Olefin Inversion. 2. Sodium Iodide Reductions of *vic*-Bromochlorides and *vic*-Dichlorides

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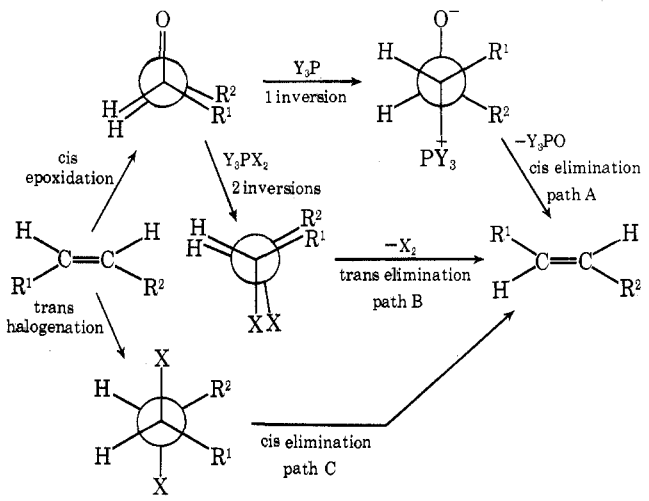
The stereochemistry of sodium iodide dehalogenations of *vic*-bromochlorides and *vic*-dichlorides was investigated and was found to be stereospecifically cis. This is opposite to the previously observed trans eliminations of *vic*-dibromides. It is proposed that the "cis" eliminations involve an initial SN2 displacement of Cl^- or Br^- by I^-, and that the resulting iodohalides then rapidly undergo trans elimination of ICl or IBr. A simple two-step sequence of halogenation (with Cl_2 or BrCl) and dehalogenation (with I^-) thus provides an efficient method of interconverting geometric isomers of olefins.

In the accompanying paper[1] we briefly reviewed methods of inverting geometries of olefins via their epoxides. Procedues that had been previously described involved SN2 openings of the epoxide by phosphides followed ultimately by cis eliminations of the oxygen and phosphorus moieties[2,3] (Scheme I,

Scheme I. Olefin Inversion (Exemplified by *Z*–*E* Conversions)



path A). Unsaturated hydrocarbons and acetates have frequently been identified as insect pheromones,[4] and simple means of inverting double bonds of pheromones would be extremely useful. Unfortunately, the methods just mentioned are not compatible with base-sensitive groups such as esters,[2] and we described complementary methods that did not affect that functional group.[1] In our processes, epoxides were converted to *vic*-dihalides with inversion of configuration at each of the oxygenated carbons (Scheme 1, path B). Trans elimination of the two halogens then provided olefins of geometries opposite those of the initial epoxides.

Reductive eliminations of bromine from *vic*-dibromides initiated either by metals such as zinc[5] or by iodide ion[6] generally proceed in a trans fashion, and have occasionally been utilized as means of purifying olefins via (trans) bromination–(trans) debromination sequences.[7] However, deviations from absolute overall stereospecificity have been noted,[8] a dramatic one being the observation that the ethylene produced by sodium iodide reduction of isotopically labeled 1,2-dibromoethane was formed entirely by a net cis elimination.[9] We noted that *vic*-dichlorides and *vic*-bromochlorides were reduced less readily than were *vic*-dibromides by any of several reagents and that zinc reductions of the less reactive dihalides were less stereoselective than those of the dibromides.[1] In contrast, the NaI/DMF reduction of a *vic*-bromochloride was highly stereospecific, but not in the anticipated (trans) sense: the threo 7,8-bromochlorides of 2-methyloctadecane (a mixture of *threo*-7-bromo-8-chloro and *threo*-8-bromo-7-chloro) were cleanly converted to (*E*)-2-methyl-7-octadecene. Thus a net cis elimination had occurred. This was interesting and appeared potentially useful. Since direct additions of halogens to olefins proceed trans,[10] a general procedure for cis elimination of the added halogens would provide an even simpler means of inverting double bonds (Scheme I, path C). We therefore investigated iodide-promoted eliminations of a few dichlorides, bromochlorides, and dibromides to evaluate their potential for olefin inversions.

