an insoluble crystalline product, 70 mg., m.p. 255–259°, was isolated by filtration and identified as α-methylDOPA dimethyl ether (IV). From the filtrate there was obtained, after concentration on the steam bath, 230 mg. of the dipeptide acid IXa, m.p. 213–222°. Recrystallization from acetone gave an analytical sample with m.p. 220–221°, $[\alpha]^{pyridine}D$ −37.9.

Anal. Calcd. for $C_{26}H_{34}N_2O_8$: C, 62.13; H, 6.83; N, 5.58; neut. equiv., 502. Found: C, 61.59; H, 6.53; N, 5.88; neut. equiv., 486.

The infrared and n.m.r. spectra were in agreement with the assigned structure.

The filtrate from the isolation of the dipeptide acid IXa was shown by thin-layer chromatography to contain, in addition to IXa, a small amount of the methyl ester of the N-acetyl dimethyl ether IIIa.

Substitution of ethyl for methyl alcohol in the above reaction gave analogous results. However, no reaction was observed with *t*-butyl alcohol.

B.—To a solution of 263 mg. of the dimethoxy azlactone VIIa in 30 ml. of dry pyridine was added 239 mg. of α-methylDOPA dimethyl ether. The amino acid gradually dissolved as the suspension was refluxed gently for 18 hr. The reaction mixture was cooled to room temperature, filtered, and concentrated *in vacuo*. Crystallization of the residue from acetone afforded 150 mg. of the dipeptide acid IXa, m.p. 219–2221°, identical with that described in A preceding.

Dipeptide Azlactone X.—A solution of 100 mg. of dipeptide acid IXa in 2 ml. of pyridine was treated with 2 ml. of acetic anhydride and allowed to stand at room temperature for 18 hr. The reagents were evaporated *in vacuo* and flushed by toluene distillation. The residue was dissolved in ether, filtered, and crystallized from the same solvent to provide 50–60 mg. of X, m.p. 105–108°; $\lambda_{max}^{CHCl_3}$ 2.94 (N–H), 5.46 (azlactone), 5.98 and 6.58 (amide), and 6.2 and 6.25 (aromatic).

Anal. Calcd. for $C_{26}H_{32}N_2O_7$: C, 64.46; H, 6.61; N, 5.78. Found: C, 64.42; H, 6.57; N, 5.83.

The Synthesis of 3,3'-Bipyrrolidines in Both Configurational Series[1a]

PHILIP L. SOUTHWICK, JULIUS A. VIDA, AND DAVID P. MAYER[1b]

Department of Chemistry, Carnegie Institute of Technology, Pittsburgh 13, Pennsylvania

Received December 16, 1963

New compounds in the 3,3'-bipyrrolidine series have been obtained from the aldol condensation product of 1-cyclohexyl-2,3-dioxopyrrolidine, the enol of 1,1'-dicyclohexyl-3-hydroxy-2,4',5'-trioxo-3,3'-bipyrrolidine (I). Sodium borohydride reduction of I yielded a mixture of diastereoisomeric 1,1'-dicyclohexyl-3,4'-dihydroxy-2,5'-dioxo-3,3'-bipyrrolidines (II) from which one of the four possible racemic forms was separated. Lithium aluminum hydride reduction of compounds of structure II yielded 1,1'-dicyclohexyl-3,4'-dihydroxy-3,3'-bipyrrolidines (III); two of the four possible racemic forms were separately characterized. The dehydration product of I, 1,1'-dicyclohexyl-2,4',5'-trioxo-3,3'-bipyrrolidylidene (IV), yielded the enol of 1,1'-dicyclohexyl-2,4',5'-trioxo-3,3'-bipyrrolidine (V) when hydrogenated. Sodium borohydride reduction of V produced a mixture of the four possible racemic forms of 1,1'-dicyclohexyl-4'-hydroxy-2,5'-dioxo-3,3'-bipyrrolidine (VI), all of which were separated. These four compounds were converted to 1,1'-dicyclohexyl-3,3'-bipyrrolidines (VIII); as expected, two of the forms yielded the symmetric (*meso*) structure (VIIIa) and two yielded the racemic form of the dissymmetric structure (VIIIb). Lithium aluminum hydride reduction of the four racemic forms of VI yielded corresponding forms of 1,1'-dicyclohexyl-4-hydroxy-3,3'-bipyrrolidine (IX). Compounds of types III and IX yielded bismethiodides. Stereoisomer IIIb displayed antiinflammatory and hypotensive effects, but also toxicity.

It was pointed out previously[2] that the very facile aldol condensation of those 2,3-pyrrolidinediones which are unsubstituted in the 4-position provides ready synthetic access to compounds in the little-known[3] 3,3'-bipyrrolidine series. The present investigation was undertaken with the objective of developing procedures for preparing other types of 3,3'-bipyrrolidine derivatives from the initial condensation products (I), and thereby permitting examination of the potential physiological activity of compounds in the series. As had been anticipated, the formation of mixtures of stereoisomers constituted the principal difficulty in the synthetic operations which were conducted. The assignment of configurations to the stereoisomers obtained was another desirable objective which presented difficulties but was accomplished in part.

The work to be described here is concerned with a series of compounds having the cyclohexyl substituent on both nitrogen atoms. The pyridine-catalyzed self-condensation of 1-cyclohexyl-2,3-dioxopyrrolidine, which approaches completion within a few minutes at room temperature, was described previously,[2] and it had been observed that product I was enolized. Since the enol I would contain only one asymmetric carbon atom, only one racemic form should exist, and the product did, in fact, behave as a single substance rather than a mixture. Reduction of I with sodium borohydride (see Chart I) reduced the enolic function to yield the 1,1'-dicyclohexyl-3,4'-dihydroxy-2,5'-dioxo-3,3'-bipyrrolidine structure (II) in the form of a mixture of solid diastereoisomers. One racemic form (IIa, m.p. 229.5–231°) crystallized in *ca.* 18% yield after this mixture had been dissolved in an acetone–ethanol solvent mixture. Efforts to induce the separation of other isomers were not successful.

