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THE STEREOCHEMISTRY OF THE HYDROGENOLYSIS OF ARYL OXIRANES

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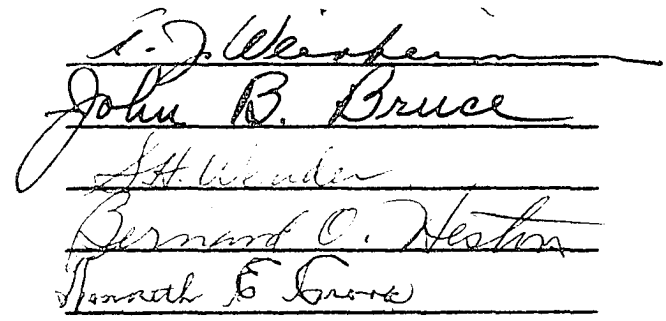
THE STEREOCHEMISTRY OF THE HYDROGENOLYSIS OF ARYL OXIRANES

APPROVED BY



DISSERTATION COMMITTEE

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To Mother and Dad

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THE STEREOCHEMICAL COURSE OF THE HYDROGENOLYSES OF ARYL OXIRANES

INTRODUCTION

There is a considerable body of data available on the stereochemistry involved in the catalytic hydrogenation of carbon-carbon multiple bonds (1, 2), but certain other aspects of the catalytic action of metal catalysts have received comparatively little attention, particularly the stereochemistry of hydrogenolysis reactions.

In general Raney nickel is the most useful catalyst for hydrogenolyses. This catalyst is particularly effective in the hydrogenolysis of carbon-sulfur bonds since ordinary catalysts, as Pd or Pt, are poisoned by sulfur compounds.

$$Ar\text{-}\overset{O}{\overset{\|}{C}}\text{-}SR \xrightarrow{Ra.Ni} ArH + Ar\text{-}Ar + RSH \qquad (3)$$

$$Ar\text{-}SH \xrightarrow[EtOH]{Ra.Ni} ArH \qquad (4)$$

$$\phi_2C(SEt) \xrightarrow[EtOH]{Ra.Ni} \phi CH_2\text{-}\phi \qquad (5)$$

Raney nickel catalyzed hydrogenolyses also occur with resultant cleavage of many carbon-halogen, and benzyl-nitrogen and benzyl-oxygen bonds, either with added hydrogen or hydrogen adsorbed on the catalyst. The more common examples are of a debenzylation type.

$$\phi\text{-}\overset{\text{Me}}{\overset{|}{C}}(Cl)\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH_2 \xrightarrow[EtOH]{Ra.Ni} \phi\text{-}\overset{\text{Me}}{\overset{|}{C}}H\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH_2 \qquad (6)$$

$$\phi_2C(Cl)\text{-}COOEt \xrightarrow[EtOH]{Ra.Ni} \phi_2CH\text{-}COOEt \qquad (7)$$

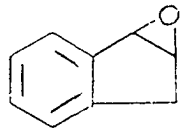
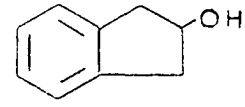
$$pHO\text{-}C_6H_4\text{-}CH_2\text{-}\overset{\text{Me}}{\overset{|}{N}}\text{-}CH_2\phi\cdot HCl \xrightarrow[EtOH]{Ra.Ni,H_2} p\text{-}HO\text{-}C_6H_4\text{-}CH_2\overset{\text{Me}}{\overset{|}{N}}H\cdot HCl \qquad (8)$$

$$(\phi CH_2)_2N\text{-}(CH_2)_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}Me \xrightarrow[NH_3]{Ra.Ni,H_2} \phi CH_2\text{-}NH\text{-}(CH_2)_3\text{-}\overset{\text{Me}}{\overset{|}{C}}H\text{-}NH_2 \qquad (9)$$

$$o\text{-}Me\text{-}C_6H_4\text{-}O\text{-}CH_2\text{-}\phi \xrightarrow[200\ atm.]{Ra.Ni,H_2} o\text{-}Me\text{-}C_6H_4\text{-}OH \qquad (10)$$

$$o\text{-}MeOOC\text{-}C_6H_4\text{-}O\text{-}CH\text{-}\phi \xrightarrow[200\ atm.]{Ra.Ni,H_2} o\text{-}MeOOC\text{-}C_6H_4\text{-}OH \qquad (10)$$

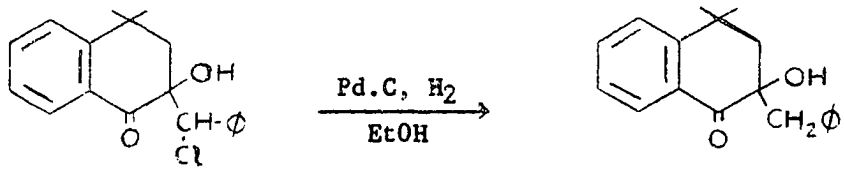
$$\phi\text{-}\overset{O}{\overset{/\ \backslash}{CH}}\text{—}CH_2 \xrightarrow[EtOH]{Ra.Ni,H_2} \phi\text{-}CH_2\text{-}CH_2OH \qquad (11)$$

$$\xrightarrow[EtOH]{Ra.Ni,H_2} \qquad (12)$$

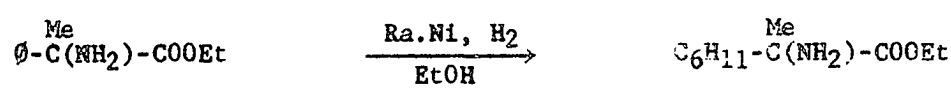
Those hydrogenolyses catalyzed by palladium-charcoal are more uniquely of a debenzylation type (i.e., cleavage of a C-X bond where C is a benzyl carbon atom and X is halogen, O, or N), although halogen is occasionally lost from an aromatic ring. As was mentioned above Pd is not effective in the hydrogenolysis of sulfur compounds. Two typical examples of the Pd.C catalyzed debenzylation reaction involving cleavage of the carbon-chlorine bond are:

$$\phi_2C(Cl)\text{-}COOEt \xrightarrow[EtOH]{Pd.C,\ H_2} \phi_2C(H)\text{-}COOEt \qquad (7)$$

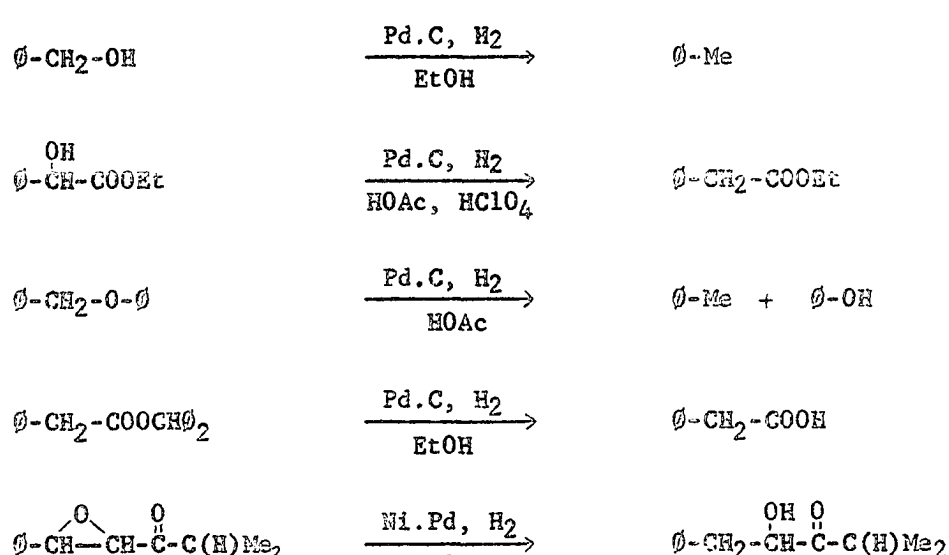


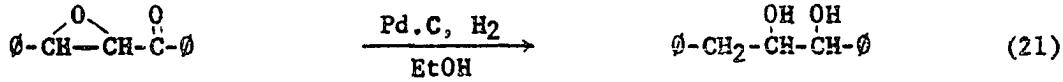
(13)

Dahn (14, 15) has shown that certain benzyl amines (benzyl, p-phenylbenzyl, benzhydryl, and 9-fluorenyl amines), as their hydrochlorides, undergo palladium-charcoal catalyzed replacement of the amino group by hydrogen. Dahn (14) found that palladium gave a cleaner reaction than Raney nickel since the latter gave ring hydrogenation as well as hydrogenolysis. This observation is supported by Bonner (6). Ethyl 2-phenyl-2-aminopropionate on treatment with Raney nickel in refluxing ethanol gave ethyl 2-cyclohexyl-2-aminopropionate.



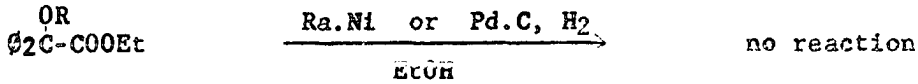
A few typical examples of palladium catalyzed benzyl carbon-oxygen cleavage are shown in the following equations.





(21)

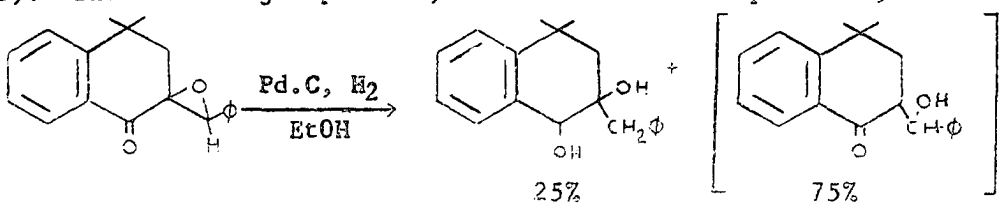
Isogai (7) found that no reaction occurred in the attempted hydrogenolysis of an ester of benzilic acid or its derivatives in the presence of either Raney nickel or palladium. This lack of reaction was attributed



(where R is H, Ac, Ø, or Bz)

to the combined effects of steric hindrance of the reduction site and to the strength of the benzyl carbon-oxygen bond. Isogai explained the ease of hydrogenolysis of the chloro-ester (see above) by assuming a chlorine compound was more strongly adsorbed to the catalyst surface than the analogous oxygen derivatives.

An apparent deviation in the generally observed benzyl carbon-oxygen cleavage of the debenzylation reaction has been demonstrated by Cromwell (13). The crude major product, which could not be purified, was assigned



the bracketed structure from its infrared spectrum and weak chemical evidence.

Little racemization should be effected in low temperature hydrogenolysis if the group which is removed is not attached to an asymmetric carbon atom. Thus, the Raney nickel desulfuration of derivatives of mercapto amino acids (derivatives of cysteine, for example) leads to optically pure amino acids (22, 23). Similarly, cleavage by Raney

nickel of the tosyl group in optically active 2-sec-butylphenyl-p-toluenesulfonate affords 2-phenylbutane with negligible loss of optical purity (24). And the hydrogenolysis of 2-bromo-cis-decalin with Raney nickel and hydrogen at room temperature gave pure cis-decalin (25). In this last example lack of epimerization rather than lack of racemization diagnosed the stereochemistry.

However, it has been found by Bonner (26) that slow racemization of compounds such as (+)-ethyl 2-phenylpropionate and (+)-2-phenylpropionamide occurs under the influence of Raney nickel in boiling ethanol. Bonner (27) also noted that in hydrogen-deuterium exchange studies of (+)-2-phenylpropionamide, the α-deuterated product was formed with 14% loss of optical purity at the asymmetric center. When optically active 3-methylhexane was passed over nickel on kieselguhr at 90-130°, Burwell (28) found that the recovered 3-methylhexane was optically inactive. Racemization of this type appears to require dehydrogenation-hydrogenation at the asymmetric center.

In contrast, there are no known examples of deuterium exchange with carbon bound hydrogen over palladium on charcoal catalyst. Thus, e.g., the conversion of a carbonyl adjacent to a benzene ring to a methylene group, via the alcohol, by the palladium on charcoal hydrogenolysis of optically active α-phenyl-β-benzylpropionic acid gives a product of high optical purity (29).

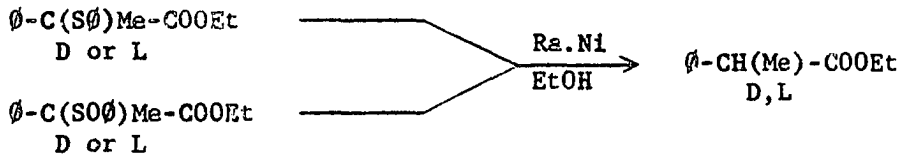
The hydrogenolysis of optically active N-benzyl-1-amino-2-propanol with palladium on charcoal gave 1-amino-2-propanol of high rotation, but the data given did not permit conclusions about the degree of racemiza-

tion, if any, which occurred (30). The palladium on charcoal catalyzed hydrogenolysis of an essentially optically pure sample of α,α'-dimethyldibenzylamine gave α-methylbenzylamine of 97.5% optical purity (31).

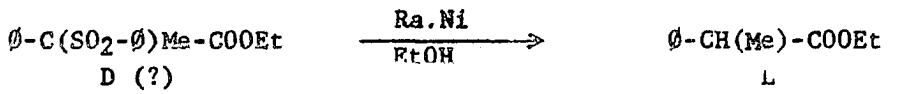
These reactions demonstrate that hydrogenolysis often may be effected without racemization when the asymmetric carbon is more or less remote from the site of reaction.

Those compounds in which the group being hydrogenolyzed is attached to the asymmetric carbon atom are of more fundamental interest since the stereochemical course of the reaction should provide a basis for the interpretation of the hydrogenolysis mechanism. A wide variety of stereochemical results have been reported from such studies. The conclusions on the mechanisms are frequently divergent, and the situation is quite complex. Some of the most pertinent available examples are derived from atrolactic acid (2-phenyl-2-hydroxypropionic acid) and hydratropic acid (2-phenylpropionic acid).

Bonner and other workers have investigated the hydrogenolysis of several optically active derivatives of these acids by refluxing the reactant with excess Raney nickel in ethanol, a method somewhat different from the usual room temperature, low pressure catalytic hydrogenolysis conducted in a Parr apparatus. Bonner found that the optically active ethyl esters of the α-thio ether (32) and α-sulfoxide (33) derived from hydratropic acid gave inactive products. Bonner (32, 33) proposed a free radical mechanism for the reductive desulfurations. This mechanism was thought to be consistent with the complete racemization observed.



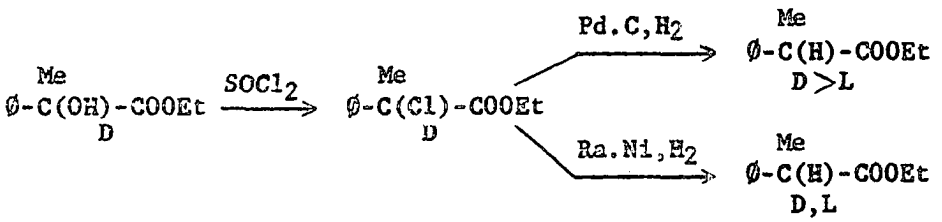
Bonner (32) found that the ethyl ester and amide of the corresponding α-



sulfone gave optically active products with some loss of optical purity. He proposed that the reaction involved inversion of configuration, but the configurational relationship of reactant and product was not certain. Bonner explained this course of reaction as occurring via an S_N2 like attack of a hydride from the catalyst surface on the side of the adsorbed species (adsorption occurring through the oxygen atoms of the sulfone, the benzene ring, and the carbonyl oxygen). He noted that since the reductive dusulfuration of sulfides and sulfoxides prceeded with complete racemization, these compounds could not be intermediates in the reductive desulfuration of sulfones. Imaizumi (34, 35) obtained similar results.

