was concentrated under reduced pressure until the acetone was removed. A little additional water was added to the remaining mixture, which was then extracted with four 35-ml portions of methylene chloride. The extract was dried and concentrated under reduced pressure. The oily product (0.721 g) crystallized. An infrared spectrum showed that some alcohol remained. The product was dissolved in acetone (50 ml) and oxidized at 40° with Jones reagent (1 ml). The isolation procedure used following the first oxidation was repeated, giving a crystalline product (0.660 g). The product in acetone solution was decolorized with activated charcoal. The acetone was replaced by Skellysolve B, and an initial deposit of crystals (**23**) in this solvent was removed by filtration. Crystallization of **24** from the filtrate at room temperature gave a first crop of 0.204 g of crystals, mp 75–77°. A second crop of colorless needles (0.085 g, total 0.289 g, 0.00189 mol, 30%), mp 76–78°, was collected: RD (*c* 0.535, CH_3OH) $[\phi]_{400}$ +572°, $[\phi]_{320}$ +1087°, $[\phi]_{314}$ +1573°, $[\phi]_{306}$ +1745°, $[\phi]_{294}$ 0°, $[\phi]_{266}$ −2975°, $[\phi]_{257}$ −2850, $[\phi]_{239}$ −3160°; ν_{NH} 3230, $\nu_{C=O}$ 1705 cm^{-1} in Nujol.

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.27; H, 9.84; N, 9.11.

(**4a***S*,**8a***S*)-*trans*-**Decahydroquinolin-6-one (25).**—A solution of **22** (0.862 g, 0.00555 mol) in hot acetone (200 ml) was oxidized with Jones reagent (2.5 ml). The reaction was worked up following the procedure described above for **24**. A solid crystalline product was obtained, which was separated into starting material (0.124 g, identified by an infrared spectrum) and product by the insolubility of the starting material in ether. The product (0.214 g) crystallized from Skellysolve B, giving colorless needles: mp 82–83°; RD (*c* 0.584, CH_3OH), $[\phi]_{589}$ +63°, $[\phi]_{400}$ +281°, $[\phi]_{350}$ +592°, $[\phi]_{320}$ +1610°, $[\phi]_{316}$ +1972°, $[\phi]_{307}$ +2323°, $[\phi]_{290}$ 0°, $[\phi]_{263}$ −2320°, $[\phi]_{231}$ −894°; ν_{NH} 3230, 3220, $\nu_{C=O}$ 1710 cm^{-1} in Nujol.

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 69.76, 69.86; H, 9.69, 9.77; N, 8.93.

(**4a***S*,**8a***S*)-*trans*-**Decahydroquinolin-7-one (26).**—A cold solution of **18** (0.487 g, 0.00314 mol) in 7 *M* sulfuric acid (2 ml) was oxidized with the dropwise addition of a solution of chromium trioxide (0.222 g) in 7 *M* sulfuric acid (3 ml) (method of Grob and Wilkens[16]). After 15 min at room temperature, the solution was made basic by the slow addition of aqueous 20% sodium hydroxide while keeping the solution cold. A precipitate formed. A saturated potassium carbonate solution (1 ml) was added. The resulting mixture was stirred with chloroform (15 ml) for 1 hr and then was extracted with four 20-ml portions of additional chloroform. The chloroform solution was dried and concentrated under reduced pressure. A crystalline product was obtained, which was shown to contain some starting alcohol by an infrared spectrum. The solid was then oxidized as described for the preparation of **24** with Jones reagent. Following the same work-up procedure, a crystalline product was obtained. Crystallization from Skellysolve B gave two crops (0.288 g, 0.00188 mol, 60%) of colorless crystals, mp 120–122°. Two recrystallizations from Skellysolve B gave colorless needles: mp 121–123°; RD (*c* 0.644, CH_3OH), $[\phi]_{370}$ +24.6°; $[\phi]_{320}$ +59.6, $[\phi]_{310}$ +95°, $[\phi]_{301}$ +114, $[\phi]_{290}$ +102°, $[\phi]_{282}$ +86°, $[\phi]_{267}$ + 102°, $[\phi]_{250}$ +176°; ν_{NH} 3220, 3210; $\nu_{C=O}$ 1710 cm^{-1} in Nujol; *m/e* 153 (M^+).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.38; H, 9.73; N, 9.88.