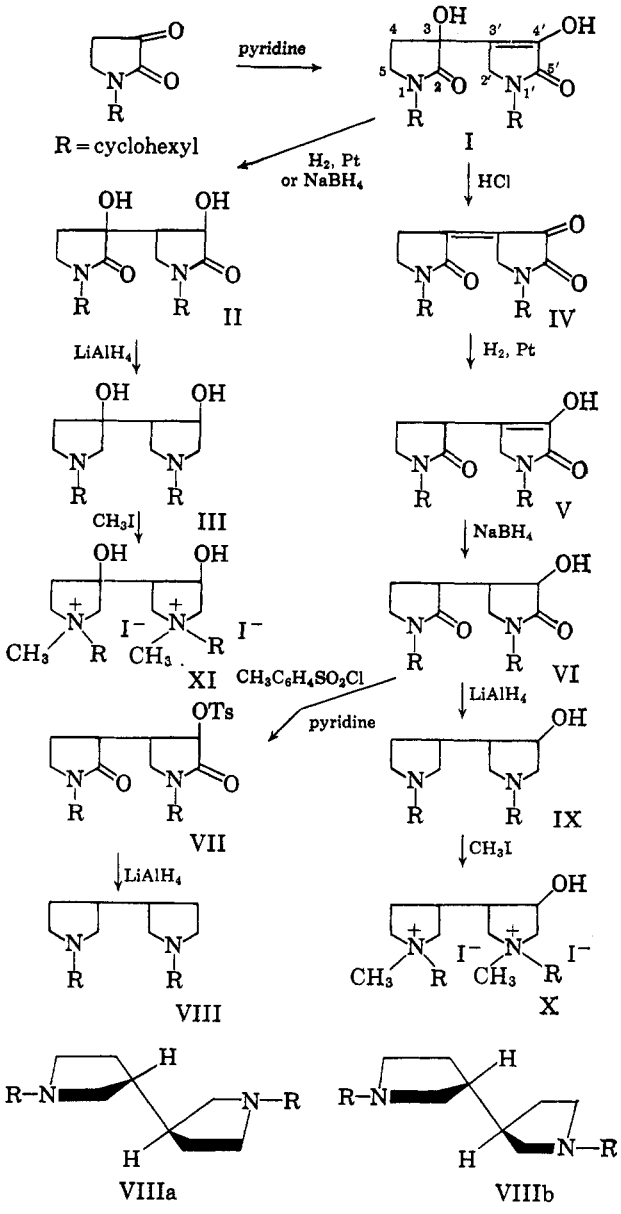
Lithium aluminum hydride reduction of IIa yielded one of the racemic forms of 1,1'-dicyclohexyl-3,4'-dihydroxy-3,3'-bipyrrolidine (IIIa, m.p. 123.5–125°). On the other hand, reduction by the same procedure of the total unseparated mixture of diastereoisomers of structure II yielded a mixture of diastereoisomers of structure III from which a second, higher melting form (IIIb, m.p. 185–186°) was separated by fractional crystallization. Thus two of the four possible racemic forms of III were separately characterized, whereas only one of the four forms of II was so characterized.

(1) (a) This investigation was supported by a research grant (RG-4371) from the National Institutes of Health, Public Health Service. Parts of the work are described in theses submitted by J. A. Vida (1960) and D. P. Mayer (1958) in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Carnegie Institute of Technology; (b) Allied Chemical Corp. Fellow, 1957–1958.

(2) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).

(3) A few other compounds in the 3,3'-bipyrrolidine series have been described by S. Gabriel [*Ber.*, **47**, 3033 (1914)], E. B. Knott [*J. Chem. Soc.*, 1196 (1947)], and E. Buchta and K. Greiner [*Chem. Ber.*, **94**, 1331 (1961)]. No work on the stereochemistry of these compounds has been reported to this time.

CHART I



Preliminary tests for physiological activity[4a] which were conducted on compounds IIIa and IIIb indicated that compound IIIb, as well as the unseparated mixture of stereoisomers of structure III, had a rather prolonged hypotensive effect[4b] and some antiinflammatory action.[4c] Unfortunately, toxicity was also evident. On the other hand, the stereoisomer IIIa was devoid of hypotensive or antiinflammatory effects. It seems apparent that biological activity will be strongly influenced by configuration in the 3,3′-bipyrrolidine series. Unfortunately, although some progress has been made in elucidating the configurations of other members of the 3,3′-bipyrrolidine series (*vide infra*), similar efforts applied to compound IIIb have been unsuccessful.

As described previously,[2] the condensation product I is dehydrated in high yield by heating with hydrochloride acid to yield 1,1′-dicyclohexyl-2,4′,5′-trioxo-3,3′-bipyrrolidylidene (IV). Catalytic hydrogenation of IV over a platinum catalyst (Adams' platinum oxide) saturated only the olefinic bond to yield the enol form (V) of 1,1′-dicyclohexyl-2,4′,5′-trioxo-3,3′-bipyrrolidine. The compound appeared to be highly enolized; its infrared spectrum completely lacked the carbonyl band near 5.67 μ which is characteristic of the ketonic carbonyl at position 3 of 2,3-pyrrolidinediones,[2,5] but had a broad hydrogen-bonded hydroxyl absorption at 3.20–3.32 μ, was soluble in aqueous sodium hydroxide, and gave an intense purple color with ferric chloride. There were no indications of the presence of diastereoisomers such as might have been expected if the substance had existed in the keto form and contained two asymmetric carbons. The compounds represents another example of the enolic character of 2,3-pyrrolidinediones which carry one substituent in the 4-position.[2,5]

Sodium borohydride reduction of compound V reduced the enolic function to yield 1,1′-dicyclohexyl-4′-hydroxy-2,5′-dioxo-3,3′-bipyrrolidine (VI) in the form of an amorphous solid representing a mixture of diastereoisomers. Since the structure VI contains asymmetric carbons at positions 3, 3′, and 4′, four racemic forms are possible. By a combination of fractional crystallization and chromatography on alumina four crystalline isomers were separated from the mixture. The yields of the separated forms were as follows: VIa (m.p. 240°), 25%; VIb (m.p. 166°), 20%; VIc (m.p. 156°), 1.9%; and VId (m.p. 140°), 8%.

By removing the hydroxyl and carbonyl groups from structure VI the 1,1′-dicyclohexyl-3,3′-bipyrrolidine structure VIII would be obtained. Stereoisomerism in VIII would be limited to that arising from the like asymmetric centers at positions 3 and 3′; only a symmetric (*meso*) form (see formula VIIIa) and a dissymmetric (racemic) form (see formula VIIIb) could result from carrying out such an operation on any of the four forms of VI. In the staggered conformation shown in Chart I, structure VIIIa possesses a center of symmetry. It could also assume an eclipsed conformation with a plane of symmetry. Neither element of symmetry is present in structure VIIIb. Thus, the 3,3′-bipyrrolidines can be subdivided into a symmetric (abbreviated *sym*) and a dissymmetric (abbreviated *dissym*) series according to whether the system of two rings has the configuration present in structure VIIIa or in VIIIb; the parent compounds of the two series could be called *sym*-3,3′-bipyrrolidine and *dissym*-3,3′-bipyrrolidine. Such terminology, which describes the symmetry of the ring systems only, and not necessarily that of the molecule as a whole, will be used in the remainder of the paper to designate ring system con-

(4) (a) The authors are indebted to the Lilly Research Laboratories and to the Endocrine Evaluation Branch of the Cancer Chemotherapy National Service Center, National Institutes of Health (CCNSC), for biological testing. (b) A small (8% maximum) hypotensive effect of 6-hr. duration was observed in the hypertensive (Goldblatt) rat at an oral dose of 20 mg./kg. (Lilly, results obtained under the direction of Dr. Francis Henderson). The compound was highly toxic to rats at 100 mg./kg. (c) A preliminary bioassay (CCNSC) indicated that at a subcutaneous dose of 24 mg., the mixed isomers produced an apparent reduction in the granuloma induced by a cotton pellet in the immature adrenalectomized rat averaging about 25%. This effect was slightly less than that produced by 1.2 mg. of cortisol. The material showed no antiinflammatory activity at a dose of 1.2 mg. and no thymolytic activity at doses up to 24 mg., or glucocorticoid activity (promotion of liver glycogen deposition in mature adrenalectomized rats) at doses up to 15 mg.

