[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TORONTO, AND THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

The Conditions for Optical Inactivity. Synthesis of an Image-Superposable Molecule which Contains No Plane or Center of Symmetry[1,2]

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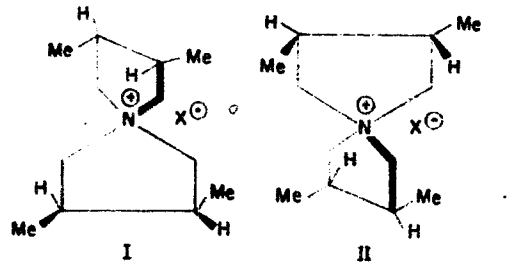
A compound (*meso* diastereomer of the spirane I) has been synthesized whose molecule contains no plane or center of symmetry but is nevertheless superposable upon its mirror image, due to the presence of a *fourfold alternating axis of symmetry*. In accordance with prediction, the compound is optically inactive. It is believed that this compound provides the first experimental demonstration of the inadequacy of the plane/center test for optical inactivity. The three diastereomers of I were also prepared. The numerous new active compounds reported have been configurationally correlated with (+)-2,3-dimethylsuccinic acid, whose absolute configuration has been predicted by means of a Kirkwood theory comparison with (+)-2-methylsuccinic acid of previously known absolute configuration.

The presence of a molecular plane or center of symmetry is a sufficient condition for optical inactivity. It might also appear to be a *necessary* condition, since to the best of our knowledge every inactive non-racemic substance hitherto reported, without exception, has possessed one or both of these molecular symmetry elements. However, it was pointed out as long ago as 1903 by Mohr[5a] and Aschan, and repeatedly mentioned by later authors[5b,c,6-10] that certain molecules of the type $Z(A^+A^+A^-A^-)$ lack such a plane or center but are nevertheless image-superposable; and thus the compounds corresponding should presumably be inactive. (The group A^+ is the non-superposable mirror image of A^-, and Z is a suitable nucleus or skeleton.) Although this presumed limitation of the plane/center test has been widely recognized, no experimental verification has been provided. We wish now to report such a verification, consisting of the synthesis of the *meso* "*trans/trans*" diastereomer[11] of 3,4,3′,4′-tetramethylspiro-(1,1′)-bipyrrolidinium *p*-toluenesulfonate (I).

The molecule I is superposable on its image, as can readily be demonstrated with molecular models, and the compound I has now been found to have an optical activity of zero, within experimental error, as would be predicted.



Instead of the well-known image-superposability test, one may employ the alternative but mathematically equivalent concept of alternating axis of symmetry,[9a] and the inactivity of compound I may then be attributed to the fact that its molecule possesses a *fourfold alternating axis of symmetry*.[12] This symmetry element is a rather common one (*e.g.*, it is present in methane), but the molecule I is unique among those of known compounds in the fact that its fourfold alternating axis is not accompanied by any onefold or twofold alternating axis.

To demonstrate that this molecule does possess a fourfold alternating axis, one may rotate it (formula I) 90° about a specified axis (co-axis of the two rings), which gives it the orientation shown in formula II. If the molecule II is now reflected through a central plane perpendicular to this axis, the resulting molecule is identical and *coincident* with (I). It should be understood that these operations of rotation and reflection are not accompanied by any motion of translation, nor by any change in conformation. (In the present discussion the anion X^- is disregarded, since it has no fixed spatial position with reference to the quaternary ammonium cation, at least in the fluid state with which we are here solely concerned.)

The tetrasubstituted spirane I can exist in four diastereomeric forms (three active, one *meso*). All four have now been prepared. The stereoisomers are most conveniently depicted by the swastika-type projection formulas VI-XIII (Chart I).

(1) Presented before the Organic Division at the Dallas Meeting of the American Chemical Society, April, 1956. Taken in part from a Ph.D. Thesis submitted by Stephen Proskow to the Graduate School, University of Toronto, 1956.

