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Stereochemistry of the 2,2'-Dihydroxydicyclohexylamines. II. Synthesis of Unknown Compensated Isomers and Formation of 5-Phenyl-2,3-7,8-dicyclohexano-1-aza-4,6-dioxabicyclo[3.3.0]octanes[1]

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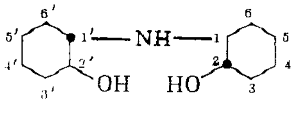
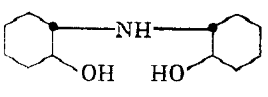
The *N*-benzoyl derivative of DL-*trans-trans*-2,2'-dihydroxydicyclohexylamine (I) was treated with thionyl chloride followed by alkali hydroxide, yielding a basic substance, $C_{19}H_{25}NO_2$ (XII), and the *cis-O*-benzoyl derivative of DL-*trans-anti-cis*-2,2'-dihydroxydicyclohexylamine which was debenzoylated to the free aminodiol (II) by hydrolysis. The former product was characterized as DL-5-phenyl-*trans*-2,3-*anti-cis*-7,8-dicyclohexano-1-aza-4,6-dioxabicyclo[3.3.0]octane (XII) on the basis of its chemical reactions and infrared spectrum. The *trans-anti-cis*-azadioxabicyclooctane (XII) was converted to DL-2-phenyl-3-(*trans*-2'-hydroxycyclohexyl)-*anti-cis*-4,5-cyclohexanoöxazolinium salts (XXII) in attempted salt-formation by anhydrous mineral acids and reversed by alkali hydroxides, suggesting an interconversion betweeen XII and XXII. DL-*cis-cis*-Dihydroxydicyclohexylamine (III) was derived from the *N*-benzoyl or the *N-cis-O*-dibenzoyl derivative of the *trans-anti-cis*-aminodiol (II) *via* the Walden inversion by thionyl chloride. The *cis-cis*-epimer (XXVIII) of XII was also formed in the analogous way to the case of XII.

The 2,2'-dihydroxydicyclohexylamines can theoretically exist in six compensated forms, of which the following four isomers have been synthesized: the DL-*trans-trans*-(I), the *meso-trans-trans*-(IV), one of the DL-*trans-cis*-(V, m.p. 147°), and the *meso-cis-cis*-(VI) isomers.[2-4] This work was started with the primary purpose of synthesis and characterization of the two isomers remaining unknown, the other (II) of DL-*trans-cis*-isomers and the DL-*cis-cis*-isomer (III). Chart I shows diagrams of the isomers projected so that both hydroxyl groups are together at the same side of an extension line of the imine bond which attaches to C_1 and C_1' in the *e*-positions. The nomenclature adopted in the preceding paper[4] is apt to confuse two different isomers of DL-*trans-cis*-configuration. Therefore, they were distinguished from each other by the application of Linstead's method[5] adopted for the nomenclature of perhydrodiphenic acids. On examining projection diagrams of both DL-*trans-cis*-isomers in Chart I, one holds two hydrogens at C_1 and C_1' respectively at opposite sides of the paper plane involving two rings, whereas the other holds them together at the same side. Hence the former is called DL-*trans-anti-cis*-2,2'-dihydroxydicyclohexylamine (II) and the latter DL-*trans-syn-cis*-diasteroisomer (V) which has been characterized,[4] m.p. 147°.

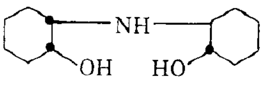
Chart I



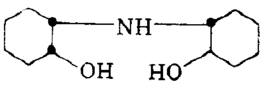
I. DL-*trans-trans*



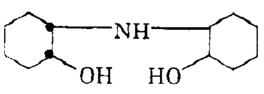
IV. *meso-trans-trans*



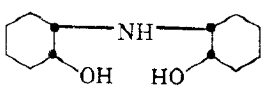
II. DL-*trans-anti-cis*



V. DL-*trans-syn-cis*



III. DL-*cis-cis*



VI. *meso-cis-cis*

The DL-*trans-trans*-aminodiol (I) gave a neutral and basic monobenzoyl derivatives, m.p.s. 216° and 103°, by the Schotten-Baumann benzoylation.[6] The neutral monobenzyl derivative was suggested to be the *N*-benzoyl derivative (VII) of I by the infrared absorption band at 1616 cm.$^{-1}$, characteristic of benzamide group, while the basic monobenzoate was identified as the *O*-benzoate (VIII) of I by the same method, the band at 1706 cm.$^{-1}$ due to ester carbonyl. Treatment of the benzamidodiol (VII) with aqueous or alcoholic hydrochloric acid effected N → O acyl migration to give VIII·HCl which, nevertheless, did not undergo the reverse acyl migration, remaining as the corresponding free base (VIII) on treatment with aqueous sodium hydroxide in the cold (see Chart II). On further benzoylation of the benzamide (VII)- and the *O*-benzoate (VIII) by the Schotten-Baumann method, only the latter was benzoylated further to give a neutral dibenzoyl derivative which was suggested to be the *N,O*-dibenzoyl derivative (IX) of I by the infrared spectrum determination, with bands at 1609 and 1709 cm.$^{-1}$ (amide and

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[1] Studies in Stereochemistry. XXV. Paper XXIV, *J. Am. Chem. Soc.*, **81**, 4322 (1959).

[2] L. Brunel, *Compt. rend.*, **137**, 199 (1903).

[3] M. Mousseron, R. Granger, G. Combes, and V. A. Pertzoff, *Bull. soc. chim. France*, 859 (1947).

[4] T. Taguchi and K. Hayashida, *J. Am. Chem. Soc.*, **80**, 2522 (1958).

[5] R. P. Linstead, W. E. Doering, Selby B. Davis, Philip Levine, and Richard R. Whestone, *J. Am. Chem. Soc.*, **64**, 1985 (1942).

[6] In every case of this paper it was carried out with one equivalent of benzoyl chloride in aqueous sodium hydroxide at room temperature, unless otherwise stated.

ester carbonyl). The *N,O*-dibenzoyl derivative (IX) underwent neither N → O acyl migration on treatment with alcoholic hydrochloric acid in the cold nor further benzoylation by the Schotten-Baumann method to give the tribenzoate.