Typical NaI reductions of *vic*-dibromides have utilized large excesses of I^- in an alcoholic medium, e.g., refluxing 2-propanol.[11] The only dibromide we investigated, *erythro*-7,8-dibromo-2-methylocatadecane, was completely reduced by excess NaI in DMF at 50–55 °C (overnight). As noted previously, bromochlorides and dichlorides were reduced less readily. Bromochlorides required overnight exposure to a tenfold excess of NaI in DMF at >80 °C for complete reduction, and an entire week was required for the same reaction to proceed to completion in refluxing 2-propanol (82 °C). The *vic*-dichlorides were still less reactive, and refluxing DMF was found to provide a suitable medium. A few other conditions were briefly investigated for NaI reductions of *erythro*-7,8-dichloro-2-methyloctadecane, all employing excess NaI: the reduction was incomplete in refluxing acetonitrile after 4 days, and the reaction in Me_2SO was slow at 90 °C and appeared to offer no advantage over the reactions in DMF or hexamethylphosphoric triamide (HMPA). Indeed, in HMPA reduction was complete (and stereospecifically cis) after 2 h at 100–110 °C. Substitution of LiI for NaI appeared to offer no advantage. The results of I^- reductions of several dihalides are given in Table I. With the exceptions of the single dibromide (entry 10) and the one reaction in 2-propanol (entry 3), the reductions were at least 93% stereoselectively cis, and many were completely stereospecific within the limits of our analyses (2–4%).

Hine[6] has reviewed the subject of NaI reductions of *vic*-dibromides (dichlorides and bromochlorides apparently have not been investigated). Reduction of *meso*-1,2-dibromo-1,2-dideuterioethane gave *cis*-1,2-dideuterioethylene[9] (cis elimination). Since the reaction rate had almost exactly the value expected for nucleophilic displacement of primary bromide by iodide ion,[12] the reaction mechanism was rationalized as involving an initial SN2 displacement of Br^- by I^- followed by nucleophilic attack of a second iodide ion upon the iodine of the resulting *vic*-bromoiodide (Scheme II, path B, R = D). Since such an elimination would be expected to be trans antiplanar, the result is a net cis elimination (one in-

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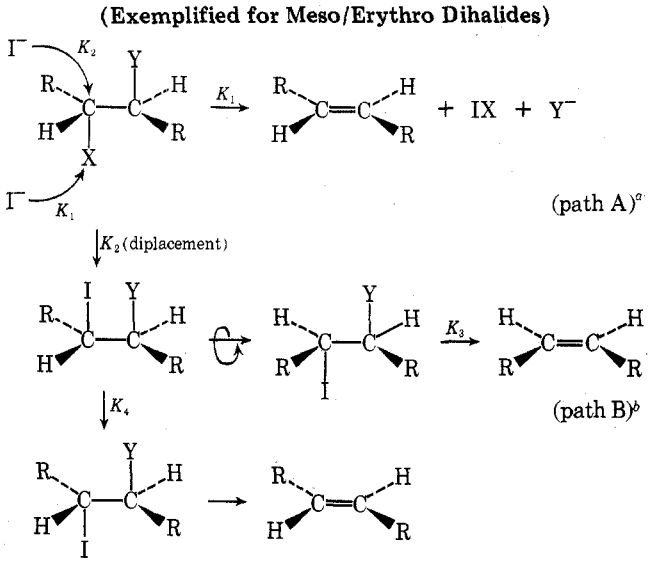
Table I. Elimination of *vic*-Dihalides