(5) For other observations on enolization of 2,3-pyrrolidinediones, see (a) W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 98, 1554, 1560 (1957); (b) W. R. Vaughan and I. S. Covey, *J. Am. Chem. Soc.*, **80**, 2197 (1958); (c) P. L. Southwick and E. F. Barnas, *J. Org. Chem.*, **27**, 98 (1962); (d) P. L. Southwick and J. A. Vida, *ibid.*, **27**, 3075 (1962).

figurations in individual compounds when such configurations have been determined.[6]

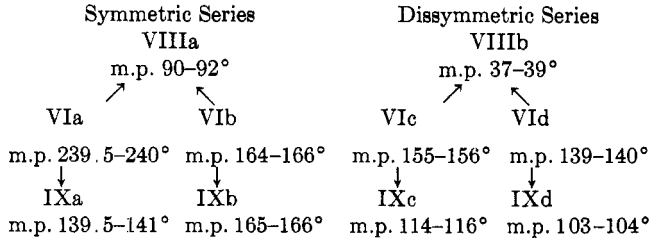
The steps required in the conversion of the four racemic forms of structure VI into the two forms of VIII involved forming the *p*-toluenesulfonates (VII) and reducing these compounds with lithium aluminum hydride. The *p*-toluenesulfonates were not fully characterized, but were directly reduced in the crude form. The two compounds of structure VIII which were produced were form A, m.p. 90–92°, obtained from compounds VIa and VIb, and forms B, m.p. 37–39°, obtained from compounds VIc and VId. The assignments of configuration to forms A and B of structure VIII were based on resolution experiments which demonstrated that form B was resolvable and therefore must represent the dissymmetric configuration depicted by formula VIIIb in the reaction chart. No indications that form A could be resolved were observed; it was concluded that A was the symmetric form represented by formula VIIIa.

Unfortunately, none of the acid resolving agents thus far tested yielded salts of the compounds of structure VIII which could be recrystallized or fractionally crystallized efficiently. The salts prepared from (+)-10-camphorsulfonic acid were unsatisfactory in this respect, as were the salts from (+)-dibenzoyltartaric acid. The salts obtained with (+)-tartaric acid itself were not easily crystallized either, but that from form A did melt over a rather narrow range (182–184°) and show a rotation unchanged by recrystallization, whereas the salts from form B melted over a considerable range and changed in both melting point and rotation upon repeated recrystallization. Form A displayed no detectable rotation when liberated from its tartrate, but form B was obtained with specific rotations in chloroform or ethanol, $[\alpha]^{25}D$, varying from $-30°$ to $+12°$ when liberated from different fractions of its tartrate. Whether the material with a specific rotation of $-30°$ represents a sample which is almost completely resolved remains to be seen; the difficulty of recrystallizing either the tartrate or the free base rendered the optical purity of the resolved product uncertain.

The configurations at the 4′-carbon in the stereoisomers of structure VI have not been determined. Results of an investigation of sodium borohydride reductions of enols of a related group of 4-substituted 2,3-pyrrolidinediones suggest that probably the more abundant product should be that in which the hydroxyl group at the 4′-position is *trans* to the bond at 3′ which joins the two rings. However, no clear evidence to support such a conclusion in the case of these 3,3′-bipyrrolidine derivatives has yet been obtained.

The four stereoisomers (racemic forms) of structure VI were also reduced directly with lithium aluminum hydride to yield the 1,1′-dicyclohexyl-4′-hydroxy-3,3′-bipyrrolidines (IX). These reductions evidently proceeded without affecting adjacent asymmetric centers; each form of VI yielded a different isomer of IX with no apparent interchange of configurations. Chart II summarizes relationships of stereoisomeric 3,3′-bipyrrolidines of the types VI, IX, and VIII.[7a]

CHART II



When compounds IIIb and IXb were treated with excess methyl iodide, bismethiodides of the expected composition (corresponding to structures XI and X) were formed in both instances. Possibly because of the opportunity for additional stereoisomerism resulting from the formation of two unlike asymmetric nitrogens in the quaternization, the methiodides were difficult to crystallize and only a low yield of compound X was obtained after recrystallization. A crystalline form of the methiodide XI, m.p. 253–253.5°, was examined for physiological effects, but failed to show activity comparable to that of the parent bipyrrolidine (IIIb).[7b]

Experimental[8,9]

The 1,1-Dicyclohexyl-3,4′-dihydroxy-2,5′-dioxo-3,3′-bipyrrolidines (II).—To 6 g. (0.158 mole) of sodium borohydride was added 200 ml. of 95% ethanol. Over a period of 30 min., 27 g. (0.074 mole) of 1,1′-dicyclohexyl-3-hydroxy-2,4′,5′-trioxo-3,3′-bipyrrolidine (I)[2] was added in portions. The reaction mixture was kept in an ice bath during the addition and swirled frequently. After the reaction mixture had been allowed to stand overnight at room temperature, 20% hydrochloric acid was added dropwise to the reaction mixture to destroy the excess hyride. The solvent was evaporated under reduced pressure to leave a gummy residue, which was treated with 200 ml. of water. The aqueous mixture was extracted twice with chloroform. The chloroform extracts were combined, dried over sodium sulfate, and evaporated under reduced pressure to yield a yellow, glassy residue, which was treated with a 2:1 mixture of petroleum ether (b.p. 30–60°) and ether and cooled to $-15°$ for an hour with frequent stirring. The glassy residue was converted into a white solid, which was removed by filtration. The dried product, m.p. 178–200°, weighed 26.71 g. (98.6% yield). Recrystallization from a 10:1 mixture of acetone and 95% ethanol with cooling only to room

(6) Although dissymmetric has become the accepted term to describe a configuration which cannot be superimposed upon its mirror image, this terminology may not have been used previously as part of the name of a compound. There are terms already in use in the names of compounds which could be applied to the designation of the configurations of these bipyrrolidine systems, but only by the modification of generally accepted meanings. Thus the terms *meso* and racemic could be applied to the symmetric and dissymmetric systems, respectively, provided that it be understood that the absence of optical activity would not be implied in all compounds carrying these designations for the ring system configurations. The application of the terms *erythro* and *threo*, as suggested by a referee, to the symmetric and dissymmetric 3,3′-bipyrrolidine systems (regarded as analogous to 1,1,2,2-tetrasubstituted ethanes) would be suitable if it were understood that the terms would in this instance not necessarily carry the usual implication of two *unlike* asymmetric centers.

