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# THE ABSOLUTE CONFIGURATION OF GENTISIC ACID NONAMETHYLENE ETHER

by

BALDEV LILLARAM BATHIJA

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1972

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirements for the degree of Doctor of Philosophy.

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Leonard H. Schwartz

2/23/73

Date

The City University of New York

To My Daughter

ANITA

Solitary Ray of Light
in an Ocean of Darkness

## ACKNOWLEDGEMENTS

It gives me great pleasure to express my sincere appreciation to my research advisor Professor Leonard H. Schwartz. He devoted a great amount of time and effort in guiding me during the years of this work. Without his critical judgement and encouragement, this problem could not have been realized. He was helpful in nonacademic matters also. His explanations helped me to understand and accept the realities of life at a very difficult and trying period of my life. I am forever indebted to him. No amount of words can ever express my gratitude.

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Mr. Miguel Mieles is due special thanks for general help in the laboratory.

## Abstract

The absolute configuration of gentisic acid nonamethylene ether (III) is established by correlation with the absolute configuration of cis-3-hydroxycyclohexanecarboxylic acid (XVI). One of the enantiomers of III, on catalytic hydrogenation gives cis-2,5-(1,9-nonamethylenedioxy)cyclohexanecarboxylic acid (X). Treatment of the methyl ester of X with potassium t-butoxide in DMSO, causes elimination and hydrolysis to give 5-(9-hydroxynonamethyleneoxy)cyclohexenecarboxylic acid (XII). Hydrogenation of XII gives 3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XIII). Treatment of XIII with 30% NaOH gives an equilibrium mixture (XIV) consisting mainly of the thermodynamically more stable cis isomer. The equilibrium mixture (XIV) is converted to its methyl ester (XV), the relay compound.

Optically active cis-3-hydroxycyclohexanecarboxylic acid (XVI) is condensed with 2-(9-bromononamethyleneoxy)tetrahydropyran (XVIII) in presence of NaH in DMF) The condensation product (XIX) is hydrolysed to hydroxy acid, XXI, which is equilibrated to XIV with 30% NaOH. The latter with diazomethane is converted to methyl ester (XV), the relay compound.

Thus (+) gentisic acid nonamethylene ether (III) is correlated with (+)-(1S,3R)-cis-3-hydroxycyclohexanecarboxylic acid (XVI). The configuration of (+) gentisic acid nonamethylene ether is therefore R.

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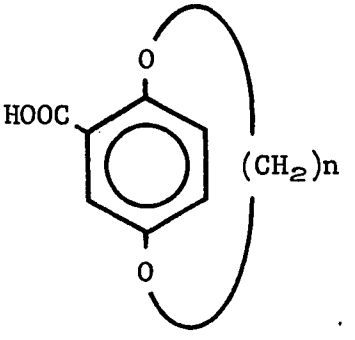
# INTRODUCTION

Ansa compounds (from the Latin for handle) are aromatic species which have one or more bridges attached to an aromatic ring in positions other than ortho or peri.

Examples of ansa compounds include gentisic acid polymethylene ethers (I). The resolution of an ansa compound




I

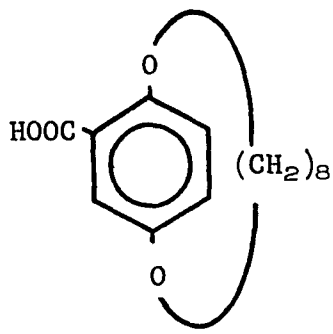
was first described by Lüttringhaus and Gralheer.[1] Lüttringhaus and his coworkers[1-3] were able to resolve gentisic acid octamethylene ether (II) and gentisic acid nonamethylene ether (III). However, they were not able to resolve gentisic acid decamethylene ether (IV).

---

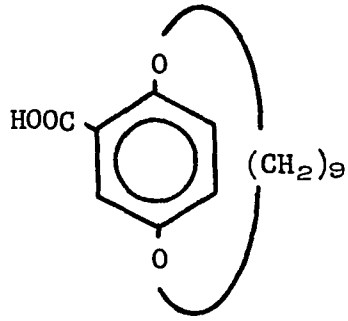
(1) A. Lüttring aus and H. Gralheer, Justus Liebigs Ann. Chem., 550, 67 (1942).

(2) A. Lüttringhaus and H. Gralheer, ibid., 557, 112 (1945).

(3) A. Lüttringhaus and G. Eyring, ibid., 604, 111 (1957).




II

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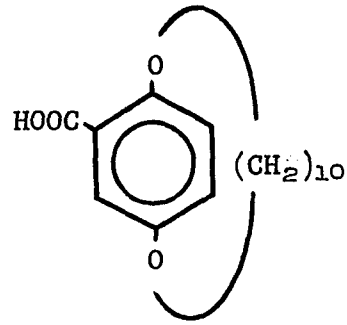



IV

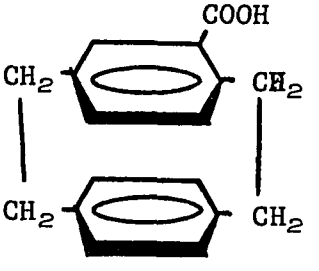
The paracyclophanes can also be included in the general class of ansa compounds. Cram and Allinger[4] resolved [2,2]paracyclophanecarboxylic acid (V). Falk and Schlögl[5] assigned the S configuration to (+)-V based on the similar topologies of V and methylferrocene-α-carboxylic acid (VI). The configurational correlation of V with VI was achieved by kinetic resolution of the anhydrides of the racemic acids. Treatment of these anhydrides with a limited quantity of (-)-α-phenethylamine in pyridine resulted in preferential reaction with (-)-enantiomer of the acid. The liberated acids were thus dextrorotatory. Assuming that the similar topologies of the reaction sites in V and VI should determine

---

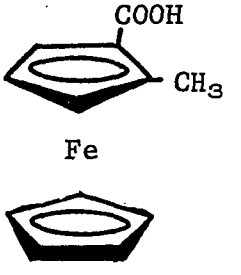
(4) D. J. Cram and N. L. Allinger, J. Amer. Chem. Soc., 77, 6289 (1955).

(5) H. Falk and K. Schlögl, Angew. Chem. Intern. Ed., Engl., 7, 383 (1968).

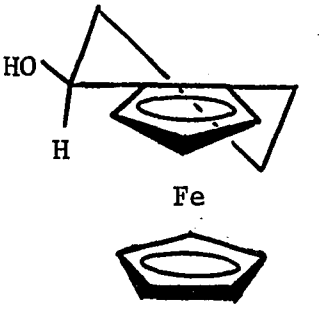
the course of kinetic resolution, it was concluded that the arrangements $COOH/CH_2$ and $COOH/CH_3$ in (+)-V and (+)-VI respectively, should have the same chiralities. Thus enantiomers of V and VI with the same sign of rotation possess the same configuration. The absolute configuration of (+)-VI had been established as 1S by chemical correlation with (1S)-(+)-ferroceno-(3-S-hydroxy)-cyclohexane (VIa).[6]




V




VI




VIa

Blomquist and Smith[7] resolved [10]paracyclophane-12-

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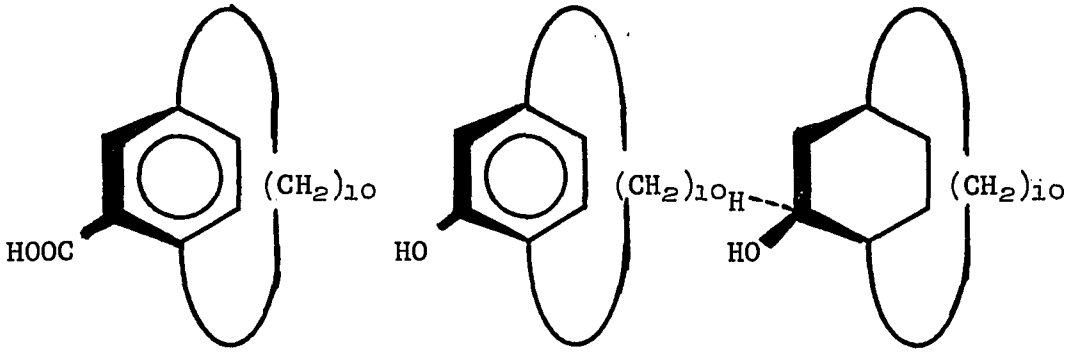
(6) K. Schlögl, "Stereochemistry of Metallocenes," in Topics in Stereochemistry, Vol. 1, N. L. Allinger and E. L. Eliel, Eds., Interscience Publishers, New York, N.Y., 1967. In this review, Schlögl discusses the different approaches to the determination of absolute configuration of centrally chiral metallocenes.

(7) A. T. Blomquist and B. M. Smith J. Amer. Chem. Soc., 82, 2073 (1960).

carboxylic acid (VII). From the results of the kinetic resolution of the anhydride of VII with (-)-α-phenethylamine, Eberhardt and Schlögl[7a] assigned to (-)-VII the S configura tion. In addition, [10]paracyclophane-12-carboxylic acid (-)-VII was converted to hydroxy-[10]-paracyclophane (-)-VIII which was hydrogenated to give the corressponding alcohol, (-)-VIIIa. The absolute configuration of the carbinol (-)-VIIIa was established as S by kinetic resolution with phenylbutyric anhydride (Horeau method).[7b]




VII VIII VIIIa

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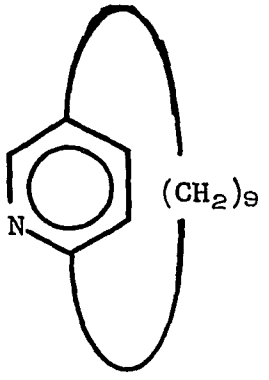
(7a) H. Eberhardt and K. Schlögl, Justus Liebigs Ann., Chem., 760, 157 (1972)

(7b) A. Horeau and H. B. Kagan, Tetrahedron, 20, 2431 (1964).

Gerlach and Huber[8] resolved [9](2,5)pyridinophane (IX) into its enantiomers.




IX

This thesis describes an attempt to establish the absolute configuration of a gentisic acid polymethylene ether, specifically gentisic acid nonamethylene ether (III). The crucial step involves a transfer of asymmetry to a compound of known absolute configuration by a mechanistically understood reaction path. The asymmetric transfer in the present case is incorporated in the transformation III to X (Scheme I, p 7). One of the enantiomers of III was converted by catalytic hydrogenation into a compound containing three asymmetric carbon atoms (X). The latter, using a series of stereochemically understood steps, was correlated with cis-3-hydroxycyclohexanecarboxylic acid (XVI) whose absolute configuration had been

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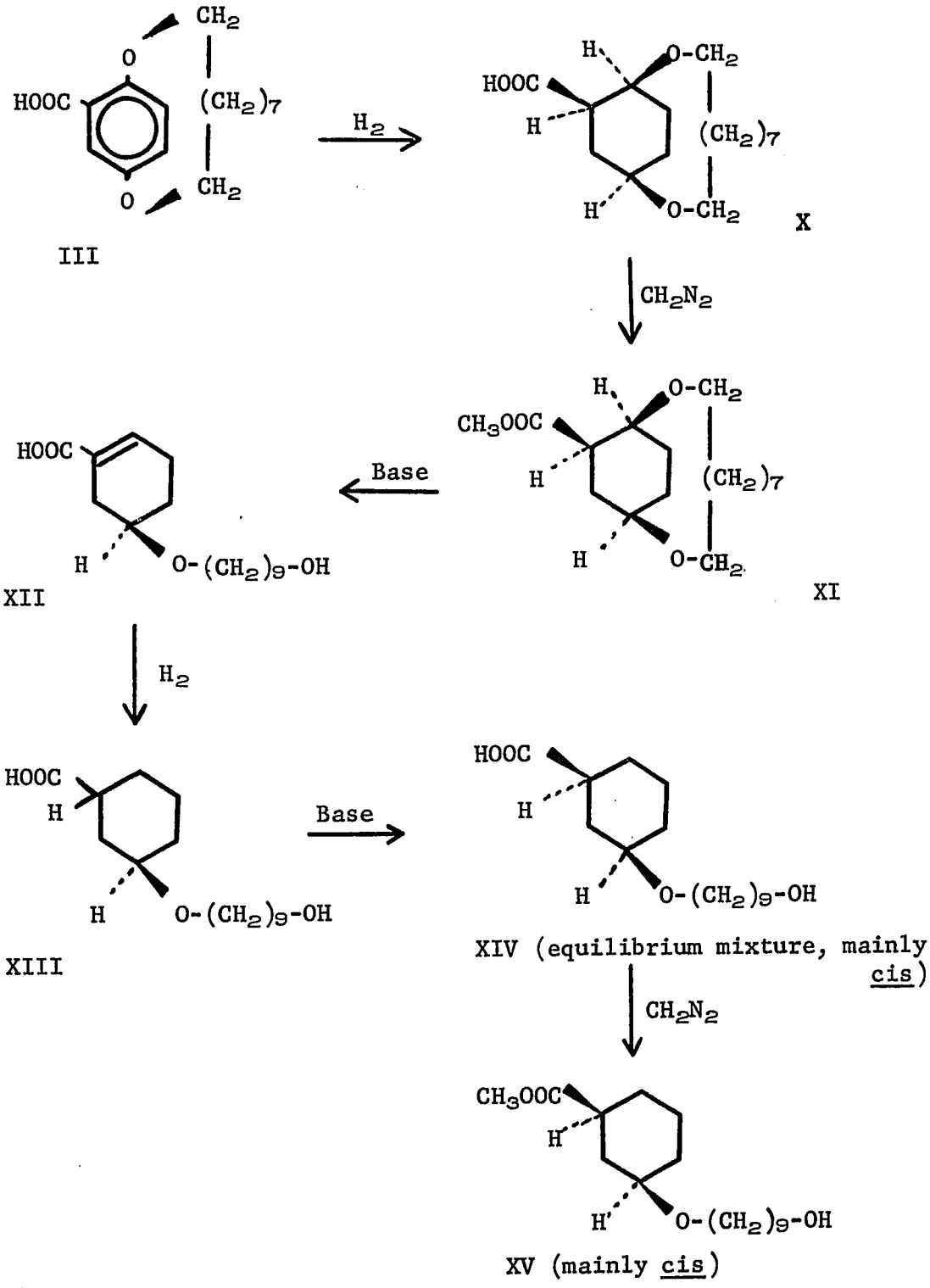
(8) H. Gerlach and E. Huber, Helv. Chim. Acta., 51, 2027 (1968).

Scheme I - Correlation for Establishing the Absolute Configuration of Gentisic Acid Nonamethylene Ether



determined by Noyce and Denney.[9]

The catalytic hydrogenation of optically active III introduced three asymmetric centers of known relative configuration into the product X. Treatment of the methyl ester of X (XI) with base caused the elimination of an $\alpha$-alkoxy group to give XII. Hydrogenation of XII gave XIII (probably a mixture of cis and trans isomers). Treatment of XIII with base gave an equilibrium mixture XIV, which consisted mainly of the thermodynamically more stable cis isomer. The methyl ester (XV) of this equilibrium mixture (XIV) is the relay compound.

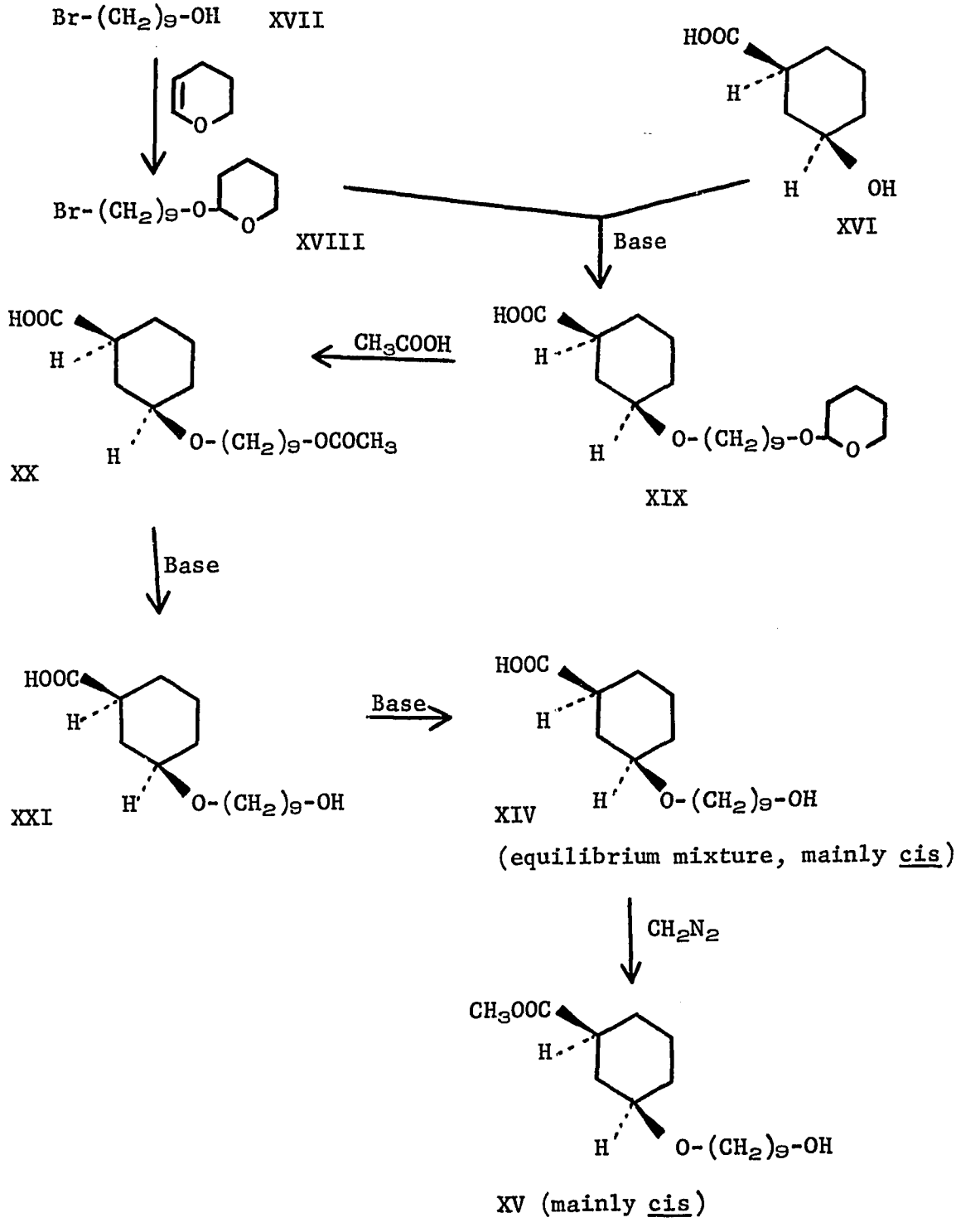
The relay compound (XV) was synthesized from cis-3-hydroxycyclohexanecarboxylic acid (XVI) (Scheme II, p 9) whose absolute configuration is known.[9] Optically active XVI was condensed with 2-(9-bromononamethyleneoxy)tetrahydropyran (XVIII). The condensation product (XIX) was hydrolysed to the free alcohol (XXI). The latter was equilibrated to XIV and the methyl ester (XV) of the equilibrium mixture (XIV) prepared.

Comparison of the sign of rotation of the relay compound (XV) obtained from the hydrogenation of gentisic acid nonamethylene ether (III) with the sign of the rotation of the relay compound (XV) synthesized from cis-3-hydroxycyclohexanecarboxylic acid (XVI) established the absolute configuration of gentisic acid nonamethylene ether.

---

(9) D. C. Noyce and D. B. Denney, J. Amer. Chem. Soc., 76, 768 (1954).

Scheme II - Synthesis of the Relay Compound, Methyl 3-(9-Hydroxy-nonamethyleneoxy)cyclohexanecarboxylate (XV)



# RESULTS AND DISCUSSION

The major decision concerning the particular gentisic acid polymethylene ether to be used had to be made at the outset of the research. Lüttringhaus[1-3] had reported the synthesis of three polymethylene gentisic acids (II, III, and IV) with chains containing eight, nine, and ten polymethylene groups respectively.

Gentisic acid octamethylene ether (II) can be resolved into its dextrorotatory and levorotatory forms using cinchonine and brucine, respectively. The methyl ester of the dextrorotatory isomer is not detectably racemized by heating at 200° for 2 hours.

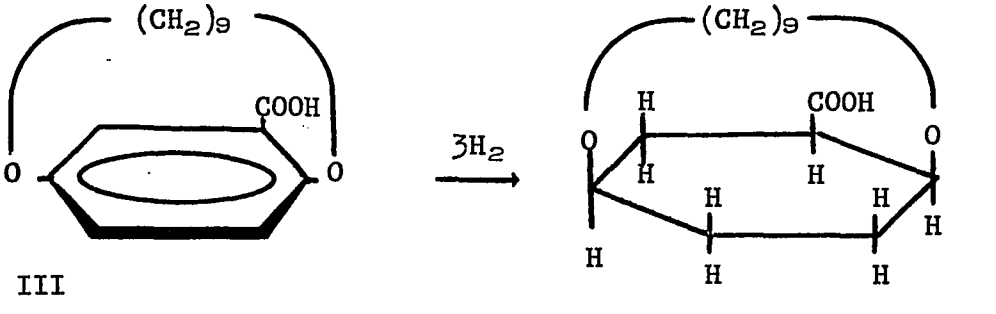
Gentisic acid nonamethylene ether (III) can be resolved into its dextrorotatory and levorotatory forms using strychnine and quinine, respectively. The methyl ester of the dextrorotatory isomer can be racemized at elevated temperatures; its half life at 95.5° is 444 min and at 82.5° is 1835 min, with an activation energy of 28.4 kcal/mol (in xylene).