Run	Dihalide	Olefin	Conditions	Yield, %	Stereospecificity, %[a]
1	*threo*-7,8-Bromochloro-2-methyloctadecane	(*E*)-2-Methyl-7-octadecene	NaI, DMF, 80 °C, 18 h	*c*	100
2	*erythro*-7,8-Bromochloro-2-methyloctadecane	(*Z*)-2-Methyl-7-octadecene	NaI, DMF, 80 °C, 18 h	88	96
3	*erythro*-7,8-Bromochloro-2-methyloctadecane	(*Z*)-2-Methyl-7-octadecene	NaI, *i*-PrOH, 82 °C, 1 week	*c*	79
4	*threo*-7,8-Bromochlorooctadecane	(*E*)-7-Octadecene	NaI, DMF, 80 °C, 18 h	67	100
5	*erythro*-8,9-Bromochlorododecan-11-ol acetate	(*Z*)-8-Dodecen-1-ol acetate	NaI, DMF, 85 °C, 16 h	95	93
6	*erythro*-7,8-Dichloro-2-methyloctadecane	(*Z*)-2-Methyl-7-octadecene	NaI, DMF, 153 °C, 25 h	95	100
7	*threo*-7,8-Dichlorooctadecane	(*E*)-7-Octadecene	NaI, DMF, 153 °C, 25 h	79	97
8	*erythro*-8,9-Dichlorododecan-1-ol acetate	(*Z*)-8-Dodecen-1-ol acetate	NaI, DMF, 153 °C, 16 h	*c*	93
9	*erythro*-7,8-Dichloro-2-methyloctadecane	(*Z*)-2-Methyl-7-octadecene	NaI, HMPA, 100 °C, 2 h	80	100
10	*erythro*-7,8-Dibromo-2-methyloctadecane	(*E*)-2-Methyl-7-octadecene	NaI, DMF, 50–55 °C, 20 h	*c*	82[d]

[a] Product olefins were epoxidized with *m*-chlorobenzoic acid in CH_2Cl_2, and the epoxides were analyzed by GLC (EGGS-X SCOT column, 1.5 m × 5 mm at 140–170 °C). Unsaturated esters were analyzed directly with this column. [b] *vic*-Bromochlorides are presumably mixtures of positional isomers. For example, *threo*-7,8-bromochlorooctadecane would be a mixture of *threo*-7-bromo-8-chlorooctadecane and *threo*-8-bromo-7-chlorooctadecane. [c] Yield not determined (in several cases the reactions were followed by periodically withdrawing samples for GLC analysis). [d] 82% trans elimination.

Scheme II. Iodide-Induced Eliminations of *vic*-Dihalides (Exemplified for Meso/Erythro Dihalides)

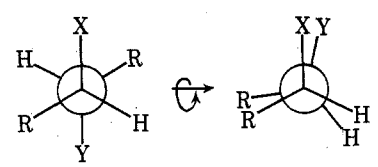


[a] Elimination. [b] Displacement followed by elimination.

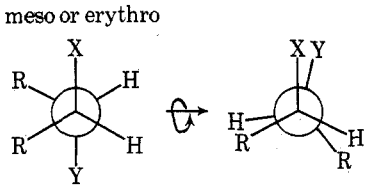
version, trans elimination). The more general case for dibromides of 1,2-disubstituted ethylenes is that of trans elimination.[10] Evidently direct displacement of Br^- by I^- (Scheme II, path B) is less favored than the attack by I^- on bromine with a concomitant expulsion of olefin and bromide (Scheme II, path A). At higher temperatures, losses in stereospecificity for this reaction were observed that were ascribed to a significant contribution from path B.

We feel that the reductions of *vic*-dichlorides and *vic*-bromochlorides probably proceed via path B. Evidently the replacement of bromine by chlorine either markedly increases the susceptibility of the other halogen to SN2 displacement, or, more probably, decreases the ability of the *vic*-dihalide to undergo the concerted reduction (path A). Interestingly, if the presumed intermediate *vic*-iodohalides are to eliminate stereospecifically, it is necessary that the iodide ion attack the bound iodine and initiate the concerted elimination (path B) much faster than it displaces the bound iodine from carbon (thus inverting that center a second time, i.e., $K_3 > K_4$). Yet iodide must first displace a chloride or bromide ion much faster than it can attack a bound bromine or chlorine to initiate a concerted elimination ($K_2 > K_1$). Apparently the nature of the halogen molecule being formed during the concerted elimination step is quite important, and the formation of I_2 is highly favored over that of IBr or ICl.