Chart II

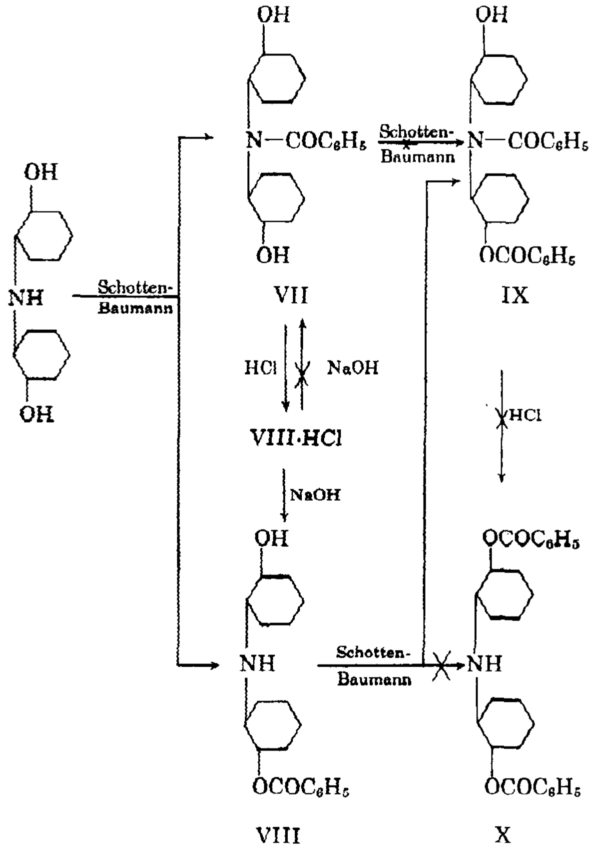
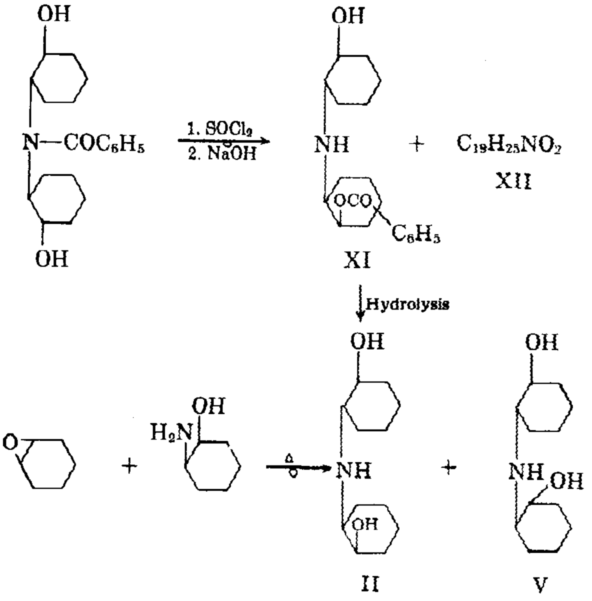


Chart III



DL-*trans-anti-cis*-2,2′-Dihydroxydicyclohexylamine (II) was prepared in the following way (see Chart III). The DL-*trans-trans*-benzamidodiol (VII) was converted to two basic substances, m.p.s. 151° and 78°, by action of thionyl chloride, followed by treatment with aqueous sodium hydroxide. The one, m.p. 151°, (XII) was given $C_{19}H_{25}NO_2$ for empirical formula, the structure and configuration of which will be discussed below. The other, m.p. 78°, (XI) was ascertained to have an *O*-benzoyl group by examining the infrared spectrum, with a band at 1710 cm.$^{-1}$ (ester carbonyl), and to give a new 2,2′-dihydroxydicyclohexylamine (II) by hydrolysis. The aminodiol (II) was identical with 2,2′-dihydroxydicyclohexylamine, m.p. 111°, which was obtained together with the epimer of m.p. 147° by reaction of *meso-cis*-cyclohexene oxide and DL-*cis*-2-aminocyclohexanol. Because it had been already established that the epimer of m.p. 147° was DL-*trans-syn-cis*-2,2′-dihydroxydicyclohexylamine[4] (V), the aminodiol of m.p. 111° (II) was characterized as the epimer of DL-*trans-anti-cis*-configuration and accordingly XI is the corresponding *cis-O*-benzoyl derivative. The conclusion is supported by the fact that the stereospecificities of reactions involved in the formation of II have been well established.

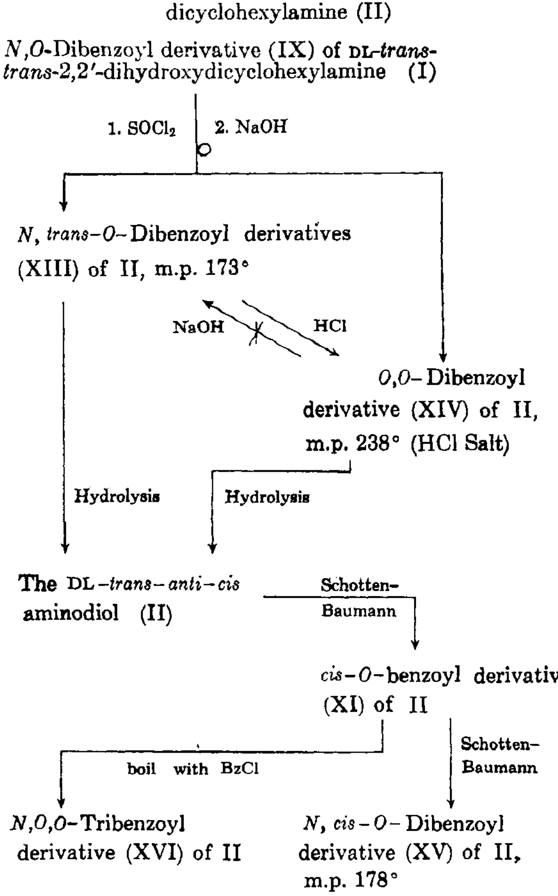
There are three isomers, *N,trans*-O-(XIII), *O,O*-(XIV), and *N,cis*-O-(XV), of the dibenzoyl derivatives of DL-*trans-anti-cis*-2,2′-dihydroxydicyclohexylamine (II), which were obtained in the following ways. The benzoylation of the DL-*trans-anti-cis*-aminodiol (II) by the Schotten-Baumann method proceeded preferentially on one of hydroxyl groups rather than on the amino group to give the corresponding *cis-O*-benzoyl derivative (XI) which took up one more equivalent of benzoyl chloride to give a neutral dibenzoyl derivative of II. The product was shown to be DL-(*trans*-2-hydroxy-*anti-cis*-2′-benzoyloxydicyclohexyl)benzamide (XV) by the infrared absorption bands at 1625 and 1718 cm.$^{-1}$, characteristics of amide and ester carbonyl groups. This phenomenon agreed with the previous finding[4] that an epimer of 2,2′-dihydroxydicyclohexylamine, which has a free hydroxyl group in the position *cis* to the amino group, does not undergo *N*-benzoylation first by Schotten-Baumann method. Boiling the *cis-O*-benzoate of II with benzoyl chloride gave the *N,O,O*-tribenzoyl derivative (XVI) of II.

II was also prepared from the *N,O*-dibenzoyl derivative (IX) of DL-*trans-trans*-aminodiol (I) on treatment with thionyl chloride followed by sodium hydroxide. The reaction gave a solid and an oily benzoyl derivative, which were both converted to the DL-*trans-anti-cis*-aminodiol (II) by hydrolysis. The solid dibenzoyl derivative gave no hydrochloride and was suggested to be DL-(*trans*-2-benzoyloxy-*anti-cis*-2′-hydroxydicyclohexyl)benzamide (XIII) with infrared absorption bands at 1607 and 1707 cm.$^{-1}$, characteristics of amide and ester carbonyl groups, and differing from the *N,cis*-

O-dibenzoyl derivative (XV) of II. The oily dibenzoyl derivative gave the hydrochloride immediately after addition of dilute hydrochloric acid and showed the infrared absorption band due to ester carbonyl at 1711 cm.$^{-1}$ and no band due to amide and hydroxyl groups, thus suggesting that it was DL-*trans-anti-cis*-2,2'-dibenzoyloxydicyclohexylamine (XIV). The *N*,*trans*-*O*-dibenzoyl derivative (XIII) suffered *N* → O acyl migration to convert it to the *O*,*O*-dibenzoyl derivative (XIV) hydrochloride after heating in concentrated hydrochloric acid on a water-bath for half an hour; it suffered no reverse acyl migration on treatment with alkali in the cold changing only to its free form (see Chart IV).