Gentisic acid decamethylene ether (IV) cannot be resolved. Although Lüttringhaus obtained crystalline salts with cinchonidine, brucine, and strychnine, which he recrystallised to constant rotation, liberation of the free acid with cold dilute sulfuric acid yielded only racemic material.

Because of its optical stability, gentisic acid octamethylene ether (II) would be most suitable for our purposes.

However, its preparation proceeds in poor yield.[3,10] Gentisic acid nonamethylene ether (III) offered the best compromise between optical stability and yield. Its methyl ester has a half life of 20.2 years at 25°. Compound II would not be expected to racemize appreciably on hydrogenation at room temperature.

The first step in the conversion of gentisic acid nonamethylene ether (III) to the relay compound (XV) involves the conversion of III into a compound containing three asymmetric carbon atoms (X). In order to relate the configuration of III and X, it is necessary to know the direction of addition of hydrogen to the aromatic ring. In the following it will be shown that there is ample evidence for <u>cis</u> addition during catalytic hydrogenation of an aromatic ring, and that hydrogen adds to the side of the ring that is adsorbed on the catalyst, i.e., the face of the aromatic ring that is not blocked by the polymethylene chain. Thus the following path is suggested (eq 1):




III X (1)

(10) L. H. Schwartz, Ph.D. Thesis, New York University, New York, N.Y., 1961.

Hydrogenation of monocyclic aromatics has been extensively covered in reviews by Smith,[11] Siegel and Dunkel,[12] and Amano and Parravano.[13] There are also excellent reviews of olefinic hydrogenation (including aromatics) by Burwell,[14] Bond and Wells,[15] and Siegel.[16] The following conclusions can be drawn from the above reviews and the numerous literature references therein.

Hydrogen is added to olefins and aromatics by a mechanism which is predominently, if not exclusively cis addition. The formation of trans addition products seems to involve olefin intermediates that have desorbed and turned over on the catalyst. There is very little evidence for direct trans hydrogenation. The benzene ring is assumed to be adsorbed with its face parallel to the surface from which hydrogen is abstracted. In those instances in which different stereoisomers may form if hydrogen adds from the alternate sides of the molecule, the main product

---

(11) H. A. Smith, Catalysis, 5, 175 (1957).

(12) S. Siegel and M. Dunkel, Advan. Catal., 9, 15 (1957).

(13) A. Amano and G. Parravano, Advan. Catal., 9, 716 (1957).

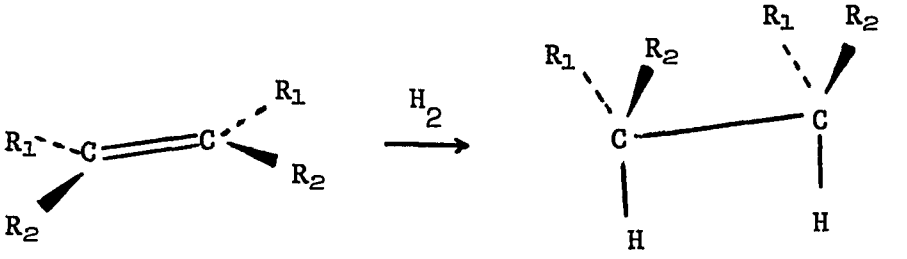
(14) R. L. Burwell Jr., Chem. Rev., 57, 895 (1957).

(15) C. G. Bond and P. Wells, Advan. Catal., 15, 91 (1964).

(16) S. Siegel, Advan. Catal., 16, 123 (1966).

is the one corressponding to the addition from the least hindered side of the molecule.

Farkas and Farkas[17] proposed that hydrogenation involves the simultaneous addition of two atoms of hydrogen to a double bond. The evidence for this point of view is that compounds of type XXII are hydrogenated to the meso compounds XXIII (eq 2).




(2)

XXII XXIII

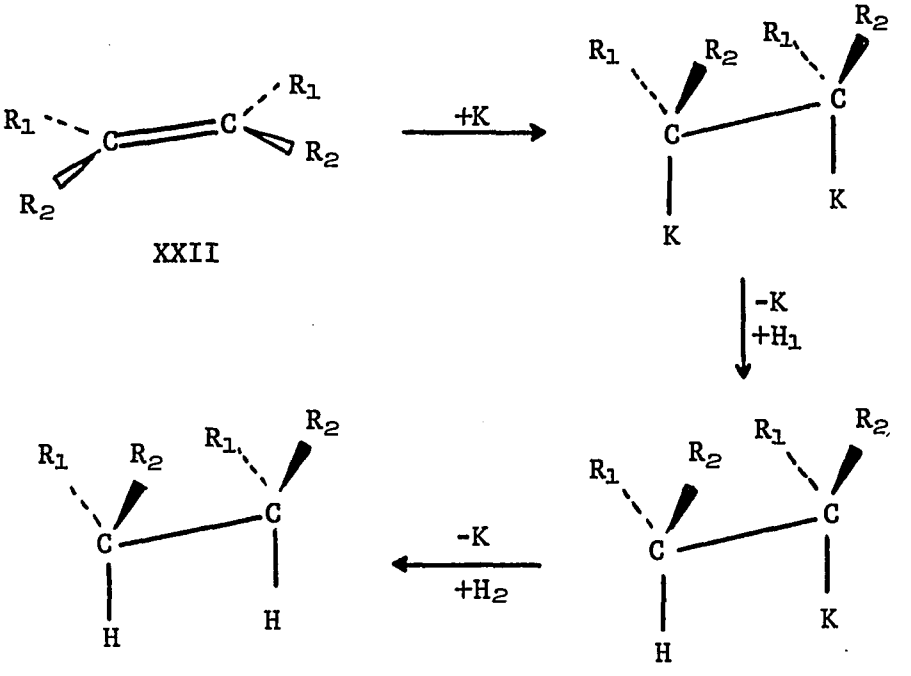
However, Greenhalgh and Polanyi[18] showed that stepwise addition of two hydrogen atoms, in which the configuration at each carbon is retained at each stage of the reaction, can also account for cis addition. This mechanism involves an $\alpha,\beta$-diadsorbed species which reacts stepwise with adsorbed hydrogen atoms at the face in contact with the catalyst. The configuration of the half hydrogenated state is not destroyed by free rotation

---

(17) A. Farkas and L. Farkas, Trans. Faraday Soc., 33, 837 (1937).

(18) R. K. Greenhalgh and M. Polanyi, ibid., 35, 520 (1939).

around the C-C axis. If the assumption is made that the breaking of the catalyst bond (-K) and substitution by atom (+H) occurs by the same steric mechanism for both $H_1$ and $H_2$, the final product is a meso compound (eq 3).




XXII

XXIII

(3)

Noyce and Dolby[19] reduced several 3-hydroxy-4-alkylbenzoic acids (XXIV) with high stereospecificity to the cis isomer (XXXV) over 5% rhodium on alumina in acetic acid (eq 4).

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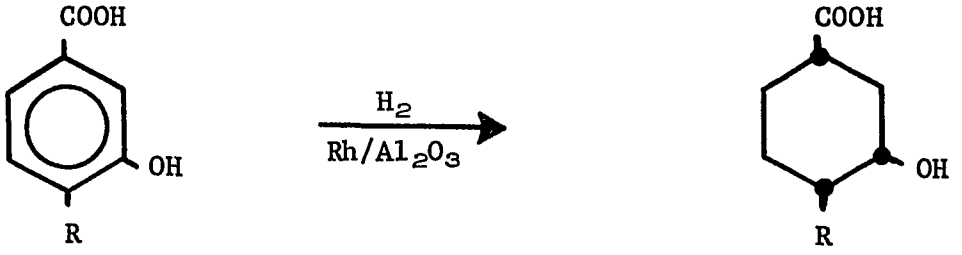
(19) D. S. Noyce and L. J. Dolby, J. Org. Chem., 26, 1732 (1961).

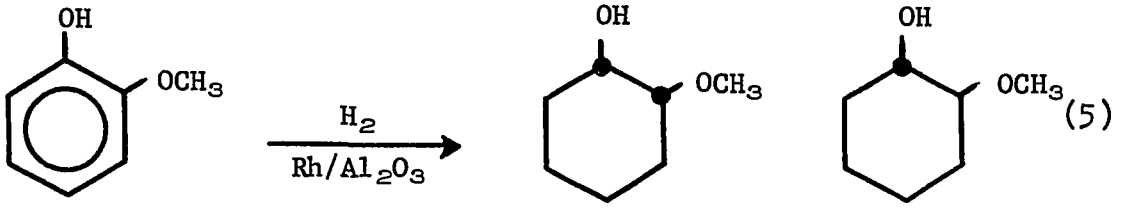



(4)

XXIV XXV

R = $-CH_3$, $-C_2H_5$, $-CH(CH_3)_2$, $-C(CH_3)_3$

Eliel and Brett[20] obtained 90.3 % cis (XXVII) and 9.7 % trans-2-methoxycyclohexanol (XXVIII) from the hydrogenation of guaiacol (XXVI) over rhodium on alumina (eq 5).



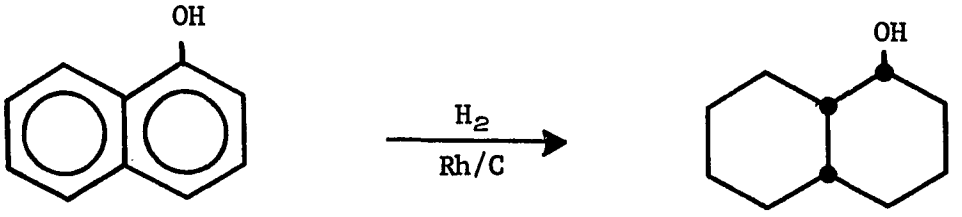

(5)

XXVI XXVII XXVIII

---

(20) E. L. Eliel and T. J. Brett, ibid., 28, 1923 (1963).

Freifelder and Stone[21] obtained a high yield of cis-cis-1-decadol (XXX) from the hydrogenation of 1-naphthol (XXIX) over 5% rhodium on carbon in ethanol (eq 6).




(6)

XXIX XXX

Burgstahler and Bithos[22] obtained cis-cis-1,2,3-cyclohexanetriol (XXXII) from the hydrogenation of pyrogallol (XXXI) over rhodium on alumina (eq 7). These workers also obtained cis-hexahydrogallic acid (XXXIV) from the hydrogenation of gallic acid (XXXIII) (eq 8).

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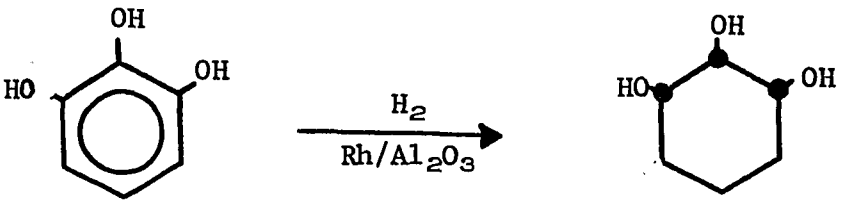
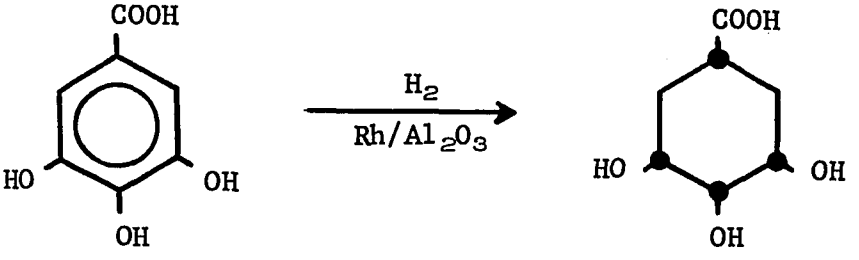
(21) M. Freifelder and G. R. Stone, J. Pharm. Sci., 53, 1134 (1964).

(22) A. W. Burgstahler and Z. J. Bithos, J. Amer. Chem. Soc., 82, 5466 (1960).




XXXI XXXII (7)




XXXIII XXXIV (8)

Many other examples can be cited where cis addition takes place during catalytic hydrogenation of aromatic compounds.

Siegel and his coworkers[23,24] considered the possibility that the hydrogenation of benzene is a stepwise process whereby hydrogen atoms are added two at a time. These workers studied

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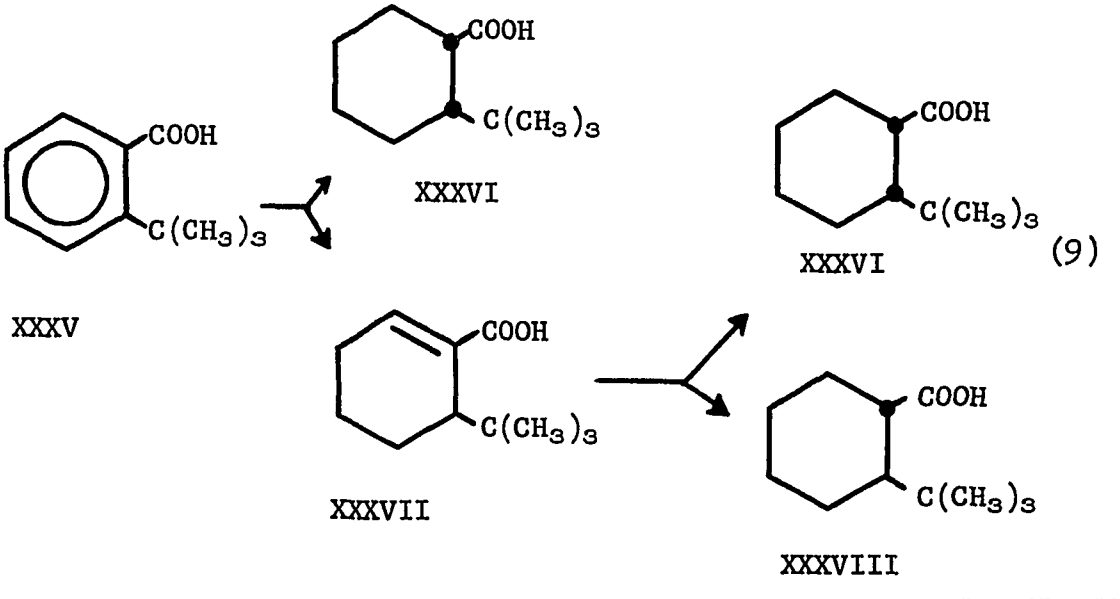
(23) S. Siegel, V. Ku, and W. Halpern, J. Catalysis, 2, 348 (1963).

(24) S. Siegel and V. Ku, Proc. 3rd Intern. Cong. Catalysis, Amsterdam, 1964, Contrib. No. I-80, North Holland Publ., Amsterdam, 1965.

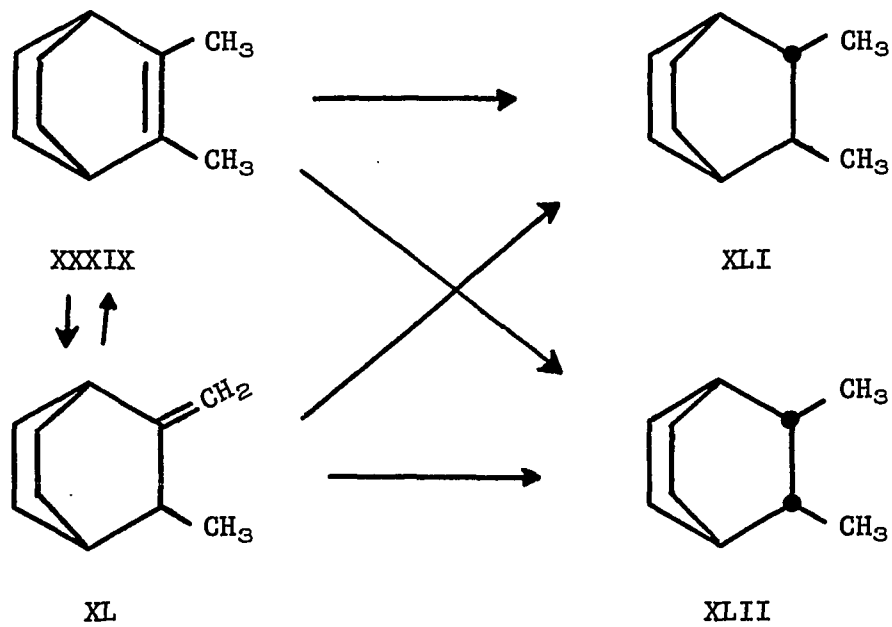
the stereochemistry of hydrogenation of several xylenes and their tetrahydro derivatives. They established that cycloalkenes which would result from cis addition of four atoms of hydrogen to the xylene molecule are released from the surface before readsorption and reduction. Van Bekkum[25] has reported that hydrogenation of 2-tert-butylbenzoic acid (XXXV) over rhodium catalyst yields cis-2-tert-butylcyclohexanecarboxylic acid (XXXVI) and 2-carboxy-3-tert-butylcyclohexene (XXXVII) (which attains a concentration of 22 mole %), and only in the final stages after most of the aromatic compound has disappeared is the trans-2-tert-butylcyclohexanecarboxylic acid (XXXVIII) formed, obviously via the hydrogenation of the tetrahydro derivative (XXXVII) (eq 9).




(9)

(25) H. Van Bekkum, Proc. 3rd Intern. Cong. Catalysis, Amsterdam, 1964, Discussion of Contrib. No. I-80, North Holland Publ., Amsterdam, 1965.

Pecque and Maurel[26] have studied the hydrogenation of 2,3-dimethylbicyclo[2.2.2]oct-2-ene (XXXIX) and 3-methyl-2-methylenebicyclo[2.2.2]octane (XL) over nickel, palladium, and platinum catalysts. They observed that over platinum the hydrogenation of the tetrasubstituted olefin (XXXIX) gave more trans product (XLI) than the hydrogenation of the methylenic isomer (XL) (eq 10). This stereochemistry cannot be explained without direct conversion of the tetrasubstituted olefin (XXXIX) into its trans saturated product (XLI). From this result, they have concluded that, at least on platinum, direct trans hydrogenation occurs.




XXXIX XLI

XL XLII

(10)

(26) M. Pecque and R. Maurel, J. Catalysis, 19, 360 (1970).

Although the mass of evidence indicates that two hydrogen atoms which add to a double bond do so in the cis sense, the direction of approach to the hydrogen acceptor has been deduced from indirect arguments. Steric factors play an important role in bringing about preferential adsorption of a substrate on catalytic surface. In those instances in which different stereoisomers may form if hydrogen adds from the alternate sides of the molecule, the main product is the one corresponding to addition from the least hindered side.

From extensive stereochemical studies on hydrogenation of octahydrophenanthrene derivatives (XLIII), Linstead and his coworkers[27] have concluded that (1) steric hindrance between the catalyst and the substrate plays a considerable part in hydrogenation, (2) the benzene ring is adsorbed with its face parallel to the catalyst surface, and (3) hydrogen is added from the side of the catalyst. Thus derivatives of cis-as-octahydrophenanthrene (XLIII) yielded almost exclusively cis-syn-cis-perhydrophenanthrenes (XVIV) (eq 11). They explained these results on the basis of the mode of adsorption of the substrate on the catalyst surface. If the aromatic ring, lying with its face parallel to the surface, anchors itself to the catalyst, two arrangements are possible.

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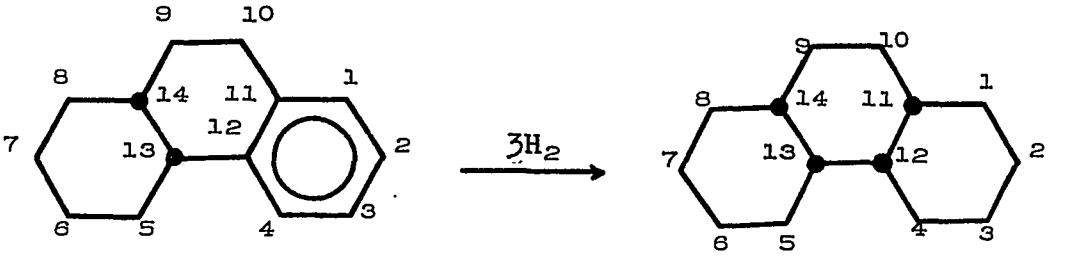
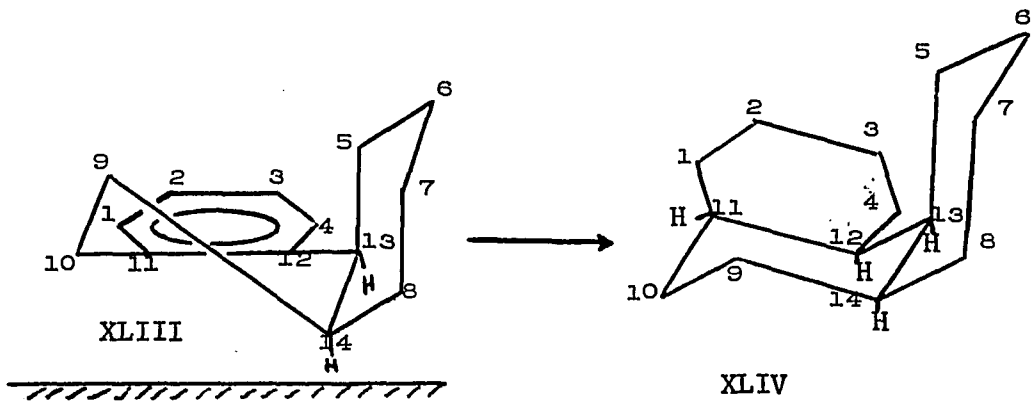
(27) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, J. Amer. Chem. Soc., 64, 1985 (1942).