(7) (a) The higher-melting isomers IXa and IXb failed to show biological activity in the rat comparable to that of compound IIIb when administered orally; there was merely a slight hypertensive effect and a slight anti-inflammatory activity at toxic dose levels (Lilly). The lower-melting isomers IXc and IXd were not tested separately because only very small amounts were available, but a mixture of all of the isomers of structure IX (obtained by lithium aluminum hydride reduction of the unseparated mixed isomers of structure VI) was also inactive in the same tests. The mixture produced a strong (maximum 43%) decrease in blood pressure of 1- to 2-hr. duration when administered intravenously to the anesthetized dog at 1 mg./kg., but the result is regarded as of questionable significance because the responses in the rat and the dog were not consistent. (b) The only biological activity found was a hypotensive effect of short duration in the dog. There was no effect on respiration in the dog and no antibacterial action was discovered.

(8) Microanalyses were by Geller Microanalytical Laboratories, Charleston, W. Va., and Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England.

(9) Infrared data were obtained with a Perkin-Elmer Model 21 spectrophotometer. Figures quoted are wave lengths of bands in μ. The letters after each number signify the following: i, intense; m, medium; w, weak; b, broad; si or sm, intense or medium band with shoulder (weak, 0–30% absorption; medium, 30–60% absorption; intense, >60% absorption).

temperature yielded 5.1 g. (18%) of white needles, m.p. 229.5–231°. When the mother liquor from the recrystallization was cooled to −15°, a white microcrystalline solid was deposited, yielding 7.30 g. (27%), m.p. 205–225°. Further recrystallization did not greatly effect this melting range.

The crystalline compound melting at 229.5–231° is the isomer designated IIa. The following spectral data were obtained for this substance (infrared spectrum, chloroform): 3.08 bm, 3.44 i, 3.49 si, 6.02 bi, 6.72 m, 6.91 i, 7.80 i, 7.97 i, 8.88 m, and 11.20 m μ.

Anal. Calcd. for $C_{20}H_{32}N_2O_4$: C, 65.90; H, 8.85; N, 7.69. Found: C, 66.26; H, 8.93; N, 7.54.

The large broad-melting fraction (m.p. 205–225°) described above had an infrared spectrum very similar to that of IIa, as did a product melting over the range *ca.* 213–220° and having the same composition as IIa, which was obtained by hydrogenation of I over a platinum catalyst (Adams' platinum oxide) in methanol. A similar hydrogenation product described previously[2] was reported to melt at 204–206°. It seems evident that all of these products have the structure II, but it is questionable whether any but the high-melting form IIa represents a single racemic form.

The 1,1′-Dicyclohexyl-3,4′-dihydroxy-3,3′-bipyrrolidines (III). The Low-Melting Form IIIa.—To 2.0 g. (0.053 mole) of lithium aluminum hydride suspended in 250 ml. of dry ether was added portionwise 3.54 g. (9.7 mmoles) of the isomer IIa of 1,1′-dicyclohexyl-3,4′-dihydroxy-2,5′-dioxo-3,3′-bipyrrolidine (m.p. 229–231°) over a period of 30 min. The reaction mixture was stirred and refluxed for an additional 5 hr., and refluxing was continued overnight. A solution of 1.48 g. of sodium potassium tartrate[10] dissolved in 6.5 ml. of water was added dropwise with stirring to the reaction mixture to destroy the excess hydride. The solid was removed from the ether solution by filtration and extracted twice with chloroform. The ether and chloroform solutions were combined, dried over sodium sulfate, and evaporated under reduced pressure to yield a clear, glassy residue. The residue was then treated with 20 ml. of a 1:1 mixture of ether and petroleum ether (b.p. 30–60°) and cooled to −15°. In a few hours the glassy residue assumed the form of a white solid, which was filtered and washed with 10 ml. of ether. The yield was 2.80 g. (85.6%), m.p. 122–123.5°. Recrystallization from a 4:3 mixture of ether and acetone gave 1.4 g. of product in the form of very fine white crystals, m.p. 123.5–125°; infrared spectrum (chloroform): 2.96–3.08 sw, 3.44 i, 3.50 i, 6.90 m, 7.28 m, 7.44 w, 8.80–9.0 bw, and 11.22 w μ.

Anal. Calcd. for $C_{20}H_{36}N_2O_2$: C, 71.38; H, 10.78; N, 8.33. Found: C, 71.17; H, 10.86; N, 8.48.

A mixture of IIIa and IIIb melted over a broad range (121.5–150°) beginning slightly below the melting point of IIIa.

The High-Melting Form IIIb.—Mixed isomers of II (7.85 g., 0.022 mole, m.p. 207–217°), obtained by sodium borohydride reduction of I, were reduced with lithium aluminum hydride (3 g. 0.07 mole) in dry ether (200 ml.) as described above for the preparation of IIIa. The crude product, obtained after the same type of work-up procedure, was a clear, light yellow glass. After it was stirred with a 3:1 mixture of petroleum ether (b.p. 30–60°) and ether at −15° for several hours, a white powder was collected by filtration. The melting point was 109–135°; yield was 6.10 g. (84.2%). Recrystallization from a 4:1 mixture of acetone and 95% ethanol cooled only to room temperature yielded 0.8 g. (29%) of white platelets, m.p. 178–181°. Repeated crystallization from the same solvent mixture raised the melting point to 185–186°; infrared spectrum (chloroform): 2.88 w, 3.42 i, 3.50 i, 6.89 m, 7.28 m, 7.43 m, 8.70–9.00 bm, and 11.22 m μ.

Anal. Calcd. for $C_{20}H_{36}N_2O_2$: C, 71.38; H, 10.78; N, 8.35. Found: C, 71.60; H, 10.53; N, 8.45.

The lithium aluminum hydride reduction of the mixed isomers of II, m.p. 213–220°, prepared by the catalytic reduction of I with platinum oxide, gave a mixture of diastereoisomers of III, m.p. 100–120°. Recrystallization of the product failed to yield any sharp-melting crystalline fractions.

The Dimethiodide (XI) of the High-Melting 1,1′-Dicyclohexyl-3,4′-dihydroxy-3,3′-bipyrrolidine (IIIb).—To 1.9 g. (5.64 mmoles) of compound IIIb (m.p. 178–181°) dissolved in 40 ml. of dioxane, 5 ml. of methyl iodide was added. The reaction mixture was allowed to stand overnight at room temperature. The solid which had formed was removed by filtration and washed with a small amount of acetone to yield 3.2 g. (92%) of very fine white crystals, m.p. 250–253°. Recrystallization of the product from 95% ethanol yielded 1.8 g. of product, m.p. 253–253.5°.