We also considered the possibility of a cis elimination with both halogens departing, more or less simultaneously, from the same side of the molecule. In the dibromide series, meso compounds react faster with I^- then do their *dl* isomers (trans eliminations), presumably because it is easier to attain the desired trans antiplanar alignment of bromines. If both halogens were to leave from the same side, the threo (or *dl*)



meso or erythro



dl or threo

isomer should more easily attain the conformation with the halogens in close proximity, and thus undergo cis elimination more readily.

Accordingly, we compared the rates of reaction of the *erythro*- and *threo*-4-bromo-5-chlorooctanes with NaI in DMF at 80–85 °C. The two reactions were run simultaneously under identical conditions, and were followed by gas chromatographic analysis of quenched aliquots. Although absolute temperature control of the heating bath was not precise enough to allow the calculation of a meaningful rate constant,

it was evident that the erythro isomer was reduced more rapidly. Thus we have no evidence to support any kind of concerted cis elimination of halogen.

The dihalides we initially reduced with NaI were those synthesized from epoxides as described in the accompanying paper.[1] Since their preparation had involved two SN2 reactions on epoxides, cis elimination of halogen simply regenerated the olefin from which the epoxide had been prepared. To illustrate the utility of the cis eliminations for olefin inversions we subjected several olefins to the two-step halogenation–dehalogenation sequence. Chlorinations of 1,2-disubstituted ethylenes can generally be controlled,[13] and entries 8 and 9 in Table I describes results of reductions of dichlorides prepared in that manner. Both the unsaturated acetate and the unsaturated hydrocarbon were efficiently inverted by this simple sequence. *erythro*-7,8-Dichloro-2-methyloctadecane, entry 9, was prepared both by chlorination of the corresponding *E* olefin and by treating *trans*-7,8-epoxy-2-methyloctadecane [the sex pheremone of the gypsy moth, *Porthetria dispar* (L.)] with triphenylphosphine dichloride.[1] Identical results were realized from both pathways.

Hageman and Havinga[14] described the in situ preparation of bromine chloride and the trans addition of the mixed halogen to several cyclohexene derivatives. We found their method, which consists of simply adding *N*-bromosuccinimide to a HCl-saturated solution of the olefin, both efficient and convenient. For example, the *erythro*- and *threo*-4-bromo-5-chlorooctanes were synthesized in 82 and 73% yields from (*E*)- and (*Z*)-4-octenes, respectively; the isomers were readily distinguished by gas chromatography, and each bromochloride was found to be free of its isomer. Entry 5, Table I illustrates an application to the principal component of the sex pheromone of the oriental fruit moth, *Grapholita molesta* (Busck). (*E*)-8-Dodecen-1-ol acetate was converted to the erythro bromochloride, and the bromochloride was treated with NaI/DMF without purification. (*Z*)-8-dodecen-1-ol acetate was obtained in an overall yield of 93%; the conversion was >93% stereospecific.

To date these methods have been successful only for inversions of 1,2-disubstituted olefins. We briefly examined (*E*)-3-methyl-3-hexene; predictably,[13] however, chlorination provided primarily substitution instead of addition products. Hageman and Havinga[14] successfully added BrCl to several 1-alkylcyclohexenes, but our single attempt to apply their procedure to (*E*)-3-methyl-3-hexene was unsuccessful since HCl addition to the double bond evidently occurred faster than BrCl was generated.

Experimental Section[15]

General experimental details (instrumentation, GLC analyses, epoxidation procedures, etc.) are described in the accompanying paper.[1]