Registry No.—(+)-**2**, 16878-36-7; (−)-**2**, 5681-50-5; (−)-**3**, 16878-16-3; (±)-**4**, 16878-38-9; (+)-**4**, 16878-35-6; (−)-**4**, 16878-34-5; (+)-**5**, 16878-39-0; **6**, 16878-17-4; (±)-**9**, 16878-18-5; **10**, 16878-19-6; (±)-**10**, 16959-97-0; **11**, 16915-92-7; **12**, 16878-20-9; perchlorate salt of **12**, 16878-21-0; **13**, 16878-22-1; **15**, 16878-23-2; **17**, 16878-24-3; **18**, 16878-25-4; **19**, 16878-26-5; **21**, 16878-27-6; **22**, 16878-28-7; (±)-**22**, 16878-29-8; **23**, 16878-30-1; **24**, 16878-31-2; **25**, 16878-32-3; **26**, 16878-33-4.

Acknowledgments.—We thank J. R. Heald, J. M. Noteboom, I. N. Pratt, M. J. Sutton, H. M. Woltersom, and S. L. Towne for technical assistance and Dr. W. A. Struck and associates for physical and analytical data.

Stereochemistry of Microbiological Hydroxylation

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Several observations concerning the stereochemistry of a number of rigid molecules, that have been hydroxylated by *Sporotrichum sulfurescens*, in relationship to possible enzyme–substrate interactions are discussed. Rigid molecules containing the 1-benzoylpiperidine ring are hydroxylated at positions outside of the piperidine ring, supporting the idea that a 5.5-Å distance between the electron-rich center and point of hydroxylation is preferred in substrates containing the amide functional group. The hydroxyl group introduced into the substrate molecule by the microorganism has been found to be oriented *trans* with respect to the amide functional group. A spatial orientation for the methylene group which is hydroxylated has been defined on the basis of a coordinate system. Mapping of the enzyme contours may then be carried out indirectly by observing the volume of space occupied by rigid molecules when they are placed into this arbitrary orientation. Preliminary results based on optically active products obtained from hydroxylation of 1-benzoyl-*trans*-decahydroquinoline indicate a preference for placing the bulk of the molecules in the upper right (UR) rear octant of the coordinate system. The dihydroxylation of certain 1-adamantanamine derivatives is observed to result from increased lipophilic character in the amide group. Finally it is suggested that the oxidation state (alcohol or ketone) of the oxygenation products depends upon the conformational mobility of the molecule in question.

A recent report from these laboratories proposed a hypothetical enzyme–substrate model to account for the preferential hydroxylation at certain sites observed during the oxygenation of macrocyclic alcohols by the microorganism, *Sporotrichum sulfurescens*.[1] This model suggests that an electron-rich center of the cyclic substrate molecule becomes attached to the hydroxylating enzyme and that hydroxylation then occurs at a carbon atom approximately 5.5 Å distant from the attachment site.[1] In the case of the macrocyclic alcohols, the hydroxyl oxygen serves as the electron-rich center. Substrates containing other electron-rich groups are also oxygenated by *S. sulfurescens* and the amide functional group has been particularly useful in this respect.[2] Among the types of amide-containing molecules, all of a cyclic nature, which we have studied are amides of azacycloalkanes,[3] azabicycloalkanes,[4]

(1) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Amer. Chem. Soc.*, **89**, 672 (1967).

(2) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Org. Chem.*, **33**, 3182 (1968).

(3) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *ibid.*, **33**, 3187 (1968).

(4) R. A. Johnson, M. E. Herr, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **33**, 3195 (1968).

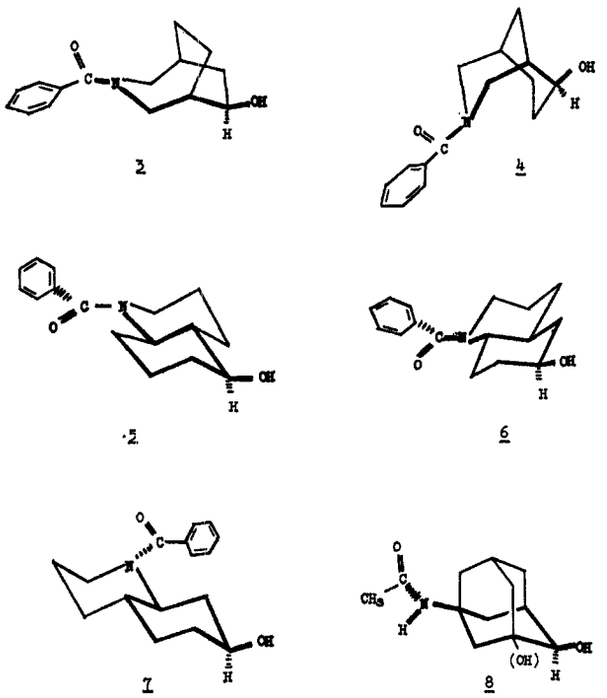
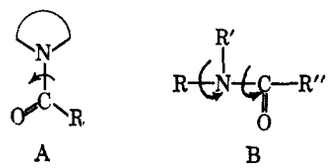