(11)

XLIII XLIV

In one arrangement, ring A is inclined away from the surface, while in the other, ring A is directed towards the surface of the catalyst. When ring A is inclined away from the surface (eq 12), the hydrogen atom at C-13 is directed towards the surface. Now, if hydrogen adds from the underside of the molecule, the hydrogen which becomes attached to C-12 is on the same side as that at C-13, and therefore a syn arrangement of the rings is obtained. The opposite holds if the molecule is adsorbed so that ring A is directed towards the surface (eq 13). The addition of hydrogen at C-12 would yield the anti arrangement with respect to C-13. That the first manner of adsorption is preferred over the second is understandable in terms of steric effects, consequently the product of cis hydrogenation predominates.

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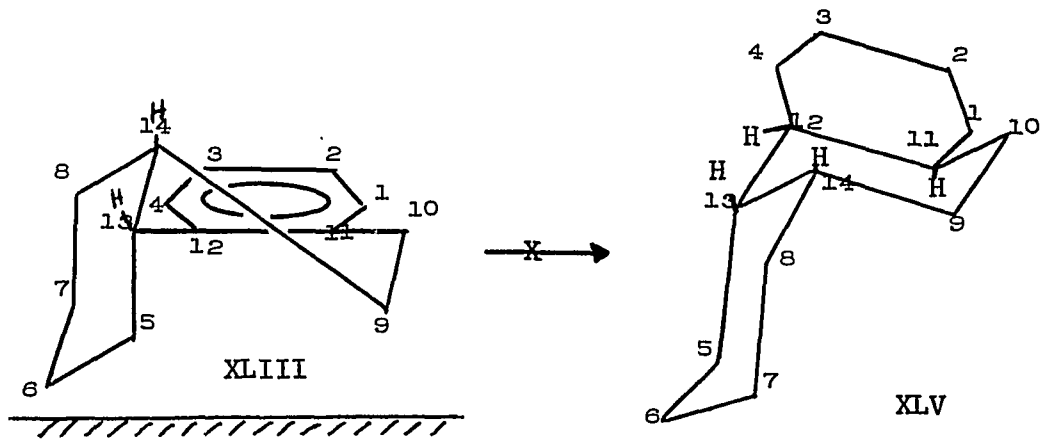


(13)

Pure <u>cis</u> addition results if both hydrogen atoms add to the plane of the olefin molecule from the side facing the catalyst or from the side facing away from the catalyst. Most workers seem implicitly to accept the first possibility. For molecules which

have one side of the double bond blocked, such as XLIII, there are two ways in which the results can be understood. The molecule is adsorbed on the catalyst on its less hindered side and hydrogen adds from the side adsorbed. Alternately the molecule is adsorbed on its more hindered side and the addition of hydrogen takes place from the side away from the catalyst. Either way the observed results can be explained. All that is required is that hydrogen add to the aromatic nucleus from the less hindered side of the ring. For the purpose of this thesis, either explanation is satisfactory although the first one seems more reasonable.

From their work on the exchange of hydrogen with deuterium in cycloalkenes, Rooney and Webb[28] have concluded that replacement of hydrogen (loss of hydrogen as well as the reverse step) utilizes surface adsorbed hydrogen or deuterium.

Adsorbed atoms of hydrogen are involved in catalytic hydrogenation of double bonds, and during the hydrogen-deuterium exchange in hydrocarbons in the presence of metal catalysts.[29] If adsorbed hydrogen atoms are involved in the catalytic hydro-

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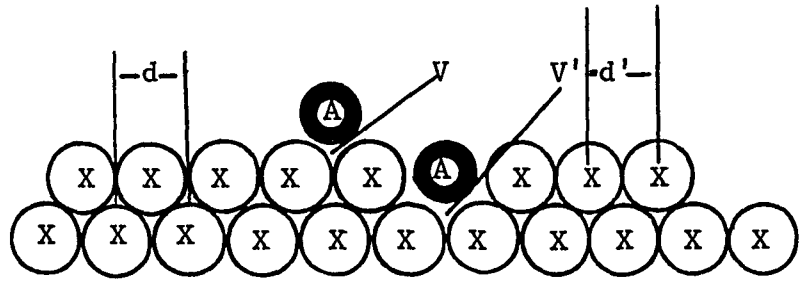
(28) J. J. Rooney and G. Webb, J. Catalysis, 3, 488 (1964).

(29) C. Wagner, "Adsorbed Atomic Species as Intermediates in Heterogenous Catalysis," in Advan. Catal., 21, 323 (1970).

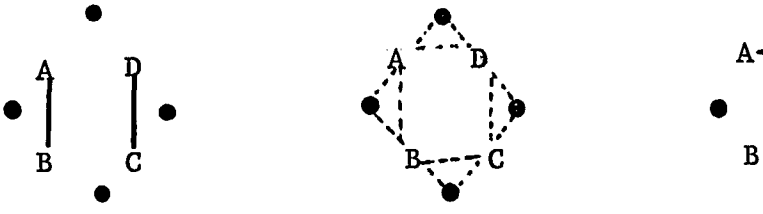
genation of aromatic hydrocarbons, then the only way the observed results with aromatics can be explained is by assuming that the adsorption of the molecule takes place on its less hindered side, and hydrogen adds from the side of the molecule adsorbed on the catalyst.

From his "Multiplet Theory", Balandin[30] has concluded that steric hindrance between the catalyst and substrate plays an important role in hydrogenation, and that hydrogen is added from the side of the catalyst. According to this theory, there are elevations on the surface of the crystal lattice of the catalyst corresponding to the atoms (X). There also exist valleys (V, V', etc.) between the atoms. The distances between the valleys (d) equal those between the elevations (d'). The reacting atoms (A) fall into the valleys between the surface of the group of atoms




(30) A. A. Balandin,"Modern State of the Multiplet Theory of Heterogenous Catalysis," in Advan. Catal., 19, 1 (1969).

of the catalyst (multiplet) and an intermediate multiplet complex is formed. The interactions of the catalyst with the substrate proceed under the influence of chemical valence forces; the bonds inside the substrate molecule are weakened. The weakened valence bonds of the multiplet complex rearrange and in the course of this rearrangement, products of the reaction are formed. Catalytic reactions of organic chemistry are considered as doublet, triplet, or sextet reactions. In a doublet reaction (eq 14), two bonds of reactants

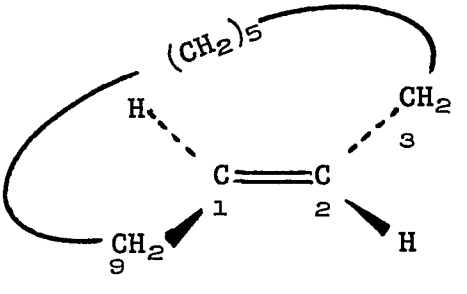



(a) (m) (b) (14)

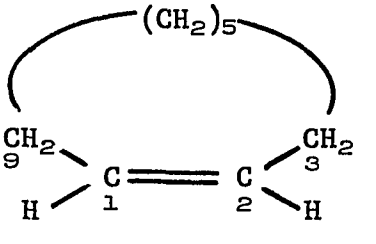
are broken (a) and two new ones are formed in the products (b); the transition from 14a to 14b is accomplished through the multiplet complex (m). Here A, B, C, and D denote reacting atoms; they may have substituents which are not shown. The atomic centers of the catalyst are shown as dots. In a triplet reaction, three bonds are broken and three new ones are formed. A sextet involves breaking and reformation of six bonds. Since the atoms of the catalyst are involved in the formation of the multiplet complex, it follows that only certain catalysts with certain interatomic distances and crystal lattices can function as catalysts

for a particular reaction. It can be easily seen that Balandin's multiplet theory is in full conformity with Linstead's results, that the less hindered side of a reacting molecule will be adsorbed on the catalyst surface, and that hydrogen is added from the side that is adsorbed on the catalyst.

trans-Cyclononene (XLVI) exists in only one relatively unstrained conformation. The four carbon atoms (marked 9, 1, 2, and 3) must lie in a plane, the two exterior carbon atoms (9 and 3) are joined by a $-(CH_2)_5-$ chain, which passes either behind or in front of the plane, thus completely blocking one side of the double bond to attack from any external reagent. It has been observed that both trans (XLVI) and cis-cyclononene (XLVII) hydrogenate readily under mild conditions. Since either the olefin or the hydrogen must be adsorbed on the catalyst, Blomquist[31] has




XLVI




XLVII

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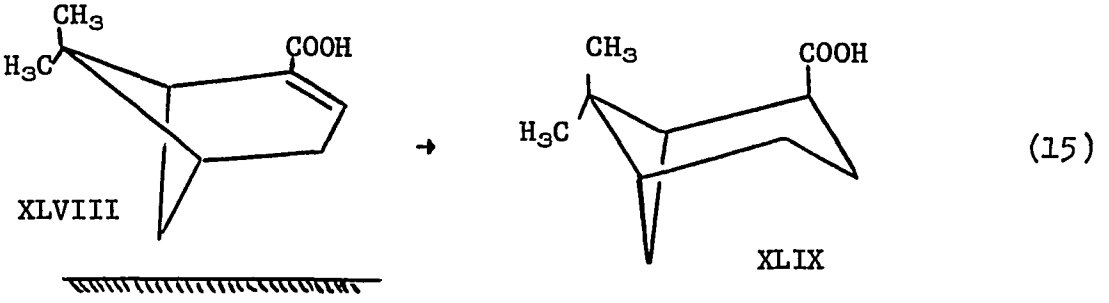
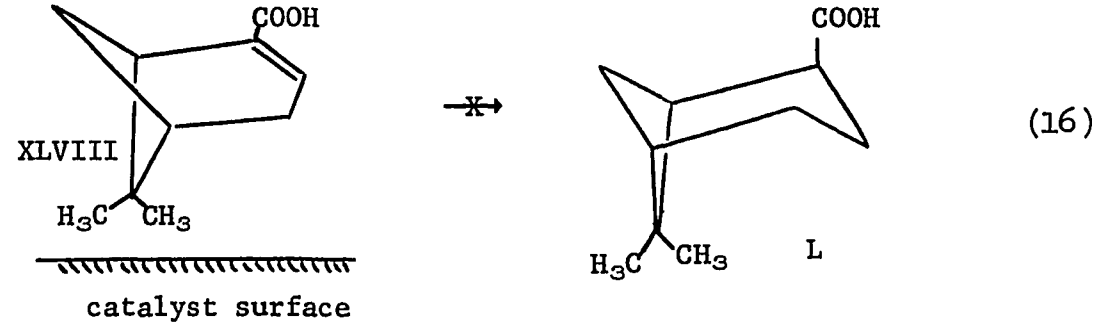
(31) A. T. Blomquist, L. H. Lin, and J. C. Bohrer, J. Amer. Chem. Soc., 74, 3643 (1952).

concluded that hydrogen must add from the direction of the surface of the catalyst.

Eigenmann and Arnold[32] have studied the hydrogenation of several α-pinene derivatives. They found that low temperature, low pressure hydrogenation of α-pinene derivatives in acetic acid or ethanol over Adams platinum catalyst proceeds in a stereospecific manner, and that the products all possess the *cis* configuration, hydrogen being added from the methylene side of the molecule. Thus myrtenic acid (XLVIII) yields <u>cis</u>-dihydromyrtenic acid (XLIX)




(15)




(16)

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(32) G. W. Eigenmann and R. T. Arnold, <u>ibid</u>., <u>81</u>, 3440 (1959).

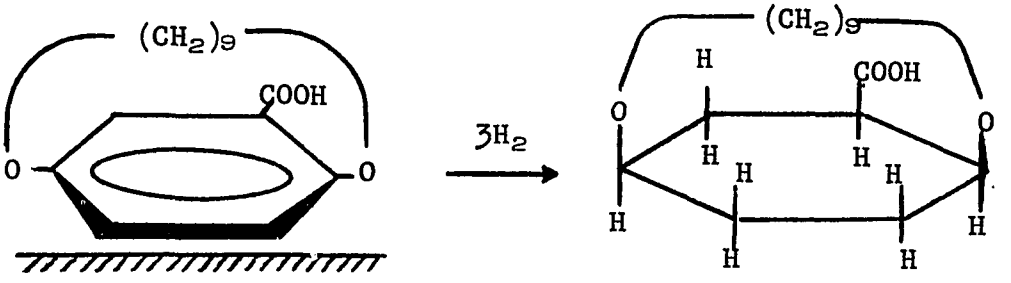
(eq 15). The adsorption of an α-pinene derivative on the catalyst surface appears to be determined largely by the steric requirements of the methylene and isopropylidene bridges. The mode of adsorption involving the methylene bridge facing the catalyst is thus preferred, and reduction under mild conditions leads to cis addition of hydrogen atoms from the methylene bridge side of the molecule. Such addition occurs in spite of the fact that it leads to the formation of the thermodynamically less stable isomer.

For the catalytic hydrogenation of gentisic acid nonamethylene ether (III), the following points have to be kept in view:

> Hydrogen is added to olefins and aromatics by a mechanism, which involves predominantly, if not exclusively, cis addition.
>
> The benzene ring is assumed to be adsorbed with its face parallel to the surface of the catalyst.
>
> The shape of the given molecule determines on which face adsorption is more likely. Steric factors determine the manner in which the molecule is adsorbed on the catalyst surface.
>
> Hydrogen is added from the side of the catalyst.

Gentisic acid nonamethylene ether (III) has one face

of the aromatic ring blocked by the polymethylene ring. Hence, the other face which is not blocked by the polymethylene ring would be adsorbed on the catalyst surface. Since hydrogen is added to the side adsorbed on the catalyst, the configuration of the saturated product (X) will be as shown below, (eq 1).




III X (1)

Methoxyl and other ethereal linkages are known to be susceptible to hydrogenolysis in the course of catalytic hydrogenation of aromatic ethers.[33]

Smith and Thomson[33] have carried out a study of the hydrogenation and hydrogenolysis of aromatic ethers. Their results which are pertinent to the present study may be summarized as follows:

The extent of cleavage is found to be

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(33) H. A. Smith and R. G. Thomson, Proc. Intern. Cong. Catalysis, Philadelphia, Penn., 1956, Contrib. No. 73, Academic Press Inc. Publ., New York, N.Y., 1957.

dependent upon the catalyst, the compound, and the reaction conditions. Rhodium on alumina results in much less hydrogenolysis than platinum catalyst. Schwartz[10] has confirmed the same conclusions. The amount of cleavage increased linearly with temp.

Hydrogenolysis of a methoxyl group does not occur prior to the hydrogenation of the aromatic ring.

Hydrogenolysis of a methoxyl group does not occur subsequent to the complete saturation of the aromatic ring.

The direction of cleavage is predominantly between the aromatic carbon and the oxygen atom.

With these facts in hand, it was decided to use 5% rhodium on alumina for the hydrogenation of gentisic acid nonamethylene ether.

Nishimura and Yoshino[34] have shown that the nature of the solvent used has a profound effect on the extent of hydrogenolysis. The rate of hydrogenolysis increases with increasing

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(34) S. Nishimura and H. Yoshino, Bull. Chem. Soc. Jap., 42, 499 (1969).

polarity of the solvent.

Results of our preliminary experiments indicated that there was less hydrogenolysis with 95% ethanol as solvent than with acetic acid. It was also found that compared with hydrogenation at atmospheric pressure, hydrogenation at three atmospheres (Parr low pressure hydrogenation apparatus) resulted in less hydrogenolysis.

Since we wanted to minimize hydrogenolysis of the ethereal linkages during conversion of III to X, it was decided to use 95% ethanol as solvent and to carry out the hydrogenation in a Parr low pressure hydrogenation apparatus.

While the writing of this thesis was in progress, a report on the hydrogenation and hydrogenolysis of aromatic ethers was published. Nishimura and his coworkers[35] studied the hydrogenation of ethyl p-tolyl ether (LI) over platinum metal catalysts in ethanol solvent. The results of this study which are pertinent to the present work are summarized as follows:

> The extent of hydrogenolysis depends on the nature of the catalyst and increases in the order Pd<Ru<Rh<Ir<Pt.
>
> Hydrogenation pathways with different

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(35) S. Nishimura, M. Uramoto, and T. Watanane, ibid., 45, 216 (1972).

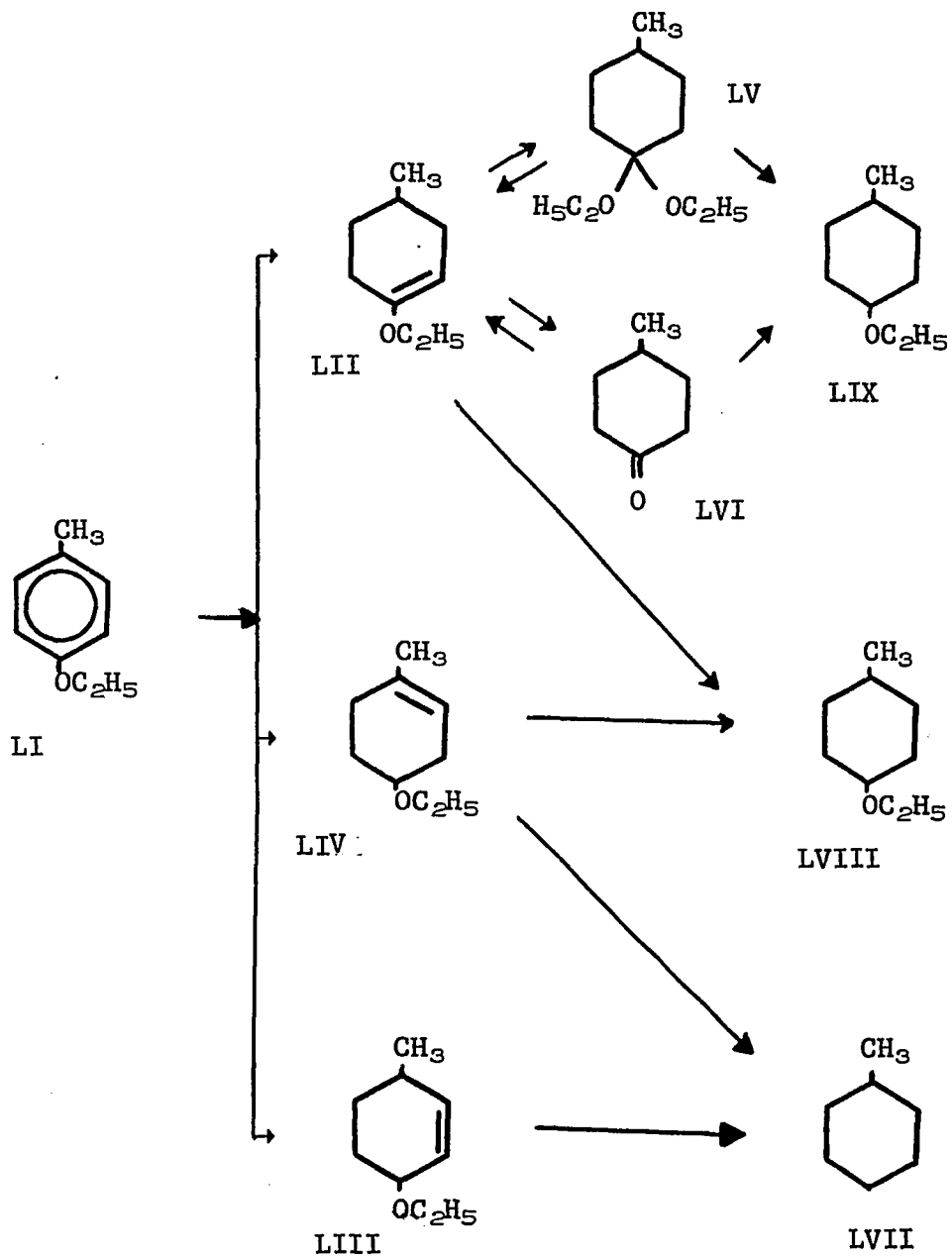
catalysts have been postulated. Tetrahydro derivatives such as enol ether (LII), allyl ether (LIII), and homoallyl ether (LIV) are concluded to be the intermediates in the hydrogenation of LI.

The nature and the amount of tetrahydro derivatives that may be desorbed depends on the catalyst used.

Depending on the catalyst used, the tetrahydro derivative may undergo hydrogenation or hydrogenolysis or both.

The postulated hydrogenation pathways over rhodium catalyst assumes that the three tetrahydro derivatives are formed equally. The enol ether (LII) is hydrogenolysed to only a slight extent, the allyl ether (LIII) is hydrogenolysed completely, while the homoallyl ether (LIV) is hydrogenolysed to the extent of only 24%. It is also to be noted that LII, LV, and LVI are scarcely hydrogenated during the hydrogenation of LI; when the amount of LI approaches almost zero, hydrogenation of LII, LV, and LVI seems to begin. The cis/trans ratio of saturated

ether LVIII is very high in the initial stages, but decreases to about 10 towards the end of hydrogenation (eq 17).