Chart IV

Dibenzoyl derivatives of DL-*trans-anti-cis*-2,2'-dihydroxydicyclohexylamine (II)



The structure and configuration of the basic substance, $C_{19}H_{25}NO_2$ (XII), in question was deduced from the infrared spectrum and chemical properties to be DL-5-phenyl-*trans*-2,3-*anti*-*cis*-7,8-dicyclohexano-1-aza-4,6-dioxabicyclo[3.3.0]octane which shows an unusual ring system containing *ortho* amide group as a part of ring constituents. The infrared spectrum of XII showed no absorption bands due to hydroxyl, amino (primary and secondary), amide, and ester groups, but it showed the characteristic bands of oxazolidine (N—C—O group and tertiary N)[7,8] in the 1050–1180 cm.$^{-1}$ region, being accompanied by some minor bands. Hydrolysis of XII were carried out under a number of conditions; (a) heating in water or dilute acetic acid at 120° in a sealed tube, (b) treatment in alcoholic potassium hydroxide, (c) allowing to stand at room temperature in hydrochloric acid, and (d) boiling in 80% ethanol for an hour. Products under (a), (b), (c), and (d) were the DL-*trans-anti-cis*-aminodiol (II) benzoate, its free base (II), the *cis*-*O*-benzoyl DL-*trans-anti-cis*-aminodiol (XI) and DL-*trans-anti-cis*-2,2'-dihydroxydicyclohexylbenzamide (XVII), respectively (see Chart V). The last product (XVII) was gained only in this way and characterized by the infrared absorption band at 1600 cm.$^{-1}$ characteristic of benzamido group and by conversion to the *cis*-*O*-benzoate (XI) hydrochloride of II on treatment with hydrochloric acid. XII was treated with methyl iodide to give the corresponding *N*-methoiodide (XVIII), identification of which was based on a positive proof of anionic iodine and on the fact that XVIII was converted to DL-*trans*-2-benz(methyl)amidocyclohexanol[9] (XIX) by heating in alcoholic potassium hydroxide (see following diagrams.)

These findings seem adequate support for the given configuration of XII, but to gain additional information, the following reactions were examined and the results were found to be reasonably explained by the configuration (see Chart VI). Hydrogenation of XII over platinum oxide[10,11] consumed two moles of hydrogen at room temperature under atmospheric pressure giving DL-*trans-anti-cis*-2,2'-dihydroxydicyclohexyl(benzyl)amine (XX) which was characterized by elemental analyses and infrared spectrum determination. Some knowledge having been gained about action of the Grignard reagent on an α-amino ether[12] and oxazolidine,[13,14] XII was submitted to this treatment. In the reaction of XII and methylmagnesium iodide in ether, use of one equivalent of the Grignard reagent caused the precipitation of crystals (presumably an addition compound of the two reactants) which resulted in the recovery of the material on the subsequent treatment with water and use of two or three equivalents gave the DL-*trans-anti-cis*-aminodiol (II) and acetophenone

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(7) E. D. Bergmann, *Chem. Revs.*, **53**, 326 (1953).

(8) E. D. Bergmann and S. Pinchas, *Rec. trav. chim.*, **71**, 237 (1952); *Chem. Abstr.*, **47**, 6401 (1953).

(9) M. Mousseron and F. Winternitz, *Compt. rend.*, **235**, 373 (1952).

(10) V. L. Flampton *et al.*, *J. Am. Chem. Soc.*, **73**, 4432 (1953).

(11) A. C. Cope and H. M. Honack, *J. Am. Chem. Soc.*, **64**, 1503 (1942). *J. Am. Chem. Soc.*, **66**, 1453 (1944). E. D. Bergmann, D. Lavie, and S. Pinchas, *J. Am. Chem. Soc.*, **73**, 5662 (1951).

(12) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, **123**, 532 (1923).

(13) L. H. Goodson and H. Christopher, *J. Am. Chem. Soc.*, **72**, 358 (1950).

(14) M. Senkus, *J. Am. Chem. Soc.*, **72**, 2178 (1950).

Chart V

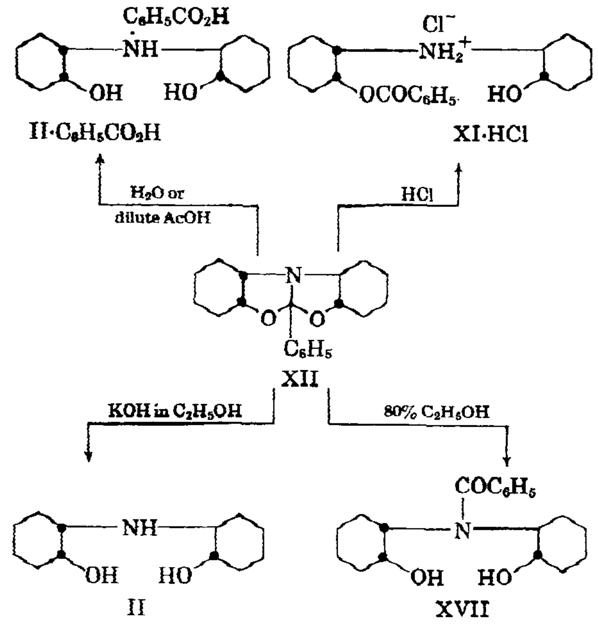
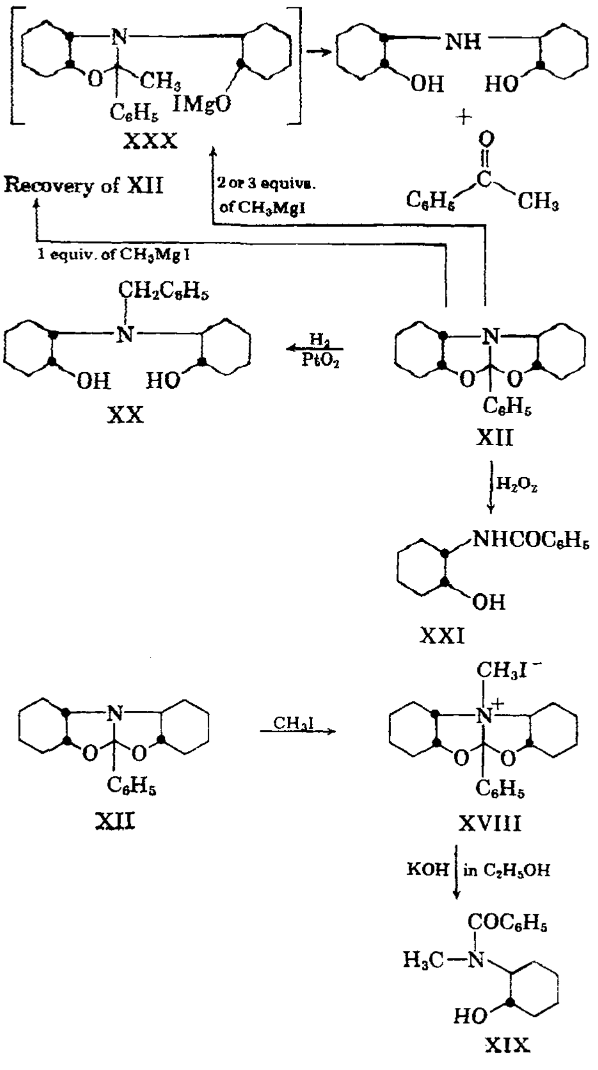
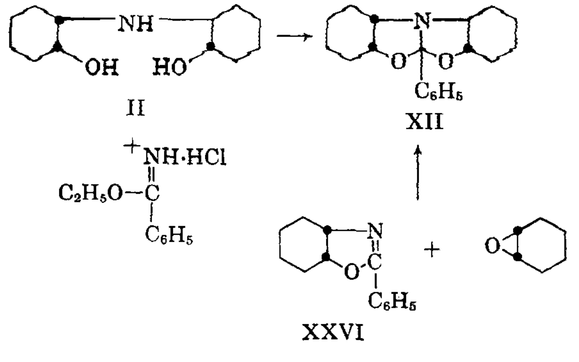