Figure 1.—Stereochemistry of products from the hydroxylation of rigid molecules with *S. sulfuescens*. Heavy lines illustrate the *trans* relationship of the hydroxyl group to the amide group.

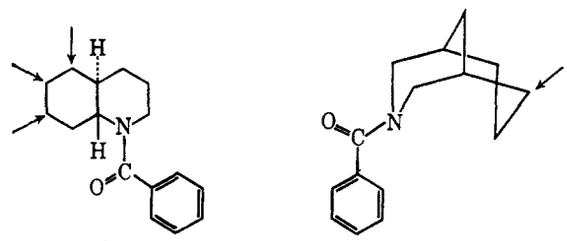
adamantanamines,[5] and *trans*-decahydroquinoline.[6] With an increasing number of examples available, it first was of interest to determine if the above enzyme–substrate model would accurately predict the products obtained from these latter substrates.[3-6] Secondly, we hoped that the patterns of hydroxylations in these molecules would be suggestive of other conformational and steric factors which may have an effect on the hydroxylation reaction.[7] Any information of this type which may be gained would be useful in predicting the course of hydroxylations of other molecules.

The requirements of an approximate 5.5-Å spacing between the electron-rich center and the site of hydroxylation appear to be largely met in these amides, assuming the amide carbonyl oxygen as the point of enzyme attachment. However, the amide group has several possible conformations, making predictions of hydroxylation sites according to the above model more difficult. If the amide nitrogen is part of a ring system (A), as in piperidine, two preferred conformations exist for the amide together with other less favorable conformations depending on rotation about the C–N amide bond.[8] If the amide nitrogen is primary, or not in a cyclic system (B), as in N-acetyl-1-adamantanamine,[5] additional rotational freedom will exist around the C–N alkyl bond. These factors result in some latitude for orientation of the electron-rich amide oxygen.



A B

Of interest with respect to the spacings between amide carbonyl and hydroxylation sites are the results obtained when relatively rigid molecules containing the piperidine ring are hydroxylated. 1-Benzoylpiperidine is hydroxylated at the 4 position.[3] The maximum distance between carbonyl oxygen and the methylene carbon at the 4 position is about 5.3 Å when the C–N amide bond is rotated so that the carbonyl is perpendicular to the plane of the piperidine ring. When the amide is in a planar conformation, this distance is reduced to about 5.0 Å. The molecules 1-benzoyl-*trans*-decahydroquinoline (**1**) and 3-benzoyl-3-azabicyclo[3.3.1]nonane (**2**) both contain the 1-benzoylpiperidine ring system, but in each case hydroxylation occurs outside of the piperidine ring. In the former (**1**), hydroxylation occurs at three sites in the ring fused to the



1 2

(arrows indicate hydroxylation sites)

piperidine while in the latter (**2**), hydroxylation occurs at one site outside of the piperidine ring. It is possible, by selecting a suitable amide conformation, to obtain spacings of 5.3 Å *or greater* between these sites and the amide carbonyl. These examples suggest that, while the 5.5-Å distance between electron-rich center and point of hydroxylation is not essential, it is nevertheless preferred in substrates containing the amide functional group.