(2) (a) For preliminary communication, see THIS JOURNAL, 77, 4688 (1955); (b) G. E. McCasland and S. Proskow, *ibid.*, 76, 6067 (1954); (c) 76, 3486 (1954); (d) G. E. McCasland and Donald A. Smith, *ibid.*, 74, 564 (1952); (e) Ph.D. Thesis, D. A. Smith, University of Toronto, 1951; (f) Ph.D. Thesis, S. Proskow, University of Toronto, 1956; (g) G. E. McCasland and S. Proskow, *J. Org. Chem.*, in press.

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(4) Fellow of the National Research Council, 1954-1955.

(5) (a) E. Mohr, *J. prakt. Chem.*, [2] 68, 382 (1903), credited O. Aschan with first noticing the unusual characteristics of the molecular type $Z(A^+A^+A^-A^-)$; (b) F. Ebel in K. Freudenberg, "Stereochemie," F. Deuticke, Leipzig, 1933, p. 601; (c) G. W. Wheland, ref. 9a.

(6) R. Adams and R. L. Shriner, ref. 10b.

(7) F. M. Jaeger, "Lectures on the Principles of Symmetry," Elsevier Press, Amsterdam, 1917.

(8) A. F. Wells, "Structural Inorganic Chemistry," 2nd ed., Clarendon Press, Oxford, England, 1950, p. 208.

(9) G. W. Wheland, "Advanced Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1949; (a) pp. 147-151, (b) p. 139, (c) p. 182.

(10) R. Adams and R. L. Shriner, Chap. IV in H. Gilman, "Organic Chemistry: An Advanced Treatise," 2nd ed., Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943; (a) p. 239, (b) pp. 317-320, (c) p. 327.

(11) C. R. Noller and several of his students at Stanford University have independently been active in the preparation of spiranes containing four asymmetric atoms and have recently reported preparation of the *m-cis/cis* diastereomer of the bipiperidinium homolog of I. See C. R. Noller and C. R. Pannell, THIS JOURNAL, 77, 1862 (1955), and references there cited (especially 3). We wish to thank Professor Noller for a personal communication in August, 1954, describing some of his results.

(12) Or fourfold axis of rotatory inversion, see P. Woodward, *Chemistry & Industry*, 1599 (1955).

The co-axis of each spirane is assumed perpendicular to the paper, and the intersecting lines represent the two rings. The short appendages on each line show whether the two substituents are *cis* or *trans*. The front ring nearer the observer's eye is indicated by heavy shading. We find it advantageous to adopt a uniform orientation for such formulas: namely, front ring always vertical, back horizontal ring with at least one substituent directed upwards and the *cis* ring placed at the back in case of *cis/trans* ring combinations.

According to "Chemical Abstracts"[13] and the Ring Index,[14] the four asymmetric ring atoms in I should be numbered 3, 4, 3′ and 4′. In order to describe *configuration*, a more explicit numbering is needed. In this article the smallest number (3) is assigned to the top front asymmetric atom of each properly oriented formula, as indicated in formulas VI–XIII.

Since no official nomenclature exists for stereoisomers such as those here described, the following conventions[15] have been employed. The symbols (+) and (−) have their usual significance (rotation, not configuration). The dimethylsuccinic acids and related open-chain compounds are designated by the symbols "D(2)A-" and "L(2)A-" for the configurations IV and V. The inclusion of position number "2" and not "3" indicates that the two methyl groups are on opposite sides of the projection formula and that the prefix D or L describes the *lowest-numbered* (methyl) group. The symbol "A" stands for "absolute" and it serves also to avoid possible confusion with carbohydrate configurational nomenclature, which by custom is based on the highest-numbered asymmetric atom.

Similarly, "D(3)A-" and "L(3)A-" are used to describe the configurations XV and XVI of the dimethylpyrrolidines, each perspective formula being vertical and perpendicular to paper, with hetero atom at back.

The prefixes "*cis/cis*," "*cis/trans*" and "*trans/trans*" are used[15] to describe the spirane diastereomeric configurations, VI, VIII and X or XII, respectively, each of the two rings of each spirane being independently classified "*cis*" or "*trans*." The "D-" or "L-" prefix for each spirane describes the position of the *lowest-numbered* (top front) methyl group in each properly oriented formula. "DL-" and "*meso*" have their usual significance.