Ott (36) showed that the chloro-ester formed (presumably with retention of configuration) by the action of thionyl chloride on optically active ethyl atrolactate suffered hydrogenolysis upon treatment with hydrogen on palladium-charcoal. The resulting active ethyl 2-phenylpropionate had the same configuration as the ethyl atrolactate (37), but the retention of optical purity was low--12% when the hydrogenolysis was conducted in glacial acetic acid and 9% when the hydrogenolysis was conducted in ether. Imaizumi (38) found that when this hydrogenolysis

was conducted in ethanol using 1% palladium on charcoal and 10% palladium on charcoal, the retention of optical purity was 13% and 16% respectively. He also found that the Raney nickel hydrogenolysis of the chloro-ester in ethanol gave a completely inactive product.



Imaizumi (38) attributed the high degree of racemization to radical cleavage of the carbon-chlorine bond due to the strong chemisorption of chlorine to the catalyst surface. To account for the small amount of retention of configuration he proposed an S_Ni mechanism in which the frontside displacement of the chlorine in the adsorbed reactant by a hydrogen species from the catalyst surface would give the retention observed.

Bonner (6) found that the methyl and ethyl esters of optically active atrolactic acid gave esters of 2-phenylpropionic acid with predominant retention of configuration, and 15 to 30% loss of optical purity. He found the methyl ethers behaved similarly.

$$\underset{L}{Ø\text{-}C(OH)Me\text{-}COOR} \xrightarrow[EtOH]{Ra.Ni} \underset{L}{Ø\text{-}C(H)Me\text{-}COOR}$$

$$\underset{L}{Ø\text{-}C(OMe)Me\text{-}COOR} \xrightarrow[EtOH]{Ra.Ni} \underset{L}{Ø\text{-}C(H)Me\text{-}COOR}$$

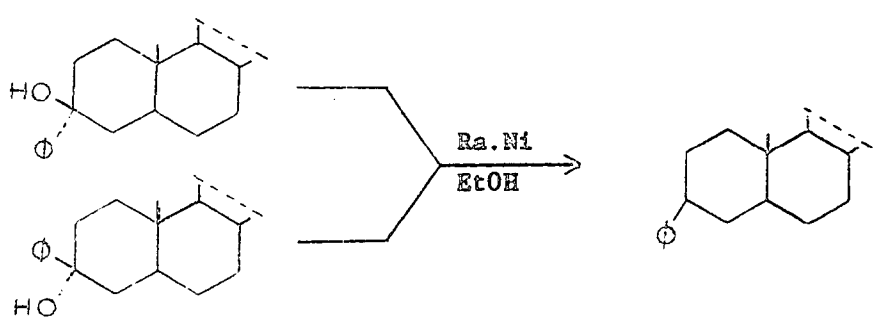
Imaizumi (38) obtained similar results from the hydrogenolysis conducted in a Parr low pressure apparatus at room temperature.

Bonner (6, 26) proposed that the course of reaction was consistent with either an adsorbed carbonium ion, formed on the catalyst, which abstracted a hydride ion from its surface, or a concerted front side attack by the hydride ion on the adsorbed substrate (an S_Ni type reaction). From work with the corresponding sulfide derivatives (32) Bonner assumed that racemization would have occurred if a free radical had been formed.

Cram and Allinger (39) found that optically active 2-hydroxy-2-phenylbutane on refluxing with Raney nickel in ethanol gave 2-phenylbutane of 64% optical purity and with retention of configuration. The optical purity of the alcohol was not known with certainty since it was made by a several step synthesis from optically pure 2-methyl-2-phenylbutyric acid.

$$\text{Me-}\overset{\overset{\text{Ø}}{|}}{\text{C}}\text{(Et)-COOH} \xrightarrow[\text{steps}]{\text{several}} \text{Me-}\overset{\overset{\text{Ø}}{|}}{\underset{\text{D}}{\text{C}}}\text{(Et)-OH} \xrightarrow[\text{EtOH}]{\text{Ra.Ni}} \text{Me-}\overset{\overset{\text{Ø}}{|}}{\underset{\text{D}}{\text{C}}}\text{(Et)-H}$$

Zderic (40) has shown that both isomers of 3-phenylcholestan-3-ol on refluxing with Raney nickel in ethanol readily undergo hydrogenolysis, the 3β-phenylcholestan-3α-ol with retention of configuration, and the 3α-phenylcholestan-3β-ol with inversion of configuration, each leading to the thermodynamically more stable 3β-phenylcholestane, in which the phenyl residue is disposed in the equatorial position.



Zderic pointed out that while it was not impossible that the configurational inversion encountered in the one case resulted from an S_N2 displacement, molecular models would not seem to support such a conclusion due to the inaccessibility of the back (alpha) side of C-3 (axial orientation of the phenyl group). He stated that a more feasible explanation may be that the catalyst adsorption occurs principally on one face of the benzene ring with the general plane of the steroid molecule being suspended perpendicularly to the surface of the catalyst. This adsorbed intermediate could then undergo dehydroxylation to produce an adsorbed "species" which, if it accepted hydrogen from the catalyst, could lead to a reaction product maintaining the original configuration. However, to explain the inversion Zderic speculated that once the reactive species had been formed the adsorption energy binding it to the surface of the catalyst was less than the repulsion energies involved in the 1:3 non-bonded interactions of the axial 3α-phenyl group. This would lead to desorption from the catalyst surface, whereupon the 3α-phenyl group would become free to assume the thermodynamically more stable 3β-equatorial position. The process could then be completed by the addition of a hydrogen species obtained either from the solvent or by readsorption to the catalyst surface.

In contrast to the retention of configuration observed by Bonner (6), and later by Imaizumi (38), in the Raney nickel dehydroxylation and demethoxylation of optically active atrolactate esters, Mitsui and Imaizumi (34, 41, 42) found that the low pressure Raney nickel hydrogenolysis of the phenyl ether, and indeed all aryl ethers investigated,

of ethyl atrolactate gave a product of over 90% optical purity and of inverted configuration. Inversion was similarly observed (34) with the acetate (67% retention of optical purity), propionate (82%), and benzoate (34%) derivatives of optically active atrolactate esters.

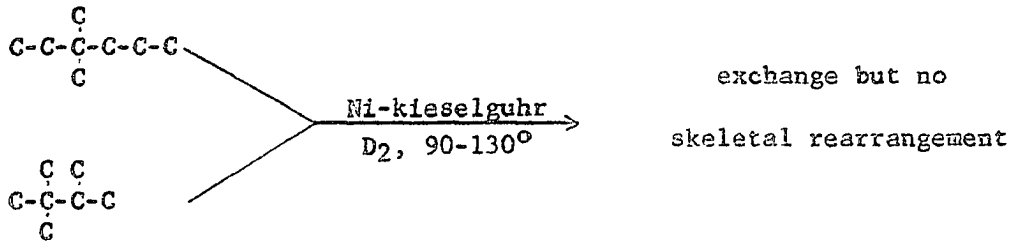
$$\underset{D}{\text{Ø-C(OAr)Me-COOEt}} \xrightarrow[EtOH]{Ra.Ni,\ H_2} \underset{L}{\text{Ø-C(H)Me-COOEt}}$$

$$\underset{D}{\text{Ø-C(O-CO-R)Me-COOEt}} \xrightarrow[EtOH]{Ra.Ni,\ H_2} \underset{L}{\text{Ø-C(H)Me-COOEt}}$$

The mechanisms proposed by Mitsui and Imaizumi (34, 41, 42) for the Raney nickel hydrogenolysis of optically active Ø-C(X)Me-COOEt, where X is OH, OR, OAr, OCOR, SAr, SOAr, SO_2Ar, or Cl, were based upon two factors: the strength of adsorption of the X group on the catalyst surface, and the steric requirements of the other adsorbing groups, i.e., the size and number of groups on the benzyl carbon which will be adsorbed to any extent on the catalyst surface. These authors stated that the observation of complete racemization in the hydrogenolysis of thiol ethers and sulfoxides indicated the initial fission of the C-S bond forming the fragments C^+, S^- or $C\cdot$, $S\cdot$, caused by the strong chemisorption of the sulfur on the catalyst. This explanation was considered consistent with the observation of partial racemization of chlorine-containing compounds which are adsorbed on the catalyst more strongly than oxygen-derivatives (7), but less strongly than sulfur-compounds. It has been proposed by Imaizumi (38) that in the case of Ø-C(X)Me-COOEt (where X is OH, OMe, or Cl) the phenyl, carbethoxy, and X groups may be adsorbed on a surface of the catalyst

holding the asymmetric carbon near the surface with the attack of a hydride ion from the catalyst surface completing the hydrogenolysis according to an S_Ni mechanism (frontside displacement) with retention of configuration. In the case of Ø-C(XAr)Me-COOEt, where X is O or SO_2, the adsorption of X and Ar on the catalyst surface determine a plane, making impossible the adsorption of the Ø- and carbethoxy groups on the same surface. Imaizumi stated that these latter two groups were considered to adsorb on another surface of the catalyst, which provided a hydride ion to attack the asymmetric center from the rear of the XAr group according to an S_N2 mechanism and thus complete the hydrogenolysis with accompanying Walden inversion.

However, from isomerization and hydrogen (or deuterium) exchange studies, Burwell (2, 28) cited evidence which opposed the formation of a carbonium ion on metallic surfaces at low temperatures. The absence of species behaving like carbonium ions was indicated by the fact that the rate of the nickel catalyzed hydrogen or deuterium exchange reaction of 3-methylhexane and heptane were very nearly the same (in a carbonium ion mechanism the 3-methylhexane would be expected to react at rates very much greater than those of heptane). Burwell (2) favored a free radical mechanism and explained the retention observed in some



$$C\text{-}C\text{-}C\text{-}C\text{-}C\text{-}C\text{-}C \xrightarrow[D_2,\ 90\text{-}130^{\circ}]{\text{Ni-kieselguhr}} \text{exchange but no skeletal rearrangement}$$

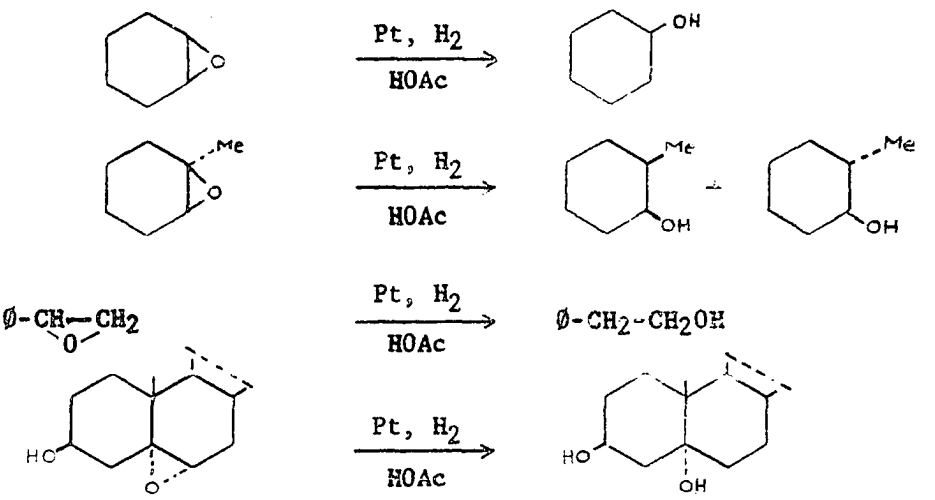
$$\begin{matrix} & & C & & \\ C\text{-}C\text{-}C\text{-}C\text{-}C\text{-}C & & & & \\ & & D & & \end{matrix} \xrightarrow[H_2,\ 90\text{-}130^{\circ}]{\text{Ni-kieselguhr}} \begin{matrix} & & C & & \\ C\text{-}C\text{-}C\text{-}C\text{-}C\text{-}C & & & & \\ & & D,L & & \end{matrix}$$

cases as occurring via "unfree" free radicals. As written, the reaction

$$RX + \begin{matrix} H & H \\ | & | \\ * & * \end{matrix} \longrightarrow \begin{matrix} R & X & H & H \\ | & | & | & | \\ * & * & * & * \end{matrix} \longrightarrow RH + HX$$

would proceed with retention of configuration, but the half-hydrogenated state R--*, is subject to racemization, as for example, via olefin formation by loss of a second hydrogen with subsequent addition of two hydrogen atoms to either side of the double bond. Burwell states such side reactions of R--* before final desorption are indicated by the reaction between (+)-phenylpropionamide and deuterated Raney nickel (27) where both exchange and racemization occur (26). However, it should be pointed out that the exchange reaction occurs much faster than racemization (see above). Burwell (2) also argued that the carbonium ion course could not be general since Raney nickel readily removed bromide from the bridgehead position of adamatane (43), a system incapable of adopting the planarity necessary to carbonium ions. In this last case, the reaction of necessity proceeded with retention of configuration.

McQuillin and Ord (44) showed cyclohexene oxide, 1-methylcyclohexene oxide, styrene oxide, and 5,6-oxidocholestan-3β-ol at platinum in acetic acid were reduced at a satisfactory rate. With the same catalyst in ethyl acetate hydrogen uptake was slow but addition of a trace of sulfuric acid initiated rapid absorption with the reactions proceeding to give the same products.

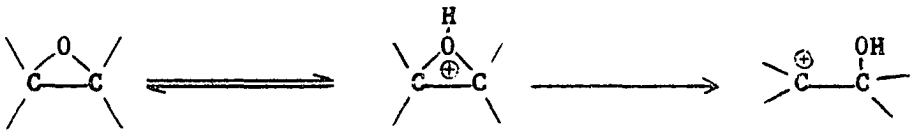


These workers felt it seemed reasonable to attribute the parallel effect of acidified ethyl acetate and acetic acid to acid catalysis.

These authors reported in a survey of steroid oxide hydrogenolysis that the simple steroid oxide hydrogenolysis had two interesting features: the principal product was, as a rule, the derived axial alcohol (via a "diaxial opening" of the oxide in which the developing hydroxyl group and the incoming hydrogen group adopt axial orientations), and the solvent had an important influence on rate of reaction and sometimes on the course of reaction.

They also pointed out a reaction sequence of acid-induced oxide $\longrightarrow$ ketone rearrangement followed by reduction would not provide a general interpretation for results of catalytic hydrogenolysis in acidic media: a cholestan-5α-ol could not arise in this way (as in the case of the hydrogenolysis of 5,6-oxidocholestan-3β-ol to cholestan-3β,5α-diol); a keto group reduction would not give exclusively the axial alcohol (45); such rearrangement could be induced by strong acid (46), but only exceptionally by acetic acid (47).

McQuillin and Ord favored the following sequence:



with initial protonolysis and ring opening in acid solution to provide a cationic intermediate intrinsically more reducible than the oxide, and a priori permitting hydrogen transfer to either face of the molecule. The mixed product from 1-methylcyclohexene oxide (the products were nearly equal amounts of cis- and trans- 2-methylcyclohexanols), and stereospecific reduction of the steroid oxides, dependent on axial opening (48) and hydrogen transfer to the less hindered face, were consistent with this model.