We now wish to examine the pattern of hydroxylations found[3-6] in these molecules with the idea of determining conformational and steric factors which may be effecting the hydroxylation reaction. The stereochemistry of the alcohols produced in the microbial hydroxylation of several rigid and partially rigid molecules has been determined.[4-6] These results are illustrated in Figure 1 and may be summarized as follows. The hydroxyl group in 3-benzoyl-3-azabicyclo[3.2.2]nonan-6-ol (**3**) is *endo* with respect to the six-membered ring[4] and in 3-benzoyl-3-azabicyclo[3.3.1]nonan-6-ol (**4**) is axial with respect to the *cyclohexane* ring.[4] Hydroxylation of 1-benzoyl-*trans*-decahydroquinoline (**1**) occurs at the 5, 6, or 7 positions, giving compound **5**, **6**, and **7** in which the hydroxyl group is equatorial in each case.[6] The major product from hydroxylation of N-acetyl-1-adamantanamine (**9**) is the 4-hydroxy compound (**8**) in which the hydroxyl group is equatorial with respect to the six-membered ring common to both the nitrogen and the alcohol.[5] A minor product from hydroxylation of **9** has the hydroxyl group at the tertiary 3 position. A stereochemical feature found in all of these products and which we believe to be important is the *trans* orientation of the hydroxyl group and the amide group with respect to each other. Thus in the

(5) M. E. Herr, R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *J. Org. Chem.*, **33**, 3201 (1968).

(6) R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *ibid.*, **33**, 3207 (1968).

(7) An assumption underlying these considerations is that the same enzyme is responsible for the hydroxylations of these varied substrates.

(8) *Cf.* H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956).

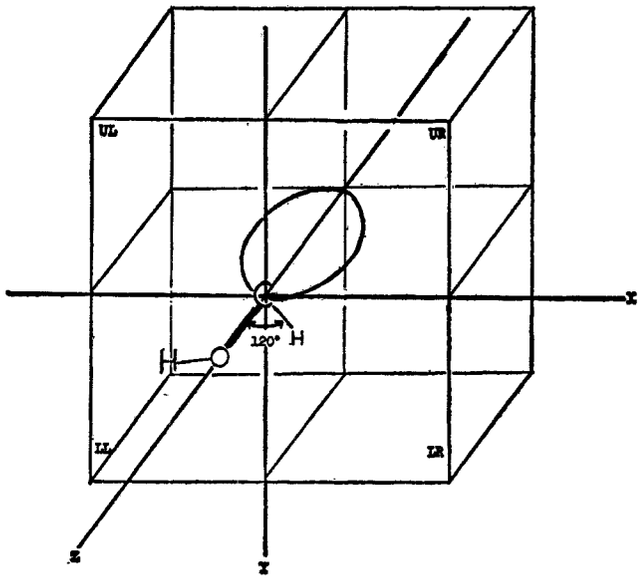


Figure 2.—Octant system for defining orientation of substrate–product molecules in space. Rear four octants are shown by boxes.

adamantanamine (**8**) and *trans*-decahydroquinoline (**5**, **6**, and **7**) examples, the hydroxyl group and the amide nitrogen are found to be 1,3- or 1,4-diequatorial substituents on a cyclohexane ring. In the two bicyclic compound (**3** and **4**), the C–O alcohol bond is oriented in a direction opposite that of the N–C amide bond. These stereochemical relationships are outlined by the heavy lines in the formulas of Figure 1. In addition to the above examples, the orientation of both hydroxyl groups in the bioconversion product N-benzoyl-N-methyl-1-adamantanamine-4α,6α-diol (**10**) has been shown to be *trans* with respect to the amide group.[5] This observation adds support to the generalization that hydroxylation occurs to give hydroxyl groups oriented *trans* to the enzyme attachment site.

Our discussions of the enzyme–substrate model to this point have centered around the electron-rich group of the substrate molecule, *i.e.*, the hydroxyl or the amide oxygen atom. We now would like to turn attention to a second important site within the enzyme, whose existence is certain. This is the site at which the oxygenation reaction occurs.[9] Although the molecular structure at this site is unknown, we will assume that the molecular geometry is quite precise at this point.[10] As the substrate molecule approaches this oxygenation site, it will undoubtedly come into contact with adjacent surfaces of the enzyme molecule. We wish to determine the contours of these surfaces indirectly by examining the stereochemical features of various rigid molecules, which have been hydroxylated successfully.

As a consequence of the precise geometry of the oxygenation site, the methylene group which is oxygenated will have a preferred orientation at this site. This in turn will determine the orientation of substrate

(9) The total enzymic site of hydroxylation of course will include both the oxygenation site and any electrophilic substrate attachment sites. However, these individual parts appear to be at opposing ends of the total site, allowing separate consideration of their character.

(10) The number of entities which must interact at this site, *i.e.*, oxygen in association with an activating moiety (such as a cytochrome), redox cofactors, enzyme bulk, and substrate molecule, suggest that a precise geometry will be required.