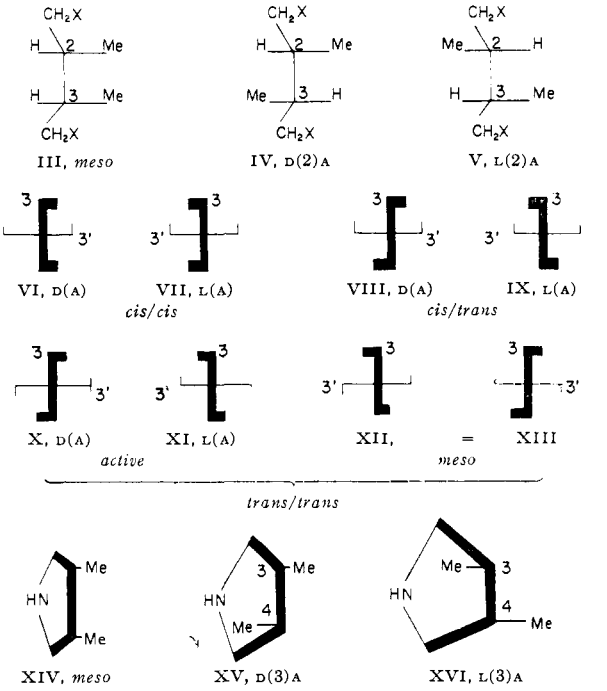
Synthesis of the Model Compound

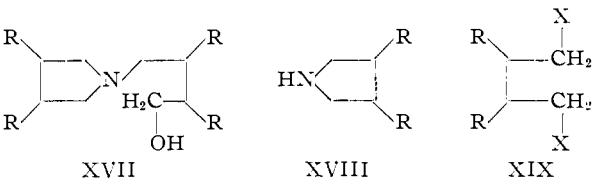
Suitable methods for preparing simple spirobipyrrolidinium (or -piperidinium) derivatives had been reported by previous investigators.[16] Two principal synthetic approaches to the more highly substituted spirane I were considered: (1) cyclization of the side chain of a pyrrolidinealkanol XVII and (2) reaction of a monocyclic secondary amine XVIII with a difunctional intermediate XIX. The first approach was partially successful, but will not be described here.[2g] The second approach was the one actually followed to completion.

CHART I

CONFIGURATIONAL FORMULAS OF SPIRANE PRODUCTS AND STARTING MATERIALS

For diacid derivatives replace H_2 by =O in formulas III, IV and V





The reactions of the racemic and the *meso* forms of 3,4-dimethylpyrrolidine and 1,4-dibromo-2,3-dimethylbutane (see Table I) were first utilized and led to successful syntheses of certain isomers. However, the *meso*-spirane could not be isolated from the *meso*-DL-*trans/trans*-spirane mixture, due to an unfavorable isomer ratio, or to relatively low solubility of the DL-form, or both.

A more certain route to the pure *meso*-spirane was found in the use of active intermediates (Table I). The needed (+)-3,4-dimethylpyrrolidine was obtained by resolution of the racemic form with ordinary (+)-tartaric acid.[17] Since the enantiomeric resolving agent, (−)-tartaric acid, is readily available, the (−)-dimethylpyrrolidine was preparable by precisely similar procedure.

(13) *C.A.*, Introduction to Subject Index, 1945.

(14) A. M. Patterson and L. Capell, "The Ring Index," Reinhold Publishing Corp., New York, N. Y., 1940.

(15) The configurational prefixes here used are in conformity with a system proposed by one of us for organic compounds in general and fully described in a pamphlet entitled "A New General System for the Naming of Stereoisomers" (1954), available from Chemical Abstracts, Columbus 10, Ohio. However, as a matter of convenience we have here employed the self-explanatory prefixes "*cis/cis*," "*cis/trans*," active "*trans/trans*" and *meso* "*trans/trans*" for the four spirane diastereomers, in preference to the corresponding numerical symbols "(3, 4, 3′, 4′)," "(3, 3′, 4′)," "(3, 3′)" and "(3, 4′)" proposed in the "General System."

(16) (a) W. Mills and E. Warren, *J. Chem. Soc.*, 2507 (1925); (b) J. von Braun, *et al.*, *Ber.*, **49**, 970 (1916); **43**, 2862 (1910); **39**, 4348 (1906); (c) A. Albert, *Ber.*, **42**, 551 (1909).