Chart VI



presumably *via* XXX as depicted in Chart VI. XII reacted with hydrogen peroxide in glacial acetic acid in the hope of gaining the corresponding *N*-oxide, but it gave an unexpected product, DL-*cis*-2-benzamidocyclohexanol (XXI). The compound XII reacted with anhydrous hydrochloric acid, hydroiodic acid and nitric acid to form salts. However, it seems probable that they were not the salts of XII itself, but DL-2-phenyl-3-(*trans*-2′-hydroxycyclohexyl)-*anti*-*cis*-4,5-cyclohexanoöxazolinium salts (XXII), a conversion product from the salts of XII, because the infrared spectra of the salts were in close similarity to that of the *syn*-oxazolinium chloride (XXIII), an epimer of XXII, which had been characterized[4] (the bands at 3448 and 1613 cm.$^{-1}$ due to hydroxy and $>C=N^+<$ groups.[7] The *anti*- and *syn*-oxazolinium chlorides (XXII and XXIII) were boiled in water to give equally the corresponding *cis*-*O*-benzoyl aminodiol hydrochlorides (XI· and XXIV·HCl). On the other hand the *anti*-oxazolinium salt (XXII) was treated with sodium hydroxide to regenerate XII in contrast to the *syn*-oxazolinium chloride (XXIII) which gave the *N*-benzoyl derivative (XXV) of DL-*trans*-*syn*-*cis*-dihydroxydicyclohexylamine (V) along the usual behavior of a *N*-alkyl oxazolinium salt. Thus there is an interconversion of XII to XXII by acids and *vice versa* by alkali (see Chart VII). This fact suggests that in the above-stated preparation method of XII from the DL-*trans*-*trans*-benzamidodiol (VII) by the use of thionyl chloride and then alkali, the reaction proceeded *via* XXII. The compound XII was also synthesized in two other ways: one was carried out by boiling benzimido ether hydrochloride with the DL-*trans*-*anti*-*cis*-aminodiol (II) and the other heating DL-*cis*-2-phenyl-4,5-cyclohexanoöxazoline (XXVI) with *meso*-*cis*-cyclohexene oxide in a sealed tube, as is shown in the following diagrams.



DL-*cis*-*cis*-2,2′-Dihydroxydicyclohexylamine (III) was obtained in the following way. The *N*,*cis*-*O*-dibenzoyl derivative (XV) of the *trans*-*anti*-*cis*-aminodiol (II) was treated with thionyl chloride and boiled in water for ten minutes to give the *O*,*O*-dibenzoate (XXVII) of another 2,2′-dihydroxydicyclohexylamine hydrochloride. XXVII was hy-

Chart VII

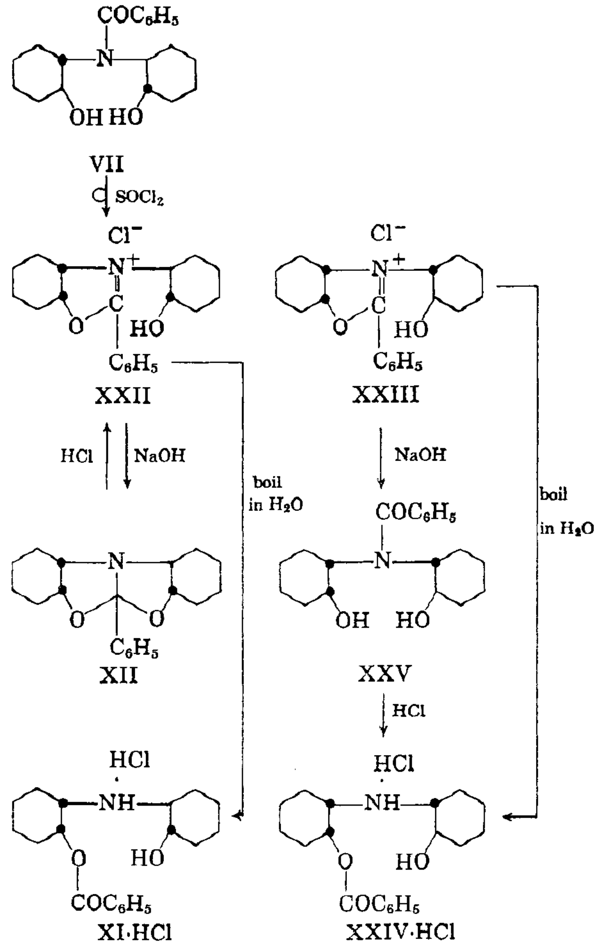
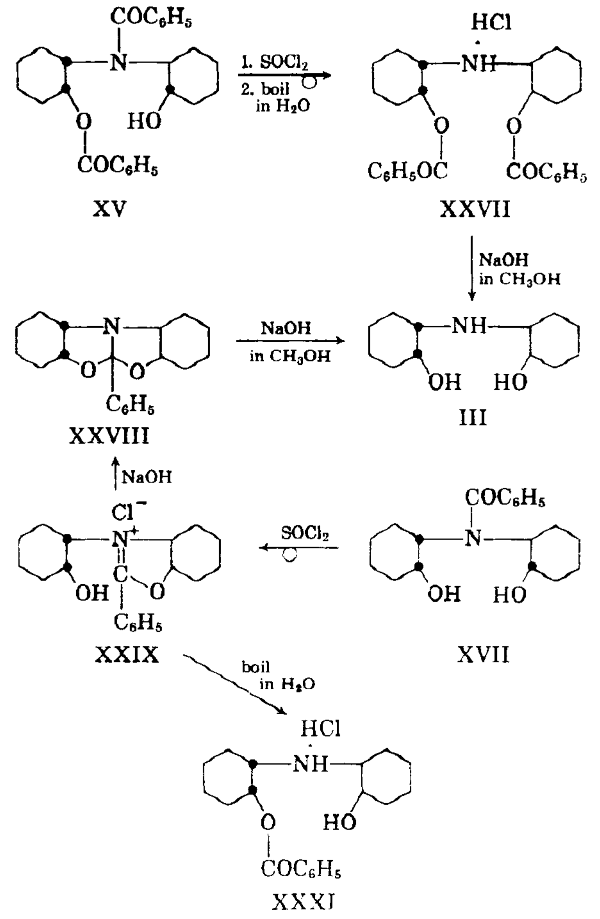


Chart VIII



drolyzed in methanolic potassium hydroxide to give a free aminodiol which was characterized as the DL-*cis-cis*-isomer (III) because of no identity with the known five isomers, suggesting that XXVII was *O,O*-dibenzoate of III·HCl. The *O*-benzoate (XXXI) of III·HCl was obtained when the reaction mixture of the *N*-benzoyl DL-*trans-anti-cis*-aminodiol (XVII) and thionyl chloride was poured into water and boiled for ten minutes, (see Chart VIII). III and its *O*-benzoate did not suffer benzoylation by the Schotten-Baumann method.