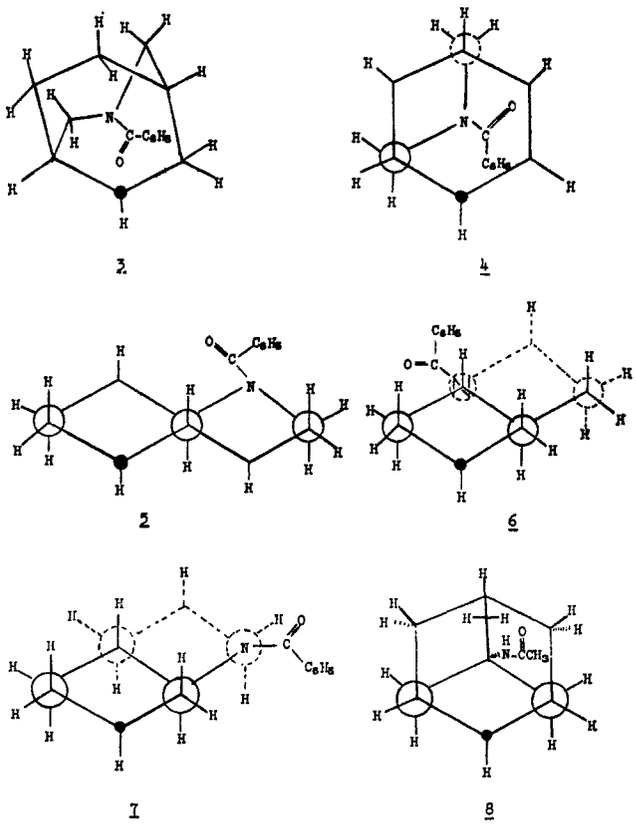


Figure 3.—Projection formulas of product molecules. Heavy dot (●) indicates C–O bond projecting toward the viewer.

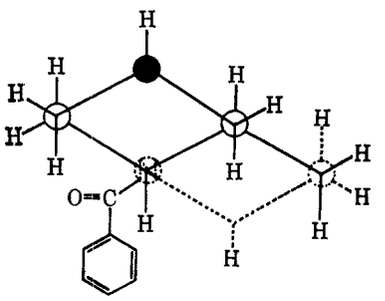
molecules having a rigid structure. The methylene group itself has tetrahedral geometry and it should be possible to transpose this from the orientation found at the oxygenation site into an arbitrarily defined spatial orientation. Such an operation will make it possible to place a variety of rigid molecules into the defined orientation so that the composite space occupied by the molecules can be mapped out. To define an arbitrary spatial orientation for the methylene group, we have chosen to place the methylene carbon at the origin of a *XYZ* coordinate system (see Figure 2). A second point then is fixed in this system by extending the C–O bond of the hydroxylated substrate molecule along the *Z* axis toward the viewer. As a third fixed point, required to prevent rotation around the C–O bond, the remaining C–H bond[11] of the hydroxymethylene group is placed in the *Y*–*Z* plane as shown in Figure 2. These three points provide the desired spatial orientation for the substrate–product molecules. As the viewer looks down the *Z* axis at molecules placed in this orientation, the atomic arrangements will be seen much as they appear in conventional Newman projection formulas. The rigid molecules discussed above are shown in such projections in Figure 3.

The mapping of the space occupied by the substrate molecules, which reflects the contours of enzyme surfaces adjacent to the oxygenation site, now may be attempted using the above orientation system. As a result of the manner in which the above model is defined, the bulk of the molecules will be found almost exclusively in the rear four octants of the coordinate

(11) In the few cases where a tertiary carbon is hydroxylated an alternative means of fixing the orientation is recognized to be necessary. This is considered briefly later in the discussion.