(17) Sufficient mineral acid was added to neutralize one-half of the racemic base (technique of W. J. Pope and S. V. Peachey, *J. Chem. Soc.*, **75**, 1066 (1899).

The active 1,4-dibromo-2,3-dimethylbutanes were prepared from the active diols, derived from the active diesters of the active 2,3-dimethylsuccinic acids. This diacid[18] was first resolved in 1913[19a] by use of the interesting reagent, (+)-triethylenediaminecobaltic bromide; however, the brucine method[19b] appeared more convenient. The first detailed account of the brucine resolution is the one given below.

Although certain spirane isomers (Table I) were successfully prepared from the active dibromides and pyrrolidines, the pure *meso*-spirane could still not be obtained. Since the optical purity of the low-rotating, liquid dibromides was dubious, we turned to the active diol di-*p*-toluenesulfonates, which were readily prepared in a crystalline optically pure condition, from the active crystalline diols. Such ditosyl diols react with amines in the same manner as dihalides.[20]

By reaction of the (−)-ditosyl diol with the (−)-pyrrolidine in hot dioxane, the desired *meso trans/trans* diastereomer (XII = XIII or I) of 3,4,3′,4′- tetramethylspiro- (1,1′)- bipyrrolidinium tosylate was finally obtained. The compound consisted of colorless crystals, m.p. 160–162°, which gave a correct analysis for carbon, hydrogen, nitrogen and sulfur, and had an optical rotation of zero[21] within experimental error.

However, reaction of the *levo* ditosyl diol with the pyrrolidine of opposite sign of rotation (and thus of the same configuration) gave a different and active *trans/trans*-spirane product, as would be predicted (see Table I).

The reactions employed were fairly standard, and the principal, and considerable, obstacle to solving the problem lay in the difficulty of finding appropriate stages at which clean-cut separations of diastereomers could be achieved. The particular route finally chosen was based on binary separations of diastereomers at three stages, namely, *meso*- from DL-diacid, (+)- from (−)-diacid (brucine salts); (+)- from (−)-pyrrolidine (tartrates). The two latter separations necessarily involve 50:50 mixtures, and the former happens to be nearly 50:50. Separations of diastereomers were then unnecessary in all subsequent steps down to the final spirane.

TABLE I

RELATION OF STARTING MATERIAL CONFIGURATIONS AND ROTATIONS TO THOSE OF PRODUCTS. REACTION OF 3,4-DIMETHYLPYRROLIDINE WITH 1,4-DITOSYLOXY-, OR 1,4-DIBROMO-, 2,3-DIMETHYLBUTANE

Starting materials: Dimethylpyrrolidine	Starting materials: Ditosyldiol (T) or dibromide[e] (B)	Product: Tetramethylspirobipyrrolidinium salt
		trans/trans Isomers
D(3)A-(+)	L(2)A-(+) B, T	*Meso*
L(3)A-(−)	D(2)A-(−) B, T	*Meso*
DL	D(2)A-(−)	*Meso* and D(A)[a,b]
DL	L(2)A-(+)	*Meso* and L(A)[a,b]
DL	DL B	*Meso* and DL[f]
D(3)A-(+)	D(2)A-(−) T	D(A)-(+)
L(3)A-(−)	L(2)A-(+) B, T	L(A)-(−)
...	...	DL[d]
		Cis/trans Isomers
D(3)A-(+)	*Meso* B	D(A)-(+)[b]
L(3)A-(−)	*Meso* T	L(A)-(−)[b]
DL	*Meso* B, T	DL[b]
		Cis/cis Isomers
Meso	*Meso* B	DL
...	...	D(A)[a,c]
...	...	L(A)[a,c]

[a] Not yet prepared. [b] Same product if starting material configurations reversed. [c] Presumably obtainable by resolving racemic form. [d] Bromide obtained from *meso*–DL mixture; tosylate from mixed enantiomers. [e] Dibromide rotation in ether. [f] Only DL actually isolated.