By working up as in the formation of the *trans-anti-cis*-azadioxabicyclooctane (XII) from the *N*-benzoyl DL-*trans-trans*-aminodiol (VII), DL-5-phenyl-*cis*-2,3-*cis*-7,8-dicyclohexano-1-aza-4,6-dioxabicyclo[3.3.0]octane (XXVIII) was derived from the *N*-benzoyl DL-*trans-anti-cis*-aminodiol (XVII). The identification of XXVIII depended upon the comparison of it with XII in the infrared spectra and on the fact that the hydrolysis of it in methanolic sodium hydroxide gave DL-*cis-cis*-2,2'-dihydroxydicyclohexylamine (III). The formation of XXVIII seems to proceed *via* DL-2-phenyl-3-(*cis*-2'-hydroxycyclohexyl)-*cis*-4,5-cyclohexanoöxazolinium chloride (XXIX) along the same mechanism with the formation reaction of XII (see Chart VIII). As has been shown in this paper and the preceding one[4] treatment of the *N*-benzoyl derivatives (VII, XVII, and XXV) of 2,2'-dihydroxydicyclohexylamines, I, II, and IV, with thionyl chloride were found to give the corresponding oxazolinium chlorides, XXII, XXIX, and XXIII, but by the subsequent treatment with alkali hydroxide XXII and XXIX were converted to the DL-*trans-anti-cis*- and DL-*cis-cis*-azadioxabicyclooctanes (XII and XXVIII) while XXIII gave the *N*-benzoyl DL-*trans-syn-cis*-aminodiol (XXV). The difference in results is presumably rationalized in terms of steric repulsion between *cis*-oriented H_1 and H_1' for XXIII in the transition state where hydroxyl group at C_2' adds to $>C{=}N^+<$, an effect that is absent in the *trans*-oriented transition state for XXII and XXIX (see Chart IX).

EXPERIMENTAL[15]

DL-*trans-trans-2,2'-Dihydroxydicyclohexylamine* (I). A solution of 10 g. of DL-*trans*-2-aminocyclohexanol and 10 g. of *meso-cis*-cyclohexene oxide in 80 ml. of ethanol was boiled for 6 hr. and cooled. After filtration of the precipitated *meso-trans-trans*-2,2'-dihydroxydicyclohexylamine (IV), the mother liquor was evaporated *in vacuo* and the remainder (I) was recrystallized from ligroin as colorless needles, m.p.

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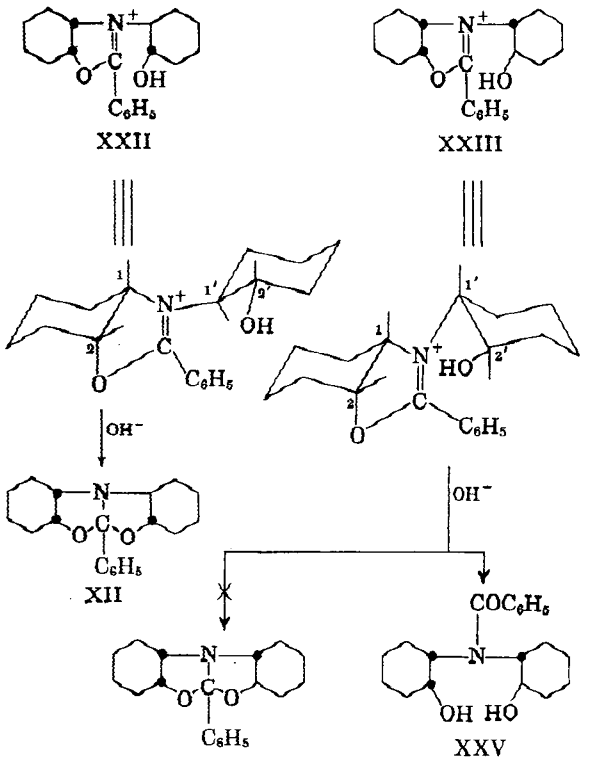
[15] Melting points are uncorrected.

Chart IX



124° (m.p. 114° by Brunel[2] and Mousseron,[3] m.p. 126° by Hawkins[16]).

Anal. Calcd. for $C_{12}H_{23}NO_2$: C, 67.56; H, 10.87; N, 6.57. Found: C, 67.79; H, 11.06; N, 6.67.

Monobenzoyl derivatives of I. (a) DL-*trans-trans-2,2'-Dihydroxydicyclohexyl benzamide* (VII). To a solution of 50 g. of I in 200 ml. of chloroform was added 500 ml. of 20% aqueous sodium hydroxide and then 72 ml. of benzoyl chloride was added dropwise while stirring. After filtration of the precipitate, the chloroform layer was separated from the aqueous layer and evaporated to one third volume to precipitate an additional crop. The combined precipitate was recrystallized from benzene as colorless needles, m.p. 216°, yield 38 g. infrared spectrum (Nujol) 1616 cm.$^{-1}$ (amide).

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.58; N, 4.41. Found: C, 72.30; H, 8.52; N, 4.33.

(b) DL-*trans-2-Hydroxy-trans-2'-benzoyloxydicyclohexylamine* (VIII). The chloroform solution after removal of VII under (a) was concentrated and the residue was recrystallized from ligroin, m.p. 103°, 15 g. of colorless needles, infrared spectrum (Nujol) 1706 cm.$^{-1}$ (ester).

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.58; N, 4.41. Found: C, 72.24; H, 8.52; N, 4.01.

Hydrochloride. A benzene solution of VIII was shaken with 10% hydrochloric acid to cause the precipitation of colorless needles, m.p. 218° after recrystallization from acetone-ether.

Anal. Calcd. for $C_{19}H_{27}NO_3 \cdot HCl$: C, 64.49; H, 7.98; N, 3.96. Found: C, 64.74; H, 8.11; N, 4.26.

DL-*trans-2-Hydroxy-trans-2'-benzoyloxydicyclohexylbenzamide* (IX). To a mixture of 100 ml. of benzene and 200 ml. of 7.5% aqueous sodium hydroxide was added 31 g. of VIII·HCl and then 15 g. of benzoyl chloride while stirring. After stirring for 5 hr., the precipitate was filtered and recrystallized from benzene as colorless needles, m.p. 171°, yield 25 g., infrared spectrum (Nujol) 1609 cm.$^{-1}$ (amide), 1709 cm.$^{-1}$ (ester).