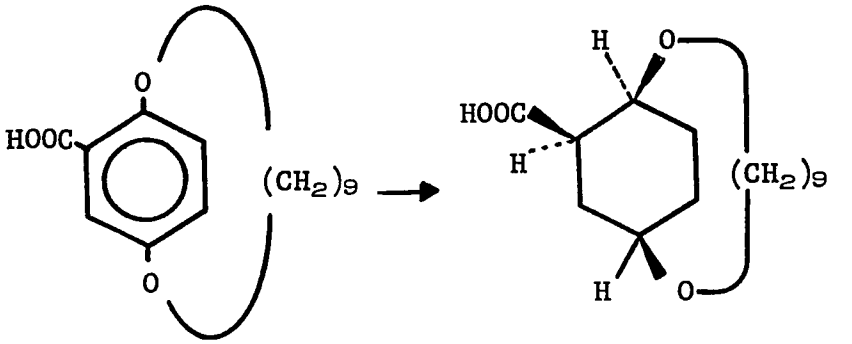

(17)

The results obtained by Nishimura and his coworkers[35] are similar to those obtained by Siegel and his coworkers[23,24] and by Van Bekkum.[25] All these workers conclude that tetrahydro derivatives (cycloalkenes) which would result from cis addition of four atoms of hydrogen to the aromatic nucleus are indeed released from the surface before readsorption and reduction. The formation of trans addition products involves these olefin intermediates that have desorbed and turned over on the catalyst.

From the results obtained by Nishimura and his coworkers,[35] it can be seen that our choice of rhodium catalyst was quite good. Use of rhodium results in comparatively less hydrogenolysis. In spite of the desorption of the tetrahydro derivatives, the fully saturated product is still predominantly a cis addition product.

Keeping in mind that hydrogen will be added to the aromatic ring of gentisic acid nonamethylene ether (III) from the side that is not blocked by the polymethylene chain, and that during hydrogenolysis the cleavage is predominantly between aromatic carbon atoms and the ether oxygen atoms, one can envisage the following products from the hydrogenation and hydrogenolysis of gentisic acid nonamethylene ether (III) (eq 18, p 36).

Gentisic acid nonamethylene ether (III) was hydrogenated in a Parr low pressure hydrogenation apparatus with 5% rhodium on alumina in 95% ethanol. The reaction mixture was separated

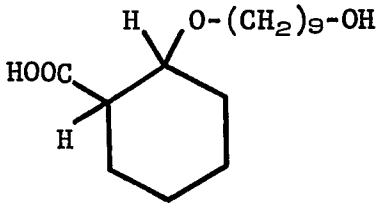



(18)

III

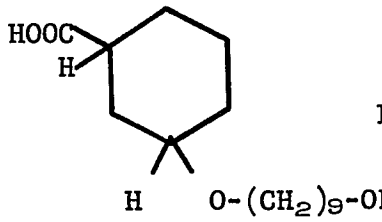
X

+



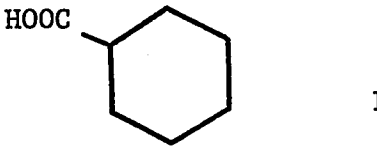

LX

+




LXI

+




LXII

+

HO-(CH2)9-OH LXIII

into acid and neutral fractions with sodium hydroxide. The neutral fraction was identified as 1,9-nonanediol (LXIII) by comparison of its nmr spectrum with that of an authentic sample.

Column chromatography of the crude acid fraction yielded four acids. The first to be eluted was compound LXII, identified as cyclohexanecarboxylic acid by comparison of its nmr spectrum with that of an authentic sample. The next to be eluted was compound X, which was followed by LX and LXI respectively. The acids X, LX, and LXI had $R_f$ values of 0.75, 0.65, and 0.60 respectively, on tlc (p 70).

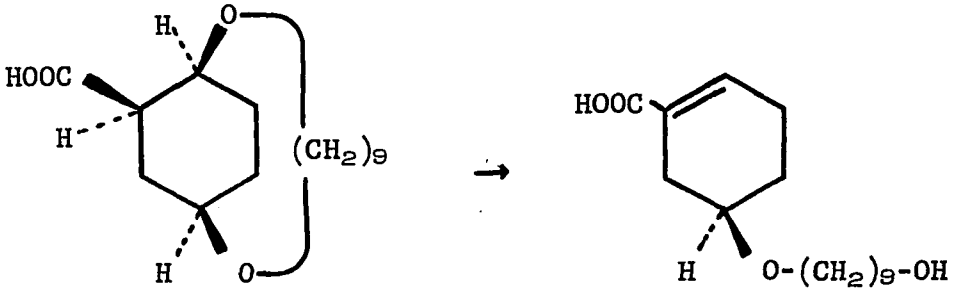
Compound LXI was tentatively assigned the structure cis-3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid. Its nmr and ir spectra and tlc properties were identical to those of cis-3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XXI) synthesized from cis-3-hydroxycyclohexanecarboxylic acid (XVI). Compound LXI was equilibrated to XIV, and the latter was converted to its methyl ester XV. Elemental analysis and a comparison of the nmr and ir spectra and the ms of XV, obtained from LXI with those of the synthetic relay compound, XV, obtained from cis-3-hydroxycyclohexanecarboxylic acid (XVI), confirmed the structure assigned to LXI as cis-3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid.

Compound X was tentatively assigned the structure cis-2,5-(1,9-nonamethylenedioxy)cyclohexanecarboxylic acid. It was

eluted immediately after cyclohexanecarboxylic acid, and had an $R_f$ value of 0.75 on tlc. Compound X was converted to its methyl ester XI. On treatment with potassium t-butoxide in dimethylsulfoxide, the methyl ester (XI) was converted to $\alpha,\beta$-unsaturated acid XII. The latter on catalytic hydrogenation yielded XIII. On equilibration with 30% sodium hydroxide solution, XIII gave the equilibrium mixture XIV. The latter was converted to its methyl ester, XV. A comparison of the nmr and ir spectra, and the ms of this XV (from X) with those of XV obtained from LXI and that synthesized from cis-3-hydroxycyclohexanecarboxylic acid (XVI), confirmed the structure of X as cis-2,5-(1,9-nonamethylenedioxy)cyclohexanecarboxylic acid.

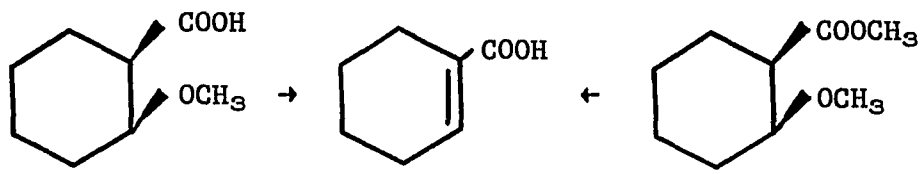
On the basis of its chromatographic properties, and its nmr spectrum, LX was tentatively assigned the structure 2-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid.

The next step in the corelation sequence (Scheme I, p 7) is the elimination reaction, i.e., X to XII (eq 19).




X XII (19)

The model compound selected for studying this type of elimination was cis-2-methoxycyclohexanecarboxylic acid (LXIV). The latter was prepared by catalytic hydrogenation of 2-methoxybenzoic acid. A base could remove an α-proton with simultaneous or subsequent loss of the β-methoxyl group to form the double bond. Either the acid (LXIV) or its methyl ester (LXV) could be used as the starting material (eq 20).



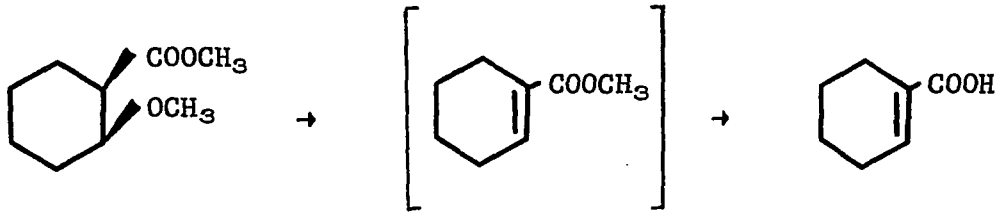

(20)

LXIV LXVI LXV

The acid (LXIV) and the ester (LXV) were separately heated with sodium methoxide in methanol. With the acid there was no elimination, and the starting material was recovered, quantitatively. With the ester, there was some elimination, some conversion to the trans-methoxy isomer, and possibly some condensation.

The best system for carrying out the required elimination reaction was found to be potassium t-butoxide in dimethylsulfoxide. With this system, it was observed that the elimination from the free acid (LXIV) was comparatively poor

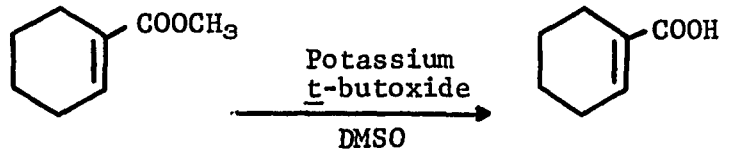
(less than 20%). However, the elimination from the methyl ester (LXV) is much better (85 to 90%). The best ratio of ester to potassium t-butoxide is 1:2.5. During the procedure, the methyl ester is hydrolysed, and the free acid (LXVI) is obtained. Since the elimination from the free acid (LXIV) takes place in very poor yield, it can be concluded that first elimination takes place from the ester (LXIV) forming methyl cyclohexenecarboxylate (LXVII) which is then hydrolysed (probably during work-up) to free cyclohexenecarboxylic acid (LXVI) (eq 21).




(21)

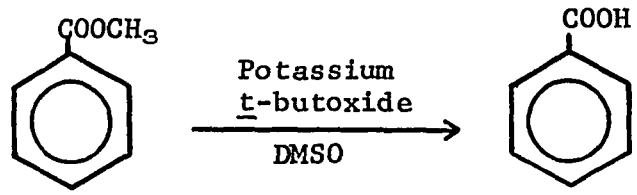
LXV LXVII LXVI

A control experiment was run, and it was found that methyl cyclohexenecarboxylate (LXVII) as well as methyl benzoate (LXVIII) were indeed hydrolysed to cyclohexenecarboxylic acid (LXVI) (eq 22) and benzoic acid (eq 23), respectively, under the work-up conditions.




(22)

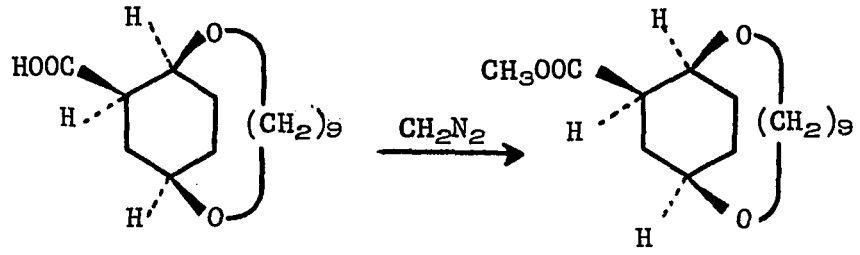
LXVII LXVI




(23)

LXVIII LXXIX

The nmr spectrum of cis-2,5-(1,9-nonamethylenedioxy) cyclohexanecarboxylic acid (X) had a broad singlet at δ 9.41 (COOH). Acid X was treated with diazomethane in ether to yield methyl ester XI (eq 24). The nmr spectrum of the methyl ester

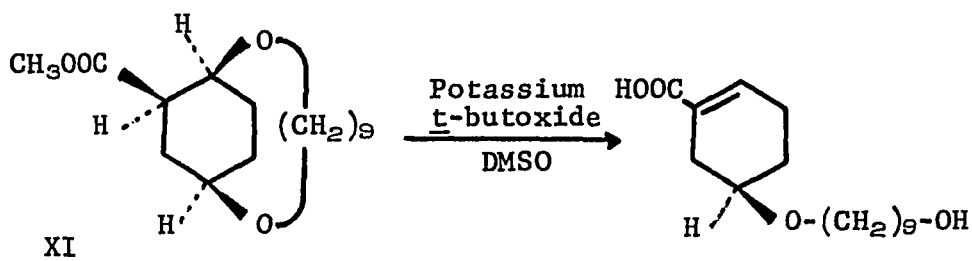



(24)

X XI

(XI) showed the absence of COOH and a sharp singlet was present at δ 3.70 ($COOCH_3$). The ir spectrum of the methyl ester (XI) showed an absorption band at 1740 $cm^{-1}$ (ester); the region 3300-3600 $cm^{-1}$ showed the absence of OH.

Methyl ester XI on treatment with potassium t-butoxide in dimethylsulfoxide yielded α,β-unsaturated acid XII (eq 25).

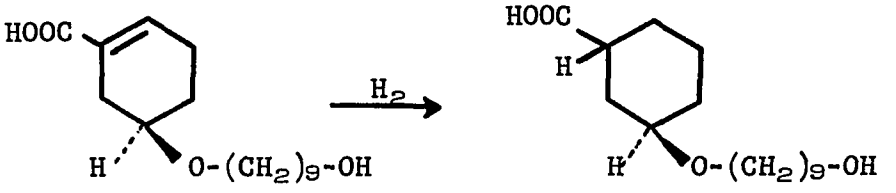



(25)

XI XII

The nmr spectrum of compound XII showed a singlet at δ 7.12 (vinyl-H) and a singlet at δ 7.55 (average for OH and COOH) which disappeared on treatment with $D_2O$. The ir spectrum of XII showed absorption bands for α,β-unsaturated acid (1690 $cm^{-1}$) and for olefin (1650 $cm^{-1}$).

On catalytic hydrogenation, unsaturated acid XII was converted to the saturated acid, XIII (stereochemistry not established) (eq 26). The nmr and ir spectra showed the absence

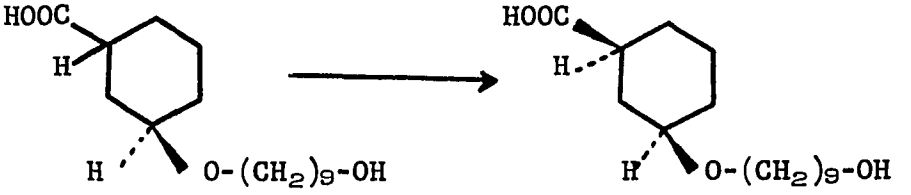



(26)

XII XIII

of any unsaturation; the singlet at δ 7.12 was absent, as was also the absorption band at 1650 $cm^{-1}$.

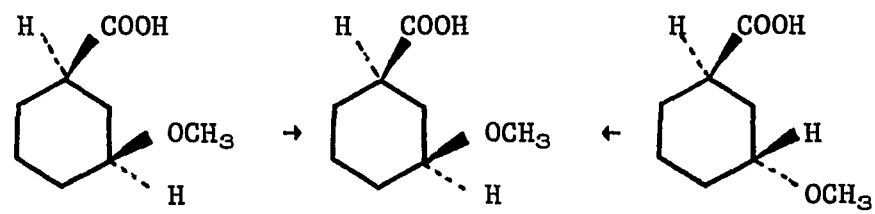
The next step in the correlation sequence (Scheme I, p 7) was the epimerization of the acid XIII to give an equilibrium mixture XIV (eq 27), which would be expected to be composed of mainly the cis isomer.




(27)

XIII XIV (equilibrium mixture) (mainly cis)

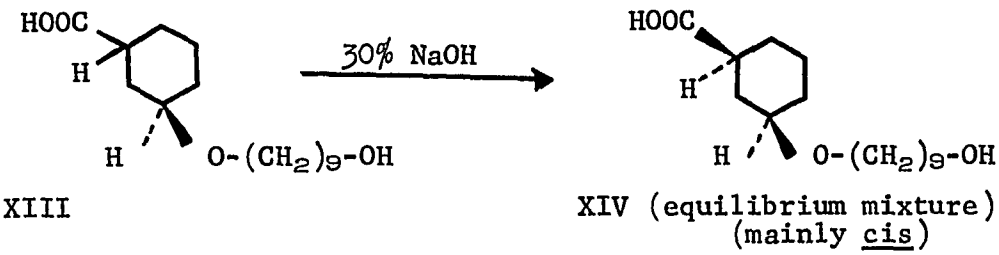
The compound selected for studying this type of equilibrium reaction was 3-methoxycyclohexanecarboxylic acid. The aim was to obtain the equilibrium mixture starting with either the cis (LXX) or the trans (LXXI) isomer of 3-methoxycyclohexanecarboxylic acid. The acids as well as their methyl esters were investigated. Sodium methoxide in methanol, potassium t-butoxide in t-butanol, and potassium hydroxide in t-butanol were tried with varying amounts of success. Some epimerization did take place, but the equilibrium composition was not reached. The best system for carrying out the required equilibration was found to be 30% sodium hydroxide. When the cis or the trans-3-methoxycyclohexanecarboxylic acid (LXX or LXXI) was heated under reflux with 30% sodium hydroxide for 65 hours, the same mixture of cis and trans isomers was obtained in 67% and 77% yield respectively (eq 28).




(28)

LXX LXXII (equilibrium mixture) (mainly cis) LXXI

The acid XIII was heated with 30% sodium hydroxide to give the equilibrium mixture XIV (eq 27). The equilibrium



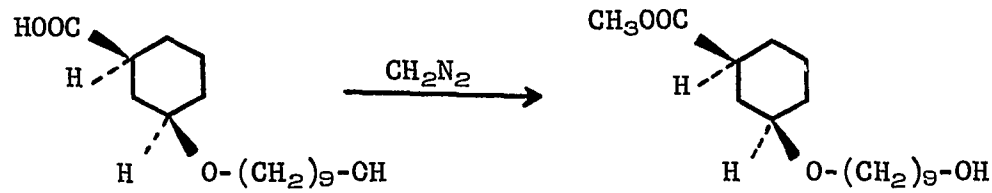

(27)

XIII

XIV (equilibrium mixture) (mainly cis)

mixture (XIV) obtained from cis-2,5-(1,9-nonamethylenedioxy)-cyclohexanecarboxylic acid (X) had the same tlc behaviour as XIV obtained from LXI and XIV synthesized from cis-3-hydroxycyclohexanecarboxylic acid (XVI).

The equilibrium mixture (XIV) obtained from X was treated with an ethereal solution of diazomethane to form the methyl ester (XV) (eq 29). Methyl ester XV was distilled under




(29)

XIV

XV (mainly cis)

reduced pressure in a short path distillation apparatus. The methyl ester (XV) showed a sharp singlet at $\delta$ 3.66 ($COOCH_3$), and an absorption band at 1770 $cm^{-1}$ (ester).

No attempt was made to purify the product of elimination (X → XII). However, before attempting the epimerization reaction, the hydroxy acid XIII was purified by column chromatography. Also, the relay compound XV was distilled to achieve purification.

The relay compound XV, which consists mainly of the cis isomer, is a viscous oil and hence quite difficult to work with. It was expected to be obtained in small quantities. Its rotation was to be compared with that of the relay compound (XV) obtained synthetically from optically active cis-3-hydroxycyclohexanecarboxylic acid (XVI). It was thus necessary to ensure that the ratio of cis-trans isomers in the relay compound from the two different sources be the same. In order to accomplish this, identical work-up procedures were necessary, before comparing their rotations. The relay compound XV was synthesized from cis-3-hydroxycyclohexanecarboxylic acid (XVI). Before epimerization, XXI, obtained from XVI, was purified by column chromatography, the equilibration being carried out under conditions identical to those used with XIV obtained from the ansa compound III. Finally the methyl ester XV was distilled in a short path distillation apparatus under conditions identical to those used with XV from the ansa compound III. Similar yields were obtained for conversion of the equilibrated hydroxy acid XIV from three different sources (X, LXI, and XVI) to the corresponding distilled methyl ester XV, the relay compound.

The first step in the synthesis of the relay compound (XV) was the preparation of cis-3-hydroxycyclohexanecarboxylic acid (XVI). 3-Hydroxybenzoic acid (LXXIII) was hydrogenated

over 5% rhodium on carbon in 95%ethanol. The crude hydrogenation mixture contained both cis and trans isomers of 3-hydroxycyclohexanecarboxylic acid together with some cyclohexanecarboxylic acid (LXXV). From this, cis-3-hydroxycyclohexanecarboxylic acid was separated by repeated crystallization from ethyl acetate.[36] This method of preparation was time consuming, and the yield was poor, because of the amount lost during the repeated crystallizations. We finally turned to a different method of separating the crude reaction product obtained from hydrogenation of 3-hydroxybenzoic acid.[37] The crude mixture of cis and trans-3-hydroxycyclohexanecarboxylic acids obtained from the catalytic hydrogenation of 3-hydroxybenzoic acid was heated. The cis isomer formed the lactone (LXXVI). The latter was separated from the trans-3-hydroxycyclohexanecarboxylic acid by fractional distillation under reduced pressure. Hydrolysis of the lactone (LXXVI) yielded cis-3-hydroxycyclohexanecarboxylic acid (XVI) (Scheme III, p 47).

The next step in the synthetic sequence (Scheme II, p 8) was the condensation of cis-3-hydroxycyclohexanecarboxylic acid (XVI) and 9-bromononanol (XVII) (eq 30, p 48).