***vic*-Bromochlorides** were prepared from epoxides as described,[1] or from olefins by the HCl–*N*-bromosucciminide method.[14] For the latter conversions, a solution of the olefin in CH_2Cl_2 (10 ml/g of olefin) was cooled to −78 °C and was saturated with anhydrous HCl. Freshly recrystallized (H_2O) *N*-bromosuccinimide (1.05 mol/mol of olefin) was added in a single portion, and the mixture was stirred and allowed to warm slowly to ca. −20 °C (while maintaining saturation of HCl). After the mixture assumed a permanent color, it was poured onto a mixture of ice and aqueous $NaHSO_3$. The layers were separated, and the organic phase was washed with H_2O, aqueous $NaHCO_3$, and again with H_2O; then it was dried ($MgSO_4$) and concentrated. The bromochlorides thus obtained were sufficiently pure for NaI reductions. Trans addition of the two halogens was established by applying the procedure to (*E*)- and (*Z*)-4-octenes (purchased from Chemical Samples Co.). In these cases the products were distilled; the former gave an 82% yield of *erythro*-4-bromo-5-chlorooctane, bp 100–105 °C (25 mm); the latter gave a 73% yield of *threo*-4-bromo-5-chlorooctane, bp 107–112 °C (24 mm). The isomeric bromochlorides were identical with those prepared from the epoxides,[1] and each isomer appeared to be free of the other as judged by gas chromatography (Carbowax or DEGS) whereby 5% would have been readily detected.

***vic*-Dichlorides** were prepared by bubbling Cl_2 through CH_2Cl_2 solutions of the appropriate olefins at −78 °C until a yellow color persisted, warming to ca. −20 °C, and following the workup procedure described for bromochlorides. Crude dichlorides were reacted with NaI without purification.

Sodium Iodide Reductions of *vic*-Dihalides. Typically, the dihalides (1 g) and NaI (10 g) were combined in DMF (or HMPA) (50 ml), and the resulting solutions were heated as described in Table I. It was convenient to follow the reactions by perioically withdrawing small aliquots and shaking them with hexane and H_2O; the hexane layer was examined by GLC for disappearance of dihalide. Workup consisted of cooling the dark solutions, pouring into H_2O, and extracting with hexane. The organic layers were washed with aqueous $NaHSO_3$, then washed twice with H_2O, and finally were dried and concentrated. The olefins thus obtained were purified by distillation or column chromatography on silica gel or were epoxidized directly for GLC analysis.

Comparative Eliminations of *erythro*- and *threo*-4-Bromo-5-chlorooctanes. Reaction mixtures containing the appropriate bromochloride (100 mg), 1-tetradecene (100 mg), NaI (1.00 g), and DMF (10.0 ml) were prepared in 25-ml flasks, and the flasks were heated simultaneously in an oil bath maintained at 78–85 °C. Aliquots (0.10 ml) were removed from each flask after 0, 1, 2, 4, and 7 h and added to small vials containing water (0.3 ml) and hexane (0.3 ml). The vials were shaken, and the hexane layers were withdrawn by pipet and analyzed by gas chromatography (SE-30, 125 °C). Peak areas of remaining bromochlorides and of the tetradecene standard were measured by planimetery. Although smooth curves were not obtained, it was evident that the erythro isomer reacted approximately twice as fast as did the threo isomer (that the erythro compound reacted faster was also apparent by visually observing the formation of iodine in the reaction mixtures).

Registry No.—*threo*-7-Bromo-8-chloro-2-methyloctadecane, 59840-17-4; *threo*-7-chloro-8-bromo-2-methyloctadecane, 59840-18-5; *erythro*-7-bromo-8-chloro-2-methyloctadecane, 59840-19-6; *erythro*-7-chloro-8-bromo-2-methyloctadecane, 59840-20-9; *threo*-7-bromo-8-chlorooctadecane, 59840-21-0; *threo*-7-chloro-8-bromooctadecane, 59840-22-1; *erythro*-8-bromo-9-chlorododecan-1-ol acetate, 59840-23-2; *erythro*-8-chloro-9-bromododecan-1-ol acetate, 59840-24-3; *erythro*-7,8-dichloro-2-methyloctadecane, 59840-25-4; *threo*-7,8-dichlorooctadecane, 59840-26-5; *erythro*-8,9-dichlorododecan-1-ol acetate, 59840-27-6; *erythro*-7,8-dibromo-2-methyloctadecane, 59840-28-7; *erythro*-4-bromo-5-chlorooctane, 59840-29-8; *threo*-4-bromo-5-chlorooctane, 59840-30-1; NaI, 7681-82-5.

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