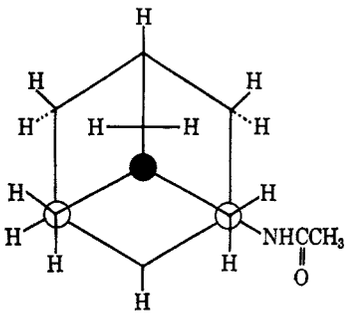
system. These octants are labeled upper left (UL), upper right (UR), lower right (LR), and lower left (LL) as seen in Figure 2. Beginning with the major product (**8**) obtained from hydroxylation of N-acetyl-1-adamantanamine,[5] we find the atoms of this symmetrical molecule evenly distributed between the UL and UR octants when seen in projection (see Figure 3). It should be remembered that the amide group in **8** may be rotated about the C–N bond. Next we examine the projection formulas of the bicyclic products **3** and **4**. Hydroxylation has introduced asymmetry into both of these molecules. Lack of significant optical rotation in **3** and **4**[4] indicates that a mixture of enantiomeric forms has been obtained in each case. Stereoselectivity of the hydroxylating enzyme for the potentially enantiomeric carbons in the bicyclic precursors to **3** and **4** is therefore absent. Projection formulas of single enantiomers of **3** and **4** (Figure 3) are also seen to be rather evenly distributed between the UL and UR octants, much as is observed for the adamantane derivative **8**. Since, qualitatively, all three of these products (**3**, **4**, and **8**) are formed rapidly and in good yield, the positions occupied by their skeletal atoms do not seriously interfere with the hydroxylation reaction. Consequently, the potential asymmetry of the substrates, which lead to **3** and **4**, is insufficient to result in a preferred steric course for the hydroxylation reaction.

It now becomes of interest to examine the projection formulas of the products obtained from hydroxylation of 1-benzoyl-*trans*-decahydroquinoline, since the optical activity of these compounds suggests that the asymmetry of the molecules is affecting the course of the reaction. The absolute configurations of these products are known and enable us to compare projection formulas in the orientation model.[6] The major products from this bioconversion were (4a*S*,5*S*,8a*R*)-1-benzoyl-*trans*-decahydroquinolin-5-ol (**5**) and (4a*S*,6*S*,8a*S*)-1-benzoyl-*trans*-decahydroquinolin-6-ol (**6**) while (4a*S*,7*S*,8a*S*)-1-benzoyl-*trans*-decahydroquinolin-7-ol (**7**) and (4a*R*,6*R*,8a*R*)-1-benzoyl-*trans*-decahydroquinolin-6-ol (**11**) were found as minor products. Placement of **5**, **6**, and **7** in the orientation model results in the projection formulas shown in Figure 3. The *S* configuration of these alcohols is reflected by the fact that greater portions of the molecules are found in the UR octant as opposed to the UL octant. The minor product (**11**) of *R* configuration at the alcohol carbon could be represented by the opposite of projection formula **6** and would have a greater portion in the UL octant. These limited examples suggest that more space is available to the substrate molecule in the UR octant with respect to the potential C–O bond.



11

Since the above orientation model has been defined in terms of the methylene group it is necessary to consider separately the case of hydroxylation of a tertiary carbon. An example of this is found in the formation of the bioconversion product N-acetyl-1-adamantanamin-3-ol (**12**).[5] This hydroxymethine carbon lacks the second C–H needed to use the above orientation model. Until more examples are available we suggest that **12** be described by a projection formula which places the axial protons of the α carbons downward in planes parallel to the XY plane. A similar orientation of minor product **11** provides an alternative to that indicated previously and places more of the molecule in the LR octant than in the UL octant. This type of orientation is considered to be much less favorable in most situations.



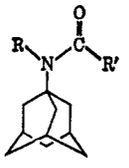
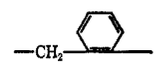
12

The general spatial orientation model which has been presented here attempts to determine important stereochemical features of the enzyme–substrate interactions during microbiological hydroxylation reactions. By examining the enzyme–substrate complex from the oxygenation site, it is hoped that this model will be complimentary to the previously outlined enzyme attachment site model[1] in predicting the course of microbial hydroxylation reactions. As the stereochemistry of other rigid molecules is determined, the validity of the present model can be tested further.

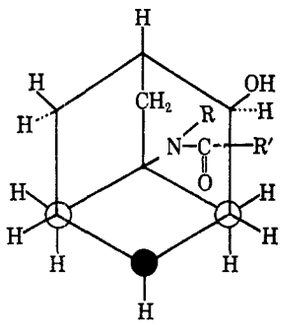
The formation of dihydroxyadamantane derivatives by the microbial hydroxylation reaction has been noted[5] and is of interest since dihydroxylation is less frequently observed. Table I shows the major product obtained from bioconversion of a series of N-substituted 1-adamantanamines with *S. sulfurescens*.[5] From the table it can be seen that the formation of dihydroxylated products is predominant where R and/or R′ are larger