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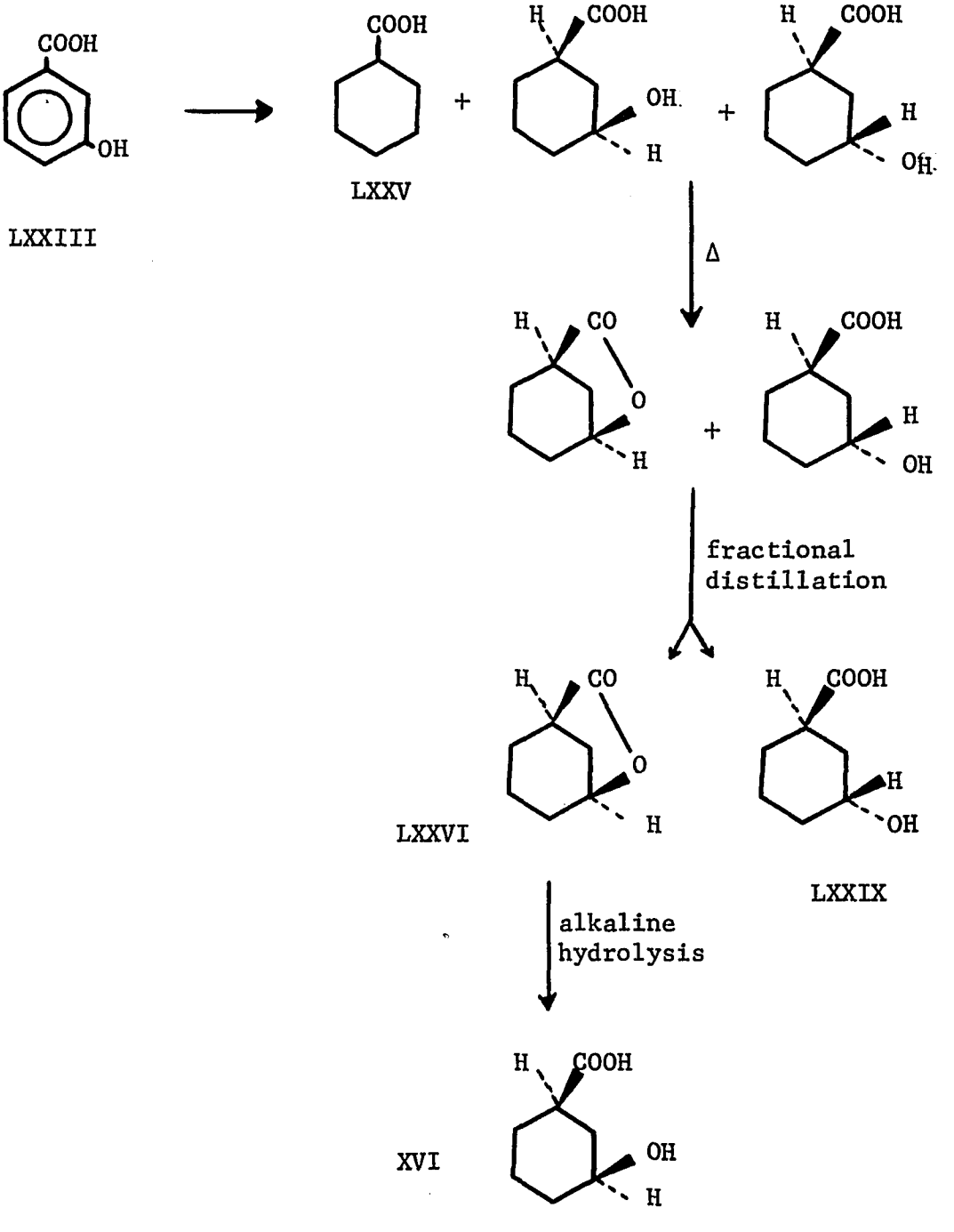
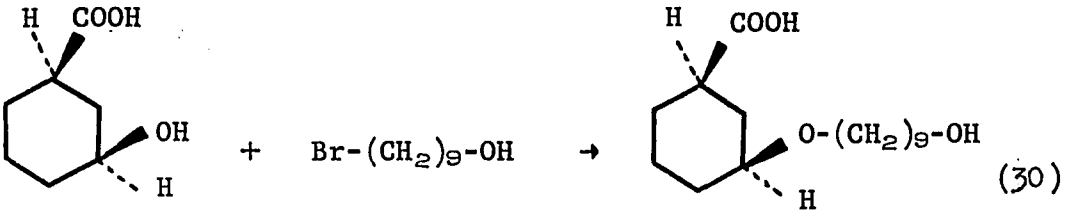
(36) D. S. Noyce and D. B. Denney, J. Amer. Chem. Soc., 74, 5912 (1952).

(37) E. J. Boorman and R. P. Linstead, ibid., 57, 258 (1935).

Scheme III - Preparation of cis-3-Hydroxycyclohexanecarboxylic Acid (XVI).






(30)

XVI XVII XXI

9-Bromononanol was prepared by the method of Butenandt and his coworkers[38] from 1,9-nonanediol (LXXVII) and hydrobromic acid (eq 31).

$$HO\text{-}(CH_2)_9\text{-}OH + HBr \rightarrow Br\text{-}(CH_2)_9\text{-}OH \qquad (31)$$

LXXVII XVII

Since the condensation of cis-3-hydroxycyclohexanecarboxylic acid (XVI) and 9-bromononanol (XVII) was to be carried out under basic conditions, the hydroxyl group of 9-bromononanol had to be suitably protected. This was achieved by reaction with 2,3-dihydropyran (LXXVIII) (eq 32).

Condensation of cis-3-hydroxycyclohexanecarboxylic acid (XVI) and 2-(9-bromononamethyleneoxy)tetrahydropyran (XVIII)

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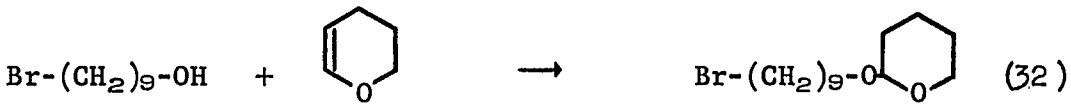
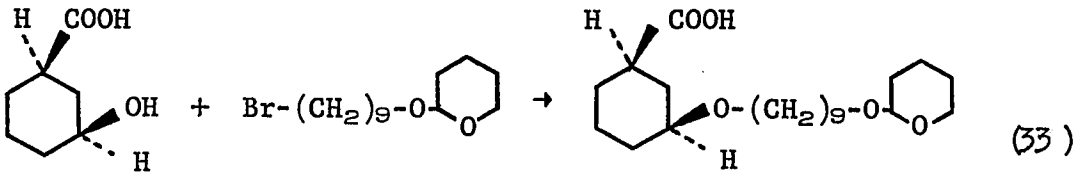
(38) A. Butenandt, E. Hecker, M. Hopp, and W. Kuch, Justus Liebigs Ann. Chem., 658, 39 (1962).

yielded XIX (eq 33).



(32)

XVII LXXVIII XVIII

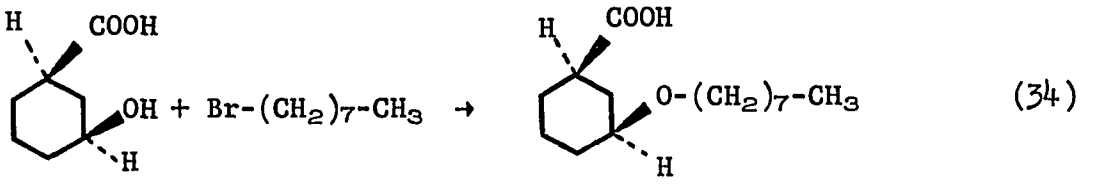


(33)

XVI XVIII XIX

Sodium methoxide in methanol was not considered a good choice for this condensation. There was a strong possibility that the methoxide ion might itself react with XVIII, forming the methyl ether. There was still another possibility that the methoxide ion might remove a proton from the carbon atom $\alpha$ to the COOH group thereby causing condensation at that carbon. Hence it was necessary to use a base which was a poor nucleophile. To conserve XVIII, n-octyl bromide (LXXIX) was used as a model compound. Condensation was attempted with both 3-hydroxycyclohexanecarboxylic acid (XVI) (eq 34) and its methyl

ester (LXXX).




(34)

XVI LXXIX LXXXI

Several attempts were made to effect this condensation without success. Among the condensing agents used were silver oxide in tetrahydrofuran, silver oxide in dimethylsulfoxide, and lithium hydride in dimethylsulfoxide.

Using sodium hydride in dimethylformamide,[39] 3-hydroxycyclohexanecarboxylic acid (XVI) was successfully condensed with n-octyl bromide (LXXIX) to yield the corresponding ether (LXXXI).

Using sodium hydride in dimethylformamide, cis-3-hydroxycyclohexanecarboxylic acid (XVI) and 2-(9-bromononamethyleneoxy)-tetrahydropyran (XVIII) were condensed together to yield the corresponding ether (XIX) (eq 33), which was recovered by acidification of the basic solution, hence it was an acid. The nmr spectrum of XIX showed a singlet at δ 4.57 (for OCHO), which was also present in the nmr spectrum of XVIII at δ 4.53. This was further indication that XVIII had condensed with XVI. A singlet was also present at δ 9.57. The chemical shift of

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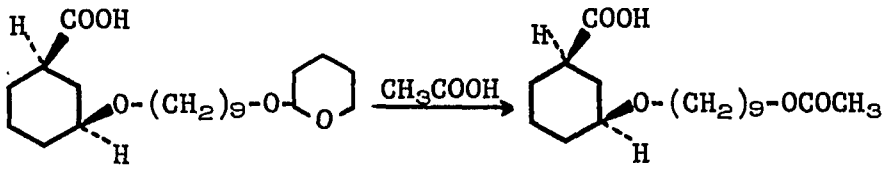
(39) We thank R. V. Flor for his suggestion.

this exchangable proton indicated the presence of only COOH and the absence of alcoholic OH (if COOH and OH both were present, the combined average signal would have appeared around δ 7.0).

When heated with acetic acid, compound XIX was converted to the corresponding acetate XX (eq 35). The nmr

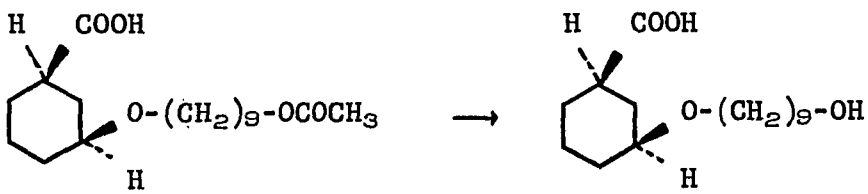



(35)

XIX XX

spectrum of XX showed the absence of OCHO (the singlet at δ 4.57 was missing). Instead, it showed the presence of $-CH_2CH_2OCOCH_3$ (triplet at δ 4.03 for $CH_2OCO$ and a sharp singlet at δ 2.0 for $OCOCH_3$). This indicated that the tetrahydropyranyloxy group of XIX was replaced by the acetoxy group.

The alkaline hydrolysis of XX gave the hydroxy acid XXI (eq 36). The nmr spectrum of XXI showed a singlet at δ 7.70




(36)

XX XXI

(average for COOH and OH) which disappeared on treatment with $D_2O$. It also showed the absence of $-CH_2CH_2OCOCH_3$ (triplet at $\delta$ 4.03 and sharp singlet at $\delta$ 2.0 were missing). This indicated that the acetoxy group of XX had been replaced by OH.

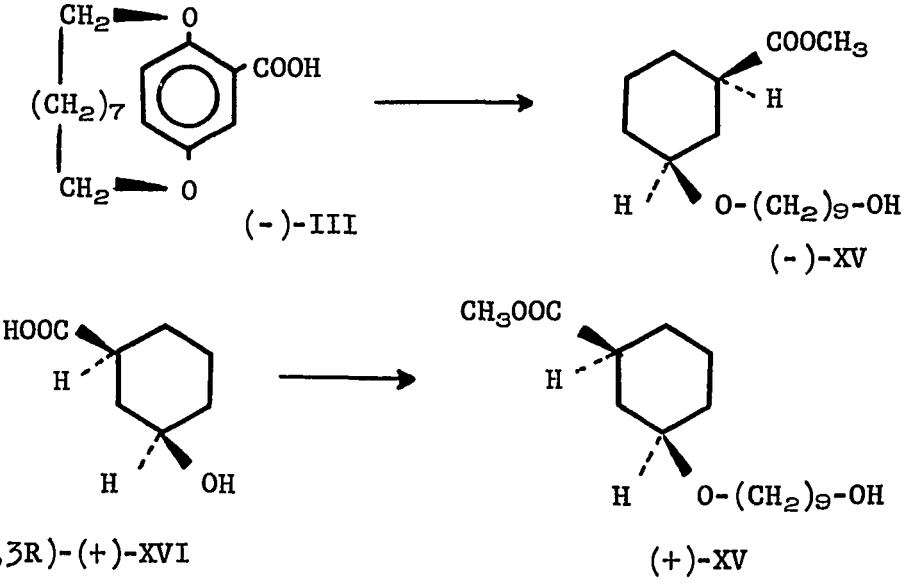
From this point onwards, hydroxy acid XXI, synthesized from cis-3-hydroxycyclohexanecarboxylic acid (XVI) and the hydroxy acid XIII, obtained from the ansa compound III, were treated under identical conditions. It was found necessary to purify the hydroxy acids XXI and XIII by column chromatography on silica gel. The purified materials had the same tlc behaviour. The remainder of our correlation sequence consisted of epimerization to form equilibrium mixture XIV followed by conversion to the corresponding methyl esters, the relay compound XV, as already described on pages 43-45.

Elemental analysis, and a comparison of the nmr and ir spectra and the ms of the relay compound, XV, synthesized from cis-3-hydroxycyclohexanecarboxylic acid (XVI), with those of the relay compound, XV, obtained from gentisic acid nonamethylene ether (III) established the structure of the relay compound XV. A comparison of their rotations established the absolute configuration of gentisic acid nonamethylene ether (III).

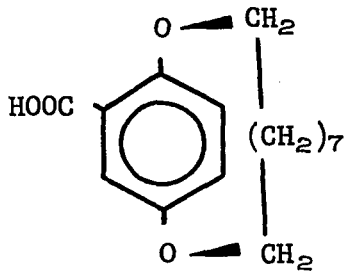
Hydrogenation of gentisic acid nonamethylene ether (III) (p 69) is also accompanied by the hydrogenolysis of the ethereal linkage. From the products, 3-(9-hydroxynonamethylene-

oxy)cyclohexanecarboxylic acid (LXI) was isolated (Chart I, p 55). Its tlc behaviour was same as that of XIII obtained from X (Chart I, p 55) and that of XXI synthesized from XVI (Chart III, p 57). Compound LXI was equilibrated to XIV, the equilibrium mixture (XIV) was converted to the methyl ester (XV) which was distilled (p 106). The reaction conditions for this sequence (LXI → XV) were identical to those used for the relay compound XV obtained from X and that synthesized from XVI. Comparison of the rotation of the relay compound XV obtained from LXI and that from X, indicates that no appreciable racemization had taken place during hydrogenolysis.

The results of our experiments are summarized in charts I, II, and III (pages 55-57). (-)-Gentisic acid nonamethylene ether [(-)-III] yielded (-)-XV. (1S,3R)-(+)-cis-3-Hydroxycyclohexanecarboxylic acid [(+)-XVI] yielded (+)-XV.



Thus, (+)-gentisic acid nonamethylene ether [(+)-III] correlates with (1S,3R)-(+)-cis-3hydroxycyclohexanecarboxylic acid [(+)-XVI]. The configuration of (+)-gentisic acid nonamethylene ether [(+)-III] is therefore R.[40]




(R)-(+)-III

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(40) R. S. Cahn, C. Ingold, and V. Prelog, Angew. Chem. Intern. Ed. Engl., 5, 385 (1966).

Chart I

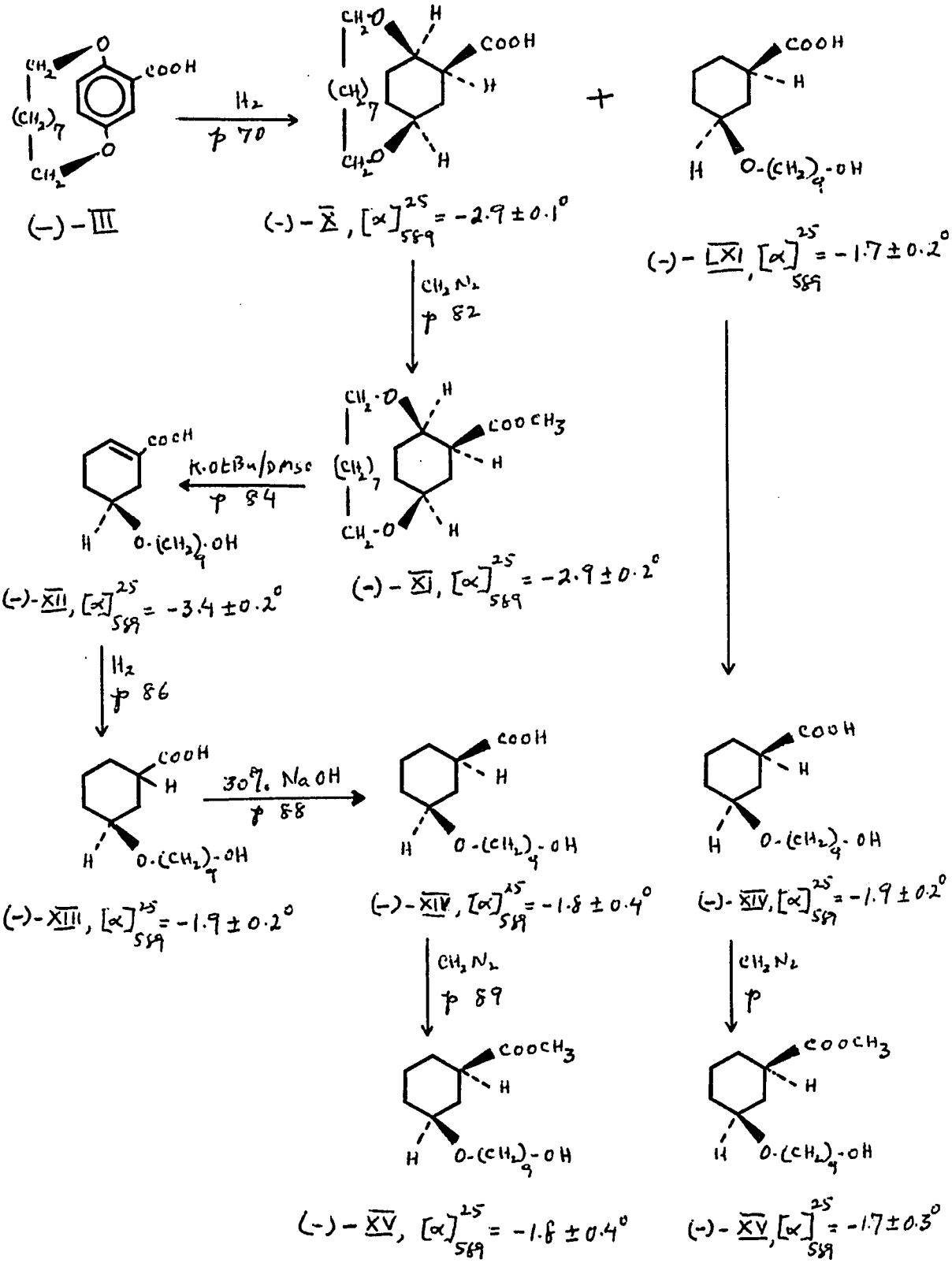
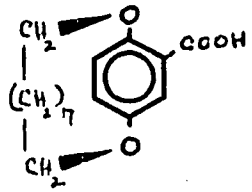

(−) − III
H2
p 70
(−) − X, [α]25 589 = −2.9 ± 0.1°
(−) − LXI, [α]25 589 = −1.7 ± 0.2°
CH2N2
p 82
(−) − XI, [α]25 589 = −2.9 ± 0.2°
K.OtBu/DMSO
p 84
(−) − XII, [α]25 589 = −3.4 ± 0.2°
H2
p 86
30% NaOH
p 88
(−) − XIII, [α]25 589 = −1.9 ± 0.2°
(−) − XIV, [α]25 589 = −1.8 ± 0.4°
(−) − XIV, [α]25 589 = −1.9 ± 0.2°
CH2N2
p 89
CH2N2
p
(−) − XV, [α]25 589 = −1.8 ± 0.4°
(−) − XV, [α]25 589 = −1.7 ± 0.3°