Anal. Calcd. for $C_{22}H_{42}I_2N_2O_2$: C, 42.59; H, 6.84; N, 4.52. Found: C, 42.15; H, 7.03; N, 4.07.

The attempted preparation of a dimethiodide from a mixture of diastereoisomers of 1,1′-dicyclohexyl-3,4′-dihydroxy-3,3′-bipyrrolidine yielded no solid material.

1,1′-Dicyclohexyl-2,4′,5′-trioxo-3,3′-bipyrrolidine (V, Enol Form). — 1,1′-Dicyclohexyl-2,4′,5′-trioxo-3,3′-bipyrrolidylinene (IV)[2] (30 g., 0.088 mole) was suspended in 300 ml. of glacial acetic acid and hydrogenated over 200 mg. of platinum oxide. The initial hydrogen pressure was 65 p.s.i.g.; the reaction period was 15 hr. At the end of this time all of the starting material had dissolved. The catalyst was removed by filtration and the light-colored solution was poured into 1.8 l. of distilled water. The mixture was allowed to stand for 24 hr. at room temperature and then filtered to collect the solid product, which was washed repeatedly with water and dried at 50°. The weight of the dried, white product was 24.1 g. (80.3% yield); the melting point was 220–222°. Repeated recrystallization from a 1:1 mixture of acetone and 95% ethanol raised the melting point to 223–226°. The compound gave a deep purple color with ferric chloride in ethanol; infrared spectrum (chloroform): 3.20–3.32 sm, 3.46, 3.50 i, 6.00 bi, 7.00 bi, 8.00 bi, and 11.20 m μ.

Anal. Calcd. for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.04. Found: C, 69.63; H, 8.56; N, 7.90.

The 1,1′-Dicyclohexyl-4′-hydroxy-2,5′-dioxo-3,3′-bipyrrolidines (VI). Preparation of the Mixed Isomers.—1,1′-Dicyclohexyl-2,4′,5′-trioxo-3,3′-bipyrrolidine (V, 122 g., 0.35 mole) was added over a period of 30 min. to a precooled solution of 36.2 g. (0.96 mole) of sodium borohydride in 1.8 l. of 95% ethanol. The addition was completed at a temperature of 0–5° and the mixture was stirred vigorously with cooling in an ice bath for an additional 3 hr. The dark solution was allowed to stand overnight at room temperature. The color of the solution faded upon acidification with 20% hydrochloric acid to pH 3. The solvent was evaporated under reduced pressure leaving a solid residue, which was treated with 1.0 l. of distilled water. The solution was extracted repeatedly with chloroform and the combined chloroform extract was dried over sodium sulfate, filtered, and evaporated at reduced pressure to yield a light yellow glass. The yield was 105 g. (86%).

The High-Melting 1,1-Dicyclohexyl-4′-hydroxy-2,5′-dioxo-*sym*-3,3′-bipyrrolidine (VIa).—The mixture of stereoisomers of VI described above was dissolved in 600 ml. of 95% ethanol with heating. The hot solution was treated with Norit A, filtered, and stored at 0° for 30 hr. The crystalline precipitate was collected by filtration, washed with cold ethanol, and dried. Recrystallization from 95% ethanol yielded 31 g. (25.3%) of platelets, m.p. 231–233°; m.p. 239–240° after further recrystallization; infrared spectrum below 8 μ (methylene chloride)[11]: 3.01 bm, 3.40 i, 3.48 i, 5.88 si, 6.01 si, 6.64 w, 6.70 m, 6.92 bm, 7.27 w, 7.48 w, and 7.72 m μ.

Anal. Calcd. for $C_{20}H_{32}N_2O_3$: C, 68.93; H, 9.26; N, 8.04. Found: C, 69.21; H, 8.90; N, 8.10.

The Low-Melting 1,1′-Dicyclohexyl-4′-hydroxy-2,5′-dioxo-*sym*-3,3′-bipyrrolidine (VIb).—The ethanol mother liquor from the separation of VIa was evaporated under reduced pressure to

(10) *Cf.* W. G. Brown, *Org. Reactions*, **6**, 469 (1951). The use of this decomposition method avoids the emulsion formation encountered with other procedures.

(11) The close similarity of the spectra of the four different isomers in methylene chloride solution supports the assumption that all of the compounds have the same structure and differ only in configuration. The following full listing of conspicuous bands for spectra taken in potassium bromide pellets is given to supplement the melting point data as a means of distinguishing between the isomers. The bands are not compared as to relative intensity, but those in parentheses are conspicuous in the spectrum of the isomer in question but much weaker or absent in two or more of the other forms.

VIa: 3.08, 3.40, 3.49, 5.94, (6.11), (6.63), 6.69, 6.88, 7.24, (7.64), 7.81, 7.94, 8.00, 8.08, 8.25, 8.34, 8.45, 8.66, (8.83), 9.09, (9.24), 9.49, 10.05, 10.18, 10.45, 11.22, 12.36, 13.37, (13.78), 14.69 μ.

VIb: 2.96, 3.41, 3.48, 5.96, 6.70, 6.87, 7.00, 7.79, 7.98, 8.30, 8.39, 8.68, 8.89, (9.52), 9.70, 9.98, 10.12, 10.24, (10.53), 11.23, 11.59, 11.92, 12.48, 12.58, (13.24) μ.

VIc: 2.90, 3.06, 3.39, 3.49, 5.94, (6.07), 6.70, 6.88, 6.99, 7.28, (7.70), 7.80, 7.94, 8.44, 8.70, 8.87, 9.03, 9.18, 9.49, 9.71, 10.16, 11.23, 11.66, 11.92, 12.30, 12.65, (13.38), 13.78, 14.76 μ.

VId: 3.03, 3.41, 3.48, 6.00, 6.68, 6.87, 7.02, 7.26, 7.58, 7.79, 7.95, 8.31, 8.70, 8.93, 9.18, 9.50, (9.67), 10.14, 11.21, 11.65, 11.94, 12.23, 12.37, (12.63), (13.36), 13.66, 14.78 μ.

give a light tan glass, which was dissolved in 80 ml. of a 3:1 petroleum ether–ether mixture. The solution was cooled at 0° for 20 hr. The crystalline precipitate was collected by filtration and washed repeatedly with boiling ether (200 ml. total) to yield 24 g. (19.6%) of cubes, m.p. 164–166°. An analytical sample of this same melting point was obtained by recrystallization from a 1:4 ethanol–water mixture; infrared spectrum below 8 μ (methylene chloride): 3.01 bm, 3.40 i, 3.48 i, 5.90 si, 6.01 si, 6.70 m, 6.92 bm, 7.27 w, 7.40 w, 7.48 bw, and 7.80 bm μ.

Anal. Calcd. for $C_{20}H_{32}N_2O_3$: C, 68.93; H, 9.26; N, 8.04. Found: C, 68.73; H, 9.36; N, 8.33.