McQuillin and Ord did not state which feature (the diaxial opening or the acid catalysis) was predominant when competition was possible in the stereochemical course of the hydrogenolysis of steroid oxides. It would appear that the course of this reaction, from the single steroid oxide they investigated, was determined by the diaxial opening since acid-catalyzed opening of the oxide ring followed by reduction should give coprostan-3β,6α-diol.

No studies have been made on the stereochemical course of the hydrogenolysis of aryl oxiranes. In such a study, the hydrogenolysis of the oxide oxygen from the benzyl position, on the basis of benzyl dehydroxylations and demethoxylations, should be a stereospecific reaction. Thus, the reaction could be useful in correlations of configurations, and could provide further information on the mechanisms of hydrogenolysis reactions.

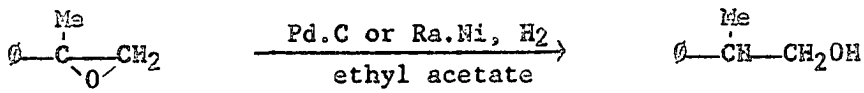
If the hydrogenolysis was found to be stereospecific, then it could be tested in a properly chosen aryl steroid oxirane to see which of the two predicted courses of reaction, "diaxial opening" or "debenzylation", would predominate.

PART I. α-METHYL STYRENE OXIDE

DISCUSSION

In the present work a study of the stereochemical course of the catalytic hydrogenolysis of oxiranes was made. The system chosen for this work was α-methyl styrene oxide (α,β-epoxy cumene). This oxide would be expected, on the basis of previous work, to undergo hydrogenolysis at the benzyl position (a so-called debenzylation reaction) to give 2-phenyl-1-propanol. Moreover, the stereochemical result of the reaction could be determined since the configuration of the compounds in the series were known or could be related easily.

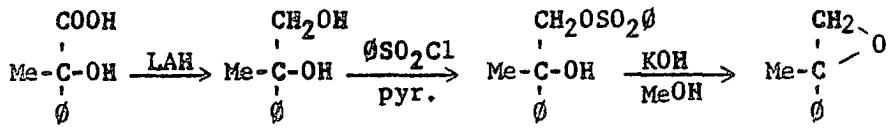
At the outset, it was confirmed that α-methyl styrene oxide (Dow free sample) did undergo hydrogenolysis in the expected fashion. With either palladium on charcoal or W-5 Raney nickel (49) in ethyl acetate, the hydrogenolysis formed 2-phenyl-1-propanol as the only isolable product. The alcohol was identified as its tosylate derivative and was found to be identical in every respect with the tosylate derivative of 2-phenyl-1-propanol prepared from the lithium aluminum hydride reduction of 2-phenyl-1-propanol (hydratropaldehyde).



Although optically active α-methyl styrene oxide had not been reported at the beginning of this work, its synthesis from atrolactic acid using the method Eliel (50) employed for the preparation of optically active styrene oxide appeared to be feasible. This approach was explored using optically inactive materials, and indeed was found to be a good method for the formation of the oxide.

Synthesis of Optically Active α-Methyl Styrene Oxide

The method of synthesis of optically active α-methyl styrene oxide from optically active atrolactic acid was an adaptation of that which Eliel and Delmonte (50) used in converting (-)-mandelic acid to (+)-styrene oxide, and which we later learned had also been used by Eliel and Ryan (54) in the synthesis of optically active α-methyl styrene oxide.



Optically active atrolactic acid was prepared initially by the method of Smith (51), using active α-methylbenzylamine as the resolving agent. During the course of this resolution, it was found that by a simple modification of his procedure both forms of atrolactic acid, of high activity and in good yields, could be obtained without the usual tedious fractional crystallization, and required only one base as opposed to the two usually needed for both forms. This improvement was made possible by the fact that the active form of the acid is considerably more soluble in dilute hydrochloric acid than the (±)-form. On cooling the solution obtained by decomposing the once recrystallized

(-) acid, (+) base salt (obtained from (±)-atrolactic acid and (+)-α-methylbenzylamine) with excess hydrochloric acid, a small amount of the (±)-acid separated permitting isolation of 90.5% (52) optically pure (-)-acid in 54% yield, increased from the calculated 72% activity of the total acid present in the salt. The mother liquors from the resolution, after similar removal of (±)-acid, afforded 84.4% optically pure (+)-acid in 56% yield, markedly increased from the calculated 37% optical purity of the acid remaining in this fraction.

A study of the change in optical purity of partially active atrolactic acid on recrystallization from several solvents was made. In each case a 3% solution of 44.6% optically pure acid was chilled, the deposited (±)-acid filtered, and the optical purity of the acid remaining in solution was calculated. In water, the optical purity of the active acid was raised to 69%; in 3 N HCl, the optical purity was raised to 81%; and in concentrated HCl, the active acid remaining in solution was found to be 89.2% optically pure. In the latter case solution of the partially active acid was effected only after prolonged heating and considerable loss of HCl vapor. The failure of the same type of fractional crystallization to separate as well the (±) and active forms of atrolactic acid using water as a solvent, emphasized the unique properties of the mineral acid used as solvent in this work.

The lithium aluminum hydride reduction of (+)-atrolactic acid, optical purity 85%, in tetrahydrofuran gave crude (+)-2-phenyl-1,2-phenyl-1,2-propanediol, optical purity 82.8% (53) presumably slightly low because no purification was performed, in 90% yield. The value for the percent optical purity of the glycol was based on the maximum value of

8.94° reported by Eliel (53) for material recrystallized to constant melting point and presumed maximum optical rotation. A similar reduction of inactive material in which ether was used as a solvent gave the crude glycol in 74% yield (Eliel reported the reduction in ether gave glycol in 69% yield).

The crude (+)-glycol on reaction with an equimolar quantity of benzene sulfonyl chloride in pyridine was converted to (+)-2-phenyl-1,2-propanediol-1-benzenesulfonate having a specific rotation of 9.74°, and calculated to be 85% optically pure based upon the maximum value of 11.44° observed for a similar sample after multiple recrystallizations.

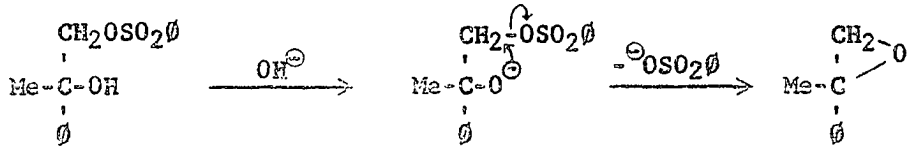
Treatment of the (+)-benzenesulfonate ester with methanolic potassium hydroxide afforded (-)-oxide, $(\alpha)_D$-8.80°, in 80% yield. At this point in the course of this study Ryan's (54) work became available to us. From several preparations of optically active α-methyl styrene oxide from (+)- or (-)-atrolactic acid, Ryan reported a calculated specific rotation of 11.22° for optically pure oxide. Thus the oxide described above would be of ca. 78.5% optical purity. Whereas Ryan made the oxide from crude 2-phenyl-1,2-propanediol-1-p-toluenesulfonate, the 2-phenyl-1,2-propanediol-1-benzenesulfonate was isolated and purified in the present work.

The loss in optical purity observed in the conversion of the (+)-benzenesulfonate ester to the (-)-oxide could be due to several factors. If the procedure used to obtain ester of maximum optical rotation failed to give optically pure material, then the calculated optical purity of the benzenesulfonate would be too high. Some loss of optically active ester may have been effected when the crude ester was washed with water

to remove pyridine. The fact that the active benzenesulfonate ester is more soluble in acetone, and thus probably more soluble in pyridine-water, than the racemic ester would support this conclusion. A loss in optical purity could also be due to racemization in the step leading to the ester formation, or in the step leading to the oxide. In any case the calculated value reported by Ryan (54) for optically pure oxide appears to be valid since it was strongly supported by the results obtained in the palladium on charcoal catalyzed hydrogenolysis of the oxide (see below).

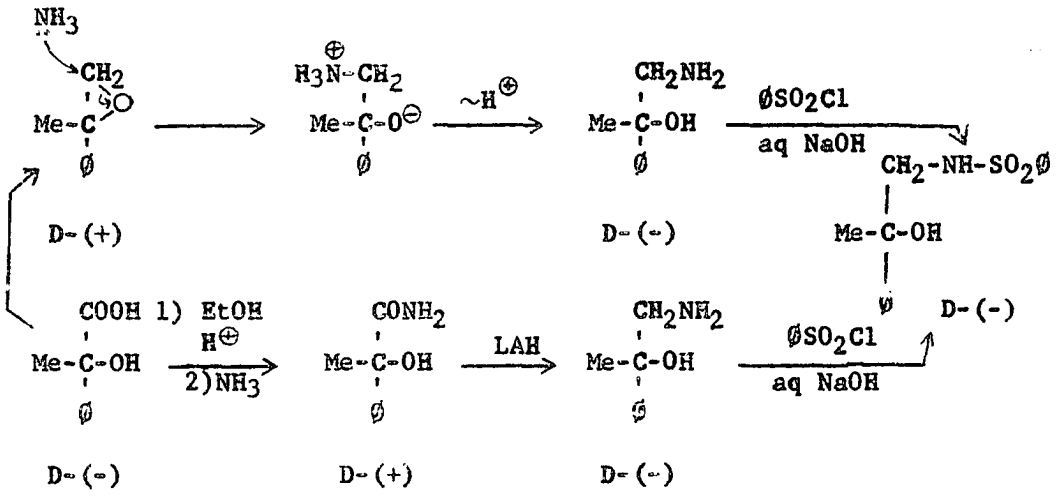
Confirmation of Configuration of α-Methyl Styrene Oxide

The configuration of the oxide is directly related by its method of synthesis to atrolactic acid, since ring closure, an intramolecular displacement by the alkoxide ion on the adjacent primary carbon atom, should not affect the configuration of the asymmetric center. This



assumption was verified independently by comparison of the amino alcohols, as the benzenesulfonamides, obtained from ammonolysis of the (+)-oxide and the lithium aluminum hydride reduction of (+)-atrolactamide. The ammonolysis of the (+)-oxide in methanolic ammonia, presumably occurring by an S_N2 type displacement by NH_3 on oxygen at the less hindered primary carbon, would give no change of configuration at the active center. The (+)-atrolactamide was derived from (-)-atrolactic acid *via* ammonolysis of its ester. Identical specimens of the

solid (-)-benzenesulfonamide were obtained from each route.



Hydrogenolyses of Optically Active α-Methyl Styrene Oxide

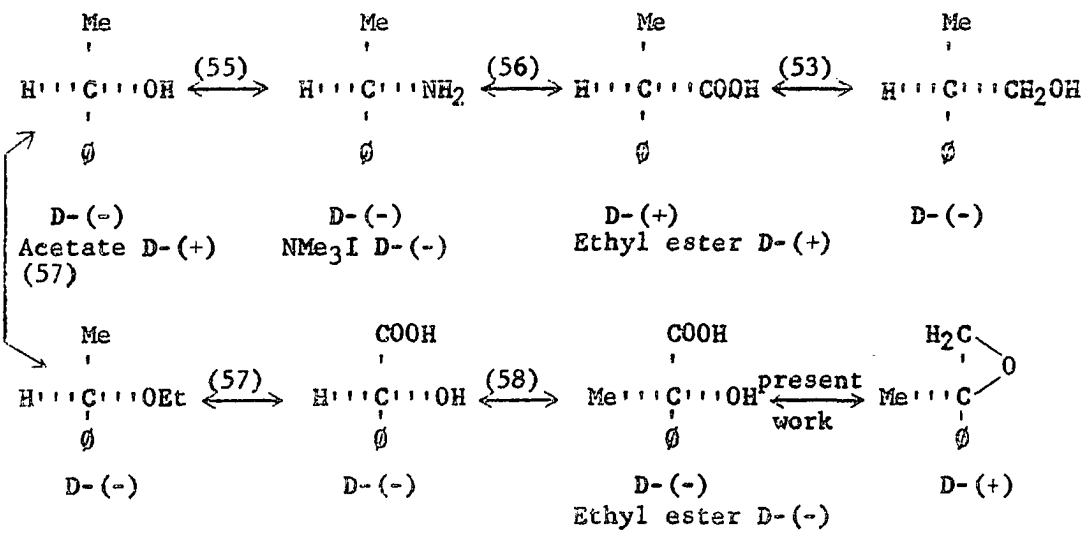
The hydrogenolyses were carried out under two to three atmospheres hydrogen pressure in ethyl acetate containing a few drops of pyridine. Pyridine was added to prevent acid catalyzed isomerization of the oxide to hydratropaldehyde, which had been observed to occur spontaneously in preliminary work with the inactive oxide. The theoretical quantity of hydrogen was consumed in several hours, and the active alcohol obtained in yields, 80%. From (-)-oxide of 82.2% optical purity the 5% Pd.C reduction gave (-)-2-phenyl-1-propanol of 80.3% (54) optical purity, and from (-)-oxide of 78.3% optical purity, the Raney nickel reduction gave (-)-alcohol of 8.16% optical purity.

Ryan felt that his value of 11.22° for the optically pure oxide could be as much as 15% low, based on the results obtained by Eliel and Delmonte (50) in the analogous synthesis of optically active styrene oxide. However, our work shows that oxide with a specific rotation of

11.22° would have to be at least 98% optically pure since the Pd.C catalyzed hydrogenolysis of the (-)-oxide occurred with 98% retention of optical purity.

Correlation of α-Methyl Styrene Oxide and 2-Phenyl-1-Propanol

The configuration of (-)-2-phenyl-1-propanol has been correlated with (-)-atrolactic acid, and thus to the (+)-oxide, through the following sequence (⟷ correlation established, not resonance):



In the correlation of D-(-)-α-methylbenzyl alcohol and D-(-)-α-methylbenzylamine, Snyder and Brewster (55) converted the D-(-)-amine to D-(-)-α-methylbenzyl trimethylammonium iodide which on treatment with silver oxide, followed by acetic acid gave the L-(-)-acetate derivative of L-(+)-α-methylbenzyl alcohol, the acetate ion displacement of $-NMe_3^{\oplus}$ presumably occurring with Walden inversion at the asymmetric center.

Bernstein and Whitmore (56) in correlating D-(+)-hydratropic acid

(2-phenylpropionic acid) and D-(-)-α-methylbenzylamine treated the D-(+)-acid with thionyl chloride, then sodium azide. Curtius rearrangement of the resulting acyl azide, known (68) to occur with retention of configuration at the asymmetric center, gave α-methylbenzylisocyanate which on decomposition provided the D-(-)-amine.

To establish the correlation of D-(+)-hydratropic acid and D-(-)-hydratropalcohol (2-phenyl-1-propanol), Eliel and Freeman (53) showed that the lithium aluminum hydride reduction of the D-(+)-acid gave D-(-)-alcohol. The maximum rotation for the alcohol was established in this work, and was confirmed by Ryan (54).

Mislow (57) demonstrated the correlation between D-(-)-mandelic acid and D-(-)-α-methylbenzyl alcohol by converting both compounds to D-(-)-ethyl-α-methylbenzyl ether. Treatment of the D-(-)-acid with ethyl iodide and silver oxide gave the D-(-)-ethyl ethoxy ester which on reduction with lithium aluminum hydride afforded D-(-)-β-ethoxy-phenethyl alcohol. The ether-alcohol was converted to D-(-)-β-ethoxy-phenethyl-p-toluenesulfonate which on lithium aluminum hydride reduction gave the same D-(-)-ethyl-α-methylbenzyl ether produced by the reaction of D-(-)-α-methylbenzyl alcohol with ethyl iodide and silver oxide.