Chart II

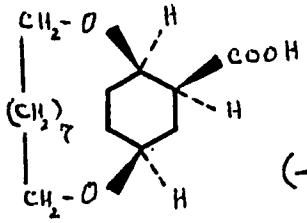


(-) - II

$[\alpha]_{589}^{25} = -4.5 \pm 0.2^{\circ}$

$H_2$

p 72

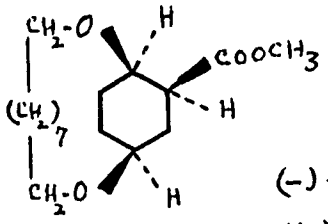


(-) - X

$[\alpha]_{589}^{25} = -4.5 \pm 0.2^{\circ}$

$CH_2N_2$

p 82

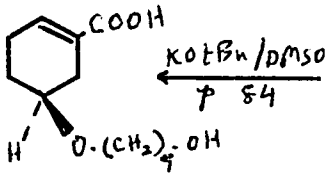


(-) - XI

$[\alpha]_{589}^{25} = -4.9 \pm 0.2^{\circ}$

KotBu/DMSO

p 84

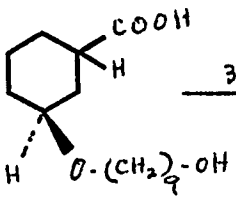


(-) - XII

$[\alpha]_{589}^{25} = -5.3 \pm 0.2^{\circ}$

$H_2$

p 86

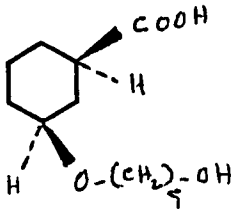


(-) - XIII

$[\alpha]_{589}^{25} = -2.1 \pm 0.2^{\circ}$

30% NaOH

p 88

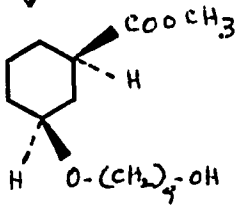


(-) - XI

$[\alpha]_{589}^{25} = -2.1 \pm 0.2^{\circ}$

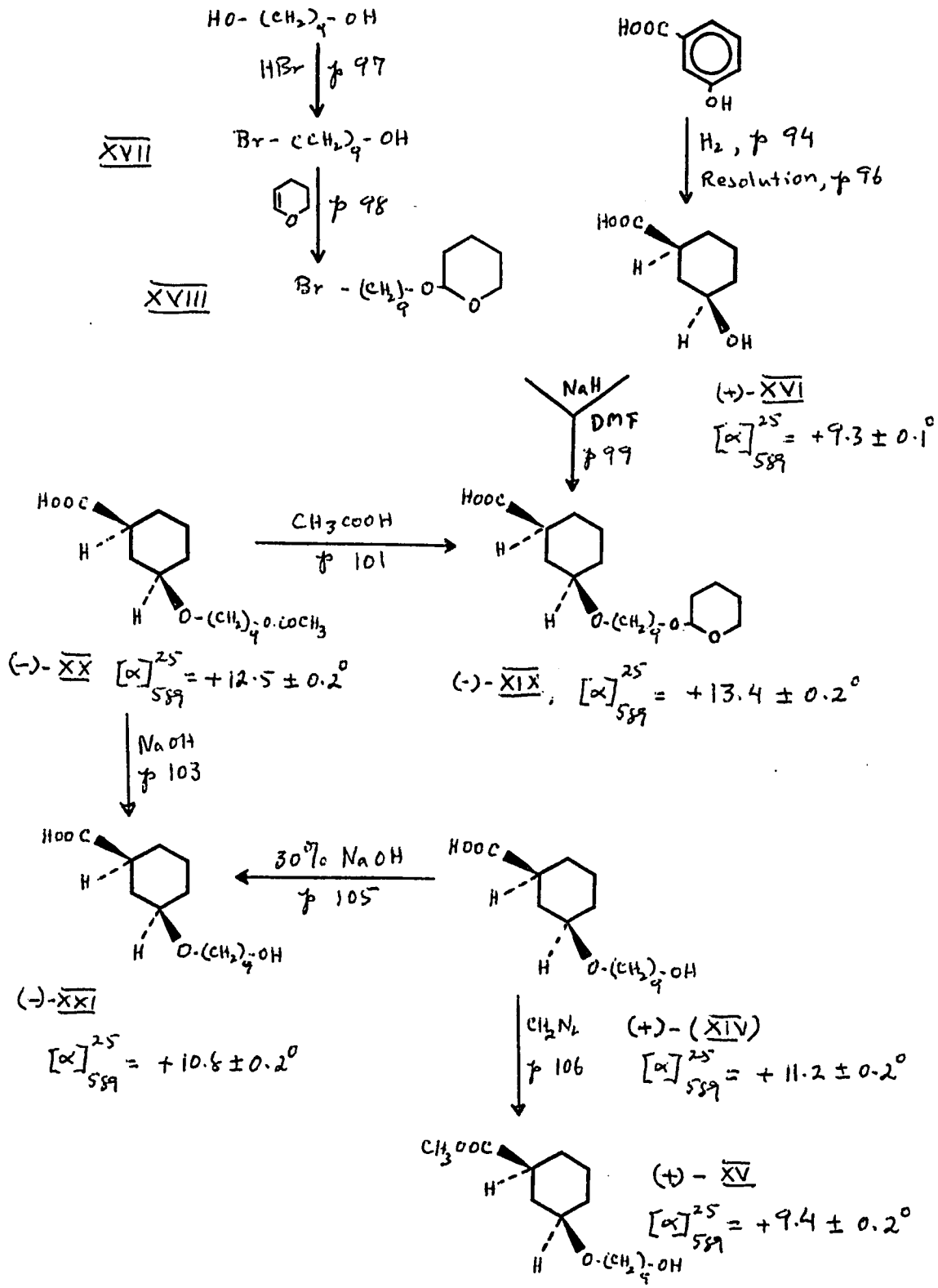
$CH_2N_2$

p 89



(-) - XV, $[\alpha]_{589}^{25} = -2.0 \pm 0.3^{\circ}$

Chart III


HO-(CH2)q-OH
HBr
p 97
Br-(CH2)q-OH
XVII
p 98
XVIII
Br-(CH2)q-O
HOOC
OH
H2, p 94
Resolution, p 96
HOOC
H
H
OH
NaH
DMF
p 99
(+)-XVI
[α]25 589 = +9.3 ± 0.1°
HOOC
H
O-(CH2)q-O.COCH3
CH3COOH
p 101
HOOC
H
O-(CH2)q-O
(-)-XX [α]25 589 = +12.5 ± 0.2°
(-)-XIX, [α]25 589 = +13.4 ± 0.2°
NaOH
p 103
HOOC
H
O-(CH2)q-OH
30% NaOH
p 105
HOOC
H
O-(CH2)q-OH
(-)-XXI
[α]25 589 = +10.6 ± 0.2°
CH2N2
p 106
(+)-(XIV)
[α]25 589 = +11.2 ± 0.2°
CH3OOC
H
O-(CH2)q-OH
(+)-XV
[α]25 589 = +9.4 ± 0.2°

## EXPERIMENTAL SECTION[41]

(41) Microanalyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn., 37921. Melting points were determined using a Thomas-Hoover apparatus, in open capillary tubes, and are corrected; boiling points are uncorrected. Mass spectra were determined using a Varian CH5 Mass Spectrometer at 70 eV under direct sample inlet conditions and linear mass scan. Infrared spectra were determined using a Perkin-Elmer 137 Spectrophotometer. Absorption maxima are expressed in wavenumbers. Proton magnetic resonance spectra were determined at 60 MHz using a Varian A-60 spectrometer. Chemical shifts are expressed in $\delta$ (ppm) downfield from internal tetramethylsilane ($\delta$=0).

## (A) Preparation, Resolution, and Hydrogenation of Gentisic Acid Nonamethylene Ether (III).

### (1) Preparation of 4-(9-Bromononamethyleneoxy)phenol (LXXXII).[3,10]

Hydroquinone (100 g, 0.91 mol), 1,9-dibromononane (550 g, 1.92 mol), and ethanol (95%, 500 ml) were placed in a 5-liter 3-necked flask equipped with a mechanical stirrer, a pressure equalizing addition funnel, and a reflux condenser. The mixture was heated to boiling. Potassium hydroxide solution (1.6 M, 285 ml) was added dropwise over a period of 1 hour to the refluxing reaction mixture. After the addition was completed, the reaction mixture was heated for an additional one hour.

The reaction mixture was extracted with warm water (ca. 70°, 1500 ml). The organic layer was dissolved in a mixture of hexane (2000 ml) and ether (300 ml). The resulting solution was extracted with three 1000 ml portions of water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated (rotary evaporator) to a brown liquid residue. The unused 1,9-dibromononane was recovered by distilling the brown liquid residue under reduced pressure [bp (0.2 mm), 85-86°]. The residue from the distillation was distilled in a short path distillation apparatus. The distillate (0.1 mm, pot 140°) was 4-(9-bromononamethyleneoxy)phenol (66.4 g

45% based on KOH used). Nmr ($CDCl_3$): δ 1.0-2.2 (complex, 14 H, side chain $CH_2$); δ 3.37 (triplet, J=6.5 Hz, 2 H, $BrCH_2$); δ 3.87 (triplet, J=6.5 Hz, 2 H, $OCH_2$); δ 6.80 (singlet, 4 H, aromatic H).

(2) Preparation of Hydroquinone Nonamethylene Ether (LXXXIII).[3,10]

The high dilution apparatus used in the following experiment was essentially that described by Leonard and Sentz[42] except for the use of a Morton flask.

Isoamyl alcohol (4 l.) and potassium carbonate (90 g, 0.65 mol) were placed in a 12-liter 3-necked Morton flask equipped with a fast stirrer and a high dilution assembly. A solution of 4-(9-bromononamethyleneoxy)phenol (LXXXII) (p 59) (45 g, 0.143 mol) in isoamyl alcohol (2.5 l.) was added dropwise over a period of 11 days to the vigorously stirred, refluxing reaction mixture in the flask. After the addition was completed, the reaction mixture was heated for additional 6 hour period.

The cooled reaction mixture was filtered, and the solvent was evaporated (rotary evaporator) to an orange-red, viscous liquid residue. The latter was thoroughly mixed with 1:3 benzene:hexane (1.5 l.) and filtered. The filtrate was extracted four times with 200 ml portions of Claisen's alkali (352 g KOH dissolved in 250 ml of water, and the resulting solution diluted to 1000 ml with methanol), and thereafter twice with water. The organic layer was dried over anhydrous

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(42) N. J. Leonard and R. C. Sentz, J. Amer. Chem. Soc., 74, 1704 (1952).

$MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to an orange solid-liquid residue. From two such experiments 43 g of crude hydroquinone nonamethylene ether was obtained.

The crude reaction product (42.5 g) was chromatographed on alumina (500 g). Hydroquinone nonamethylene ether (LXXXIII) (21 g) was eluted with benzene and 5% 1,4-dioxane/benzene as a white solid, mp 55-56° (lit[3] mp 56°), yield [from 4-(9-bromo-nonamethyleneoxy)phenol] 15.8%. Nmr ($CDCl_3$): δ 0.5-2.0 (complex, 14 H, $CH_2$); δ 4.17 (triplet, J=5.0 Hz, 4 H, $OCH_2$); δ 6.98 (singlet, 4 H, aromatic H).

(3) Preparation of Gentisic Acid Nonamethylene Ether (III).[3,10]

A solution of phenyl lithium in ether was prepared as follows: A solution of bromobenzene (20.0 g, 0.127 mol) in ether (anhydrous, 35 ml) was added dropwise over a 2 hour period to a stirred mixture of small pieces of lithium wire (2.2 g, 0.314 mol) and ether (anhydrous, 25 ml) under a nitrogen atmosphere. The reaction mixture was heated to maintain a gentle reflux. After 5 hours, almost all the lithium had dissolved. The above reaction mixture was filtered through glass wool (closed system) into a solution of hydroquinone nonamethylene ether (LXXXIII) (p 61) (15.2 g, 0.065 mol) in ether (anhydrous, 35 ml). The resulting mixture was kept in a desiccator for nine days.

The following was done in a dry box. Dry ice was broken into small lumps and washed with ether containing small lumps of sodium metal. The reaction mixture was poured over the dry ice lumps with good stirring and left in the dry box for an additional 0.5 hour. The resulting slurry was extracted with sodium hydroxide solution (5%, three times). The aqueous layer was acidified to pH 1 with hydrochloric acid and extracted with ether. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated (rotary evaporator) to yield 17.5 g of a pale brown liquid residue. The latter was

dissolved in ether and treated with an excess of a cold solution of diazomethane in ether.[43] This was left overnight in the hood to warm up to the room temperature and for the unused diazomethane to decompose. The ether solution was dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated (rotary evaporator) to yield 16.75 g of a yellow liquid residue. The latter was

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(43) An ethereal solution of diazomethane was prepared as follows: A solution of potassium hydroxide (5.0 g) in water (8 ml) and ethanol (95%, 25 ml) was placed in a 100 ml flask equipped with a Claisen head, with a pressure equalizing addition funnel and an efficient condenser delivering into two receiving flasks in series. The second receiver contained about 30 ml of ether and its inlet tube was below the surface of the liquid. Both receiving flasks were kept in an ice-salt bath. The reaction flask was immersed in an oil bath at 70°, and the temperature of the bath was maintained at 67-70° during the experiment. A solution of 21.4 g (0.1 mol) of Diazald (N-methyl-N-nitroso-p-toluenesulfonamide, Aldrich Chemical Co.) was added dropwise over a 45 minute period. The rate of addition was maintained almost equal to the rate of distillation. After complete addition, 30 ml of ether was added and the distillation continued untill the distillate was colorless. The distillate was an ethereal solution of diazomethane.

distilled (149-151°, 0.3 mm) to give 14.81 g of a clear, pale yellow, viscous oil, methyl gentisate nonamethylene ether. Nmr ($CDCl_3$): δ 0.5-2.0 (complex, 14 H, $CH_2$); δ 3.87 (singlet, 3 H, $COOCH_3$); δ 4.19 (triplet, J=5.0 Hz, 4 H, $OCH_2$); δ 7.0-7.2 (complex, 2 H, aromatic H), δ 7.35-7.65 (complex, 1 H, aromatic H).

Methyl gentisate nonamethylene ether (14.8 g) was heated with ethanolic sodium hydroxide solution (2 M, 150 ml) for four hours. The cooled reaction mixture was extracted with ether. The ether layer was extracted with 5% sodium hydroxide solution. The aqueous layers were combined and acidified to pH 1 with hydrochloric acid and extracted with ether. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated (rotary evaporator) to yield 14.0 g (77.5% based on hydroquinone nonamethylene ether) of a clear pale yellow solid, mp 63° (lit[3] mp 63°). Nmr ($CDCl_3$): δ 0.4-2.0 (complex, 14 H, $CH_2$); δ 4.22 (triplet, J=5.0 Hz, 2 H, $OCH_2$); δ 4.45 (triplet, J=5.0 Hz, 2 H, $OCH_2$); δ 7.1-7.3 (complex, 2 H, aromatic H); δ 7.65-7.85 (complex, 1 H, aromatic H); δ 11.2 (singlet, 1 H, COOH).

(4) Resolution of Gentisic Acid Nonamethylene Ether (III).[3 10]

Gentisic acid nonamethylene ether (III) (p 63) (14.0 g, 0.05 mol) and strychnine (City Chemical Corp., New York) (15.5 g, 0.464 mol, $[\alpha]_{589}^{25} = -141.0 \pm 2.0^{\circ}$, c = 1.01, $CHCl_3$) were dissolved in ethanol (95%, 200 ml). The slightly turbid solution was filtered. The filtrate was concentrated to 150 ml, and left overnight to crystallize. The resulting white crystals (CR I) weighed 11.3 g. The mother liquor (MLI) was concentrated to 50 ml and left overnight to crystallize. The filtration yielded white crystals (CR II) (5.0 g). The filtrate and washings were combined to ML II. CRI and CRII were combined and recrystallized from aqueous ethanol (50%, 150 ml) to yield white crystals (CR III) (13.2 g) and mother liquor (ML III). CR III was recrystallized from aqueous ethanol (50%, 150 ml) to yield white crystals (CR IV) (11.0 g), and mother liquor (ML IV). CR IV was recrystallized from aqueous ethanol (50 %, 125 ml) to yield white crystals (CR V) (9.0 g, $[\alpha]_{589}^{9.7} = +2.0 \pm 0.1^{\circ}$; c = 3.96, $CHCl_3$), and mother liquor (MLV). CR V was recrystallized from aqueous ethanol (50%, 100 ml) to yield crystals (CR VI) (8.4 g, $[\alpha]_{589}^{9.7} = +7.5 \pm 0.2^{\circ}$; c = 4.06, $CHCl_3$), and mother liquor (ML VI). CR VI was recrystallized from aqueous ethanol (50%, 100 ml) to yield white crystals (CR VII) (7.8 g, $[\alpha]_{589}^{9.8} = +14.5 \pm 0.1^{\circ}$; c = 5.15, $CHCl_3$), and mother liquor (ML VII). CR VII

was recrystallized from aqueous ethanol (50%, 80 ml) to yield white crystals (7.45 g, $[\alpha]_{589}^{9.5}$ = + 12.3 ± 0.1°; c = 4.18, $CHCl_3$) (lit[3] $[\alpha]_{589}^{20}$ = + 10.6°; c = 4.0, $CHCl_3$), and mother liquor (ML VIII).

ML II, ML III, and ML IV were combined, the solvent evaporated, and the pale yellow residue recrystallized from aqueous ethanol (50%) to yield white crystals (CR IX) (5.5 g, $[\alpha]_{589}^{5.0}$ = - 62.0 ± 1.0°; c = 4.3, $CHCl_3$), and mother liquor. On evaporation, this mother liquor yielded a yellowish viscous liquid residue (ML IX) (12.6 g, $[\alpha]_{589}^{5.4}$ = - 39.7 ± 0.5; c = 4.03, $CHCl_3$). ML V, ML VI, and ML VII were combined, evaporated, and the yellowish residue recrystallized from aqueous ethanol (50%) to yield white crystals (CR X), and mother liquor (ML X). ML VIII and ML X were combined, evaporated and the yellowish residue recrystallized from aqueous ethanol (50%) to give white crystals (CR XI), and a mother liquor which on evaporation of the solvent gave a yellowish viscous liquid residue (ML XI) (1.2 g). CR X and CR XI were combined to CR XII.

CR VIII (7.45 g) was dissolved in chloroform. The chloroform solution was extracted three times with 30% aqueous acetic acid, three times with 20% aqueous sulfuric acid, and finally four times with water. The chloroform layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator). The last traces of the solvent were removed

under reduced pressure (vacuum pump). The pale yellow, solid residue was optically active gentisic acid nonamethylene ether (III), $[\alpha]_{589}^{7.0} = + 21.6 \pm 0.2^{o}$, c = 4.06, $CHCl_3$; $[\alpha]_{589}^{24} = + 17.0 \pm 0.2^{o}$, c = 3.80, $CHCl_3$; (lit[3] $[\alpha]_{589}^{20} = 16.68^{o}$, c = 4.0, $CHCl_3$).

CR IX, CR XII, ML IX, and ML XI were also hydrolysed using the same procedure. ML IX yielded 12.6 g of active gentisic acid nonamethylene ether, $[\alpha]_{589}^{25} = - 4.5 \pm 0.2^{o}$ (c = 3.56, $CHCl_3$). CR IX gave 2.8 g of active gentisic acid nonamethylene ether, $[\alpha]_{589}^{25} = - 9.0 \pm 0.1^{o}$ (c = 5.39, $CHCl_3$). CR XII gave 1.8 g of active gentisic acid nonamethylene ether, $[\alpha]_{589}^{25} = + 0.9 \pm 0.1^{o}$ (c = 5.89, $CHCl_3$). ML XI gave 0.61 g of active gentisic acid nonamethylene ether.

## (5a) Hydrogenation of Gentisic Acid Nonamethylene Ether (III).[10]

Gentisic acid nonamethylene ether (III) (p 66) (0.443 g, 1.6 mmol; $[\alpha]_{589}^{25} = -4.5 \pm 0.2^{\circ}$) was dissolved in 50 ml of acetic acid, rhodium on alumina (5%, 0.95 g) was added, and the mixture was hydrogenated in a Parr low pressure hydrogenation apparatus for 16 hours. The catalyst was filtered, and the solvent was evaporated (rotary evaporator) to yield a pale yellow liquid residue. The latter was heated with 30 ml of 10% ethanolic potassium hydroxide for 12 hours. The cooled reaction mixture was extracted with ether and the resulting ether solution was extracted with water. The ether layer was dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated (rotary evaporator) to yield 0.050 g of a white solid, 1,9-nonanediol (nmr spectrum was identical with that of an authentic sample). The aqueous layer was acidified to pH 1 with HCl and extracted with ether. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to yield 0.384 g of a pale yellow liquid residue.

The above experiment was repeated four times. Thus, 0.222 g (0.8 mmol) of active gentisic acid nonamethylene ether ($[\alpha]_{589}^{25} = +0.9 \pm 0.1^{\circ}$) and 0.120 g of 5% rhodium on alumina in 35 ml of acetic acid were hydrogenated for 16 hours in a

Parr low pressure hydrogenation apparatus to yield 5 mg of 1,9-nonanediol and 0.222 g of a pale yellow liquid product. Gentisic acid nonamethylene ether (0.195 g, 0.65 mmol, $[\alpha]_{589}^{25}$ = - 4.5 ± 0.2°) with 0.105 g of the catalyst and 50 ml of acetic acid on hydrogenation for 2 hours gave 0.165 g of the product. Gentisic acid nonamethylene ether [0.215 g, 0.77 mmol, (-)-isomer of uncertain optical activity] with 110 mg of the catalyst and 50 ml of 95% ethanol solvent on hydrogenation for 13 hours yielded 0.210 g of the product; and 0.349 g (1.2 mmol) of gentisic acid nonamethylene ether [(-)-isomer of uncertain optical activity] with 200 mg of the catalyst in 50 ml of acetic acid solvent on hydrogenation for 2 hours yielded 0.352 g of the product.

The crude hydrogenation products from the above five runs were combined. Thin layer chromatography on silica gel, using the solvent system 20% dioxane/benzene with 1% acetic acid showed three spots with $R_f$ values of 0.75, 0.65, and 0.60.

The crude hydrogenation product (1.32 g) was chromatographed on 300 g of silica gel (Davidson, grade 923, mesh 100-200) (column length 25", width 0.75", eluent 10% ether/benzene).[10] Cuts approximately 15 ml in volume were collected, each in about 20-25 minutes using an automatic fraction collector. The results were monitored by tlc. Cuts showing the same $R_f$ value were combined, dried over anhydrous $MgSO_4$, filtered and the

solvent was evaporated (rotary evaporator).