TABLE I

MAJOR PRODUCTS FROM OXYGENATION OF N-SUBSTITUTED-1-ADAMANTANAMINES WITH *S. sulfurescens*

Compd	R	R′	Major product Mono OH	Major product Di OH
	H	CH_3	*	
	CH_3	CH_3	*	
	CH_3	C_6H_5		*
	H	$CH_2C_6H_5$		*
	CH_3	C_6H_{11}		*
				*
				*

groups, *i.e.*, phenyl rather than methyl, for example. The increased size of the groups R and R′ will impart greater lipophilic character to the molecule and it may be that this is sufficient to allow a second attachment of the molecule to the enzyme following the first hydroxylation. In terms of the above orientation model, the product of dihydroxylation[5] will have the following projection formula. Rotation of the adamantane nucleus 120° around the C–N bond will present a second "face" of the nucleus to the enzyme surface identical with the first. A second hydroxylation of this orientation results in the di-α-OH products which are observed.



The above argument implies that dihydroxylation occurs as two discreet steps. This is supported by following the course of the fermentation by thin layer chromatography. When this is done, a single spot corresponding to the monohydroxy product is seen first. With increasing time a second spot, corresponding to the dihydroxy product, appears and becomes stronger at the expense of the monohydroxy product. It is also possible to isolate the monohydroxy product and then add it to a fresh *S. sulfurescens* culture, which converts it into the dihydroxy product.[5]

The oxygenation of some substrates gives only hydroxylated products while in other cases both hydroxy and ketonic products are obtained. In the latter cases, the hydroxyl groups and the ketone groups are found at the same position, suggesting that the hydroxy compound is probably an intermediate in the formation of the ketone. We have observed that molecules having a higher degree of conformational mobility tend to give more ketonic products when oxygenated with *S. sulfurescens*, while highly rigid molecules give exclusively hydroxylated products. As examples, the macrocyclic alcohols (C_{12}–C_{14}) are oxygenated to mixtures of dialcohols, keto alcohols, and diketones.[1] Similarly, oxygenation of 1-benzoylhexamethylenimine, 1-benzoylheptamethylenimine, and 1-benzoyloctamethylenimine gave mixtures of alcohols and ketones in each case.[3] All of these molecules have several conformations differing in energy to a relatively small degree. On the other hand, molecules such as N-acetyl-1-adamantanamine, 3-benzoyl-3-azabicyclo[3.3.1]nonane, 2-benzoyl-2-azabicyclo[2.2.2]octane, and 1-benzoyl-*trans*-decahydroquinoline have either a rigid structure or a highly preferred conformation. All of these compounds give only hydroxy products.[4–6] Intermediate in conformational mobility are the six- and seven-membered-ring compounds. Cyclohexane derivatives may flip from one chair conformation to a second but they prefer the one in which substituents are equatorial. Cyclohexyl compounds generally give only hydroxylated products.[1,2] Cycloheptyl derivatives have a slightly greater conformational freedom and are found to give both hydroxy and ketonic products. The compound 3-benzoyl-3-azabicyclo[3.2.2]nonane contains both six- and seven-membered rings and has some conformational freedom as judged from Dreiding models. This compound also gives both a hydroxy and a ketonic product.[4] It seems plausible that the greater conformational mobility of some molecules permits them to be adapted to the alcohol dehydrogenating enzymes of the microorganism with the result that they are more readily converted from alcohols into ketones.

Steric Requirements for Free-Radical Substitutions. I. Phenyl Migration during Bromination[1]

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Steric hindrance can affect the course of free-radical brominations with N-bromosuccinimide (NBS) and with bromine. 1,1,1,2-Tetraphenylethane with NBS or Br_2 affords tetraphenylethylene resulting from a phenyl migration. 1,2,2-Triphenylpropane undergoes normal bromination with either reagent to give 1-bromo-1,2,2-triphenylpropane. 4,4,4-Triphenyl-1-butene, **11**, with NBS gives exclusively 1-bromo-4,4,4-triphenyl-2-butene, **12**, the product arising from allylic rearrangement. Both **11** and **12** give negative tests for unsaturation when treated with bromine in carbon tetrachloride.

The Wohl–Ziegler reaction[4] utilizing N-bromosuccinimide (NBS) is a valuable synthetic method for introducing a bromine atom at an allylic or benzylic position.[5] A free-radical chain sequence initiated by bromine atoms as suggested in 1953 by Goldfinger and coworkers[6] has been substantiated by others.[7] The

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