Anal. Calcd. for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 73.99; H, 7.52; N, 2.96.

DL-*5-Phenyl-trans-2,3-anti-cis-7,8-dicyclohexano-1-aza-4,6-dioxabicyclo[3.3.0]octane* (XII). (a) To 15 ml. of thionyl chloride was added 20 g. of VII slowly, the mixture allowed to stand for 3 hr. in air, poured in 150 ml. of water and made alkaline with aqueous 5*N* sodium hydroxide. The precipitate was filtered and recrystallized from acetone to give colorless cubes, m.p. 151°, yield 7.5 g.

Anal. Calcd. for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68; mol. wt., 299.40. Found: C, 76.28; H, 8.28; N, 4.56; mol. wt. (Rast), 297.9.

(b) A solution of 2.2 g. of II and 1.8 g. of benzimido ether hydrochloride in 100 ml. of dry ethanol was allowed to stand in the air for 20 days. After evaporation of ethanol the residue was extracted with acetone and recrystallized from a small volume of the same solvent, yield 0.31 g., m.p. 150° alone and on admixture with a sample prepared by method (a).

(c) Allowing to stand for 20 days in method (b) can be replaced by boiling for 1 hr., yield 0.27 g., m.p. 150°.

(d) A mixture of 3.5 g. of *meso-cis*-cyclohexene oxide and 3.5 g. of DL-2-phenyl-*cis*-4,5-cyclohexanoöxazoline[17] was heated at 180° in a sealed tube for 15 hr. After cooling, the unchanged materials were distilled *in vacuo* and the residue was recrystallized from acetone, yield 0.08 g., m.p. 150°.

DL-*trans-2-Hydroxy-cis-2'-benzoyloxydicyclohexylamine* (XI) *and its hydrochloride.* (a) The acetone solution after removal of XII in the preparation method (a) of XII was concentrated to leave a syrupy substance, which was dissolved in benzene, shaken with 200 ml. of 2*N* hydrochloric acid and set aside to cause the precipitation of colorless needles, yield 11 g., m.p. 254° after recrystallization from acetone-ether, infrared spectrum (Nujol) 1728 cm.$^{-1}$ (ester).

Anal. Calcd. for $C_{19}H_{27}NO_3 \cdot HCl$: C, 64.49; H, 7.98; N, 3.96. Found: C, 64.39; H, 8.29; N, 3.57.

To a mixture of 100 ml. of ether and 150 ml. of water containing 2 g. of sodium hydroxide was added 3.42 g. of XI·HCl. The mixture was stirred for 1.5 hr., and the ether layer separated and dried over anhydrous sodium sulfate. After evaporation of ether the residue (XI) was recrystallized from petroleum ether, yield 0.47 g., m.p. 78°, infrared spectrum (Nujol) 1719 cm.$^{-1}$ (ester). A mixed melting point with a sample of the *N*-benzoyl isomer (XVII) showed depression.

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.58; N, 4.41. Found: C, 72.34; H, 8.71; N, 4.30.

(b) To a benzene solution (100 ml.) of 10 g. of DL-*trans-anti-cis-2,2'-dihydroxydicyclohexylamine* (II) (described below) was added 7 g. of benzoyl chloride and 20 ml. of 25% aqueous sodium hydroxide. The solution was stirred for 5 hr. The benzene layer was shaken with 100 ml. of 1*N* hydrochloric acid and allowed to stand in air to precipitate colorless needles, yield 5.0 g., m.p. 254° alone and on admixture with a sample of XI·HCl prepared by method (a).

Dibenzoyl derivatives of DL-*trans-anti-cis-2,2'-dihydroxydicyclohexylamine* (II). (a) *The N,trans-O-dibenzoate* (XIII). To 18 g. of IX was added 20 ml. of thionyl chloride and the mixture set aside for 30 min. The mixture was poured into 200 ml. of water, made alkaline with aqueous sodium hydroxide and extracted with 200 ml. of chloroform. The chloroform solution was concentrated to dryness to leave an oily material which solidified on allowing to stand in air as colorless prisms of m.p. 173° after recrystallization from acetone-ether, yield 8 g., infrared spectrum (Nujol) 1607 cm.$^{-1}$ (amide), 1707 cm.$^{-1}$ (ester).

Anal. Calcd. for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 73.81; H, 7.14; N, 3.12.

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(16) L. R. Hawkins and R. A. B. Bannard, *Can. J. Chem.*, **36**, 220 (1958); *Chem. Abstr.*, **52**, 18250 (1958).

(17) M. Kojima, *Yakugaku Zasshi*, **79**, 1 (1959).

(b) *The O,O-dibenzoate* (XIV) *hydrochloride.* The acetone-ether solution after removal of XIII[18] in procedure (a) was shaken in 1*N* hydrochloric acid and allowed to stand in air to deposit crystals. Recrystallization from acetone-ether gave colorless needles of m.p. 238°, yield 5.0 g., infrared spectrum (Nujol) 1711 cm.$^{-1}$ (ester).

Anal. Calcd. for $C_{26}H_{31}NO_4 \cdot HCl$: C, 68.18; H, 7.04; N, 3.06. Found: C, 67.78 H, 7.11; N, 3.36.

(c) *The N,cis-O-dibenzoate* (XV). With good stirring, to a suspension of 2 g. of XI·HCl in chloroform was added 10 ml. of 20% aqueous sodium hydroxide and then 1 g. of benzoyl chloride. After 3 hr. agitation, the chloroform layer was concentrated and ether added to deposit crystals which were washed with petroleum benzin and recrystallized as colorless prisms, m.p. 178°, yield 2.0 g., infrared spectrum (Nujol) 1625 cm.$^{-1}$ (amide), 1718 cm.$^{-1}$ (ester).

Anal. Calcd. for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 73.85; H, 7.38; N, 3.49.

DL-*trans-anti-cis-2,2'-Dibenzoyloxydicyclohexylbenzamide* (XIV). A mixture of 1 g. of XI·HCl and 10 ml. of benzoyl chloride in 50 ml. of benzene was boiled for 5 hr. After cooling the benzene solution was evaporated under reduced pressure and the residue (XIV) was recrystallized from methanol as colorless cubes, m.p. 199.5°, yield 0.1 g.

Anal. Calcd. for $C_{33}H_{35}NO_5$: C, 75.40; H, 6.71; N, 2.73. Found: C, 74.96; H, 6.51; N, 2.49.

DL-*trans-anti-cis-2,2'-Dihydroxydicyclohexylamine* (II) *and its hydrochloride.* (a) A mixture of 5 g. of *meso-cis*-cyclohexene oxide and 2.1 g. of DL-*cis*-2-aminocyclohexanol was boiled in an oil bath for 3 hr. After cooling, the precipitated crystals were collected, m.p. 147° alone and on admixture with a sample of DL-*trans-syn-cis*-2,2'-dihydroxydicyclohexylamine[4] (IV). From the mother liquor was removed the starting materials by distillation and the residue (II) was washed with ether to give colorless needles, m.p. 111°, after recrystallization from petroleum benzin; yield 1.1 g. *Hydrochloride,* m.p. 239° after recrystallization from acetone-ether.