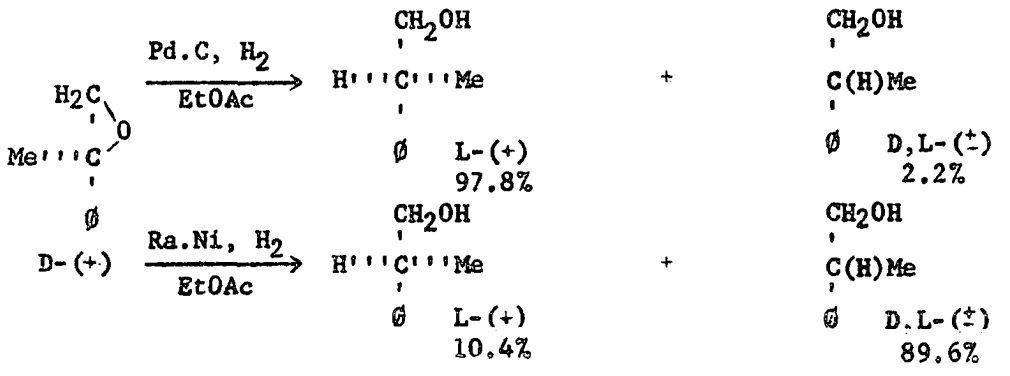
The correlation of D-(-)-mandelic acid and D-(-)-atrolactic acid which is based on systematic increments in the optical rotations in the parallel series of the acid derivatives, Freudenberg's displacement principle (66), has been supported recently by chemical evidence. Cram (58) treated L-(+)-atrolactic acid with phenyl lithium to form L-(-)-α-methyl benzoin which on sodium borohydride reduction gave (-)-threo-1,2-

diphenyl-1,2-propanediol in very low yield (2%). Roger (68) previously had obtained (+)-alpha-1,2-diphenyl-1,2-propanediol from D-(-)-mandelic acid by action of methyl magnesium iodide on D-(-)-mandelamide to form D-(-)-phenylacetyl-carbinol which on treatment with phenyl magnesium bromide provided the (+)-alpha glycol. The stereochemical course of the hydride reduction reaction (58) and the latter of Roger's Grignard reactions (68) were assumed by Cram (58) to have proceeded via Cram's rule (69), and it is upon this basis that the glycols were assigned threo configurations.

Stereochemical Course of Oxide Hydrogenolyses

Based on the above correlations of configurations, it is clear that the Pd.C catalyzed hydrogenolysis of the oxide proceeded with a high retention of optical purity (97.8%) and resulted in 98.9% inversion of configuration at the reduced center. The Raney nickel catalyzed reduction proceeded mainly with racemization, resulting in only 10.4% retention of optical purity, but again, the predominating alcohol was of inverted configuration.

The racemization observed with the Raney nickel catalyst could have been due to the optical instability of the product under the reaction conditions rather than to the course of the hydrogenolysis. However, treatment of (-)-2-phenyl-1-propanol, optical purity 69.5%, under the reaction conditions employed for the nickel hydrogenolysis of the (-)-oxide, but for 24 hours instead of the 3 hours for the hydrogenolysis, gave essentially unchanged crude (-)-alcohol, optical purity 64.8%.



The theory of organic mechanisms permits analysis of a large number of organic reactions into a series of elementary steps small enough in number to be practical (S_N1, S_N2, etc., to use Ingold's (70) terminology). It is not surprising that such development of elementary steps for heterogeneous catalytic reactions is much less advanced than it is in homogenous reactions. All the difficulties of homogeneous reactions are present plus the problem of the catalyst surface.

In considering the reaction mechanism for catalytic hydrogenolysis of epoxides, one might first examine the known mechanisms for reactions of epoxides.

Brewster (37) stated that the driving forces for the acid-catalyzed ring openings of epoxides appeared to be the strain present in the three-membered ring, the "pull" effected by protonation of the ring oxygen atom, the "push" of a nucleophilic displacing agent, and generation of partial carbonium character at the site of reaction. He pointed out that in certain reactions one or the other of these latter two driving forces could predominate. Thus tertiary or α-phenyl epoxides could develop a particularly high degree of carbonium character, even to the

point where a rearward nucleophilic "push" was not required for reaction. Brewster used this argument to explain certain ring openings in inert solvents, in which retention of configuration was observed, since nucleophilic displacement would lead to inversion of configuration. However, he also noted that the stilbene oxides reacted with aqueous hydrochloric acid to give the respective glycols with inversion of configuration. This, he stated, demonstrated that the presence of highly nucleophilic agents at large in the solution, and thus available in all directions, could permit the inverting displacement to come to the fore. Brewster did not exclude the possibility that the reactions could have proceeded *via* free radical mechanisms, but it would seem unlikely under his conditions.

The driving forces in the catalytic hydrogenolysis of epoxides could be formally analogous to those in the acid-catalyzed ring openings. Certainly the main driving force for the reaction should be the strain present in the three-membered ring. However, the ease of the debenzylation reaction in the hydrogenolysis of the epoxide could also be characteristic of the benzyl position. The "pull" could be exerted on the ring oxygen by either the catalyst surface itself (adsorption), or by the hydrogen film, in the form of protons or atoms, on the catalyst surface. The "push" could be effected by hydride ions or atoms from the catalyst. Alternatively, and probably less likely, the "pull" or "push" could arise from hydrogen species in the solution.

Molecular models of the epoxide indicate that the benzene and epoxide ring cannot assume co-planarity. Thus parallel adsorption

of the plane of the benzene ring to the catalyst surface would allow the ring oxygen to be adsorbed on the catalyst surface, or the oxygen could be projected into space away from the catalyst surface.

On the basis catalytic hydrogenolysis is usually considered to involve simultaneous addition of two hydrogen species from the catalyst surface to the adsorbed reactant, and assuming that adsorption occurs as pictured in Figure I (adsorption is indicated by dashed vertical lines), two modes of hydrogenolysis can be considered: a mechanism analogous to the S_Ni type or one similar to the S_Nl type. In an S_Ni type reaction, cleavage of the benzyl carbon-oxygen bond with simultaneous addition of hydrogen species from the catalyst surface to the benzyl carbon and ring oxygen would give a product with accompanying retention of configuration. In an S_Nl reaction type, initial cleavage of the benzyl carbon-oxygen bond would lead to a stable tertiary carbonium ion or radical. This intermediate, through desorption and nonstereospecific readsorption to the catalyst surface, could lead to a racemic product, or the adsorbed intermediate could be held close to the catalyst surface with addition of a hydrogen species to the asymmetric center to give a product with retention of configuration. However, either of these two reaction mechanisms would lead to the wrong stereochemical result for the Pd.C catalyzed hydrogenolysis of the oxide, and other mechanisms must be examined.

The observed inversion of configuration in the Pd.C hydrogenolysis of the oxide would be possible if one hydrogen species came from the catalyst surface and the other came from the solution, or if one

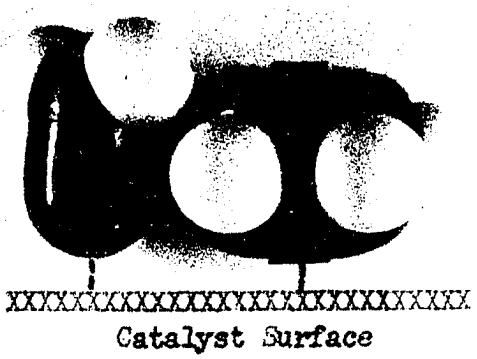


FIGURE I

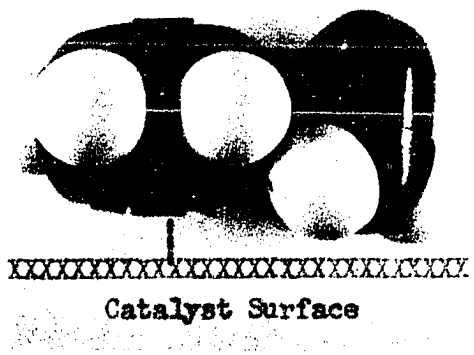


FIGURE II

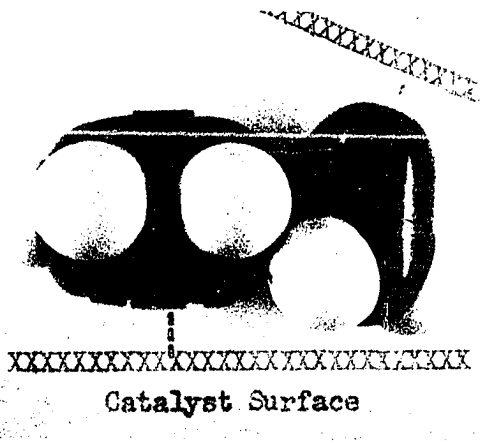


FIGURE III

hydrogen species came from each of two catalyst surfaces.

If the oxide were adsorbed on the catalyst surface as pictured in Figure II, i.e., adsorption occurring only through the benzene ring with the ring oxygen projected into space or away from the catalyst surface, an S_N2 type mechanism could be proposed. In this type of mechanism a hydrogen species from the catalyst surface could attack the adsorbed molecule at the benzyl carbon with resultant ring opening and would afford a product, formed after the oxygen adds a hydrogen species either from the solution or subsequently from the catalyst surface, of inverted configuration. Thus the driving forces for this type of reaction, using the analogy of the acid-catalyzed ring openings, would be the strain present in the three-membered ring, the "push" exerted by the nucleophilic hydrogen species from the catalyst surface, and the possible, but not necessarily needed, "pull" of a hydrogen species in solution.

If adsorption occurs as pictured in Figure III, where the benzene ring is adsorbed on one catalyst surface and the ring oxygen adsorbed on another, then attack of a hydrogen species by an S_N2 type mechanism would effect ring opening and lead to a product of inverted configuration. Mitsui and Imaizumi (60) propose such a mechanism to explain the inversion of configuration observed in the Pd.C catalyzed hydrogenolysis of ethyl α-phenyl-α-phenoxypropionate to ethyl hydratropate. As evidence, these workers state in yet to be published work that ethyl hydratropate produced in the catalytic hydrogenolysis of optically active ethyl α-phenyl-α-phenoxypropionate was accompanied

by retention of configuration when the catalyst-carrier ratio was low and inversion of configuration when the catalyst-carrier ratio was high. No such variation was looked for in our work, but it seems improbable that the very clean inversion of configuration observed could have resulted when a competitive mechanism giving retention of configuration was possible.

It is impossible to say at this time which of these two mechanisms is correct. However, the S_N2 mechanism involving the adsorption of the molecule through the benzene ring on a single catalyst surface is preferred. This mechanism certainly would be consistent with the high retention of optical purity and predominant inversion of configuration observed in the Pd.C hydrogenolysis.

In the Raney nickel catalyzed hydrogenolysis of (+)-oxide to (+)-alcohol the predominant racemization with partial inversion of configuration observed might be considered as occurring via either of two combinations of reaction paths: a completely stereospecific reduction, with 55% of reaction occurring by inversion of configuration and 45% by retention of configuration; or a partially stereospecific reduction with 10% inversion of configuration and 90% racemization at the reduced center.

In the case of a combined completely stereospecific reduction the product of inverted configuration could arise from an S_N2 type attack of hydrogen species from the catalyst surface at the asymmetric center of the adsorbed molecule (Figure II). The product formed with retention of configuration could be obtained via an S_Ni or S_N1 type mechanism, as explained earlier, involving an adsorbed reactant as shown in Figure I.

This interpretation would require that the stereochemical course of the reaction depends upon the conformation of the adsorbed oxide and would infer that the adsorption as depicted in Figure II is slightly preferred to that shown in Figure I. The apparent difference in preferred adsorbed conformations between Raney nickel and palladium-charcoal could be attributed to differences in the catalyst surfaces.

Alternatively, in the partially stereospecific Raney nickel reduction the alcohol of inverted configuration could be obtained by the S_N2 mechanism described above, while the predominantly racemized product could arise via an S_N1 type mechanism. In this latter case, the adsorbed intermediate (adsorption as depicted in Figure I with ring opening effected by attack of a hydrogen species on the ring oxygen) could, through desorption and non-stereospecific readsorption before addition of a second hydrogen species, form inactive alcohol. In this interpretation the stereochemical course of the reduction again would be dependent upon the conformation of the adsorbed reactant. Apparently the predominant initial reaction step would be the rupture of the oxide ring followed by a non-stereospecific addition of a hydrogen species to the benzyl center to give a racemic product.

Hydrogenolysis of D-(-)-Ethyl Atrolactate

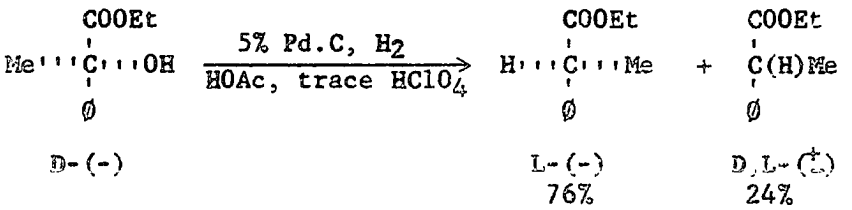
Bonner (6, 26) showed that the Raney nickel catalyzed hydrogenolysis of D-(-)-ethyl atrolactate to D-(+)-ethyl hydratropate occurred with predominant retention of configuration and ca. 80% retention of optical purity.

Since the Pd.C hydrogenolysis of optically active α-methyl styrene

oxide proceeded with inversion of configuration, an examination of the Pd.C catalyzed dehydroxylation of optically active ethyl atrolactate was undertaken to see if the inversion observed was uniquely due to the Pd.C catalyst or to some feature of the aryl oxirane system.

Hydrogenolysis of inactive ethyl atrolactate with Pd.C did not occur in ethyl acetate, ethanol, or in acetic acid alone, but did proceed at a satisfactory rate in acetic acid containing a trace of 70% perchloric acid.

The 5% Pd.C catalyzed hydrogenolysis of D-(-)-ethyl atrolactate, optical purity 33.3% (59), in acetic acid containing a trace of perchloric acid gave L-(-)-ethyl hydratropate, optical purity 24.5% (60), in 52.4% yield. Since the reactant and product have been correlated <u>via</u> the acids (see correlation chart above), the hydrogenolysis proceeded with <u>predominant inversion of configuration</u> (87%) at the reduced center and with 74% <u>retention of optical purity</u>.



The possibility that the observed racemization was due to the effect of acid on the ester was eliminated by showing that (-)-ethyl atrolactate was recovered unchanged after standing 28 hours in the acetic acid-perchloric acid solution.

In the Pd.C catalyzed hydrogenolysis of (-)-ethyl atrolactate to (-)-ethyl hydratropate, the reactant could be adsorbed on the catalyst surface as pictured in Figure IV or Figure V.

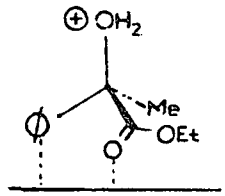


Figure IV

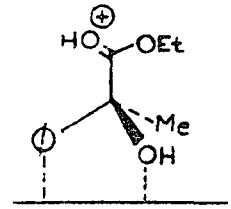


Figure V

Protonation of the benzyl oxygen would cause the molecule to be adsorbed through the benzene ring and the carbonyl oxygen (Figure IV). An S_N2 type attack of a hydrogen species from the catalyst surface on the asymmetric center of the adsorbed reactant with simultaneous debenzylation as water is formed would give a product of inverted configuration. Since the benzyl carbon oxygen in the ester would be stronger than the benzyl carbon oxygen bond of the strained three-membered ring in an α-phenyl epoxide, the necessary driving forces of the reduction of the ester in acid media should include a "pull" effected by protonation of the benzyl oxygen as well as the "push" of the nucleophilic species from the catalyst surface. The fact that in more basic solvents such as ethyl acetate and ethanol the reduction doesn't proceed at a measurable rate would tend to support these conclusion.