A mixture of VIa and VIb melted at 135–144°, a mixture of VIb and VIc at 130–135°.

In order to assure the complete removal of VIb from the remaining mixture of stereoisomers, the mother liquor was combined with the ether washings described above and the combined solution (volume 290 ml.) was seeded with VIb and stored at 0° for 20 hr. A white solid (10 g., m.p. 92–164°) was filtered out. Fractionation of this material yielded only an insignificant additional amount of VIb in pure form.

The High-Melting 1,1′-Dicyclohexyl-4′-hydroxy-2,5′-dioxo-*dissym*-3,3′-bipyrrolidine (VIc).—After separation of VIb and the mixed solids described above, the mother liquor was evaporated under reduced pressure, and 280 ml. of a 4:1 ether–petroleum ether mixture was added with heating to dissolve the residue. The solution was cooled at 0° for 20 hr. The white crystals which separated were collected by filtration. The yield was 10 g. (8.15%) of material melting at 84–92°.

This mixture was fractionated by means of chromatography, using a column containing 100 g. of adsorption alumina (Fisher Scientific Co., 80–200 mesh). The material was placed on the column using 100 ml. of carbon tetrachloride. The column was washed successively with 500 ml. of petroleum ether and 500 ml. of carbon tetrachloride, then eluted with 1.5 l. of benzene, followed by 4.0 l. of ether and 4.5 l. of chloroform. The residue from evaporation of the ether eluate was crystallized from a 1:1 mixture of benzene and *n*-hexane to yield 2.2 g. (1.88%) of white crystals, m.p. 155–156°; infrared spectrum below 8 μ (methylene chloride): 2.99 bm, 3.40 i, 3.48 i, 5.96 si, 6.20 w, 6.70 m, 6.88 bm, 7.27 w, 7.40 w, 7.48 w, and 7.74 bm μ.

Anal. Calcd. for $C_{20}H_{32}N_2O_3$: C, 68.93; H, 9.26; N, 8.04. Found: C, 69.13; H, 8.94; N, 7.85.

The Low-Melting 1,1′-Dicyclohexyl-4′-hydroxy-2,5′-dioxo-*dissym*-3,3′-bipyrrolidine (VId).—After separation of the fraction containing VIc, the mother liquor was evaporated. The residue was a light-colored oil. The oil was treated with 200 ml. of a 1:3 mixture of petroleum ether and ether. The mixture was kept at room temperature for 24 hr. and filtered to yield 12 g. (9.8%) of material melting at 90–150°. This mixture was fractionated by means of chromatography on a column containing 200 g. of alumina (Fisher Scientific Co., 80–200 mesh). The material was placed on the column using 50 ml. of carbon tetrachloride. The column was washed with 500 ml. of petroleum ether, 500 ml. of high-boiling (65–110°) petroleum ether, and 2 l. of carbon tetrachloride, then eluted first with 2 l. of ether, next with 3 l. of chloroform. The residue from evaporation of both eluates was crystallized from benzene–*n*-hexane mixtures (1:1) to give white crystals, m.p. 139–140°. The yield from the ether eluate was 5 g., that from the chloroform eluate 5.1 g. The total was thus 10.1 g. (8.25%); infrared spectrum below 8 μ (methylene chloride): 3.00 bm, 3.40 i, 3.48 i, 5.95 si, 6.70 m, 6.88 bm, 7.27 w, 7.40 w, 7.48 bw, 7.76 bm μ.

Anal. Calcd. for $C_{20}H_{32}N_2O_3$: C, 68.93; H, 9.26; N, 8.04. Found: C, 68.91; H, 9.21; N, 8.31.

A mixture of VIc and VId melted at 99–112°.

After separation of the fraction which yielded VId, the mother liquor was evaporated under reduced pressure and treated with 300 ml. of petroleum ether (b.p. 30–60°). The mixture was kept at room temperature for 4 days. The mixture was filtered to remove 12 g. of material melting at 84–130°. The attempted fractionation of this mixture by means of chromatography yielded only mixtures of stereoisomers with wide melting ranges.

The 1,1′-Dicyclohexyl-4′-hydroxy-3,3′-bipyrrolidines (IX).—Over a period of 30 min. the diastereoisomeric 1,1′-dicyclohexyl-4′-hydroxy-2,5′-dioxo-3,3′-bipyrrolidines (VI) were added with vigorous stirring to suspensions of lithium aluminum hydride in dry ether, using 0.45–0.54 g. of lithium aluminum hydride and 24–30 ml. of ether per gram of the bipyrrolidine to be reduced. The reaction mixtures were refluxed with stirring for 5 hr. Refluxing was then continued for 16–20 hr. without stirring. Excess lithium aluminum hydride was destroyed by dropwise addition with stirring of 25% solutions of potassium sodium tartrate in water, using *ca.* 4 g. of solution per gram of lithium aluminum hydride originally present. After an additional hour of stirring the solutions were filtered and the filter cake was washed with chloroform on the filter, then twice broken up, and extracted with boiling chloroform. The combined filtrate and washings were dried over sodium sulfate and concentrated under reduced pressure. Solid products were obtained in all cases.

Crystallization was carried out by using acetone or acetone–ethanol and treating the hot solutions with Norit, filtering, and cooling the hot filtrates to 0° for 24 hr. Results with the individual compounds are given below.

The Low-Melting 1,1′-Dicyclohexyl-4-hydroxy-*sym*-3,3′-bipyrrolidine (IXa).—The reduction of compound VIa, m.p. 234–236° (7.16 g., 0.021 mole), yielded 6.7 g. (100%) of crude IXa, m.p. 135–137°. Following recrystallization from a 3:7 mixture of 95% ethanol and acetone, 4.0 g. (59.5%) of white needles were obtained, m.p. 139.5–141°.

Anal. Calcd. for $C_{20}H_{36}N_2O$: C, 74.95; H, 11.32; N, 8.74. Found: C, 75.04, 74.65; H, 11.42, 11.00; N, 8.63, 8.60.

The High-Melting 1,1′-Dicyclohexyl-4-hydroxy-*sym*-3,3′-bipyrrolidine (IXb).—The reduction of compound VIb, m.p. 164–166° (23 g., 0.066 mole), yielded 13.15 g. (62.5%) of compound IXb as white crystals, m.p. 165–166°, following recrystallization from 400 ml. of a 1:1 mixture of 95% ethanol and acetone.

Anal. Calcd. for $C_{20}H_{36}N_2O$: C, 74.95; H, 11.32; N, 8.74. Found: C, 74.83; H, 11.34; N, 8.63.

A mixture of IXa and IXb softened at 135° and melted at 138.5–144°.

The High-Melting 1,1′-Dicyclohexyl-4-hydroxy-*dissym*-3,3′-bipyrrolidine (IXc).—The reduction of compound VIc, m.p. 155–156° (2.1 g., 0.0060 mole), yielded 1.5 g. (77.5%) of compound IXc as white crystals, m.p. 110–112°, following recrystallization from 40 ml. of acetone. Recrystallization from 25 ml. of acetone yielded 1.25 g. (64.6%) of a product, m.p. 114–116°; melting point unchanged by further recrystallization.