Cuts 171-294 ($R_f$ 0.75) yielded 0.605 g (42.5%) of a white solid, $[\alpha]_{589}^{25} = -2.9 \pm 0.1^{\circ}$ (c = 6.0, $CHCl_3$). Nmr ($CDCl_3$): δ 0.7-2.9 (complex, 21 H, CH and $CH_2$); δ 3.2-4.2 (complex, 6 H, OCH and $OCH_2$); δ 9.41 (broad singlet, 1 H, COOH). This white solid has been assigned the structure cis-2,5-(1,9-nonamethylenedioxy)cyclohexanecarboxylic acid (X) (p 37).

Cuts 429-458 ($R_f$ 0.65) yielded 0.218 g (15.3%) of a pale yellow, viscous liquid. Nmr ($CDCl_3$): δ 0.8-2.9 (complex, 23 H, COCH, ring and side chain $CH_2$); δ 3.2-4.2 (complex, 5 H, OCH and $OCH_2$); δ 6.65 (broad singlet, 2 H, OH and COOH). This pale yellow viscous liquid has been assigned the structure 2-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (LX) (p 38).

Cuts 533-580 ($R_f$ 0.60) yielded 0.380 g (26.7%) of a pale yellow, viscous liquid, $[\alpha]_{589}^{25} = -1.7 \pm 0.2^{\circ}$ (c = 3.6, $CHCl_3$). Nmr ($CDCl_3$): δ 0.8-2.9 (complex, 23 H, COCH, ring and side chain $CH_2$); δ 2.9-4.0 (complex, 5 H, OCH and $OCH_2$); δ 7.33 (broad singlet, 2 H, OH and COOH). This pale yellow, viscous liquid has been assigned the structure cis-3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (LXI) (p 37).

(5b) Hydrogenation of Gentisic Acid Nonamethylene Ether (III).[10]

Gentisic acid nonamethylene ether (III) (2.75 g, 9.89 mmol, $[\alpha]_{589}^{25} = -4.5 \pm 0.2^{\circ}$; c = 3.56, $CHCl_3$) was dissolved in ethanol (95%. 120 ml), rhodium on alumina (5%, 2.8 g) was added, and the mixture was hydrogenated in a Parr low pressure hydrogenation apparatus for 20 hours. The catalyst was filtered, and the solvent was evaporated (rotary evaporator) to a white residue. The latter was heated with 200 ml of 5% ethanolic sodium hydroxide for 3 hours. The cooled reaction mixture was extracted with ether and the resulting ether solution was extracted with water. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to yield 0.110 g of a white solid residue, identified as 1,9-nonanediol (nmr spectrum was identical to that of authentic sample). The aqueous layer was acidified to pH 1 with HCl and extracted with ether. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to yield 2.7 g of white solid, $[\alpha]_{589}^{25} = -4.2 \pm 0.1^{\circ}$ (c = 4.11, $CHCl_3$).

This white solid showed three spots on tlc place (silica gel) with $R_f$ values 0.75, 0.65, and 0.60 (20% dioxane/benzene with 1% acetic acid). It (2.6 g) was chromatographed on silica gel (Davidson, grade 923, mesh 100-200) (500 g, column length 38", width 1", eluent 10% ether/benzene). Fractions each

approximately 15 ml in volume were collected , each in about 15-25 minutes using an automatic fraction collector. The results were monitored by tlc.

Cuts 301-720 (R value 0.75) were combined, dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to yield 0.89 g (32.0% based on gentisic acid nonamethylene ether used) of white solid, $[\alpha]_{589}^{25} = -4.5 \pm 0.2^{\circ}$ (c = 2.81, $CHCl_3$). Nmr ($CDCl_3$): $\delta$ 0.7-2.9 (complex, 21 H, CH and $CH_2$); $\delta$ 3.2-4.2 (complex, 6 H, OCH and $OCH_2$); $\delta$ 9.3 (broad singlet, 1 H, COOH). This white solid was assigned (p 37) the structure <u>cis</u>-2,5-(1,9-nonamethylenedioxy)cyclohexanecarboxylic acid (X); its nmr spectrum was identical to that of X obtained previously (p 71).

(B) Elimination Studies.

(1) Preparation of cis-2-Methoxycyclohexanecarboxylic Acid (LXIV).

2-Methoxybenzoic acid (15.2 g, 0.1 mol) was dissolved in 130 ml of acetic acid, rhodium on alumina (5%, 5.0 g) was added, and the mixture was hydrogenated in a Parr low pressure hydrogenation apparatus. In the first hour, the hydrogen uptake was 27.7 psig. The calculated uptake (volume of system 4.5 l.) was 24.5 psig. There was no further uptake of hydrogen in the next hour. The catalyst was filtered and the solvent was evaporated (rotary evaporator) to yield 15.3 g of a clear, pale blue, viscous liquid.

Column chromatography on silica gel (Davison, grade 923, mesh 100-200) (eluent benzene) resulted in partial separation. Several fractions were taken. The first fraction was cyclohexanecarboxylic acid. The next few fractions were mixtures of cis-2-methoxycyclohexanecarboxylic acid (LXIV) with decreasing amounts of cyclohexanecarboxylic acid. After that cis-2-methoxycyclohexanecarboxylic acid (8.1 g, 51.3%) was obtained as a clear, colorless, viscous liquid. Nmr ($CDCl_3$): $\delta$ 0.9-2.8 (complex, 9 H, ring CH and $CH_2$); $\delta$ 3.33 (singlet, 3 H, $OCH_3$); $\delta$ 3.7-4.0 (complex, 1 H, OCH); $\delta$ 11.8 (singlet, 1 H, COOH). Nmr spectrum

was identical to a literature spectrum.[44]

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(44) A. Munoz, J. Pazan, J. Pascual, and J. Castells, An. Real Soc. Espan. Fis. Quim., Ser. B, 63, (4) 455 (1967).

(45) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co. Inc., New York, N.Y., 1962, p 213.

(2) Preparation of Methyl cis-2-Methoxycyclohexanecarboxylate (LXV).

A cold solution of diazomethane in ether[43] (p 64) was slowly and carefully added to a solution of cis-2-methoxycyclohexanecarboxylic acid (LXIV) (p 74) (2.4 g, 15 mmol) in ether untill the yellow color persisted. This was left overnight in the hood to warm up to room temperature and for the unused diazomethane to decompose. The ether solution was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to yield a clear, colorless liquid (2.38 g). The yield of crude ester was 90.8%. Nmr ($CDCl_3$): δ 1.0-2.7 (complex, 9 H, ring $CH_2$ and COCH); δ 3.28 (sharp singlet, 3H, $OCH_3$); δ 3.6-4.0 (complex, with a sharp singlet at δ 3.67, 4 H, $COOCH_3$ and OCH).

(3) Conversion of Methyl cis-2-Methoxycyclohexanecarboxylate (LXV) to 1-Cyclohexenecarboxylic Acid (LXVI).

A 100-ml flask was equipped with a magnetic stirrer, a pressure equalizing addition funnel, and a reflux condenser fitted with a drying tube. Methyl cis-2-methoxycyclohexanecarboxylate (LXV) (p 76) (0.442 g, 2.57 mmol) and potassium t-butoxide (0.497 g, 7.1 mmol) were placed in the flask, and 50 ml of dimethyl sulfoxide (dried over activated molecular sieve, Linde type 4A, 80-100 mesh) were added from the addition funnel. The reaction mixture was stirred for 48 hours at room temperature.

The reaction mixture was poured over ice and extracted with ether. The ether layer was extracted with water. The aqueous layers were combined, acidified to pH 1 with HCl, and extracted with ether. This ether extract was dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated (rotary evaporator) to yield 0.272 g (84%) of a clear, colorless liquid, 1-cyclohexenecarboxylic acid (LXVI). The nmr spectrum was identical with that of authentic material (Frinton Laboratories, So. Vineland, N.J.).

(C) Equilibration Studies.

(1) Hydrogenation of 3-Methoxybenzoic Acid.

3-Methoxybenzoic acid (15.2 g, 0.1 mol) was dissolved in ethanol (95%, 200 ml), rhodium on carbon (5%, 4.0 g) was added, and the mixture was hydrogenated in a Parr low pressure hydrogenation apparatus. In the first 2 hours, the uptake of hydrogen was 28 psig. The calculated uptake of hydrogen was 24.5 psig. There was no further uptake of hydrogen in the next 3 hours. The catalyst was filtered and the solvent was evaporated to a clear, colorless, liquid residue. The latter was extracted with ether. The ether solution was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to yield 15.1 g of a clear, colorless, liquid residue.

Column chromatography on silica gel (Davison, grade 923, mesh 100-200) resulted in partial separation. Several fractions were taken. The first few fractions (eluent benzene) contained only cyclohexanecarboxylic acid. The next few fractions consisted of trans-2-methoxycyclohexanecarboxylic acid[46] (LXXI) with a little of the cis-isomer (LXX). Nmr

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(46) We believe LXXX to be the cis and LXXI to be the

($CDCl_3$): δ 0.9-2.8 (complex, 9 H, $CH_2$ and COCH); δ 2.9-3.8 (complex with sharp singlets at δ 3.28 and δ 3.35, 4 H, OCH and $OCH_3$); δ 10.55 (singlet, 1 H, COOH). In the next few fractions, the ratio of the cis isomer increased until only the cis isomer (LXX) was obtained. Nmr ($CDCl_3$): δ 0.9-2.6 (complex, 9 H, $CH_2$ and COCH); δ 2.9-3.5 (complex with a sharp singlet at δ 3.35, 4 H, OCH and $OCH_3$); δ 10.9 (singlet, 1 H, COOH).

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trans isomer of 3-methoxycyclohexanecarboxylic acid because of the following:

(a) Catalytic hydrogenation of aromatic systems under not too high pressures, is known to give predominantly the cis product. The nmr spectrum of the crude hydrogenation product showed two sharp singlets due to the methoxyl hydrogens at δ 3.28 and 3.35. The peak at δ 3.35 was much larger, hence it must be for the cis $OCH_3$.

(b) On equilibration with 30% NaOH, both LXX and LXXI gave the same equilibrium mixture, LXXII (pages 80-81). This equilibrium mixture is expected to consist of mainly the more stable[45] cis isomer. The nmr spectrum of the equilibrium mixture LXXII showed the peak at δ 3.35 to be much larger than the peak at δ 3.28. Hence the peak at δ 3.35 must be due to the cis $OCH_3$ and the peak at δ 3.28 due to the trans $OCH_3$.

(2) Equilibration of cis-3-Methoxycyclohexanecarboxylic Acid (LXX).

3-Methoxycyclohexanecarboxylic acid, mainly the cis isomer (LXX) (p 78) (1.08 g, 6.8 mmol) and aqueous sodium hydroxide solution (30%, 25 ml) were heated under reflux (bath temperature 125-130°) for 65 hours. The reaction mixture was cooled, diluted with water, and extracted with ether. The ether layer was rejected. The aqueous layer was acidified to pH 1 with HCl and extracted with ether. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated (rotary evaporator) to a clear, colorless, liquid residue (0.724 g, 67%), the equilibrium mixture (LXXII).[47] Nmr ($CDCl_3$): δ 0.8-2.8 (complex CH and $CH_2$); δ 2.9-3.8 (complex with two sharp singlets at δ 3.28 and 3.35, OCH and $OCH_3$); δ 9.52 (singlet, COOH).

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(47) The ratio of peak heights at δ 3.35 and δ 3.28 was about 1.5 to 1. However, the peak at δ 3.35 was significantly wider than the one at δ 3.28. The actual molar ratio is thus greater than 1.5 to 1. The cis-trans ratio in the equilibrium mixture of 3-methoxycyclohexanecarboxylate salts can also be calculated using the average "A values".[48] The calculated value is 2.3.

(48) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co. Inc., New York, 1962, p 236.

(3) Equilibration of trans-3-Methoxycyclohexanecarboxylic Acid (LXXI).

3-Methoxycyclohexanecarboxylic acid, mainly the trans isomer (LXXI) (p 78) (0.67 g, 4.24 mmol) and aqueous sodium hydroxide solution (30%, 25 ml) were heated under reflux (bath temperature 125-130°) for 65 hours. The reaction mixture was cooled, diluted with water, and extracted with ether. The ether layer was rejected. The aqueous layer was acidified to pH 1 with HCl and extracted with ether. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated (rotary evaporator) to a clear, colorless, liquid residue, the equilibrium mixture (LXXII) (0.515 g, 77%). Nmr ($CDCl_3$): δ 0.8-2.8 (complex, CH and $CH_2$); δ 2.9-3.8 (complex with two sharp singlets at δ 3.28 and 3.35, OCH and $OCH_3$); δ 9.7 (singlet, COOH). The nmr spectrum was identical to that of LXXII obtained from LXXI (p 80). The ratio of peak heights at δ 3.35 and 3.28 was also same.

## (D) Conversion of cis-2,5-(1,9-Nonamethylenedioxy)cyclohexanecarboxylic Acid (X) from the Hydrogenation of Gentisic Acid Nonamethylene Ether (III) to the Methyl Ester of equilibrated 3-(9-Hydroxynonamethyleneoxy)cyclohexanecarboxylic Acid (XV).

### (1) Preparation of Methyl cis-2,5-(1,9-Nonamethylenedioxy)cyclohexanecarboxylate (XI).

A cold ethereal solution of diazomethane[43] (p 64) was slowly and carefully added to a solution of cis-2,5-(1,9-nonamethylenedioxy)cyclohexanecarboxylic acid (X) (p 71) (0.605 g, 2.13 mmol; $[\alpha]_{589}^{25} = -2.9 \pm 0.1^{\circ}$; c = 6.0, $CHCl_3$) in 50 ml of ether. An excess of diazomethane was used. The reaction mixture was left overnight in the hood to warm up to room temperature and for the unused diazomethane to decompose. The ether solution was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to yield 0.324 g (the low yield is due to an accidental spillage) of a clear, colorless liquid residue, $[\alpha]_{589}^{25} = -2.9 \pm 0.2^{\circ}$ (c = 3.24, $CHCl_3$). Nmr ($CDCl_3$): $\delta$ 0.7-3.0 (complex, 21 H, COCH and $CH_2$); $\delta$ 3.1-4.3 (complex, with a sharp singlet at $\delta$ 3.70, 9 H, OCH, $OCH_2$, and $COOCH_3$); ir (neat liquid): 1740 $cm^{-1}$ (ester), 1090 $cm^{-1}$ (dialkyl ether).

A similar experiment starting with 0.890 g (3.13 mmol) of cis-2,5-(1,9-nonamethylenedioxy)cyclohexanecarboxylic acid (X) (p 73) ($[\alpha]_{589}^{25}$ = - 4.5 ± 0.2°; c = 6.0, $CHCl_3$) yielded 0.942 g of methyl cis-2,5-(1,9-nonamethylenedioxy)cyclohexanecarboxylate (XI), $[\alpha]_{589}^{25}$ = - 4.9 ± 0.2° (c = 3.38, $CHCl_3$).

(2) Conversion of Methyl cis-2,5-(1,9-Nonamethylenedioxy)cyclohexanecarboxylate (XI) to 5-(9-Hydroxynonamethyleneoxy)-cyclohexenecarboxylic Acid (XII).

A 100-ml flask was equipped with a magnetic stirrer, a pressure equalizing addition funnel, and a reflux condenser fitted with a drying tube. Methyl cis-2,5-(1,9-nonamethylenedioxy)cyclohexanecarboxylate (XI) (p 82) (0.315 g, 1.09 mmol, $[\alpha]_{589}^{25} = -2.9 \pm 0.2^{\circ}$; c = 3.24, $CHCl_3$) and potassium t-butoxide (0.330 g, 2.9 mmol) were placed in the flask, and 30 ml of dimethyl sulfoxide (dried over activated molecular sieve, Linde type 4A, 80-100 mesh) were added from the addition funnel. The reaction mixture was stirred for 48 hours at room temperature.

The unused potassium t-butoxide was decomposed by addition of crushed ice to the cooled reaction mixture. The latter was extracted with ether. The ether layer was rejected. The aqueous layer was acidified to pH 1 with HCl and extracted with ether. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to yield 0.257 (85.7%) of a pale brown liquid residue, $[\alpha]_{589}^{25} = -3.4 \pm 0.2^{\circ}$ (c = 2.5, $CHCl_3$). Nmr ($CDCl_3$): $\delta$ 0.7-3.0 (complex, 20 H, $CH_2$); $\delta$ 3.1-4.1 (complex, 5 H, OCH and $OCH_2$); $\delta$ 6.9-7.5 (two overlapping singlets at $\delta$ 7.12 and 7.30 in the ratio ca.

1:2, 3 H, vinyl H, OH, and COOH); ir (neat liquid): 3350 $cm^{-1}$ (hydroxyl), 1690 $cm^{-1}$ ($\alpha,\beta$-unsaturated acid), 1650 $cm^{-1}$ (olefin), 1070 $cm^{-1}$ (dialkyl ether).

A similar experiment starting with 0.940 g (3.15 mmol) of methyl <u>cis</u>-2,5-(1,9-nonamethylenedioxy)cyclohexanecarboxylate (XI) (p 83) ($[\alpha]_{589}^{25}$ = - 4.9 ± 0.2°; c = 3.88, $CHCl_3$) and potassium <u>t</u>-butoxide (0.984 g, 8.77 mmol) yielded 0.760 g (84.6%) of 5-(9-hydroxynonamethyleneoxy)cyclohexenecarboxylic acid (XII), $[\alpha]_{589}^{25}$ = - 5.3 ± 0.2° (c = 1.76, $CHCl_3$).

(3) Hydrogenation of 5-(9-Hydroxynonamethyleneoxy)cyclohexene-carboxylic Acid (XII).

5-(9-Hydroxynonamethyleneoxy)cyclohexenecarboxylic acid (XII) (p 84) (0.240 g 0.845 mmol; $[\alpha]_{589}^{25} = -3.4 \pm 0.2^{\circ}$; c = 2.5, $CHCl_3$) was dissolved in ethanol (95%, 50 ml), rhodium on carbon (5%, 0.21 g) was added, and the mixture was hydrogenated for 2 hours in a Parr low pressure hydrogenation apparatus. The catalyst was filtered and the solvent was evaporated (rotary evaporator) to yield 0.235 g of a pale brown, liquid residue. The crude hydrogenation product (0.235 g) was chromatographed on 30 g of silica gel (Davison, grade 923, mesh 100-200) (column length 8", width 0.75"). 3-(9-Hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XIII) (0.172 g, $[\alpha]_{589}^{25} = -1.9 \pm 0.2^{\circ}$; c = 1.7, $CHCl_3$) was eluted with 40% ether/benzene. Nmr ($CDCl_3$): $\delta$ 0.7-2.8 (complex, 23 H, COCH, ring and side chain $CH_2$); $\delta$ 2.9-3.9 (complex, 5 H, OCH and $OCH_2$); $\delta$ 7.32 (singlet, 2 H, OH and COOH); ir (neat liquid): 3300 $cm^{-1}$ (carboxylic acid), 1080 $cm^{-1}$ (dialkyl ether).

A similar experiment starting with 0.76 g (2.68 mmol) of 5-(9-hydroxynonamethyleneoxy)cyclohexenecarboxylic acid (XII) (p 85) ($[\alpha]_{589}^{25} = -5.3 \pm 0.2^{\circ}$; c = 1.76, $CHCl_3$) yielded 0.520 g (low yield is due to an accidental spillage) of crude hydrogenation product. The latter was chromatographed to give 0.385 g

of 3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XIII), $[\alpha]_{589}^{25} = -2.1 \pm 0.2^{o}$ (c = 2.95, $CHCl_3$).

(4) Equilibration of 3-(9-Hydroxynonamethyleneoxy)cyclohexanecarboxylic Acid (XIII).

3-(9-Hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XIII) (p 86) (0.290 g 1.0 mmol; $[\alpha]_{589}^{25} = -2.1 \pm 0.2^{\circ}$; c = 2.95, $CHCl_3$) and aqueous sodium hydroxide solution (30%, 30 ml) were heated under reflux (bath temperature 125°) for 75 hours. Water (150 ml) was added to the cooled reaction mixture. The latter was acidified to pH 1 with HCl and extracted with ether. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated (rotary evaporator) to yield 0.258 g (89%) of a viscous, yellow, liquid residue (XIV), $[\alpha]_{589}^{25} = -2.1 \pm 0.2^{\circ}$ (c = 2.58, $CHCl_3$). Nmr ($CDCl_3$): δ 0.7-2.8 (complex, 23 H, COCH and $CH_2$); δ 2.9-3.9 (complex, 5 H, OCH and $OCH_2$); δ 7.40 (singlet, 2 H, OH and COOH); ir (neat liquid): 3300 $cm^{-1}$ (hydroxyl), 1700 $cm^{-1}$ (carboxylic acid), 1085 $cm^{-1}$ (dialkyl ether).

A similar experiment starting with 0.170 g (0.6 mmol) of 3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XIII) (p 86) ($[\alpha]_{589}^{25} = -1.9 \pm 0.2^{\circ}$; c = 1.7, $CHCl_3$) and 50 ml of aqueous sodium hydroxide solution yielded 0.145 g (85.3%) of equilibrium mixture (XIV), $[\alpha]_{589}^{25} = -1.8 \pm 0.4^{\circ}$ (c = 1.45, $CHCl_3$).

(5) Preparation of Methyl Ester of equilibrated 3-(9-Hydroxynonamethyleneoxy)cyclohexanecarboxylic Acid (XV).