The loss in optical purity could be attributed to an initial protonation of the benzyl hydroxyl group and subsequent loss of water in solution to give a stable carbonium ion intermediate which could add a hydrogen specie from either side to give a racemic product. However, optically active ethyl atrolactate was recovered unchanged when allowed to stand in acid media. A more feasible explanation for the observed

loss in optical purity might be that some reduction occurred involving an adsorbed reactant as shown in Figure V. An S_Ni type reaction in which two hydrogen species from the catalyst surface add concurrently to the benzyl oxygen and asymmetric center in a completely stereospecific reaction would lead to a product with retention of configuration. In an S_N1 type reaction in which debenzylation would lead to a stable carbonium ion intermediate, the reaction could proceed as described earlier for the oxide. Desorption of the intermediate from the catalyst surface and non-stereospecific readsorption before addition of a hydrogen species to the asymmetric center would lead to a racemic product. If the stable carbonium ion intermediate were held closely to the catalyst surface, addition of a hydrogen species from the surface to the asymmetric center would give a product with retention of configuration.

Thus the predominant course of reaction would occur <u>via</u> an S_N2 type mechanism to give a product of inverted configuration. The loss in optical purity could be due to part of the reduction occurring by a non-stereospecific S_N1 type reaction leading to racemization of the asymmetric center, or by a stereospecific S_Ni or S_N1 type reaction leading to a product with retention of configuration.

TABLE I

MAXIMUM ROTATIONS OF PERTINENT COMPOUNDS

Compound	$(\alpha)_D$	Temperature	Concentration (g./100 ml)	Solvent	Density	Ref.
D-(+)-Atrolactamide	12.6	14	1.866	EtOH	--	64
L-(+)-Atrolactic acid	37.9	23	3.60	EtOH	--	52
D-(-)-Ethylatrolactate	-26.7	13	neat	--	d_4^{13} 1.097	59
D-(+)-α-Methyl styrene oxide	11.22	25	8.00	Et_2O	--	54[a]
L-(+)-2-Phenyl-1-propanol	17.92	25.5	neat	--	d_4^{20} 1.000	54
L-(+)-2-Phenyl-1,2-propanediol	8.94	27	6.76	Et_2O	--	53[b]
D-(+)-Ethyl hydratropate	67.5	16	neat	--	d_4^{16} 1.02	60

[a]Calculated from oxide $(\alpha)_D$ -9.69° (c 8.00, ether) assumed to be 86.4% optically pure.

[b]Based upon material recrystallized to constant melting point, 47.5-48.5°.

PART I

EXPERIMENTAL

All melting points and boiling points are uncorrected. Unless otherwise specified, the melting points were taken in sealed tubes.

(±)-2-Phenyl-1-Propanol from Pd.C Reduction of (±)-α-Methyl Styrene Oxide.--A solution of 10.60 g. (0.079 mole) of (±)-α-methyl styrene oxide in 40 ml. of ethyl acetate containing 5 drops of pyridine was shaken with 0.50 g. of 5% palladium on charcoal in a Parr apparatus for 5 hours at a pressure of 2 1/2 atmospheres of hydrogen at room temperature. The catalyst was filtered (Celite), and the solvent removed at reduced pressure. The remaining yellow oil (10.40 g., 96%) on vacuum distillation gave 8.32 g. (77%) of the alcohol collected at 103-104.5° (9 mm.), n_D^{25} 1.5236. The recorded constants are b.p. 108-109° (12 mm.), n_D^{20} 1.5252 (54), and b.p. 105-106° (11 mm.), n_D^{25} 1.5230 (53).

(±)-2-Phenyl-1-Propanol-1-p-Toluenesulfonate.--To a chilled (3°) solution of 1.00 g. (0.007 mole) of (±)-2-phenyl-1-propanol in 10 ml. of pyridine 2.00 g. (0.010 mole) of p-toluenesulfonyl chloride was added. After storing at 0° for 24 hours, the reaction mixture was poured into dilute sulfuric acid containing crushed ice, and 2.15 g. (quant.) of crystalline material, m.p. 45-48°, was collected by

filtration. A single recrystallization from 95% ethanol gave 2.00 g. (93%) of colorless crystals, m.p. 52-53°, unchanged by further recrystallization. The literature (63) value is m.p. 50-51°.

Anal. Calculated for $C_{16}H_{18}O_3S$: C, 66.19%; H, 6.25%. Found: C, 66.11%; H, 6.15%.

(±)-2-Phenyl-1-Propanol from (±)-2-Phenyl-1-Propanal.--Using the procedure of Winstein and Schreiber (62), the lithium aluminum hydride reduction of 24.28 g. (0.18 mole) of (±)-2-phenyl-1-propanal gave 20.85 g. (84.5%) of alcohol collected at 103-104° (9 mm.), n_D^{26} 1.5228. The tosylate derivative, m.p. 52-53°, was obtained in similar yield by the procedure described above. A mixed melting point with the tosylate derivative of the (±)-alcohol from the Pd.C reduction of (±)-α-methyl styrene oxide showed no depression, m.m.p. 52-53°.

(±)-2-Phenyl-1-Propanol from Raney Nickel Reduction of (±)-α-Methyl Styrene Oxide.--A solution of 8.00 g. (0.059 mole) of (±)-α-methyl styrene oxide in 40 ml. of ethyl acetate was shaken with 4 ml. of W-5 Raney nickel (49) in a Parr apparatus for 3 hours under a pressure of 2 1/2 atmospheres of hydrogen at room temperature. The catalyst was filtered (Celite), and concentration of the filtrate *in vacuo* gave 7.50 g. (93%) of a colorless oil, n_D^{25} 1.5240. The oil on vacuum distillation gave 6.40 g. (80%) of alcohol collected at 83-84° (3 mm.), n_D^{25} 1.5236. The p-toluenesulfonate derivative was prepared as was described above in 90% yield, m.p. 52-53°. The material was identical in every respect with the tosylate derivative of the alcohol

from the Pd.C catalyzed hydrogenolysis of the oxide, m.m.p. 52-53°.

Partial Resolution of Atrolactic Acid.--Active α-methylbenzylamine (38.7 g., 0.32 mole), $(\alpha)_D$ 39.5° (neat, d 0.934), was dissolved in a warm solution of (±)-atrolactic acid (56 g., 0.32 mole) in 180 ml. of water, and stored overnight at 5° in a refrigerator. The salt obtained was dissolved in 120 ml. of hot water, and after 4 hours at 5° the (+)-amine, (-)-acid salt was isolated by filtration. The filtrates from this and the previous crystallization were combined for the isolation of the (+)-acid.

(-)-Atrolactic Acid.--The wet salt isolated above was dissolved in 100 ml. of 3 N hydrochloric acid, and after chilling, 3.90 g. of (±)-atrolactic acid was removed by filtration. The filtrate was extracted with ether (three 50 ml. portions) and the residue obtained on evaporation of the combined extracts was recrystallized (5°) from 25 ml. of boiling water to give 15.10 g. (54%) of acid, $(\alpha)_D$ -34.3° (c 3.2, ethanol), optical purity 90.5% (52). Samples for optical rotation were dried at 60° in vacuo.

(+)-Atrolactic Acid.--After acidification of the combined mother liquors to pH 1 with concentrated hydrochloric acid, separation of 20.50 g. of (±)-acid from the chilled solution, and isolation as described above, there was obtained 15.70 g. (56%) of acid, $(\alpha)_D$ +31.9° (c 3.1, ethanol), optical purity 84.4%.

In another experiment, similar treatment of the salt and mother liquor obtained in the original crystallization, calculated to contain acid of acids of 37% optical purity, gave (-)-acid in 24% yield and

61% optical purity, and (+)-acid in 19% yield and 68% optical purity.

Recrystallization of Partially Active Atrolactic Acid from Other Solvents.--Water: 3 g. of 44.6% optically pure (-)-acid in 100 ml. of water deposited 1.07 g. of (±)-acid on chilling. The acid remaining in solution was calculated to be 69.4% optically pure.

3 N Hydrochloric Acid: 3 g. of 44.6% optically pure (-)-acid in 100 ml. of this solvent deposited 1.40 g. of slightly active acid, $(\alpha)_D$-1.23°. The acid remaining in solution was calculated to be 81.0% optically pure.

Concentrated Hydrochloric Acid: 3 g. of 44.6% optically pure (-)-acid dissolved in 100 ml. of this solvent only after heating and considerable loss of HCl vapor. The solution deposited 1.50 g. of (±)-acid leaving acid of 89.2% (calculated) optical purity in solution.

(+)-2-Phenyl-1,2-Propanediol.--A solution of 35.6 g. (0.214 mole) of (+)-atrolactic acid $(\alpha)_D$ 32.10°, optical purity 85%, in 150 ml. of tetrahydrofuran was added to 16.8 g. (0.42 mole) of lithium aluminum hydride in 200 ml. of tetrahydrofuran. After addition was complete (about 1 1/2 hours), the reaction mixture was heated under reflux for one hour. The flask was then cooled, and the excess hydride was decomposed by the addition of 50 ml. of water. After standing overnight Celite was added, the mixture filtered, and the filter cake washed well with ether (three 100 ml. portions). The combined organic phases were dried over anhydrous sodium sulfate and on concentration in vacuo gave 29.4 g. (90%) of crude (+)-2-phenyl-1,2-propanediol, $(\alpha)_D$ +7.40° (c 6.28, ether), optical purity 82.8% (53). A similar reduction in

which ether was used as solvent gave a crude yield of 74%.

(+)-2-Phenyl-1,2-Propanediol-1-Benzenesulfonate.--To a chilled (3°), well-stirred solution of 29.2 g.(0.192 mole) of crude (+)-2-phenyl-1,2-propanediol, $(\alpha)_D$ +7.40° (optical purity 82.8%), and 32 g. (0.40 mole) of pyridine in 50 ml. of ether, a solution of 30 ml. (0.24 mole) of benzene sulfonyl chloride in 50 ml. of ether was added over a period of 15 minutes. The reaction was allowed to come to room temperature, and stirring was continued for a total reaction time of 48 hours. A 20% solution of sodium chloride in water (100 ml.) was then added to the mixture, the phases separated, and the organic phase extracted with 100 ml. of water. The combined brine and aqueous phase was extracted with benzene (three 25 ml. portions). Concentration of the combined organic phases at room temperature and atmospheric pressure gave an orange paste (73 g.), which, after washing on the filter with three 50 ml. portions of water, was dried in vacuo to give 52.50 g. (94%) of white crystals, m.p. 72-75°, $(\alpha)_D$ +9.74° (c 6.26, chloroform), optical purity 85%. The optical purity of the ester was based upon $(\alpha)_D$ +11.44° (c 6.14, chloroform), m.p. 80-82°, for material crystallized several times from acetone to constant optical purity.

(-)-α-Methyl Styrene Oxide.--(+)-2-Phenyl-1,2-propanediol-1-benzenesulfonate (25.00 g., 0.086 mole), $(\alpha)_D$ +9.74°, optical purity 85%, was added to a chilled (5°) solution of 23.2 g. (0.351 mole) of potassium hydroxide in 150 ml. of methanol. The course of the reaction was followed by standard acid titration of aliquots of the reaction mixture and found to be complete after a total reaction time of 25

minutes. Water (200 ml.) was added, and the chilled mixture was extracted with pentane (one 50 ml. and four 25 ml. portions). After the organic phase was dried over anhydrous sodium sulfate the solvent was removed *in vacuo* to give 10.24 g. (89.2%) of oil, n_D^{25} 1.5172. Vacuum distillation gave 9.80 g. (80%) of oxide collected at 92° (17 mm.), n_D^{25} 1.5172, $(\alpha)_D$ -8.80° (c 8.25, ether), α_D^{30} -16.55° (neat), optical purity 78.5% (54). The recorded constants (54) are b.p. 47° (1.7 mm.), n_D^{20} 1.5210.

(±)-2-Phenyl-1-Amino-2-propanol from (±)-Atrolactamide.--A solution of 16.5 g. (0.10 mole) of (±)-atrolactamide, m.p. 99.5-101°, literature (64) gives 102°, in 50 ml. of tetrahydrofuran was added to a stirred, chilled (3°) solution of 10.00 g. (0.25 mole) of lithium aluminum hydride in 250 ml. of ether. After addition was complete (*ca.* 1 hour), the ice bath was removed, and the mixture stirred at room temperature for 2 hours. The mixture was then chilled, and the excess hydride decomposed by the cautious addition of water (30 ml., 70% excess). After stirring overnight the salts were removed by filtration (Celite), and concentration of the filtrate *in vauco* gave 16.40 g. of viscous oil. The infrared spectrum indicated incomplete reduction since the amide carbonyl adsorption (6.02 microns, 45% absorption) was still present. The (±)-amino alcohol was isolated from the crude reaction mixture by the Hinsberg method whereby 3.00 g. of the mixture in 20 ml. of 10% sodium hydroxide with 4 ml. of benzene sulfonyl chloride gave, after acidification, 2.55 g. of the crude benzenesulfonamide, m.p. 130-135°. Recrystallization of the crude material from 95% ethanol

gave 2.00 g. (37.6% based on atrolactamide) of colorless crystals, m.p. 136-137.5°.

Anal. Calculated for $C_{15}H_{17}NO_3S$: C, 61.85%; H, 5.88%; N, 4.81%; S, 10.98%. Found: C, 61.66%; H, 5.72%; N, 4.70%; S, 10.81%.

(-)-Ethyl Atrolactate.--A solution of 31.2 g. (0.188 mole) of atrolactic acid, $(\alpha)_D$ -34.00°, optical purity 90%, in absolute ethanol (100 ml.) containing 1 g. of p-toluenesulfonic acid was refluxed overnight. The cooled solution was shaken with sodium carbonate (5 g.), and after filtration was concentrated in vacuo. The residual oil was dissolved in ether (60 ml.), washed with 10% sodium carbonate, and then with water (two 25 ml. portions). After drying over anhydrous sodium sulfate the ether was removed in vacuo and there remained 31.70 g. (87%) of oil, n_D^{25} 1.5024, $(\alpha)_D$ -22.40° (neat, d 1.09), optical purity 84% (59).

(+)-Atrolactamide.--A solution of 10.00 g (0.052 mole) of (-)-ethyl atrolactate, optical purity 84%, in 100 ml. of chilled (3°) methanol was saturated with ammonia gas and stored at 0° for seven days. After removal of the excess ammonia and solvent on a steam bath, the residue was taken up in boiling benzene and on cooling gave 5.90 g. (69%) of colorless crystalline amide, m.p. 56-58°, $(\alpha)_D$ +10.00° (c 2.05, ethanol), optical purity 79.4% (64).