Anal. Calcd. for $C_{20}H_{36}N_2O$: C, 74.95; H, 11.32; N, 8.74. Found: C, 74.66; H, 11.12; N, 8.80.

The Low-Melting 1,1′-Dicyclohexyl-4-hydroxy-*dissym*-3,3′-bipyrrolidine (IXd).—The reduction of compound VId, m.p. 139–140° (10 g., 0.0287 mole), yielded 6.25 g. (67.3%) of compound IXd, m.p. 101–102°, following crystallization from 240 ml. of acetone. Recrystallization from acetone yielded 5.0 g. (53.7%) of a product, m.p. 103–104°; melting point unchanged by further recrystallization; m.m.p. 101–112° with IXc.

Anal. Calcd. for $C_{20}H_{36}N_2O$: C, 74.95; H, 11.32; N, 8.74. Found: C, 74.69; H, 11.34; N, 8.55.

The infrared spectra of the four isomers did not differ significantly. The following data were obtained from compound IXb (infrared spectrum, Nujol mull): 3.24 bm, 3.42 i, 3.49 i, 3.62 sm, 6.85 bi, 7.27 m, 7.44 m, 7.52 sw, 7.70 w, 7.98 w, 8.06 w, 8.24 w, 8.42 w, 8.68 bm, 8.94 m, 9.22 bw, 9.36 bm, 9.58 w, 9.80 w, 10.20 w, 10.86 w, 11.33 mb, 11.90 bw, and 12.65 bw μ.

The 1,1′-Dicyclohexyl-3,3′-bipyrrolidines (VIII).—To solutions of each of the isomeric 1,1′-dicyclohexyl-4′-hydroxy-2,5′-dioxo-3,3′-bipyrrolidines (VI) in pyridine (10 ml. of pyridine per gram of bipyrrolidine) were added solutions of *p*-toluenesulfonyl chloride in dry pyridine (4 to 4.5 g. of *p*-toluenesulfonyl chloride and 10 ml. of pyridine per gram of bipyrrolidine). The reaction mixtures were allowed to stand for an extended period of time, then were poured onto cracked ice (50 to 100 g. of ice per gram of bipyrrolidine). The resulting mixtures were usually allowed to stand for 1 to 2 hr. (24 hr. at 0° in the case of the isomer VIc) and then filtered to collect the precipitated tosylates. The crude products were washed with water and dried in a desiccator or purified by further crystallization.

Solutions of the tosylates in tetrahydrofuran (8 to 30 ml. of tetrahydrofuran per gram of tosylate) were added with vigorous stirring to refluxing suspensions of lithium aluminum hydride in tetrahydrofuran, using at least 4 g. (a large excess) of lithium aluminum hydride and 40–65 ml. of tetrahydrofuran per gram of the tosylate to be reduced. Refluxing and stirring were continued for 20 to 24 hr. and the reaction mixtures were then allowed to stand at room temperature for 24 to 48 hr.

Excess lithium aluminum hydride was destroyed by dropwise addition with stirring of 25% solutions of potassium sodium tartrate in water, using *ca.* 4 g. of solution per gram of lithium aluminum hydride originally present. After an initial hour of

stirring, ethyl acetate was added (50 to 150 ml. per gram of tosylate reduced), and the mixture was heated to the reflux temperature. The hot solutions were filtered and the filter cake was washed with ethyl acetate on the filter, then twice broken up, and extracted with boiling ethyl acetate. The combined filtrate and washings were dried over sodium sulfate and concentrated under reduced pressure. From the first and second isomers (VIa and VIb) a solid product was obtained at this point, but the third and fourth isomers (VIc and VId) yielded oils.

These crude products were crystallized by dissolving them in hot acetone (6–7 ml. per gram of tosylate reduced), treating the hot solutions with Norit A, filtering, and cooling the filtrates to −15° for 36 hr. The crystalline products which separated were collected by filtration, washed with cold acetone (*ca.* 1 ml. per gram of tosylate reduced), and dried in a desiccator.

1,1′-Dicyclohexyl-*sym*-3,3′-bipyrrolidine (VIIIa). From Compound VIa.—The tosylate from 20 g. (0.0575 mole) of VIa (m.p. 231–233°), obtained after a reaction period of 12 hr. at room temperature, was crystallized from a mixture of 200 ml. of ethanol and 100 ml. of water with decolorization of the solution by charcoal. The crystalline precipitate was collected after the solution had been kept at 0° overnight. The yield was 20 g. (68.4%) of white crystals, m.p. 138–140°. Reduction of this product yielded 10 g. (83%) of 1,1′-dicyclohexyl-*sym*-3,3′-bipyrrolidine (VIIIa) as white cubes, m.p. 90–92°. A mixture of VIIIa and VIIIb (*vide infra*) melted over the range 35–89°.[12] The following spectral data were obtained for VIIIa (infrared spectrum, Nujol mull): 3.42 i, 3.49 i, 3.62 m, 6.85 i, 7.27 i, 7.42 m, 7.58 w, 7.66 w, 7.96 w, 8.04 w, 8.28 w, 8.70 m, 8.79 m, 8.84 sm, 10.90 w, and 11.20 m μ.

Anal. Calcd. for $C_{20}H_{36}N_2$: C, 78.88; H, 11.92; N, 9.20. Found: C, 78.91; H, 11.78; N, 9.18.

From Compound VIb.—From 2.0 g. (0.0058 mole) of compound VIb (m.p. 164–166°) there was obtained after a reaction period of about 12 hr. at room temperature 1.4 g. (48.6%) of the crude tosylate, m.p. 80–84°, which was reduced to yield 0.3 g. (35%) of VIIIa, m.p. 88–90°. The infrared spectrum was the same as that of the sample obtained from VIa, and there was no melting point depression.

1,1′-Dicyclohexyl-*dissym*-3,3′-bipyrrolidine (VIIIb). From Compound VIc.—From 4.0 g. (0.0116 mole) of VIc (m.p. 155–156°) there was obtained after a reaction period of 24 hr. at 0° (solution cooled at 0° before mixing) and 48 hr. at room temperature, 2.6 g. (45%) of the tosylate, m.p. 66–70°, which was reduced to yield 0.44 g. (29%) of compound VIIIb, m.p. 36–38°; infrared spectrum (Nujol mull): 3.42 i, 3.49 i, 3.62 m, 6.85 i, 7.27 i, 7.42 m, 7.58 w, 7.66 w, 7.96 w, 8.04 w, 8.28 w, 8.70 m, 8.78 m, 8.84 m, 10.90 w, and 11.20 m μ.

Anal. Calcd. for $C_{20}H_{36}N_2$: C, 78.88; H, 11.92; N, 9.20. Found: C, 79.02; H, 11.91; N, 9.09.