A cold ethereal solution of diazomethane[43] (p 64) was slowly and carefully added to a solution of equilibrated 3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XIV) (p 88) (0.248 g, 0.867 mmol; $[\alpha]_{589}^{25} = -2.1 \pm 0.2^{\circ}$; c = 2.58, $CHCl_3$) in 50 ml of ether. An excess of diazomethane was used. The reaction mixture was left overnight in the hood to warm up to room temperature and for unused diazomethane to decompose. The ether solution was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to yield 0.280 g (89.1%) of a pale yellow, liquid residue. The latter was distilled under reduced pressure in a short path distillation apparatus. The pale yellow distillate (0.1-0.5 mm, bath temperature 180-195°) was methyl ester of equilibrated 3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid [0.171 g, 65.8% based on 3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid used] (XV), $[\alpha]_{589}^{25} = -2.0 \pm 0.3^{\circ}$ (c = 1.71, $CHCl_3$). Nmr ($CDCl_3$): $\delta$ 0.7-2.8 (complex, 24 H, COCH and $CH_2$, and OH; the peak at $\delta$ 2.50 disappeared on treatment with $D_2O$); $\delta$ 2.9-3.9 (complex with a sharp singlet at $\delta$ 3.66, 8 H, OCH, $OCH_2$, and $COOCH_3$); ir (neat liquid): 3400 $cm^{-1}$ (hydroxyl),

1770 $cm^{-1}$ (ester), 1100 $cm^{-1}$ (dialkyl ether); ms, major peaks at m/e 300, 282, 269, 267, 241, and 226.

A similar experiment starting with 0.145 g (0.483 mmol) of equilibrated 3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XIV) (p 88) ($[\alpha]_{589}^{25}$ = - 1.8 ± 0.4°; c = 1.45, $CHCl_3$) yielded 0.150 g (98.6%) of crude methyl ester, which gave 0.74 g (48.6% based on XIV used) of distillate (0.1-0.5 mm, bath temperature 180-190), the relay compound (XV), $[\alpha]_{589}^{25}$ = - 1.8 ± 0.4° (c = 0.74, $CHCl_3$).

(E) Conversion of 3-(9-Hydroxynonamethyleneoxy)cyclohexanecarboxylic Acid (LXI) from Hydrogenation of Gentisic Acid Nonamethylene Ether (III) to the Methyl Ester of Equilibrated 3-(9-Hydroxynonamethyleneoxy)cyclohexanecarboxylic Acid (XV).

(1) Equilibration of 3-(9-Hydroxynonamethyleneoxy)cyclohexanecarboxylic Acid (LXI).

3-(9-Hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (LXI) (p 71) (0.380 g, 1.33 mmol; $[\alpha]_{589}^{25} = -1.7 \pm 0.2^{o}$; c = 3.8, $CHCl_3$), obtained directly from the hydrogenation of gentisic acid nonamethylene ether (III), and aqueous sodium hydroxide solution (30%, 45 ml) were heated under reflux (bath temperature 125-130°) for 85 hours. The reaction mixture was acidified to pH 1 with HCl and extracted with ether. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to yield 0.320 g (84.2%) of a viscous, yellow, liquid residue (XIV), $[\alpha]_{589}^{25} = -1.9 \pm 0.2^{o}$ (c = 3.15, $CHCl_3$). Nmr ($CDCl_3$): δ 0.8-2.9 (complex, COCH and $CH_2$); δ 2.9-3.9 (complex, OCH and $OCH_2$); δ 7.37 (singlet, OH and COOH); ir (neat liquid): 3300 $cm^{-1}$ (hydroxyl), 1700 $cm^{-1}$ (carboxylic acid), 1085 $cm^{-1}$ (dialkyl ether).

(2) Preparation of Methyl Ester of Equilibrated 3-(9-Hydroxy-nonamethyleneoxy)cyclohexanecarboxylic Acid (XV).

A cold ethereal solution of diazomethane[43] (p 64) was slowly and carefully added to a solution of equilibrated 3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XIV) (p 91) (0.320 g, 1.12 mmol; $[\alpha]_{589}^{25} = -1.9 \pm 0.2^{\circ}$; c = 3.15, $CHCl_3$) in 50 ml of ether. An excess of diazomethane was used. The reaction mixture was left overnight in the hood. The ether solution was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to yield 0.360 g of a pale yellow, liquid residue. The latter was distilled in a short path distillation apparatus. The pale yellow distillate (0.3-0.5 mm, bath temperature 180-185°) was the relay compound, methyl ester of equilibrated 3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XV), $[\alpha]_{589}^{25} = -1.7 \pm 0.3^{\circ}$ (c = 1.91, $CHCl_3$). The yield of distilled methyl ester XV was 0.191 g (57% based on the acid XIV used). Nmr ($CDCl_3$): δ 0.8-2.9 (complex, 24 H, COCH, $CH_2$ and OH); δ 2.9-3.9 (Complex with a sharp singlet at δ 3.66, 8 H, OCH, $OCH_2$ and $COOCH_3$); ir (neat liquid): 3400 $cm^{-1}$ (hydroxyl), 1665 $m^{-1}$ (ester), 1100 $cm^{-1}$ (dialkyl ether).

Anal. Calcd for $C_{17}H_{32}O_4$: C, 67.96; H, 10.74;

Found: C, 67.88; H, 10.55.

(F) Synthesis of Methyl Ester of Equilibrated 3-(9-Hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XV) from cis-3-Hydroxycyclohexanecarboxylic Acid (XVI).

(1) Preparation of cis- and trans-3-Hydroxycyclohexanecarboxylic Acid (XVI and LXXIV).[37]

3-Hydroxybenzoic acid (27.6 g, 0.2 mol) was dissolved in ethanol (95%, 175 ml), rhodium on carbon (5%, 3.0 g) was added, and the mixture was hydrogenated in a Parr low pressure hydrogenation apparatus. During the first 9 hours the uptake of hydrogen was 55.5 psig. The calculated uptake of hydrogen was 49.0 psig. There was no further uptake of hydrogen in the next 11 hours. The catalyst was filtered, and the solvent was evaporated (rotary evaporator) to a pale yellow, viscous liquid containing some solid.

The above product was heated to 170° for one hour, cooled, and the distilled under reduced pressure, using a Vigreux column. A first fraction (11.1 g) was collected between 104-120° (7 mm). It was a clear, colorless liquid, part of which solidified on cooling to room temperature. A second fraction (2.8 g) was collected between 110-135° (1 mm). The Vigreux column was replaced by a Claisen head. The third fraction (5.1 g) distilled between 150-153° (1 mm). It was a

clear, colorless liquid, which solidified on cooling to room temperature (mp 60-100°).

The first fraction was dissolved in sodium hydroxide solution (aqueous, 2 M, 50 ml) and heated to 90-95° for one hour. The reaction mixture was acidified to pH 1 with HCl and extracted with ether. The ether extract was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to a white solid. The latter was washed with hexane and recrystallized from ethyl acetate to give 2.85 g of white crystals, melting at 131-132° (lit[37] mp 131.5-132°). This was cis-3-hydroxycyclohexanecarboxylic acid (XVI). The infrared spectrum was identical to a literature spectrum.[49]

The third fraction was recrystallized from ethyl acetate to give 3.32 g of white crystals (mp 115-120°). Washing with hexane raised the mp to 119-120° (lit[37] mp 120°). This was trans-3-hydroxycyclohexanecarboxylic acid (LXXIV). The ir spectrum was identical to a literature spectrum.[50]

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(49) Infrared spectrum no. 21669, Sadtler Standard Spectra, Sadtler Research Laboratories, Philadelphia, Penn.

(50) Infrared spectrum no 21668, ibid.

(2) Resolution of cis-3-Hydroxycyclohexanecarboxylic Acid (XVI).[36]

cis-3-Hydroxycyclohexanecarboxylic acid (XVI) (p 94) (17.34 g, 0.12 mol) was dissolved in methanol (40 ml). This solution was added to a solution of quinine (J. T. Baker Chemical Co., Phillipsburg, N.J.) (46 g, 0.12 mol) in methanol (100 ml). The mixture was kept in a warm water bath (50°) and allowed to cool slowly. After two days in a refrigerator, the mixture was filtered to give 44 g of white crystals. Two further recrystallizations from methanol gave 15 g of quinine salt.

The quinine salt (15 g) was added to a solution of 2 g (0.05 mol) of sodium hydroxide in 75 ml of water. The mixture was stirred and warmed on a steam bath for one hour and stirred at room temp for 4 hours. The reaction mixture was filtered. The residue was dissolved in 75 ml of chloroform. The chloroform solution was extracted with 50 ml of 10% aqueous sodium hydroxide solution. The combined basic extracts were acidified to pH 1 with cold 18 N sulfuric acid solution, and the acidified solution continuously extracted with ether. The ether extract was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to a white solid, $[\alpha]_{589}^{25} = +9.3 \pm 0.1^{\circ}$ (c = 4.0, $CHCl_3$) (lit[36] $[\alpha]_{589}^{23.6} = +9.75^{\circ}$).

(3) Preparation of 9-Bromononanol.[38]

1,9-Nonanediol (25 g, 0.156 mol) and HBr (48%, 125 ml, 0.75 mol) were placed in the extraction chamber of a continuous extraction apparatus. Heptane (extracting solvent) was heated to maintain a vigorous flow of solvent through the reaction mixture in the extraction chamber. This was also sufficient to maintain the extraction chamber at 55-60°. The reaction mixture was stirred (magnetic stirrer) for 16 hours. Ether was added to the cooled heptane layer. The ether solution was extracted twice with 5% aqueous sodium bicarbonate solution and three times with water. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to yield 31.5 g (90.4%) of a clear, pale yellow, liquid residue which on standing solidified to a white solid.

From four runs, 125 g of crude 9-bromononanol was obtained. Distillation under reduced pressure (6 mm, 144-146°) gave 9-bromononanol (XVII) (108 g, overall yield 77%) as a clear, colorless liquid which on cooling to room temperature solidified to a white solid, mp 32-34° (lit[38] mp 31.5-33°). Nmr ($CDCl_3$): δ 0.8-2.3 (complex, 14 H, $CH_2$); δ 3.1-3.8 (two overlapping triplets, 4 H; δ 3.39, J = 6.5 Hz, $BrCH_2$; δ 3.55, J = 6.5 Hz, $OCH_2$); δ 4.0 (singlet, 1 H, OH, disappears on treatment with $D_2O$).

(4) Preparation of 2-(9-Bromononamethyleneoxy)tetrahydropyran (XVIII).[38]

9-Bromononanol (XVII) (p 97) (85 g 0.381 mol) and 2,3-dihydropyran (92 g, 1.095 mol) were placed in a flask equipped with a magnetic stirrer. About 1 ml of conc. HCl was added, and the reaction mixture stirred for 12 hours at room temperature. Ether (400 ml) was added, and the reaction mixture was extracted with 5% aqueous sodium bicarbonate solution twice and with water three times. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to a clear, yellow, liquid residue. The latter was distilled (1 mm, 143-145°) over anhydrous potassium carbonate (2 g) to give 2-(9-bromononamethyleneoxy)tetrahydropyran (XVIII) (98 g, 83.8%). Nmr ($CDCl_3$): δ 1.0-2.2 (complex, 20 H, ring and side chain $CH_2$); δ 3.05-4.15 (complex, 6 H, $OCH_2$, and $BrCH_2$); δ 4.53 (singlet, 1 H, OCHO).

(5) Preparation of cis-3-[9-(2-Tetrahydropyranyloxy)nonamethyleneoxy]cyclohexanecarboxylic Acid (XIX).

cis-3-Hydroxycyclohexanecarboxylic acid (XVI) (p 95) (1.61 g, 11.1 mmol) and sodium hydride (57% oil emulsion, 2.8 g, 66.5 mmol) were placed in a 3-necked flask equipped with a magnetic stirrer, two pressure equalizing addition funnels, and a reflux condenser fitted with a drying tube. N,N-Dimethylformamide (25 ml) was added and the mixture was stirred for 5 minutes. A solution of 2-(9-bromononamethyleneoxy)tetrahydropyran (XVIII) (p 98) (15.05 g, 48.9 mmol) in N,N-dimethylformamide (20 ml) was added dropwise over a period of 20 minutes and the reaction mixture was heated for 2.5 hours at 75-80°. The unused NaH was decomposed by addition of ice to the reaction mixture. The latter was extracted with ether and the ether layer was rejected. The aqueous layer was acidified to pH 1 with HCl and extracted with ether. The ether extract was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to yield 1.42 g (41.5%) of a viscous, yellow, liquid residue. This was crude cis-3-[9-tetrahydropyranyloxy)nonamethyleneoxy]cyclohexanecarboxylic acid (XIX). Nmr ($CDCl_3$): δ 0.8-2.8 (complex, 29 H, COCH and $CH_2$); δ 2.8-4.3 (complex, 7 H, OCH and $OCH_2$); δ 4.57 (singlet, 1 H, OCHO); δ 9.57 (singlet, 1 H, COOH); ir (neat liquid): 3600

$cm^{-1}$ (hydroxyl), 1730 $cm^{-1}$ (carboxylic acid).

A similar experiment starting with 2.0 g (14 mmol) of optically active cis-3-hydroxycyclohexanecarboxylic acid (XVI) (p 96) ($[\alpha]_{589}^{25}$ = + 9.3 ± 0.2°; c = 4.0, $CHCl_3$), 3.5 g of sodium hydride (57% oil emulsion, 83 mmol), and 20.0 g (65 mmol) of 2-(9-bromononamethyleneoxy)tetrahydropyran (XVIII) yielded 1.56 g (30.3%) of crude optically active cis-3-[9-(2-tetrahydropyranyloxy)nonamethyleneoxy]cyclohexanecarboxylic acid (XIX), $[\alpha]_{589}^{25}$ = + 13.4 ± 0.2° (c = 3.1, $CHCl_3$).

(6) Conversion of cis-3-[9-(2-Tetrahydropyranyloxy)nonamethyleneoxy]cyclohexanecarboxylic Acid (XIX) to cis-3-(9-Acetoxynonamethyleneoxy)cyclohexanecarboxylic Acid (XX).[51]

cis-3-[9-(2-Tetrahydropyranyloxy)nonamethyleneoxy]-cyclohexanecarboxylic acid (crude, 1.4 g, ca. 3.8 mmol) (XIX) (p 99) and acetic acid (35 ml) were heated under reflux (bath temperature 125-130°) for 18 hours. The cooled reaction mixture was extracted with ether and the ether extract was washed with water. The aqueous layer was rejected. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to yield 1.012 g (81.5%) of a pale brown, liquid residue, crude cis-3-(9-acetoxynonamethyleneoxy)cyclohexanecarboxylic acid (XX). Nmr ($CDCl_3$): δ 0.7-2.8 (complex with a sharp singlet at δ 2.0, $CH_2$, COCH, and $OCOCH_3$); δ 2.9-3.8 (complex, OCH and $OCH_2$); δ 4.03 (triplet, J = 5.5 Hz, $COOCH_2$); δ 10.35 (broad singlet, COOH).

A similar experiment starting with 1.54 g (crude, ca. 4.7 mmol) of optically active cis-3-[9-(2-tetrahydropyranyloxy)-nonamethyleneoxy]cyclohexanecarboxylic acid (XIX) (p 100) ($[\alpha]_{589}^{25}$

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(51) Patterned after W.G. Dauben and H. L. Bradlow, J. Amer. Chem. Soc., 74, 559 (1952).

= + 13.4 ± 0.2°; c = 3.1, $CHCl_3$) and acetic acid (60 ml) yielded 1.23 g (90.1%) of a pale brown, liquid residue, crude optically active cis-3-(9-acetoxynonamethyleneoxy)cyclohexanecarboxylic acid (XX), $[\alpha]_{589}^{25}$ = + 12.5 ± 0.2° (c = 3.99, $CHCl_3$).

(7) Hydrolysis of cis-3-(9-Acetoxynonamethyleneoxy)cyclohexanecarboxylic Acid (XX).

cis-3-(9-Acetoxynonamethyleneoxy)cyclohexanecarboxylic acid (XX) (p 101) (crude, 1.01 g, ca. 3.1 mmol) and ethanolic potassium hydroxide solution (1.5 M, 50 ml) were heated under reflux (bath temperature 110°) for 3 hours. Water (50 ml) was added to the cooled reaction mixture, and the latter was extracted with ether. The ether layer was rejected. The aqueous layer was acidified to pH 1 with HCl, and extracted with ether. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaprator) to yield 0.784 g (77.6%) of a pale brown, liquid residue. The crude product was chromatographed on 130 g of silica gel (Davison, grade 923, mesh 100-200) (length of column 18", width 0.75"). cis-3-(9-Hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XXI) (0.58 g) was eluted with 10% ether/benzene as a pale brown, viscous liquid. Nmr ($CDCl_3$): δ 0.8-2.9 (complex, 23 H, COCH and $CH_2$); δ 2.9-3.9 (complex, 5 H, OCH and $OCH_2$); δ 7.70 (singlet, 2 H, OH and COOH, disappears on treatment with $D_2O$); ir (neat liquid): 3400 $cm^{-1}$ (hydroxyl), 1700 $cm^{-1}$ (carboxylic acid), 1085 $cm^{-1}$ (dialkyl ether).

A similar experiment starting with 1.18 g (crude, ca. 3.6 mmol) of optically active cis-3-(9-acetoxynonamethyleneoxy)

cyclohexanecarboxylic acid (XX) (p 101) ($[\alpha]_{589}^{25}$ = + 12.5 ± 0.2°; c = 3.99, $CHCl_3$) yielded 0.874 g (84.9%) of a pale brown, liquid residue. The crude product (0.87 g) was chromatographed on 150 g of silica gel (Davison, grade 923, mesh 100-200). Optically active cis-3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XXI) (0.48 g), $[\alpha]_{589}^{25}$ = + 10.8 ± 0.2° (c = 4.7, $CHCl_3$), was eluted with 30% ether/benzene.

(8) Equilibration of cis-3-(9-Hydroxynonamethyleneoxy)cyclohexanecarboxylic Acid (XXI).

cis-3-(9-Hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XXI) (p 103) (0.58 g, 2.03 mmol) and aqueous sodium hydroxide solution (30%, 55 ml) were heated (bath temperature 125-130°) under reflux for 85 hours. Water (75 ml) was added to the cooled reaction mixture. The latter was acidified to pH 1 with HCl, and extracted with ether. The ether layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated (rotary evaporator) to yield 0.375 g (64.6%) of a viscous, pale brown, liquid residue, the equilibrated 3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XIV). Nmr ($CDCl_3$): δ 0.8-2.9 (complex, COCH and $CH_2$); δ 2.9-3.9 (complex, OCH and $OCH_2$); δ 6.50 (singlet, OH and COOH); ir (neat liquid): 3350 $cm^{-1}$ (hydroxyl), 1700 $cm^{-1}$ (carboxylic acid), 1085 $cm^{-1}$ (dialkyl ether).

A similar experiment starting with 0.475 g (1.66 mmol) of optically active cis-3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XXI) (p 104) ($[\alpha]_{589}^{25}$ = + 10.8 ± 0.2°; c = 4.7, $CHCl_3$) yielded 0.324 g (66.1%) of a viscous, pale brown, liquid residue, the equilibrated 3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XIV), $[\alpha]_{589}^{25}$ = + 11.2 ± 0.2° (c = 3.2, $CHCl_3$).

(9) Preparation of Methyl Ester of Equilibrated 3-(9-Hydroxynonamethyleneoxy)cyclohexanecarboxylic Acid (XV).

A cold ethereal solution of diazomethane[43] (p 64) was slowly and carefully added to a solution of equilibrated 3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid (XIV) (p 105) (0.375 g, 1.31 mmol) in ether (50 ml). The reaction mixture was left overnight in the hood at room temperature. The ether solution was dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated (rotary evaporator) to yield 0.390 g (99%) of a pale yellow, liquid residue. The latter was distilled in a short path distillation apparatus. The pale yellow distillate (0.3-0.5 mm, bath temperature 180-185°) was the methyl ester of equilibrated 3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid, the relay compound (XV). Nmr ($CDCl_3$): δ 0.7-2.8 (complex, 24 H, COCH, $CH_2$, and OH, the peak at δ 2.01 disappeared on treatment with $D_2O$); δ 2.9-3.9 (complex, with a sharp singlet at δ 3.65, 8 H, OCH, $OCH_2$, and $COOCH_3$); ir (neat liquid): 3375 $cm^{-1}$ (hydroxyl), 1730 $cm^{-1}$ (ester), 1095 $cm^{-1}$ (dialkyl ether); ms: major peaks at m/e 300, 282, 269, 267, 241, and 226.

Anal. Calcd for $C_{17}H_{32}O_4$: C, 67.96; H, 10.74; Found: C, 67.81; H,10.49.

A similar experiment starting with 0.315 g (1.1 mmol) of optically active, equilibrated 3-(9-hydroxynonamethyleneoxy) cyclohexanecarboxylic acid (XIV) (p 105) ($[\alpha]_{589}^{25}$ = + 11.2 ± 0.2°; c = 3.2, $CHCl_3$) yielded 0.304 g (92.2%) of crude methyl ester, which gave 0.184 g (55.8% based on the acid used) of distillate (0.1 mm, bath temperature 180-210°), the methyl ester of equilibrated 3-(9-hydroxynonamethyleneoxy)cyclohexanecarboxylic acid, the relay compound (XV), $[\alpha]_{589}^{25}$ = + 9.4 ± 0.2° (c = 1.84, $CHCl_3$).