acid reduce, in greater than 70% yield, just the chlorine atom *anti* to the double bond in the title compound. Catalytic reduction, on the other hand, does not affect either of the geminal bridge chlorines, but instead reduces and dechlorinates the vinyl system.

ALTHOUGH the reduction of halogenated compounds is not an uncommon reaction the stereochemistry of reductive dehalogenation has received little attention. The purpose of the present work was to compare the stereochemistry of three representative reductive dehalogenation reactions: dissolving metal (zinc-acetic acid), homogeneous transition metal cation (chromous acetate), and catalytic (Pd-C). The system chosen for study was 1,2,3,4,7,7-hexachloro-5-*endo*-acetoxybicyclo[2.2.1]-2-heptene (1) which possesses vinyl, geminal, and bridgehead chlorines. We have studied monodechlorination paying particular attention to the two geminal Cl atoms on the bridge. Two powerful tools have made this investigation possible: analytical and preparative gas chromatography and 100 MHz NMR spectroscopy.

RESULTS AND DISCUSSION

The Diels-Alder adduct 1 was prepared in 65% yield, m.p. 43–44°, by refluxing equimolar quantities of vinyl acetate and hexachlorocyclopentadiene.¹ The adduct is regarded, in accordance with Alder's second rule,² to be the *endo* isomer. This assignment of configuration is also in agreement with our previous NMR study of this and related compounds.³

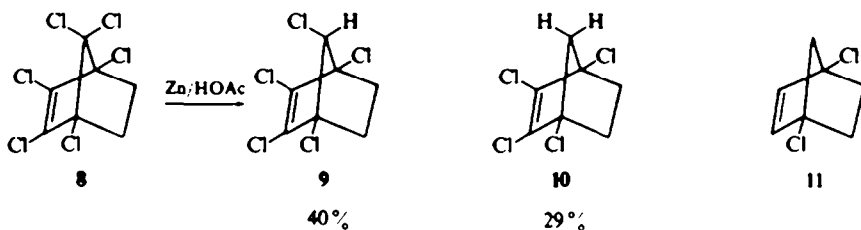
Zinc Dust. Reduction of 1 with zinc dust in refluxing acetic acid for 2 hr gave (GLC) 70% of the *syn*-7-chloro compound 2, 9% of the *anti*-7-chloro compound 3, and two other compounds which on the basis of spectral evidence are regarded as the *anti*-7-acetoxy compound 4 (15% yield) and the 7,7-dihydro compound 5 (6% yield). Although it is only natural to assume that the dihydro compound, 5, results from further reduction of 2 or 3 and that the diacetate, 4, could result from acetate

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relative area 3 was assigned to the acetate Me leaving the peak at *ca.* 4 ppm with relative area 1 being assigned to the bridge proton. That this proton is on the bridge follows from the chemical shift which is too far upfield for a vinyl proton and from lack of coupling to the 5 and 6-*exo* protons which would be evident if the proton were on the bridgehead carbon. It is then possible to distinguish 2 from 3 because only 3 has protons in the coplanar W conformation which can couple over four bonds ($J_{H,H_6} = 2.2$ Hz). Such coupling of *anti* with *endo* protons in bicyclic systems, first noted by Meinwald,^{6a} is now well established.^{6b}

We can now state that zinc reduction of chlorinated compounds of the type represented by 1 proceeds with a rather high degree of stereospecificity to give monohydro products of the type represented by 2. This conclusion is completely in accord with the results of Wilcox and Zajacek⁷ who reduced 8 to 9 and 10 in the course of synthesizing 11. Refluxing 8 with zinc dust in acetic acid for 8 hr gave 9



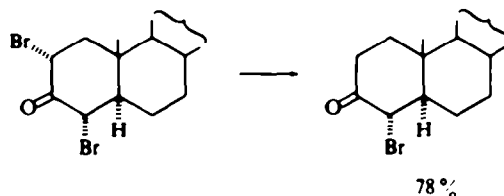
in 40% yield and 10, their desired compound, in 29% yield. They tentatively assigned the *syn* configuration for the chlorine at C-7 in compound 9 because 9, like 8 failed to reduce over Adams' catalyst while 10 is readily reduced under the same conditions. This they attributed to blocking of the double bond by *syn* chlorine atoms in 9 and 10.