Anal. Calcd. for $C_{12}H_{23}NO_2$: C, 67.56; H, 10.87; N, 6.57. Found: C, 67.89; H, 11.12; N, 6.38.

Anal. Calcd. for $C_{12}H_{23}NO_2 \cdot HCl$: C, 57.70; H, 9.69; N, 5.74. Found: C, 57.42; H, 9.70; N, 5.48.

(b) Half a gram of XI dissolved in 5 ml. of 10% methanolic potassium hydroxide was heated on a water bath for 30 min. and the methanol was evaporated to dryness. The remainder was dissolved in 10 ml. of water, extracted with 20 ml. of chloroform, dried over anhydrous sodium sulfate, and concentrated to dryness. The residue was recrystallized from petroleum benzin; yield 0.15 g., m.p. 111° alone and on admixture with a sample of II prepared by method (a).

(c) Half a gram of XI in 10 ml. of concd. hydrochloric acid was boiled for 3 hr. After cooling the precipitated benzoic acid was filtered off and the mother liquor was concentrated to leave crystals which were recrystallized from acetone-ether, yield 0.08 g., m.p. 239° alone and on admixture with a sample of II·HCl.

(d) Working up exactly as in method (b) gave II, m.p. 111°, from XIII or XIV.

Reaction of DL-*5-phenyl-trans-2,3-anti-cis-7,8-dicyclohexano-1-aza-4,6-dioxabicyclo[3.3.0]octane* (XII). (a) *Hydrolysis in ethanolic potassium hydroxide.* One gram of XII was dissolved in 30 ml. of ethanol containing 0.5 g. of potassium hydroxide and heated on a water bath for 5 hr. After cooling and filtration of precipitated potassium benzoate, the mother liquor was concentrated to dryness and the residue was recrystallized from petroleum benzin to afford pure II, m.p. 111°, yield 0.1 g.

(b) *Hydrolysis in water.* One gram of XII in 20 ml. of water was heated at 120° in a sealed tube for 6 hr. After cooling, the reaction mixture was made alkaline with sodium hydroxide, extracted with chloroform, dried over anhydrous sodium sulfate and evaporated to leave II, m.p. 111°, yield 0.3 g.

(c) *Hydrolysis in acetic acid.* One gram of XII in 10 ml. of 10% acetic acid was treated just as hydrolysis (b) and gave 0.3 g. of II, m.p. 111°.

(d) *Hydrolysis in hydrochloric acid.* To 3.8 g. of XII dissolved in 3 ml. of concd. hydrochloric acid was added 10 ml. of water and set aside until the precipitation of crystals ceased, yield 1.8 g., m.p. 254° alone and on admixture with a sample of XI·HCl.

(e) *Hydrolysis in ethanol: formation of* DL-*trans-anti-cis-2,2'-dihydroxydicyclohexyl benzamide* (XVII). One gram of XII was dissolved in 50 ml. of ethanol, 10 ml. of water added, and boiled for 2 hr. The reaction mixture was cooled, 200 ml. of water added, extracted with 100 ml. of chloroform, dried over anhydrous sodium sulfate, and evaporated to dryness. Recrystallization from acetone gave colorless needles, m.p. 175°; yield 1.0 g., infrared spectrum, (Nujol) 1609 cm.$^{-1}$ (amide).

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.58; N, 4.41. Found: C, 71.73; H, 8.73; N, 4.46.

(f) *Action of methyl iodide. Formation of the N-methoiodide* (XVIII) *of* XII. A mixture of 3.27 g. of XII, 10 ml. of methyl iodide, and 2.0 g. of anhydrous sodium carbonate was refluxed for 5 days avoiding moisture. The unchanged methyl iodide was distilled and the residue was extracted with boiling ethanol and cooled to deposit yellow crystals; yellow rhombs, m.p. 204° dec. after recrystallization from ethanol; yield 0.75 g.

Anal. Calcd. for $C_{20}H_{28}NO_2I$: C, 54.43; H, 6.39; N, 3.17; I, 28.76. Found: C, 54.33; H, 6.58; N, 3.18; ionic I, 28.84 (the Volhard method).

(g) *Catalytic hydrogenation over platinum oxide. Formation of* DL-*(trans-anti-cis-2,2'-dihydroxydicyclohexyl)benzylamine* (XX). One and two hundredth grams of XII in 20 ml. of ethanol was hydrogenated at room temperature at atmospheric pressure over 0.025 g. of platinum oxide.[10] After absorption of 140 ml. of hydrogen the mixture was filtered and evaporated to dryness. The residue was recrystallized from petroleum benzin, m.p. 108°, yield 1.0 g., infrared spectrum (Nujol) 3539 cm.$^{-1}$ (hydroxyl), no (amide), no (ester).

Anal. Calcd. for $C_{19}H_{29}NO_2$: C, 75.20; H, 9.63; N, 4.62. Found: C, 75.44; H, 9.50; N, 4.52.

(h) *Action of methylmagnesium iodide. Formation of acetophenone and* II. (1) To methylmagnesium iodide (0.042 mole) prepared from 1.0 g. of magnesium and 5.6 g. of methyl iodide in 50 ml. of ether was slowly added a solution of 6.0 g. (0.021 mole) of XII in 400 ml. of ether, refluxed for 11 hr. and then allowed to stand for 48 hr. at room temperature. The whole reaction was conducted under good stirring and avoiding moisture. To the ethereal solution was added ice water, and then ammonium chloride with agitation. Concentration of the ether layer to a small volume gave 0.2 g. of II. The mother liquor after removal of II afforded acetophenone; the 2,4-dinitrophenylhydrazone, m.p. 250°, yield 0.3 g. (2) Use of the Grignard reagent and XII in molar ratio 3:1 gave same products as procedure 1 did.

(i) *Action of hydrogen peroxide. Formation of* DL-*cis-2-benzamidocyclohexanol* (XXI). A mixture of 1.0 g. of XII, 5 ml. of glacial acetic acid and 2 ml. of 30% hydrogen peroxide was concentrated to one third volume under reduced pressure. The remainder was made neutral with potassium carbonate, extracted with chloroform, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was recrystallized from acetone; yield 0.3 g., m.p. 184° alone and on admixture with a sample of DL-cis-2-benzamidocyclohexanol.

The Hofmann degradation of XVIII. *Formation of* DL-*trans-2-benz(methyl)amidocyclohexanol* (XIX). One and three tenth grams of XVIII in 50 ml. of 4% ethanolic potassium hydroxide was boiled for 0.5 hr., concentrated under reduced pressure, extracted with chloroform, dried over

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[18] After treatment with 1*N* hydrochloric acid XIII remained undissolved and unchanged.

anhydrous sodium sulfate, and evaporated to dryness. Recrystallization from ligroin gave 0.2 g. of colorless needles, m.p. 140° alone and on admixture with a sample of DL-*trans*-2-benz(methyl)amidocyclohexanol.[9]

DL-*2-Phenyl-3-(trans-2'-hydroxycyclohexyl)-anti-cis-4,5-cyclohexanoöxazolinium salts* (XXII). (a) *The chloride.* To a solution of 1 g. of XII in 50 ml. of dry ether was introduced hydrogen chloride dried over phosphorus pentoxide. The resulting precipitate was collected and washed with ether; yield 1.0 g., m.p. 181°, infrared spectrum (Nujol) 3140 cm.$^{-1}$ (hydroxyl), 1616 cm.$^{-1}$ ($>C{=}N^{+}<$).