(-)-2-Phenyl-1-Amino-2-Propanol from (+)-Atrolactamide.--A solution of 5.60 g. (0.034 mole) of (+)-atrolactamide, optical purity 79.4%, in 50 ml. of tetrahydrofuran was added to a stirred, chilled (3°) solution of 4.00 g. (0.10 mole) of lithium aluminum hydride in

100 ml. of tetrahydrofuran. After additon was complete (ca. 1 hour) the ice bath was removed, and the mixture was heated at reflux for 2 1/2 hours. The mixture was then chilled, and the excess hydride decomposed by the cautious addition of water (15 ml., 100% excess). After standing overnight, the solids were removed by filtration (Celite), and concentration of the filtrate in vacuo gave 5.30 g. of oil, $(\alpha)_D$ -2.52° (c 4.14, ethanol), (amide carbonyl absorption, 50%, present at 6.03 microns in the infrared spectrum). The benzenesulfonamide derivative was prepared: 2.00 g. of the crude (-)-amino alcohol in 20 ml. of 10% sodium hydroxide with 4 ml. of benzene sulfonyl chloride gave after acidification 2.00 g. of oily solid, which on recrystallization from 95% ethanol gave 1.50 g. (40.3% based on the actrolactamide) of colorless crystals, m.p. 107-109°, $(\alpha)_D$ -22.30° (c 4.12, ethanol).

(-)-2-Phenyl-1-Amino-2-Propanol from (+)-α-Methyl Styrene Oxide.--A homogeneous solution of 4.40 g. (0.033 mole) of α-methyl styrene oxide, $(\alpha)_D$ +9.06°, optical purity 80.6%, in 35 ml. of methanol containing 35 ml. of concentrated ammonium hydroxide (d 0.90) was stored at room temperature in a stoppered flask for seven days. The two phase mixture obtained after removal of the excess ammonia and methanol on a steam bath was extracted with ether (three 15 ml. portions). The combined ether extracts were dried over anhydrous sodium sulfate and gave on concentration in vacuo 3.80 g. of an oily residue (78.6%), $(\alpha)_D$ -10.38° (c 4.34, ethanol). The benzenesulfonamide derivative was prepared as described above, 2.00 g. of crude (-)-amino alcohol giving 2.60 g. (51.3% based on the oxide) of crude crystalline material.

Recrystallization from 95% ethanol gave 1.30 g. of colorless crystals, m.p. 106.5-108.5°, $(\alpha)_D$ -23.90° (c 2.08, ethanol).

Anal. Calculated for $C_{15}H_{17}NO_3S$: C, 61.85%; H, 5.88%; N, 4.81%; S, 10.98%. Found: C, 61.50%; H, 5.76%; N, 4.70%; S, 10.74%.

Concentration of the mother liquor gave an additional 0.90 g. of crystals, m.p. 107-109°, $(\alpha)_D$ -24.70° (c 2.00, ethanol). A mixture of the (-)-benzenesulfonamide derivatives prepared from the crude (-)-amino alcohols from the lithium aluminum hydride reduction of (+)-atrolactamide, and the ammonolysis of (+)-α-methyl styrene oxide showed no depression of melting point, m.m.p. 107-109°.

(-)-2-Phenyl-1-Propanol from Pd.C Reduction of (-)-α-Methyl Styrene Oxide.--A solution of 8.00 g. (0.059 mole) of α-methyl styrene oxide, $(\alpha)_D$ -9.23°, optical purity 82.2%, in 40 ml. of ethyl acetate containing five drops of pyridine was shaken with 0.50 g. of 5% palladium on charcoal under the reaction conditions described for the (±)-oxide. The customary isolation gave 8.00 g. (99%) of yellow oil which on vacuum distillation gave 6.25 g. (79%) of the (-)-alcohol collected at 103-104° (9 mm.), n_D^{25} 1.5232, $(\alpha)_D$ -14.38° (neat, d 1.000), optical purity 80.3% (54).

(+)-2-Phenyl-1-Propanol-1-p-Toluenesulfonate.--The tosyl derivative was prepared by the procedure described for the (±)-alcohol. The crude red crystalline material (2.00 g., 93%), derived from 1.00 g. of 80.3% optically pure 2-phenyl-1-propanol, was dissolved in boiling 95% ethanol and treated with Norite. On cooling, rhombihedral plates, m.p. 62-63°, were deposited, $(\alpha)_D$ +9.21° (c 3.04, chloroform).

Anal. Calculated for $C_{16}H_{18}O_3S$: C, 66.19%; H, 6.25%, Found: C, 66.36%; H, 6.11%.

(-)-2-Phenyl-1-Propanol from Raney Nickel Reduction of (-)-α-Methyl Styrene Oxide.--Under the reaction conditions employed for the (±)-oxide, 4.35 g. (0.034 mole) of (-)-α-methyl styrene oxide, $(\alpha)_D$ -8.80°, optical purity 78.3%, in 40 ml. of ethyl acetate with 4 ml. of W-5 Raney nickel gave 3.60 g. (81.6%) of oil, n_D^{25} 1.5228, $(\alpha)_D$ -1.46° (neat, d 1.000). The oil on distillation gave 2.00 g. (46%) of material collected at 104-105° (10 mm.), n_D^{25} 1.5228, $(\alpha)_D$ -1.46° (neat,) d 1.000), optical purity 8.16%.

Optical Stability of (-)-2-Phenyl-1-Propanol on Treatment with Raney Nickel.--A solution of 1.00 g. of (-)-2-phenyl-1-propanol, α_D^{30} -12.65° (neat), optical purity 69.3%, in 20 ml. of ethyl acetate was shaken with 4 ml. of Raney nickel under the conditions described above for 24 hours. The customary isolation gave 0.85 g. of undistilled oil, α_D^{30} -11.80° (neat), optical purity 64.8%.

(-)-Ethyl Hydratropate (Ethyl 2-Phenylpropionate) from Pd.C Reduction of (-)-Ethyl Atrolactate.--(-)-Ethyl atrolactate, optical purity 33.3%, (2.00 g., 0.010 mole), b.p. 94° (1.8 mm.), in 10 ml. of glacial acetic acid containing 4 drops of 70% perchloric acid was catalytically hydrogenated at atmospheric pressure in the presence of 0.50 g. of 5% palladium on charcoal. After absorption of 272 ml. of hydrogen (theoretical, 264 ml. at 27° and 728 mm.) in 27 hours, the catalyst was filtered (Celite), and the filtrate made basic with aqueous sodium

carbonate. The hexane extract (40 ml.) was dried over anhydrous sodium sulfate and on concentration in vacuo gave 1.80 g. (98%) of colorless oil, n_D^{25} 1.4908, $(\alpha)_D^{25}$ -15.31° (neat, d 1.02), optical purity 22.7% (60). The infrared spectrum indicated that the product was contaminated with a small amount of starting material (3% absorption at 2.90 microns, indicative of a hydroxyl group). Distillation of 1.50 g. of the crude oil gave 0.81 g. (52.4%) of (-)-ethyl hydratropate collected at 83-84° (2.2 mm.), n_D^{25} 1.4890, $(\alpha)_D^{25}$ -16.46° (neat, d 1.02), optical purity 24.5%. Literature (65) values are b.p. 100.5° (8 mm.), n_D^{18} 1.4943.

In other experiments in which ethyl acetate, ethanol, or acetic acid were used as solvents, the Pd.C catalyzed hydrogenolysis of the ester failed to proceed at measurable rates.

Optical Stability of (-)-Ethyl Atrolactate in Acid Solution.--A solution of 1.94 g. (0.01 mole) of ethyl atrolactate, α_D^{25} -9.50° (neat), n_D^{25} 1.5008, in 10 ml. of glacial acetic acid containing 4 drops of 70% perchloric acid was allowed to stand 28 hours. The solution was made basic with aqueous sodium carbonate, and extracted with hexane (three 15 ml. portions). The organic phase was dried over anhydrous sodium sulfate and on concentration in vacuo gave 1.90 g. (quant.) of colorless oil, α_D^{25} -9.44° (neat), n_D^{25} 1.5008.

PART I

SUMMARY

1. (±)-α-Methyl styrene oxide was shown to give a single product, (±)-2-phenyl-1-propanol, on Pd.C or W-5 Raney nickel catalyzed hydrogenolysis.
2. An improved resolution of atrolactic acid was developed.
3. L-(+)-Atrolactic acid was converted to a L-(-)-α-methyl styrene oxide.
4. Confirmation that no change in configuration at the asymmetric center occurred in the synthesis of optically active α-methyl styrene oxide from optically active atrolactic acid was shown.
5. L-(-)-α-Methyl styrene oxide gave D-(-)-2-phenyl-1-propanol on Pd.C catalyzed hydrogenolysis with a very high retention of optical purity and with inversion of configuration at the reduced center.
6. The Raney nickel catalyzed hydrogenolysis of L-(-)-α-methyl styrene oxide gave D-(-)-2-phenyl-1-propanol with predominant racemization, but some inversion of configuration.
7. D-(-)-Ethyl atrolactate on Pd.C catalyzed hydrogenolysis gave L-(-)-ethyl hydratropate (ethyl 2-phenylpropionate) with high retention of optical purity and inversion of configuration at the reduced center.

PART I

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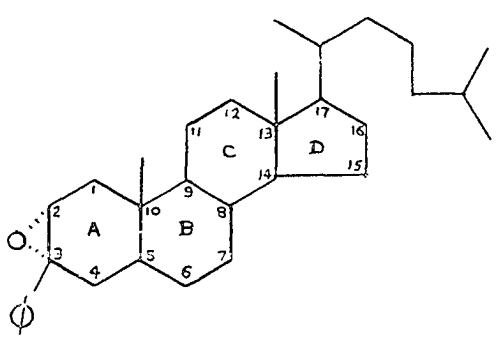
PART II. 2α,3α-OXIDO-3β-PHENYLCHOLESTANE

DISCUSSION

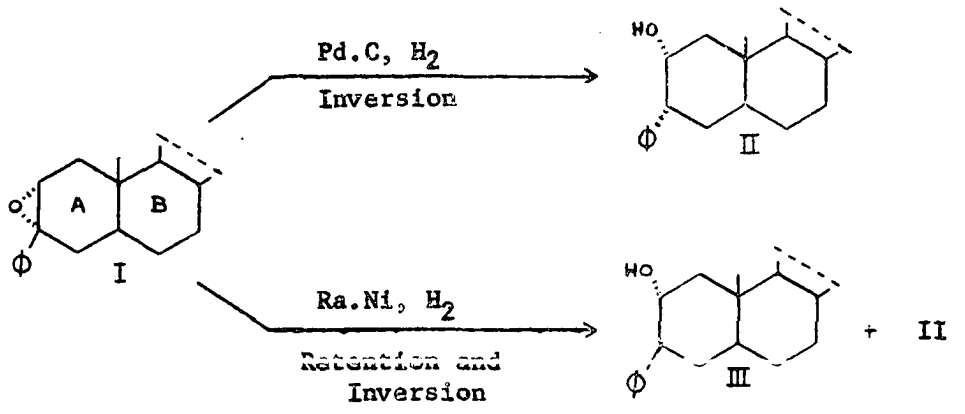
In extending the study of the stereochemical course of the catalytic hydrogenolysis of an aryl oxirane of an acyclic system (Part I) to one of a more rigid alicyclic system possessing greater stereo requirements, some facets of the reaction may be elucidated.

The model chosen for this study was 2α, 3α-oxido-3β-phenylcholestane (I).



I

From the study of the hydrogenolysis of α-methyl styrene oxide, one might predict the following courses of reaction:

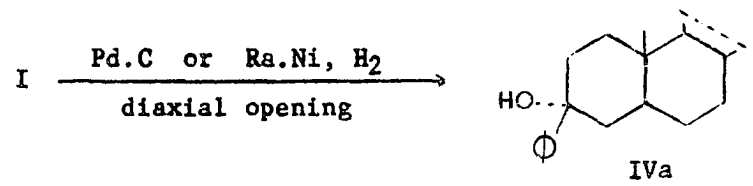


the Pd.C hydrogenolysis giving a single product, and the Raney nickel, being somewhat less stereospecific, giving two products.

Should the Raney nickel debenzylation reaction proceed via the completely stereospecific combination of reactions described in Part I (55% inversion of configuration, 45% retention of configuration), the reduction could give nearly equal quantities of isomers, II and III, differing in configuration at the benzyl center. However, if the reaction occurs via the predominantly non-stereospecific combination of reactions (i.e., 90% racemization, 10% inversion), then the carbonium ion or free radical intermediate, which gave (±)-product in the acyclic case, should give the thermodynamically more stable isomer III (1) as the major product in an alicyclic system. Thus, the ratio of isomers from the hydrogenolysis of the oxirane could permit a choice between these two modes of reaction.

Oxide I was also chosen because it permits the examination of one other possible course of reaction. The known preference for diaxial opening (2) in alicyclic epoxides, leading in this case to axial orientations for the hydroxyl group and the incoming hydrogen, would

result in formation of IVa, rather than II as predicted on the basis of the debenzylation-inversion case observed in the simpler system.



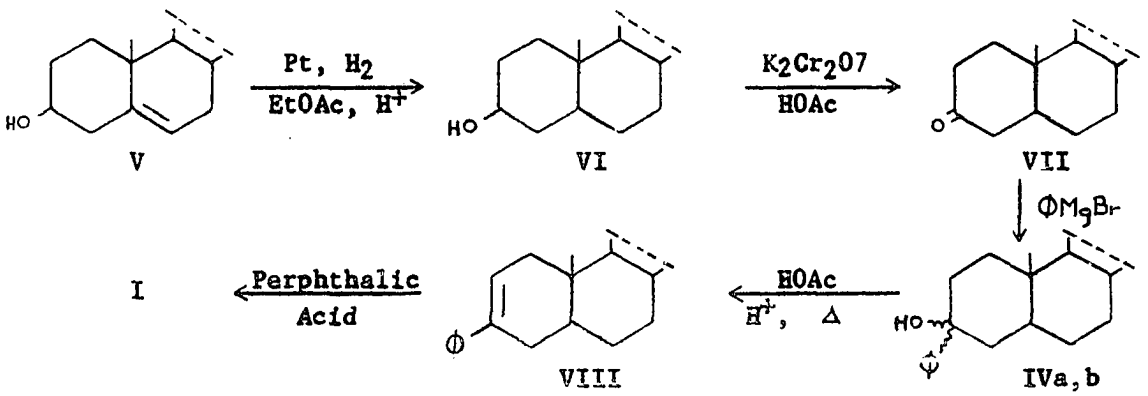
IVa

The product distribution between II and IVa, then, would permit an evaluation of the relative importance of the two "competing" courses, and thus give a way to measure the intensity of the high degree of stereospecificity and inversion of configuration observed in the Pd.C hydrogenolysis of α-methyl styrene oxide.

Though the sterols, II and III, were not known, they could be readily identified by oxidation to the known (3, 4) 3α-phenyl and 3β-phenylcholestan-2-one (XI and XII). Cookson and Hudec (3, 4), in reporting reactions of I in connection with another problem, stated that the 3α-phenyl isomer (XI) was unstable due to the axial orientation of the phenyl group, and that on treatment with acid, XI was converted to the more stable 3β-isomer (XII) where the phenyl group has an equatorial orientation.