Zinc-acetic acid reduction of (–)-2-chloro-2-phenylpropanoic acid occurs with inversion of configuration.⁸ Brewster⁹ interprets this as indicative of a mechanism involving attack of the electron-rich metal surface on the chlorine atom to produce a carbanion which is immediately protonated from the rear by the solvent. Annino *et al.*¹⁰ found that zinc reduction of 1-bromo-2,2-diphenylcyclopropane carboxylic acid gave 21% of the inversion product. No direct chemical evidence was found for the presence of either a free radical or carbanion intermediate. In the present work the mechanism of the reaction remains to be explored.

Chromous acetate. Refluxing the hexachloroacetate 1 with chromous acetate in acetic acid under nitrogen for 16 hr gave almost the same results as zinc-acetic acid reduction: the *syn* chloro compound 2 was formed in 78% yield and the *anti*-chloro compound 3 in 18% yield (GLC). By comparison with the zinc reduction the chromous ion reduction was much cleaner; the two monohydro products being formed in a combined yield of 96%.

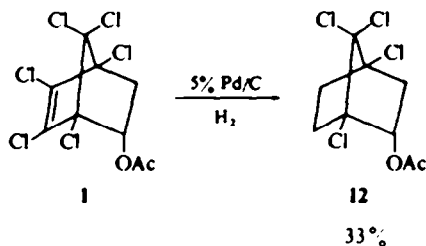
The mechanisms of chromous ion reduction of alkyl halides have, unlike the zinc reduction, been explored, chiefly through the careful work of Castro *et al.*¹¹ In the most recent work on geminal halides^{11b} it has been found that the order of reactivity is $\text{CCl}_4 > \text{CHCl}_3 > \text{CH}_2\text{Cl}_2 \gg \text{CH}_3\text{Cl}$ for homogeneous reduction by chromous sulfate in dimethylformamide at room temp. This reactivity sequence precludes a stepwise reduction of the type $\text{CCl}_4 \rightarrow \text{CHCl}_3 \rightarrow \text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_3\text{Cl} \rightarrow$

CH₄. Consequently Castro and Kray^{11b} propose a mechanism involving α -halo-methyl-radicals and carbenes as intermediates in the reduction process. In the present work we have of course noted a stepwise reduction for 79% of the products, but under conditions (chromous acetate, refluxing acetic acid) that make comparison with Castro's work rather difficult. We have previously noted the highly selective reduction of 2 α ,4 α -dibromocholestane-3-one to 4 α -bromocholestane-3-one in 78% yield with



chromous acetate¹² which we attributed to steric hindrance at C-4 compared to C-2.

Palladium on charcoal. The hexachloroacetate **1** was hydrogenated over 5% Pd-C in ethanol containing triethylamine at room temperature and atmospheric pressure. The reaction was stopped after the uptake of one mole of hydrogen and analyzed by analytical and preparative GLC. Only two products were isolated – starting material in 60% yield (by analytical and preparative GLC) and a crystalline product, m.p. 55–56°, in 33% yield which we have formulated as **12** on the basis of IR, NMR and mass spectroscopy. The IR spectrum of **12** shows a characteristic

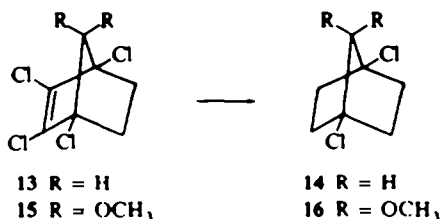


acetate carbonyl absorption and lacks the olefin absorption at 6.28 μ . The NMR spectrum has a large singlet at 2.03 ppm assigned to the acetate Me, a multiplet at 5.08 ppm assigned to the proton on the acetate bearing C atom and a very complex pattern of peaks at 1.65 to 2.96 ppm. The absence of any absorption in the region 3.5 to 4.5 ppm rules out all compounds with hydrogen on a chlorine bearing C atom.* The mass spectrum has a molecular ion peak at 290 amu corresponding to the empirical formula C₉H₁₀Cl₄O₂.†

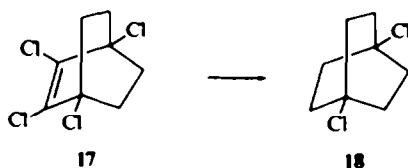
* In **2** and **3** the bridge proton absorbs at 4.3 and 4.0 ppm. LeBel¹⁴ has noted in a large number of 5,6-dihalonorbornanes that the 5 and 6 protons all absorb in the range 3.5 to 4.5 ppm.