From Compound VId.—From 10.0 g. (0.0288 mole) of VId (m.p. 138–140°), 6 g. (45.7%) of crude tosylate (m.p. 162–164°) was obtained using a 24-hr. reaction period at room temperature. It was reduced to yield 1.0 g. (27.6%) of compound VIIIb, m.p. 37–39°. The infrared spectrum was identical with that of the sample of VIIIb from compound VIc, and there was no melting point depression.

Resolution Experiments with 1,1′-Dicyclohexyl-3,3′-bipyrrolidines (VIII). The Bisbitartrate of 1,1′-Dicyclohexyl-*sym*-3,3′-bipyrrolidine (VIIIa).—1,1′-Dicyclohexyl-*sym*-3,3′-bipyrrolidine, m.p. 90–92° (1.0 g., 0.00328 mole), and 1.0 g. (0.00663 mole) of (+)-tartaric acid were dissolved in 20 ml. of boiling absolute methanol. The solution was cooled to 30°, 10 ml. of absolute ether was added, and the mixture was kept at room temperature for 1 hr., then at 0° for 2 hr. The crystals which separated were filtered out and washed with ether. The yield was 1.95 g. (97.5%) of white crystals, m.p. 182–184°. The salt was recrystallized from 20 ml. of absolute methanol with cooling to 0°. The recovery was 0.860 g. (43%) of material melting at 183–184°, $[\alpha]^{25}D$ +12.80° (*c* 2.5%, 50% ethanol). The analysis indicated that the salt was a bisbitartrate, formed from 2 moles of tartaric acid and from 1 mole of the bipyrrolidine.

Anal. Calcd. for $C_{28}H_{48}N_2O_{12}$: C, 55.70; H, 8.00; N, 4.64. Found: C, 55.82; H, 8.11; N, 4.74.

Repeated crystallization did not change the melting point or specific rotation. Material recovered from the mother liquors of recrystallizations was also identical in melting point, rotation, and composition. When any of the fractions of the tartrate were dissolved in water and treated with concentrated ammonium hydroxide, the liberated base was devoid of optical activity.

Partial Resolution of 1,1′-Dicyclohexyl-*dissym*-3,3′-bipyrrolidine (VIIIb).—1,1′-Dicyclohexyl-*dissym*-3,3′-bipyrroldine, m.p. 37–39° (0.500 g., 0.00164 mole), and 0.500 g. (0.003315 mole) of (+)-tartaric acid were dissolved in a mixture of 20 ml. of isopropyl alcohol (carefully dried) and 15 ml. of absolute ethanol with heating. The solution was allowed to cool to room temperature and to stand for 14 hr. The separated crystals were filtered out and dissolved in 30 ml. of boiling ethyl acetate. The solution was allowed to stand at room temperature for 24 hr. and filtered to collect the product. The yield was 0.400 g. (40%) of white crystals, m.p. 138–140°.

The salt was dissolved in 10 ml. of water and the solution was decolorized with Norit A and filtered. Concentrated ammonium hydroxide was then added. An oil separated. After addition of 60 ml. of a saturated potassium carbonate solution, the mixture was extracted several times with ethyl acetate. The combined ethyl acetate solutions were dried over sodium sulfate, filtered, and evaporated under reduced pressure to leave an oily residue. The residue was dissolved in 5 ml. of boiling acetone, and the solution was cooled at −15° for 24 hr. The separated crystals were filtered out and washed with cold acetone. The yield was 0.056 g. of white crystals, m.p. 37–39°, $[\alpha]^{25}D$ −30° (*c* 1%, chloroform).

The mother liquor remaining after separation of the first 400-mg. fraction was evaporated under reduced pressure to leave an oily residue. This was dissolved in 10 ml. of water and the solution was decolorized with Norit A, filtered, and treated with concentrated ammonium hydroxide. After addition of 50 ml. of saturated potassium carbonate solution, the mixture was extracted several times with ethyl actate. The combined ethyl acetate solutions were dried over sodium sulfate, filtered, and evaporated under reduced pressure to leave an oily residue. The residue was dissolved in 5 ml. of boiling acetone and the solution was cooled at −15° for 24 hr. The separated crystals were collected by filtration and washed with cold acetone. The yield was 0.053 g. of white crystals, m.p. 37–39°, $[\alpha]^{25}D$ +12° (*c* 1%, chloroform).

Analysis of the salts obtained in other similar experiments showed that they were bisbitartrates. Thus a salt prepared in a methanol–ether mixture and crystallized from ethyl acetate showed the m.p. 120–121°, $[\alpha]^{25}D$ +5.6° (*c* 2.5%, 50% ethanol).

Anal. Calcd. for $C_{28}H_{48}N_2O_{12}$: C, 55.70; H, 8.00; N, 4.64. Found: C, 55.42; H, 7.95; N, 4.56.

After separation of the fraction described above, the residue obtained from the mother liquors was crystallized from *n*-butyl alcohol. White crystals, m.p. 140–144°, $[\alpha]^{25}D$ +18.8° (*c* 2.5%, 50% ethanol), separated.

Anal. Calcd. for $C_{28}H_{48}N_2O_{12}$: C, 55.70; H, 8.00; N, 4.64. Found: C, 55.37; H, 7.76; N, 4.82.

The 1,1′-Dicyclohexyl-4′-hydroxy-3,3′-bipyrrolidine Dimethiodide (X). From Compound IXb.—The compound IXb (1.1 g., 3.13 mmoles) was dissolved in 20 ml. of dioxane. To the solution was added *ca.* 3 ml. of methyl iodide and the mixture was allowed to stand overnight at room temperature. The light yellow solid which separated was removed by filtration and washed with a small amount of acetone to remove the yellow color. The very fine white crystals weighed 1.7 g. (85% yield) and melted at 257–259°. Recrystallization from a 2:1 mixture of acetone and 95% ethanol yielded 0.5 g. of small white platelets melting at 267–268.5°.

Anal. Calcd. for $C_{22}H_{42}I_2N_2O$: C, 43.72; H, 7.02; N, 4.64. Found: C, 42.90; H, 7.02; N, 4.44.

Recrystallization of the product from 95% ethanol with cooling only to room temperature raised the melting point to 278–280°.

Anal. Found: C, 43.25; H, 6.91; N, 5.45, 4.27.

(12) The lack of a pronounced melting point depression might conceivably indicate that the samples of m.p. 37–39° are actually eutectic mixtures containing the symmetric isomer VIIIa as well as the dissymmetric form VIIIb demonstrated by the resolution experiments. However, it seems very unlikely that much of the form melting at 92° could have been present, since it did not become evident during the fractionations involved in the resolution procedures. The fact that partial resolution did not change the melting point of VIIIb would seem to indicate that the enantiomorphs of VIIIb form solid solutions, and the same may be true of mixture of VIIIa with VIIIb.