Synthesis of 2α,3α-Oxido-3β-Phenylcholestane

The oxide (I) was synthesized, in 21.5% over-all yield, from cholesterol by the following sequence:

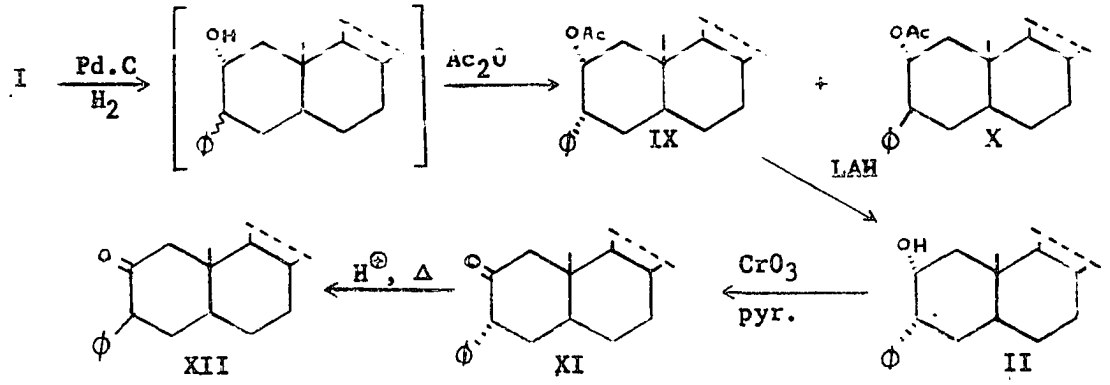


The platinum catalysed hydrogenation of cholesterol (V) in ethyl acetate containing a trace of 70% perchloric acid gave 3β-cholestanol (VI). This saturated sterol on treatment with sodium dichromate in acetic acid afforded cholestan-3-one (VII), which was converted to a mixture of 3β-phenylcholestan-3α-ol (IVa) and 3α-phenylcholestan-3β-ol (IVb) by the action of phenylmagnesium bromide. The crude mixture of these latter two sterols, on warming in acetic acid, then provided 3-phenylcholest-2-ene (VIII), which, on treatment with perphthalic acid, afforded 2α,3α-oxido-3β-phenylcholestane. Arguments pertinent to the assignment of the double bond to the 2- rather than the 3- position, as well as to the configuration of the oxide, are discussed by Zderic (5). It is interesting that the strong chromophoric effect observed on melting the olefin has been mentioned in only one of the previous reports (6).

The Hydrogenolyses of 2α,3α-Oxido-3β-Phenylcholestane

The Pd.C hydrogenolysis of the oxide in hexane-ethanol (the oxide is insoluble in ethanol alone) was complete in six hours under 2.3 atmospheres of hydrogen. The separation of the sterols in the crude reduction mixture was effected by acetylation and fractional crystal-

lization to provide 3α-phenyl-2α-cholestanyl acetate (IX) in 83% crude yield and 3β-phenyl-2α-cholestanyl acetate (X) in 5% crude yield as the only isolable products. Thus, the ratio of the sterol isomers from the hydrogenolysis was 24 parts II to 1 part III.



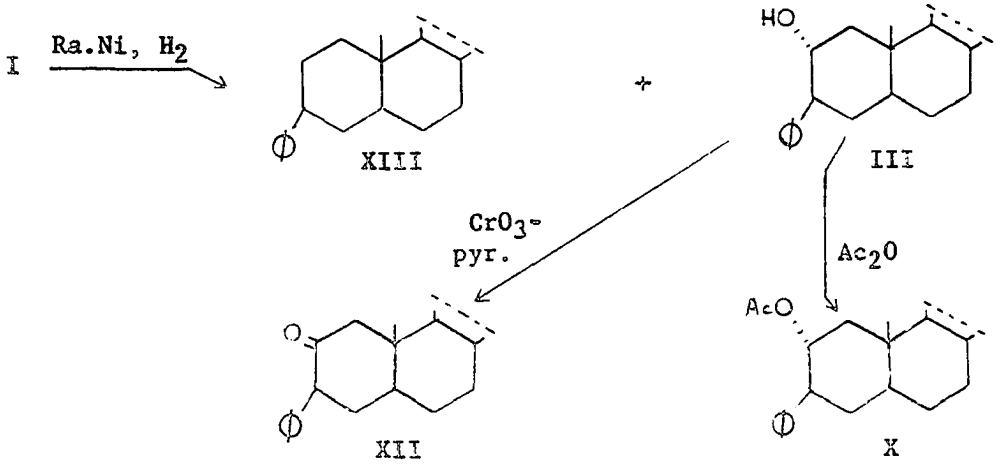
Lithium aluminum hydride reduction of the major acetate (IX) provided the free 3α-phenylcholestan-2α-ol (II) in 88% yield. The configuration of this major product was shown by its oxidation with chromium trioxide-pyridine complex (7) to the known (3,4) 3α-phenylcholestan-2-one (XI). This unstable ketone was isomerized under acid conditions to the more stable 3β-phenylcholestan-2-one (XII). The expected equatorial (α) orientation of the hydroxyl group at the 2-position was verified by the infrared spectrum of the acetate (IX), which had a single absorption band at 8.17 microns. Fieser (8) has observed that C—O band in the 8.00 to 8.50 micron region of sterol acetates would be a doublet or triplet if the acetate were in an axial position, while an equatorial group would have a single band.

The sterol (II) gave a poor elemental analysis for carbon (0.58% low). However, the elemental analysis for the acetylation product,

IX, was good. Also, the infrared spectrum of the sterol, 2.90 and 9.70 microns (OH), and its oxidation to the known 3α-phenylcholestan-2-one leave no doubt that the sterol has the structure proposed.

The 3β-phenyl-2α-cholestanyl acetate (X), isolated as the minor product in the acetylation of the crude reduction mixture, was identical in all respects with a specimen obtained in the Raney nickel hydrogenolysis of the oxide (see below).

The Raney nickel catalyzed hydrogenolysis of the steroid oxide was carried out in hexane-ethanol and was complete in four hours. The crude mixture on column chromatography gave pure 3β-phenylcholestane (XIII) in 29% yield (36% crude yield) and pure 3β-phenylcholestan-2α-ol (III) in 40% yield (43% crude yield) as the only isolable products.



The hydrocarbon (XIII) was identical in all respects with an authentic specimen prepared by the Pd.C hydrogenation of 3-phenylcholest-2-ene, a reaction known to occur on the basis of the rule of rear attack (9, 10).

Mild oxidation of the sterol (III) with chromium trioxide-pyridine

gave only the more stable ketone (XII), indicating the equatorial orientation of the phenyl group. Its acetate (X) was identical to the acetate isolated as the minor product in the Pd-C hydrogenolysis of the oxide, and had a single absorption band at 8.18 microns, which indicated the oxygen function had an equatorial (α) configuration (see above).

As in the case of the sterol (II) obtained in the Pd.C hydrogenolysis, the 3β-phenylcholestan-2α-ol (III) from the nickel hydrogenolysis gave a poor elemental analysis for carbon (0.68% low). However, as in the previous case, the formation of an acetate showing satisfactory elemental analysis, the expected infrared spectrum (hydroxyl group absorption at 2.98 and 9.71 microns), and oxidation to the known ketone (XII) definitely show the structure given for III is correct.

In another experiment, for some unexplainable reason, the phenylcholestane, isolated in 27% yield from the crude Raney nickel reduction mixture, was not pure. Although the infrared spectra of the impure material and authentic 3β-phenylcholestane were identical, a mixed melting point of the two samples showed a depression. These erratic results were observed in two of the four hydrogenolysis reactions performed.

The possibility that the hydrocarbon (XIII) was formed by further reduction of either 3α-phenylcholestan-2α-ol (II) or 3β-phenylcholestan-2α-ol (III) was eliminated when these sterols, in separate experiments, were subjected to the nickel hydrogenolysis conditions of the oxide, and were recovered unchanged.

Zderic (5) has shown that both 3β-phenylcholestan-3α-ol (IVa)

and 3α-phenylcholestan-3β-ol (IVb) on refluxing with excess Raney nickel in ethanol gave 3β-phenylcholestane (XIII). Thus, the hydrocarbon XIII, isolated from the nickel hydrogenolysis of the oxide, could arise via a two step reaction: a diaxial opening of the oxide to give IVa, followed by hydrogenolysis of the sterol to give XIII. However, it was shown that the course of reaction was not this simple. Under our conditions, the Raney nickel catalyzed hydrogenolysis of a mixture of the isomeric 3-phenylcholestan-3-ols (IVa,b) was found to proceed at a very slow rate to give some 3β-phenylcholestane (8%), but the predominant product was unchanged starting material (76%).

IVa,b $\xrightarrow[\text{hexane-ethanol}]{\text{Ra.Ni, } H_2}$ XIII (8%) + IVa,b (76%)

Stereochemical Course of the Oxide Hydrogenolyses

The Pd.C hydrogenolysis of the oxide occurred with a very high degree of stereospecificity and inversion of configuration at the asymmetric benzyl center to give 3α-phenylcholestan-2α-ol (24 parts) and 3β-phenylcholestan-2α-ol (1 part) as the only isolable products in high yield.

The Raney nickel hydrogenolysis gave 3β-phenylcholestan-2α-ol (1 part) and 3β-phenylcholestane (0.82 parts) as the only isolable products in high yield. The sterol and hydrocarbon were formed with accompanying retention of configuration at the benzyl center.

The adsorption of the steroid oxide on the catalyst surface may be pictured as occurring several ways. In Figure VI, the molecule is

absorbed on the beta (front) side through the benzene ring, the aromatic ring and the rest of the steroid molecule both lying in the same general plane. In Figure VII, the molecule is adsorbed on the alpha (front) side through the benzene ring and the ring oxygen, the angle between the plane of the steroid molecule and the catalyst surface being approximately 45°. A third type of adsorption (not shown) would be a combination of VI and VII, i.e., adsorption involving two catalyst surfaces, with the adsorption through the benzene ring occurring on one surface and the ring oxygen adsorption occurring on another.

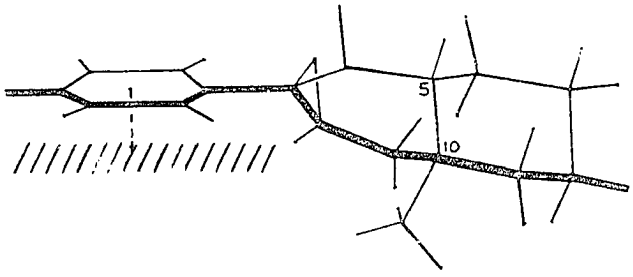


FIGURE VI

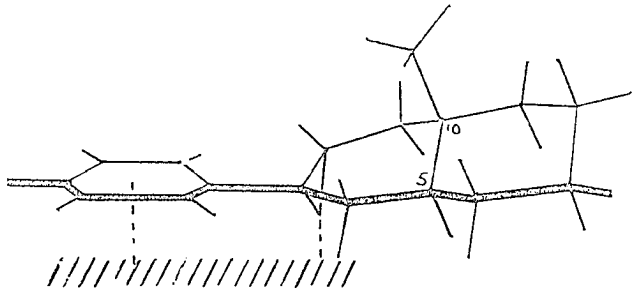


FIGURE VII

In the Pd.C hydrogenolysis, the initial step would be the addition of a hydrogen species from the catalyst surface to the benzyl carbon with resultant cleavage of the benzyl carbon oxygen bond. This addition could occur on the adsorbed reactant as shown in Figures VI or VII or

the combination of these two. However, the stereochemical result of the hydrogenolysis, inversion of configuration, permits elimination of the adsorbed reactant as depicted in Figure VII. No conclusion can be made at this time concerning the preference between an adsorbed reactant as shown by Figure VI and the combination.

In the Raney nickel hydrogenolysis, the sterol formed with retention of configuration could arise via an S_Ni and/or an S_Nl type of reaction with adsorption occurring as shown in Figure VII. Since a "pull" on the ring oxygen is needed in either of these reaction sequences, adsorption as indicated in Figure VI may be eliminated.

The initial step in the Raney nickel catalyzed formation of the hydrocarbon would be the addition of a hydrogen species from the catalyst surface at the 2- position (assuming a diaxial opening of the oxide). This step could be explained as S_N2 type attack of a hydrogen species from the catalyst surface on an adsorbed reactant as shown in Figure VI or the combination. The second step would be desorption-readsorption or simply a turning over of the intermediate (this intermediate cannot be 3β-phenylcholestan-3α-ol, see above), and completion of the sequence with hydrogenolysis of the intermediate via an S_Ni or a stereospecific S_Nl type reaction leading to a product, 3β-phenylcholestane, with accompanying retention of configuration.

PART II

EXPERIMENTAL

All melting points are uncorrected and were taken in sealed tubes. All rotations were determined in chloroform.

Hydrogenation of Cholesterol to 3β-Cholestanol.--By the procedure of Hershberg (11), 42.3 g. (0.109 mole) of cholesterol, m.p. 146-148°, in 600 ml. of ethyl acetate containing 2 drops of 70% perchloric acid was catalytically reduced at atmospheric pressure in the presence of 0.50 g. of platinum oxide. After adsorption of ca. 3000 ml. of hydrogen (theoretical 2860 ml. at 30° and 731 mm.) in 72 hours, the catalyst was filtered (Celite), and the filtrate was stored overnight at 5° in a refrigerator. There was thus obtained 23.3 g. of 3β-cholestanol, m.p. 140-142.5°. The recorded melting point is 139-142° (11). Concentration of the mother liquor gave an additional 19.5 g. of material, maximum melting point 105°, infrared adsorption peaks 5.80 and 8.10 microns (acetate). Hershberg reported crude 3β-cholestanyl acetate from the reduction reached a maximum melting point of 104°. The crude acetate (19.5 g., ca. 0.05 mole) was refluxed for 1 hour with 6.60 g. (0.10 mole) of potassium hydroxide in 200 ml. of methanol. After cooling, an additional 16.7 g. of 3β-cholestanol, m.p. 140-142°, was

obtained, thus giving a total yield of 36.2 g. (85%).

Oxidation of 3β-Cholestanol to Cholestan-3-one.--Following the procedure of Fieser (12), a hot solution of 41.5 g. (0.139 mole) of sodium dichromate dihydrate in 260 ml. of glacial acetic acid was added to a suspension of 40.0 g. (0.103 mole) of 3β-cholestanol in 240 ml. of glacial acetic acid, and the mixture was heated on a steam bath to effect solution, and then let stand overnight. The resulting paste was treated with 200 ml. of water, and precipitated cholestan-3-one was collected, washed well with water, and crystallized from 350 ml. of 4:1 ethanol-acetone; yield 25.3 g. (63.7%), m.p. 129-130°. Fieser (12) reported m.p. 127-128°.

Action of Phenylmagnesium Bromide on Cholestan-3-one.--Cholestan-3-one (22.8 g., 0.059 mole), dissolved in 175 ml. of ether, was added to an ethereal solution of phenylmagnesium bromide prepared from 4.50 g. (0.21 mole) of magnesium turnings and 22.5 g. (15 ml., 0.15 mole) of bromobenzene. After refluxing overnight, the reaction mixture was decomposed with 200 ml. of saturated aqueous ammonium chloride, the phases separated, and the aqueous layer extracted four times with 50 ml. portions of ether. The crude material (26.0 g.) obtained on evaporation of the dried ether extracts was recrystallized from ethanol-acetone to give 23.6 g. (85%) of a mixture of 3β-phenylcholestan-3α-ol and 3α-phenylcholestan-3β-ol.