† We are indebted to Dr. H. D. Hobercht of Olin, New Haven, Conn. for running and interpreting the mass spectra.

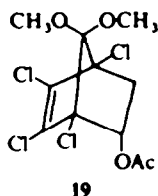
Catalytic reduction of chlorinated bicyclic compounds has been reported in various preparative schemes. Wilcox and Zajacek⁷ reduced **13** to **14** in 82% yield



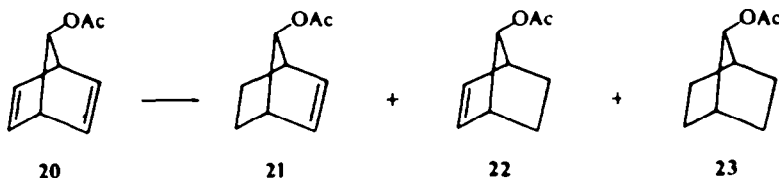
employing Raney nickel in the presence of excess base. Sherer¹³ hydrogenated **15** over 5% Pd-C in ethanol and obtained **16** in 93% yield. As an intermediate in the synthesis of some diamino compounds Kauer¹⁴ hydrogenated **17** over platinum oxide to give **18**.



Catalytic hydrogenation of these bicyclic systems is subject to steric hindrance. As mentioned above Wilcox and Zajacek⁷ assigned the *syn* chlorine configuration to compound **9** because it failed to reduce over Adams' catalyst and Sherer¹³ found



that **19** could not be reduced using palladium. Franzus *et al.*¹⁵ found that platinum catalyzed reduction of **20** gave predominantly **21** along with a small amount of **22** and a trace of **23**.



In the present work the vast difference in reactivity of the chlorines is noteworthy. Only unreacted starting material and product **12** corresponding to uptake of *three* moles of hydrogen were detected and isolated. Presumably **12** arises from initial

hydrogenation of the double bond followed by elimination and reduction or hydrolysis of the chlorines on the two carbon bridge.

Thus we have seen that homogeneous reduction (with chromous ion) and dissolving metal reduction (zinc-acetic acid) of 1 give highly stereospecific mono-reduction products while catalytic reduction (Pd-C) selectively reduces and dehalogenates the dichloro-vinyl system without affecting the geminal chlorines.¹⁶ We plan to investigate the stereochemistry of other dissolving metal (e.g. sodium in ethanol, lithium in *t*-butyl alcohol) and catalytic (e.g. Raney nickel, rhodium, platinum) reductions on this system as well as electrochemical reduction.

EXPERIMENTAL

IR spectra were taken on a Perkin-Elmer Model 137 spectrometer as 10% solns in CS₂. VPC was done on an Aerograph Autoprep Model 705 gas chromatograph equipped with a $\frac{1}{8}$ in \times 10 ft 20% SF-96 on 80/100 mesh chromosorb W column or a $\frac{1}{8}$ in \times 20 ft 30% SE-30 on 60/80 mesh chromosorb P column. M.p.s were taken on a Thomas Hoover capillary m.p. apparatus. Elemental analyses were done by Spang Microanalytical Laboratory, Ann Arbor, Mich. NMR spectra were run on a Varian HA-100 spectrometer. Spectra were taken at 100 MHz as ca. 10% solns in CS₂ with TMS as an internal reference. Coupling patterns were established by frequency swept double resonance experiments.

1,2,3,4,7,7-Hexachloro-5-endoacetoxybicyclo[2.2.1]-2-heptene (1) This adduct was prepared according to the procedure of Fields.⁷ It was recrystallized at 0° from *n*-hexane to give a 65% yield of prisms, m.p. 43-44°, IR λ_{max} : 5.75, 6.28, 8.30, 8.65, 10.05, 12.70 μ . The reported yield is 69%, m.p. 44°.

Zinc-acetic acid reduction of 1 A modification of the procedure used by Wilcox *et al.*⁷ for the reduction of 1,2,3,4,7,7-hexachlorobicyclo[2.2.1]heptene was employed.