Anal. Calcd. for $C_{19}H_{26}NO_2Cl$: C, 67.94; H, 7.80; N, 4.17. Found: C, 67.84; H, 7.89; N, 4.22.

The chloride changed to XI·HCl by boiling in water.

(b) *The nitrate.* To a suspension of 1.3 g. of XII in 2 ml. of acetic anhydride was added 0.7 ml. of nitric acid (s.w. 1.53) and then 2 ml. of acetic anhydride at −17°. Agitation was continued for 3 hr. keeping the temperature. The reaction mixture was poured into a small volume of water, filtered, washed with water, and recrystallized from methanol-ether, m.p. 200° dec., yield 1.1 g.

Anal. Calcd. for $C_{19}H_{26}N_2O_5$: C, 62.98; H, 7.23; N, 7.73. Found: C, 63.35; H, 7.05; N, 7.72.

(c) *The iodide.* To 1 g. of XII dissolved in 10 ml. of acetone was added 0.5 ml. of hydroiodic acid (s.w. 1.70) and allowed to stand in air. The resulting precipitate was filtered and recrystallized from acetone-ether; yield 0.6 g. of colorless needles, m.p. 210° dec., infrared spectrum (Nujol) 3373 cm.$^{-1}$ (hydroxyl), 1624 cm.$^{-1}$ ($>C{=}N^{+}<$).

Anal. Calcd. for $C_{19}H_{26}NO_2I$: C, 53.40; H, 6.13; N, 3.28. Found: C, 53.30; H, 6.12; N, 3.29.

Conversion of XXII *to* XII *on treatment with alkali hydroxide.* Aqueous solutions of XXII (chloride, nitrate, and iodide) were treated with aqueous sodium hydroxide to afford XII, m.p. 151°.

DL-*cis-cis-2,2'-Dibenzoyloxydicyclohexylamine hydrochloride* (XXVII). To 4 ml. of thionyl chloride was added 2 g. of XV under ice cooling; the mixture was allowed to stand at room temperature for 1 hr., poured into 100 ml. of water, and boiled for 20 min. After cooling, the precipitated crystals were filtered and recrystallized from acetone, m.p. 242°, yield 1.5 g., infrared spectrum (Nujol) 1711 cm.$^{-1}$ (ester).

Anal. Calcd. for $C_{26}H_{31}NO_4{\cdot}HCl$: C, 68.18; H, 7.04; N, 3.06. Found: C, 68.15; H, 7.05; N, 2.81.

DL-*cis-2-Hydroxy-cis-2-benzoyloxydicyclohexylamine* (XXXI) *hydrochloride.* The *N*-benzoyl DL-*trans-anti-cis*-aminodiol (XVII) was treated as in the previous paragraph to give XXXI·HCl as colorless cubes, m.p. 213°, after recrystallization from acetone yield 36%.

Anal. Calcd. for $C_{19}H_{27}NO_3{\cdot}HCl$: C, 64.49; H, 7.98; N, 3.96. Found: C, 64.77; H, 8.11; N, 4.01.

XXXI·HCl was converted to the DL-*cis-cis*-aminodiol (III). After hydrolysis in methanolic potassium hydroxide, m.p. 95.5° alone and on admixture with a sample of III.

DL-*cis-cis-2,2'-Dihydroxydicyclohexylamine* (III) *and its hydrochloride.* To 50 ml. of 1% methanolic sodium hydroxide was added 1 g. of XXVII, boiled for 45 min., evaporated to dryness, extracted with chloroform and evaporated to dryness. The residue was dissolved in petroleum ether (b.p. 30–70°), dry hydrogen chloride introduced and the precipitated crystals were collected, yield 0.35 g., m.p. 296° after recrystallization from methanol-ether.

Anal. Calcd. for $C_{12}H_{23}NO_2{\cdot}HCl$: C, 57.70; H, 9.67; N, 5.74. Found: C, 57.40; H, 9.50; N, 5.34.

The hydrochloride was treated with 1*N* sodium hydroxide and the resulting crystals were collected as colorless needles, m.p. 95.5°, after recrystallization from petroleum ether, yield 0.1 g. Mixed melting points of the product with other five epimers showed depression.

Anal. Calcd. for $C_{12}H_{23}NO_2$: C, 67.56; H, 10.87; N, 6.57. Found: C, 67.47; H, 10.73; N, 6.41.

DL-*5-Phenyl-cis-2,3-cis-7,8-dicyclohexano-1-aza-4,6-dioxabicyclo[3.3.0]octane* (XXVIII). One gram of XVII was treated as in the preparation of XII from VII to give colorless prisms, m.p. 104°, after recrystallization from petroleum ether; yield 0.47 g., infrared spectrum, no (hydroxyl, carbonyl).

Anal. Calcd. for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.52; H, 8.49; N, 4.59.

Alkaline hydrolysis of XXVIII. Two tenth grams of XXVIII in 5 ml. of 10% methanolic sodium hydroxide was boiled for 30 min., concentrated to dryness, extracted with ether, and freed of ether. The residue was recrystallized from petroleum ether, yield 0.1 g., m.p. 95.5° alone and on admixture with a sample of III.

Attempted acyl migration reactions of benzoyl derivatives of 2,2'-dihydroxydicyclohexylamines. General methods. (*a*) *N* → *O:* To concd. hydrochloric acid were added amides, the mixture boiled for 30 min., a large volume ofwater added and set aside.

(*b*) *N* → *O:* To ethanol saturated with dry hydrogen chloride were added amides, the mixture allowed to stand over night and evaporated to dryness.

(*c*) *O* → *N:* To a mixture of 2*N* sodium hydroxide and ether were added ester hydrochlorides and the mixture stirred till the hydrochlorides disappeared. After allowing to stand over night the ether layer was washed with water and evaporated to dryness. For results see Table I.

TABLE I

Aminodiols	*N*-benzoyl derivatives	Migrate or not (method)	*O*-benzoyl derivatives (hydrochloride)
DL-*trans-trans*-Isomer (I)	*N*-benzoyl (VII)	$\mathrm{N} \xrightarrow{\text{a or b}} \mathrm{O}$ $\mathrm{N} \underset{\text{c}}{\nleftarrow} \mathrm{O}$	*O*-benzoyl (VIII)
	N,*O*-dibenzoyl (IX)	$\mathrm{N} \xrightarrow{\text{a or b}} \mathrm{O}$	*O*,*O*-dibenzoyl (X)
DL-*trans*-Anti-*cis*-isomer (II)	*N*-benzoyl (XVII)	$\mathrm{N} \xrightarrow{\text{a}} \mathrm{O}$ $\mathrm{N} \underset{\text{c}}{\nleftarrow} \mathrm{O}$	*cis*-*O*-benzoyl (XI)
	N-*trans*-*O*-dibenzoyl (XIII)	$\mathrm{N} \xrightarrow{\text{a}} \mathrm{O}$ $\mathrm{N} \underset{\text{c}}{\nleftarrow} \mathrm{O}$	*O*,*O*-dibenzoyl (XIV)

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