3-Phenylcholest-3-ene.--The crude 3-phenylcholestan-3-ol mixture (23.6 g., 0.051 mole) in 500 ml. of glacial acetic acid containing 6 drops of 70% perchloric acid was heated on a steam bath for three

hours. After addition of water and cooling, filtration gave 24 g. of crude crystalline material, which was dissolved in hexane, and filtered through neutral alumina. Concentration of the hexane filtrate gave 19.7 g. of 3-phenylcholest-2-ene, m.p. 139.5° (chromophoric effect 139.5-148°). A second crop of crystals (1.70 g.) was obtained on evaporation to dryness of the hexane filtrate. The combined first and second crops (21.4 g.) on recrystallization from 400 ml. of 10:1:5 ethyl acetate-methanol-hexane gave 18.0 g. (78%) of 3-phenyl-cholest-2-ene, m.p. completely at 140.5° (chromophoric effect 140.5-148°), $(\alpha)_D$ +68.4° (c 0.988). The recorded constants are m.p. 131-132°, chromophoric effect 143-144°, $(\alpha)_D$ +65° (c 1, chloroform) (6); m.p. 126-127°, $(\alpha)_D$ +53° (c 1, chloroform) (5); and m.p. 139-140°, $(\alpha)_D$ +71° (c 0.47, chloroform) (3).

Monoperphthalic Acid.--In the preparation of monoperphthalic acid from phthalic anhydride, sodium hydroxide, and hydrogen peroxide according to Payne's (13) procedure, 75.0 g. (0.50 mole) of the anhydride gave 0.417 moles (83%) of the peracid, as determined by titration of an aliquot of the ethereal acid solution.

2α,3α-Oxido-3β-Phenylcholestane from Treatment of 3-Phenylcholest-2-ene.--A solution of 11.90 g. (0.027 mole) of 3-phenylcholest-2-ene in 400 ml. of ether was cooled to 5°, and then treated with 800 ml. of 0.52 N ethereal monoperphthalic acid. The resulting mixture was maintained at 5°. Aliquots (2 ml.) of the reaction mixture were added to excess sodium iodide solution (2 g. sodium iodide, 50 ml. water, 5 ml. chloroform, and 5 ml. acetic acid), and the liberated iodine

was titrated with 0.100 N sodium thiosulfate solution. The reaction was found to be complete after a total reaction time of eight days. The ethereal solution was washed consecutively with 5% aqueous sodium bicarbonate and water, and after drying and evaporation there was obtained 12.0 g. (96.4%) of crystalline material, m.p. 118-128°. Filtration of the crude oxide (2.00 g.) in hexane through 50 g. of neutral alumina gave on removal of the solvent in vacuo 1.80 g. of material, m.p. 130.5-132.5°, which on recrystallization from acetone-hexane gave 1.20 g. (58%) of 2α,3α-oxido-3β-phenylcholestane, m.p. 135-135.5°, $(\alpha)_D$ +65.5° (c 0.994). The values reported in the literature are m.p. 132.5-133.5°, $(\alpha)_D$ +63° (c 1.00, chloroform) (3); and m.p. 133-135°, $(\alpha)_D$ +63° (c 1.00, chloroform) (5).

Pd.C Catalyzed Hydrogenolysis of 2α,3α-Oxido-3β-Phenylcholestane.--A solution of 0.924 g. (0.002 mole) of 2α,3α-oxido-3β-phenylcholestane in 100 ml. of 1:1 hexane-ethanol containing 4 drops of pyridine was shaken with 0.50 g. of 5% Pd.C in a Parr apparatus for six hours under a pressure of 2.3 atmospheres of hydrogen. The catalyst was filtered (Celite), and concentration of the filtrate in vacuo gave 0.92 g. (quant.) of oily crystalline material. The crude reduction product was heated under reflux with 5 ml. of acetic anhydride for 4 hours, and on cooling and filtration 837.5 mg. (83%) of crude acetate, m.p. 122-126°, was collected. On recrystallization from acetone there was obtained 584 mg. (57.6%) of 3α-phenyl-2α-cholestanyl acetate as colorless crystals, m.p. 132-133.5°, $(\alpha)_D$ +87.5° (c 1.020), infrared absorption (KBr) singlet at 8.17 microns.

Anal. Calcd. for $C_{35}H_{54}O_2$: C, 82.95; H, 10.74. Found: C, 82.70; H, 1056.

Concentration of the acetone mother liquor gave an additional 55 mg. of acetate, m.p. 131.5-133°, thus raising the total yield to 639 mg. (63.2%).

The mother liquor from the acetylation of the crude reduction product was made basic with aqueous sodium carbonate, and the mixture was extracted four times with 10 ml. portions of hexane. The combined hexane extracts were dried over anhydrous sulfate and on evaporation to dryness gave 120 mg. of crude oily material. Chromatography of the residue on 5.0 g. of neutral alumina provided 50 mg. (4.9%) of crude crystalline material in the hexane-benzene (9:1, 200 ml.) eluates. Recrystallization from acetone then afforded 30 mg. (2.9%) of 3β-phenyl-2α-cholestanyl acetate, m.p. 147-149°, identical in all respects with 3β-phenyl-2α-cholestanyl acetate from Raney nickel hydrogenolysis of the oxide (see below), m.m.p. 147.5-149.5°.

3α-Phenylcholestan-2α-ol from the Lithium Aluminum Hydride Reduction of 3α-Phenyl-2α-Cholestanyl Acetate.--To a solution of 59.2 mg. (2.96 mmole) of lithium aluminum hydride in 40 ml. of anhydrous ether, 150 mg. (0.298 mmole) of 3α-phenyl-2α-cholestanyl acetate was added, and the resulting mixture was heated under reflux for two hours. After decomposition of the excess lithium aluminum hydride and product complex with 1 ml. of water, the mixture was allowed to stand overnight. The insoluble salts were removed by filtration (Celite), and concentration of the filtrate *in vacuo* gave 116.7 mg. (88%) of colorless 3α-phenyl-

cholestan-2α-ol, m.p. 58-60°, $(\alpha)_D$ +66.7° (c 1.020), infrared absorption (KBr) at 2.90, 7.70 microns. A satisfactory solvent could not be found for recrystallization, but trituration of the sterol with methanol raised its m.p. to 59.61°.

Anal. Calcd. for $C_{33}H_{52}O$: C, 85.28; H, 11.28. Found: C, 84.70; H, 11.09.

3α-Phenylcholestan-2-one from Oxidation of 3α-Phenylcholestan-2α-ol with Pyridine-Chromium Trioxide.--To 2 ml. of pyridine containing 90 mg. (0.90 mmoles) of chromium trioxide (7) was added 86.5 mg. (0.186 mmole) of 3α-phenylcholestan-2α-ol. After standing overnight at room temperature, the mixture was diluted with 80 ml. of ethyl acetate and filtered through 20 g. of neutral alumina. Evaporation of the solution to dryness left 73.5 mg. (85%) of material, m.p. 153-162°, which after recrystallization from ethanol gave 44 mg. (51%) of 3α-phenylcholestan-2-one, m.p. 160-162°, $(\alpha)_D$ +151.3° (c 0.794). The recorded constants are m.p. 162-164°, $(\alpha)_D$ 152° (c 1.33, chloroform) (3).

3β-Phenylcholestan-2-one from Acid Catalyzed Isomerization of 3α-Phenylcholestan-2-one.--A solution of 40 mg. (0.086 mmoles) of 3α-phenylcholestan-2-one in 20 ml. of ethanol containing 2 drops of concentrated hydrochloric acid was warmed on a steam bath for 30 minutes. On cooling 33.5 mg. (84%) of 3β-phenylcholestan-2-one, m.p. 159-161°, $(\alpha)_D$ +12.1° (c 0.662) was collected. The reported values are, m.p. 160-162°, $(\alpha)_D$ +12° (c 0.58, chloroform) (3).

Authentic 3β-Phenylcholestane from the Catalytic Reduction of

3-Phenylcholest-2-ene.--A solution of 200 mg. (0.45 mmoles) of 3-phenylcholest-2-ene in 35 ml. hexane-ethyl acetate (2:5) containing 0.10 g. of 5% Pd.C was shaken in a Parr apparatus for 2 1/2 hours under a pressure of 2.3 atmospheres of hydrogen. The mixture was filtered, and evaporation of the filtrate to dryness followed by a single recrystallization from ethanol gave 140 mg. (70%) of 3β-phenylcholestane, m.p. 112-114°, $(\alpha)_D$ +26.1° (c 0.688). The recorded constants are m.p. 113-114°, $(\alpha)_D$ +31 (c 1.00, chloroform) (5); and m.p. 112-113°, $(\alpha)_D$ 26° (c 1.00, chloroform) (3).

Raney Nickel Catalyzed Hydrogenolysis of 2α,3α-Oxido-3β-Phenylcholestane.--A solution of 462.7 mg. (1.00 mmoles) of 2α,3α-oxido-3β-phenylcholestane in 100 ml. of 1:1 hexane-ethanol was shaken with 2 ml. of W-5 Raney nickel in a Parr apparatus for thirteen hours under a pressure of 2.3 atmospheres of hydrogen. The catalyst was filtered (Celite), and concentration of the filtrate in vacuo gave 0.46 g. (quant.) of crystalline material. Chromatography of the residue on 10 g. of neutral alumina gave in the hexane eluates (100 ml.) 160 mg. (35.6%) of crystals, m.p. 102-113°. Recrystallization from acetone then provided 129 mg. (28.7%) of 3β-phenylcholestane, m.p. 115-116°, $(\alpha)_D$ +28.5° (c 1.00). A mixed melting point with authentic 3β-phenylcholestane, m.p. 112-114°, prepared from the Pd.C catalyzed hydrogenation of 3-phenylcholest-2-ene showed no depression, m.m.p. 112-114°.

Upon further elution of the column there was obtained in the benzene-ethyl acetate (1:1, 200 ml.) fractions 200 mg. (43%) of crystals,

m.p. 155-168°. Recrystallization from acetone gave 182 mg. (40.3%) of 3β-phenylcholestan-2α-ol, m.p. 174-175.5°, $(\alpha)_D$ +23.5° (c 0.96), infrared absorption (KBr) 2.98, 9.71 microns.

Anal. Calcd. for $C_{33}H_{52}O$: C, 85.28; H, 11.28. Found: C, 84.60; H, 11.10.

A solution of 100 mg. (0.215 mmoles) of the sterol in 5 ml. of acetic anhydride was refluxed for 3 hours. On chilling and filtration, 75 mg. (68.8%) of crude material was collected, m.p. 146-148.5°. A single recrystallization from acetone gave 60 mg. (55%) of 3β-phenyl-2α-cholestanyl acetate, m.p. 151-152°, $(\alpha)_D$ -16.72° (c 1.194), infrared absorption (KBr) singlet at 8.18 microns.

Anal. Calcd. for $C_{35}H_{54}O_2$: C, 82.95; H, 10.74. Found: C, 82.69; H, 10.78.

In another experiment 472 mg. (1.02 mmoles) of the steroid oxide in 30 ml. of hexane-ethanol (2:1) was shaken with 2 ml. of W-5 Raney nickel in a Parr apparatus for thirteen hours under a pressure of 2.5 atmospheres of hydrogen. Isolation as described above gave ca. 0.48 g. (quant.) of crude crystalline material. Chromatography of the residue on 10 g. of neutral alumina gave in the hexane eluates (100 ml.) 150 mg. (33%) of crystals, m.p. 95-105°. Recrystallization from acetone then afforded 120 mg. (26.4%) of crystals $(\alpha)_D$ +32.5° (c 1.082), whose m.p. 107-110°, was not changed by further recrystallization. A mixture melting point with authentic 3β-phenylcholestane, prepared

above, showed a depression, m.m.p. 98-108°. The infrared spectra of the reduction product and the authentic specimen were identical.

Upon further elution of the column there was obtained in the benzene-ethyl acetate (1:1, 250 ml.) fractions 255 mg. (54.6%) of crystals, m.p. 148-160°. A single recrystallization from ethanol gave 240 mg. (51.4%) of 3β-phenylcholestan-2α-ol, m.p. 172-176°, $(\alpha)_D$ +23.6° (c 0.998).

3β-Phenylcholestan-2-one from Oxidation of 3β-Phenylcholestan-2α-ol with Pyridine-Chromium Trioxide.--To 2.2 ml. of pyridine containing 111 mg. (1.10 mmoles) of chromium trioxide was added 111 mg. (0.238 mmoles) of 3β-phenylcholestan-2α-ol. Isolation as described above gave 50 mg. (45%) of 3β-phenylcholestan-2-one, m.p. 158-160° (ethanol), $(\alpha)_D$ +12.7° (c 0.942).

Stability of 3β-Phenylcholestan-2α-ol to Raney Nickel.--A solution of 92 mg. (0.199 mmoles) of 3β-phenylcholestan-2α-ol in 30 ml. of hexane-ethanol (1:1) was shaken with 2 ml. of W-5 Raney nickel for six hours under the reduction conditions described earlier. Isolation as described above gave ca. 0.88 g. (95%) of crude crystals. Chromatography on 4 g. of neutral alumina gave no material in the hexane eluates (150 ml.). Further elution gave in the hexane-benzene (100 ml.) fractions 75 mg. (82%) of crystals, m.p. 169-171°. A single recrystallization from ethanol gave 70 mg. (76%) of the starting material, m.p. 172-174°.

Stability of 3α-Phenylcholestan-2α-ol to Raney Nickel.--A solution of 30 mg. (0.063 mmoles) of 3α-phenycholestan-2α-ol in 30 ml. of hexane-ethanol (1:1) was shaken with 2 ml. of W-5 Raney nickel for six

hours under the reduction conditions described earlier. Isolation as described above gave 21 mg. (70%) of the starting material, m.p. 57-59°, as the only isolable product.

Raney Nickel Catalyzed Reduction of the 3-Phenylcholestan-3-ols.--A solution of 367.7 mg. (0.79 mmoles) of a mixture of 3β-phenylcholestan-3α-ol and 3α-phenylcholestan-3β-ol in 50 ml. of hexane-ethanol (3:2) was shaken with 2 ml. of W-5 Raney nickel catalyst for 10 hours under the usual reduction conditions. Customary isolation gave ca. 0.36 g. (quant.) of crystalline material. Chromatography on 4 g. of neutral alumina gave in the hexane fractions (100 ml.) 40 mg. (9.7%) of crystals, m.p. 107-111°. A single recrystallization from ethanol gave 30 mg. (7.7%) of 3β-phenylcholestane, m.p. 112-114°, $(\alpha)_D$ +26.6° (c 0.60).

Upon further elution of the column the benzene-ethyl acetate (1:1, 200 ml.) fractions afforded 280 mg. (76%) of the starting sterol mixture, identified by its infrared spectrum.

PART II

SUMMARY

1. 2α,3α-Oxido-3β-phenylcholestane was prepared from cholesterol in 21.5% over-all yield.
2. The Pd.C hydrogenolysis of the steroid oxide occurred in high yield, with a very high degree of stereospecificity and inversion of configuration to give 3α-phenylcholestan-2α-ol (24 parts) and 3β-phenylcholestan-2α-ol (1 part).
3. The Raney nickel hydrogenolysis of the oxide occurred in high yield to give 3β-phenylcholestan-2α-ol (1 part) and 3β-phenylcholestane (0.82 parts).
4. The structures of the two new sterols, 3α-phenylcholestan-2α-ol and 3β-phenylcholestan-2α-ol, were assigned on the basis of the infrared spectra of their acetates, and their oxidation to the known corresponding ketones, 3α-phenylcholestan-2-one and 3β-phenylcholestan-2-one.
5. It was shown that under the conditions for Raney nickel hydrogenolysis of the oxide, 3β-phenylcholestan-3α-ol was only slowly converted to 3β-phenylcholestane, and that neither of the isomeric 3-phenylcholestan-2α-ols underwent any change.

PART II

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