To a soln of 20 g (0.056 mole) of 1 in 125 ml magnetically stirred and refluxing glacial AcOH was added, through Gooch tubing,¹⁷ over 0.5 hr, 18.3 g (0.28 mole) of Mallinkrodt analytical reagent grade Zn dust. The mixture was refluxed for an additional 4 hr, then cooled to room temp. The unreacted Zn was removed by filtration through glass wool and the filtrate poured into 1 l. cold water. The mixture was extracted 3 times with 300-ml portions of pentane. The pentane was washed with water, 10% Na₂CO₃ aq. and water until neutral to litmus. The soln was dried over MgSO₄ and the pentane distilled through a Vigreux column to leave 13 g (65% yield of pentachloro products) of a viscous yellow oil which spontaneously crystallized on cooling. The crystals of 2 were separated by suction filtration and recrystallized at 0° from *n*-hexane. The yield was 6.42 g (36%) of white prisms, m.p. 79-81°. One-half gram of the filtrate was chromatographed on 25 g of alumina collecting 250-ml fractions. The first fraction, eluting with 40-60 pet. ether, contained compound 3 and after an intermediate fraction (5% benzene in pet. ether), compound 2 was eluted by 20% benzene in pet. ether.

In another run the reaction was terminated at the end of 2 hr and the crude product analyzed by preparative gas chromatography (column temp 215°, injector 245°, SE-30 column, flow rate 200 ml of He/min). Four compounds were eluted.

1,2,3,4-syn-7-Pentachloro-5-endoacetoxybicyclo[2.2.1]-2-heptene (2) was the third compound eluted (168 min retention time, 69% yield). A sample for analysis, recrystallized from *n*-hexane, had m.p. 83.5-84°. Prominent IR peaks were at 5.64, 8.19, 9.35, 9.94 and 12.91 μ . The NMR spectrum showed a sharp singlet for the C-7 proton at 4.35 ppm (Table I). (Found: C, 33.11; H, 2.12. Calc. for C₉H₂O₂Cl₅: C, 33.32; H, 2.18%).

1,2,3,4-anti-7-Pentachloro-5-endoacetoxybicyclo[2.2.1]-2-heptene (3) was the second compound eluted (147 min retention time, 9.4% yield). A sample for analysis, recrystallized from *n*-hexane, had m.p. 88-91°. Prominent IR peaks were at 5.64, 8.18, 8.55, 9.45 and 12.70 μ . The NMR spectrum showed a one proton multiplet at 5.05 ppm with splittings of 2.2, 0.4 and 0.2 Hz which corresponded to similar splittings of the C-5 and C-6 protons (Table I). (Found: C, 33.51; H, 2.34. Calc. for C₉H₂O₂Cl₅: C, 33.32; H, 2.18%).

1,2,3,4-Tetrachloro-7-anti-5-endodiacetoxybicyclo[2.2.1]-2-heptene (4) was the fourth compound eluted (203 min retention time, 15.0% yield). A sample for analysis had m.p. 91-92.5°. Prominent IR peaks were at 5.68, 5.73, 8.22, 8.40, 8.56, 9.41, 10.45, 10.72, 10.96 and 12.69 μ . The NMR spectrum showed two 3-proton singlets at 2.16 and 2.00 ppm assigned to the two acetate methyls and a one-proton multiplet at 5.05 ppm assigned to the C-7 proton. Splittings of 2.10, 0.3 and 0.3 Hz indicated coupling to the C-5 and C-6 protons

and therefore a 7-*anti* configuration for the acetate group (Table 1). (Found: C, 37.72; H, 2.78. Calc. for $C_{11}Cl_4H_{10}O_4$: C, 37.96; H, 2.90%.)

1,2,3,4-Tetrachloro-5-endoacetoxybicyclo[2.2.1]-2-heptene (5) was the first compound eluted (92 min retention time, 5.7% yield). This viscous liquid had prominent IR peaks at 5.75, 7.36, 7.85, 8.01, 8.23, 8.85, 9.25, 9.44, 9.80, 10.35, 10.56, 10.89 and 13.14 μ . The NMR spectrum showed a two proton AB quartet centered at 2.40 ppm. The proton at 2.36 ppm showed splittings of 3.5 Hz indicating coupling to the 6-*endo* proton and was therefore assigned the 7-*syn* configuration. The proton at 2.44 ppm was also coupled to the 6-*endo* proton, the splitting being 0.9 Hz. (Found: C, 37.11; H, 2.68. Calc. for $C_9Cl_4H_8O_2$: C, 37.28; H, 2.78%.)

Attempted zinc dust reduction of 2. To a stirred, refluxing soln of 0.70 g of 2, m.p. 83–5–84°, in 5 ml AcOH was added over a $\frac{1}{2}$ hr period 0.72 g of Mallinkrodt analytical reagent grade Zn dust. The mixture was refluxed for an additional 8 hr and the product isolated as above. Gas chromatography indicated only one compound. The crude product (0.64 g, 92%) had an IR spectrum identical with starting material. Recrystallization from hexane gave 0.47 g of prisms, m.p. 83–84° undepressed on admixture with authentic 2.

Diels Alder synthesis of 2, 3 and 7. To 3.10 g (0.013 mole) of pentachlorocyclopentadiene,⁴ b.p. 47.5° at 0.19 mm, was added 1.38 g (0.016 mole) of freshly distilled vinyl acetate in 50 ml of *p*-xylene. The reaction mixture was heated at 120° for 8 hr at which time IR spectroscopy indicated the absence of the diene. Evaporation of the solvent gave 4.4 g of a viscous yellow oil that upon gas chromatography (SE-30 column) gave 3 peaks—first compound 3 (47.7% yield), then 2 (45.1% yield), and finally 7 in 7.2% yield. Compound 7 had significant IR bands at 5.72, 7.35, 8.25, 8.42, 9.46, 9.95, 11.35 and 13.40 μ . The NMR spectrum showed a 3 proton singlet at 2.10 ppm assigned to the acetate Me, a sharp singlet at 4.56 ppm assigned to the 7-*anti* proton and chemical shifts and coupling constants for the C-5 and C-6 protons characteristic of *exo* substitution (Table 1) (Found: C, 33.53; H, 2.24. Calc. for $C_9H_7O_2Cl_3$: C, 33.32; H, 2.18%.)

Chromous acetate reduction of 1. Chromous acetate (10 g, 0.059 mole), prepared according to the procedure of Williamson and Johnson,¹² was dissolved in 100 ml AcOH containing 2.5 g (0.0069 mole) of 1 in a 250-ml flask equipped with a reflux condenser and N_2 inlet. The reaction mixture was refluxed for 16 hr under N_2 at which time gas chromatography indicated the absence of 1 (at 4, 8 and 12 hr the percentages of 1 in the reaction mixture were 22%, 7% and 2% respectively). The AcOH was removed at reduced press, the residue dissolved in ether, washed with water, 10% Na_2CO_3 aq. water, and then dried over $MgSO_4$. The ether was removed to leave 2.25 g of a viscous yellow oil which was shown by preparative gas chromatography (SE-30 column) to consist of 78% of 2 and 18% of 3 as shown by collection of the components and comparison of IR spectra.

Catalytic reduction of 1. To an efficiently stirred mixture of 0.05 g of 5% Pd/C and 0.50 g (0.0049 mole) of Et_3N in 5 ml of 95% EtOH, which had been completely hydrogenated, 0.96 g (0.0027 mole) of 1 in 20 ml EtOH was added. The reaction was stopped after the uptake of one mole H_2 . The catalyst was removed by filtration, the EtOH removed under reduced press, and the residue dissolved in ether. The ether soln was washed with dil HCl and water and then dried over $MgSO_4$. Evaporation of the ether gave 0.90 g of a viscous yellow oil. Preparative gas chromatography (SF-96 column, 250°) gave 12 in 33% yield followed by unreacted 1 in 60% yield. The reduced product, 12, had m.p. 55–56° and significant IR bands at 5.72, 8.20, 9.68, 11.30 and 12.85 μ . The IR spectrum in $CHCl_3$ lacked the 6.28 μ olefin band. The NMR spectrum showed a sharp 3-proton singlet at 2.03 ppm (acetate Me), a one-proton multiplet at 5.08 ppm assigned to the proton on the acetate bearing C atom and a complex pattern of peaks between 1.65 and 2.96 ppm (6 protons). Mass spectral analysis at 10 and 70 eV indicated a parent peak at 290 amu corresponding to $C_9H_{10}Cl_4O_2$ and significant fragmentation peaks at 255, 212, 195, 177, 168 and 159 amu along with peaks attributed to starting material. (Found: C, 37.44; H, 3.87. Calc. for $C_9H_{10}Cl_4O_2$: C, 37.02; H, 3.40%.)

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