Relative and Absolute Configurations.—From the experimental data now available it can be deduced that *if* (+)-2,3-dimethylsuccinic acid has the D(2)A-configuration IV, then the derivatives listed in Table II have this same configuration. It will be noted that four compounds in this correlated series have a reversed sign of rotation. Each rotation, of course, is also subject to possible reversal if observed under markedly different experimental conditions from those noted; an actual reversal was observed in the case of the dibromide when the solvent (ether) was omitted.

TABLE II

RELATIVE CONFIGURATIONS: OBSERVED ROTATIONS OF COMPOUNDS HAVING THE SAME CONFIGURATION AS (+)-2,3-DIMETHYLSUCCINIC ACID ("D" SERIES)

Compound	Rotation
2,3-Dimethylsuccinic acid	+
Di-(−)-brucine salt	−
Dimethyl ester (no solvent)	−
Anhydride	+
2,3-Dimethylbutane-1,4-diol	+
Dibromide (in ether)	−
Ditosylate	−
3,4-Dimethylpyrrolidine	+
Tosylate	+
Hydrogen (+)-tartrate	+
Tetramethylspirobipyrrolidinium salt	
trans/trans	+
cis/trans	+

(18) (a) W. Bone and C. Sprankling, *ibid.*, **75**, 839 (1899); (b) most reported preparations of the racemic dimethylsuccinic acid have had a low m.p. We find that the pure compound is best obtained by brief hydrolysis of the anhydride (m.p. 91°) in warm water (2 parts). On addition at 0° of 12 *M* hydrochloric acid (1 part), crystals of m.p. 128–129.5° (preheat to 124°) were obtained; reported m.p. 129° (B. and S.).

(19) (a) A. Werner and M. Basyrin, *Ber.*, **46**, 3229 (1913); see also E. Ott, *ibid.*, **61**, 2134 (1928). The lower-melting (130°) dimethylsuccinic acid was incorrectly designated *meso* in the 1909 edition of Beilstein. Although the error was corrected in the 1919 supplement on the basis of W. and B.'s resolution, it has persisted in much subsequent literature. For example, on page 384 of the 1951 edition of F. Whitmore's "Organic Chemistry" it is incorrectly stated that the higher-melting acid (210°) is racemic and that "All attempts to separate either acid into optically active forms have failed." (b) E. Berner and R. Leonardsen, *Ann.*, **538**, 1 (1939).

(20) D. D. Reynolds, *et al.*, THIS JOURNAL, **73**, 3519 (1951); **72**, 1597 (1950).

(21) It appears improbable that the observed inactivity of the *meso*-spirane is due merely to racemization, since the (+)-*trans/trans*-spirane prepared under similar conditions retained its activity. Active quaternary ammonium ions of the simple type $N(RR'R''R''')^+$ sometimes racemize easily because of dissociation (into tertiary amine and alkyl halide) and recombination. However, the complex quaternary ammonium ions here described could racemize only by inversions at all four *carbon* atoms, and one would not expect this to take place easily.

The correlation of the (+)-pyrrolidine with the (+)-diacid and the resultant assignment of configuration D(3)A (XV) to the (+)-pyrrolidine was not based on chemical interconversion but on the fact that the ditosyl diol and the pyrrolidine which combine to yield *meso*-spirane must have opposite configurations.

Correlations of the (+)-*cis/trans*- and the (+)-*trans/trans*-spiranes with this series are based on their pyrrolidine and ditosyl diol components (Table I) and would lead to assignment of the D(A) configuration in each case. The active *cis/cis*-spiranes are not yet known and might be difficult to correlate if prepared by resolution of the DL-form.

It will then be possible to assign absolute configurations to this entire series if the absolute configuration of any one of them can be established, either by direct physical proof[22] or by correlation with some reference compound of known absolute configuration.

The most suitable reference compound appears to be the (+)-anhydride XXII (Chart II) of (+)-2-methylsuccinic acid, whose (D(2)A) configuration XXV has been firmly established by a long series of quasiracemate studies[23b] and chemical conversions,[23a,c-e] leading ultimately to correlations with cholesterol, menthol, D(2)A- (+)-tartaric acid and D(2,3)A- (−)-isoleucine. The absolute configurations of tartaric acid and isoleucine have been directly proved by X-ray studies.[22c]

It remains only to correlate the monomethyl and dimethyl anhydrides XXI and XXII. This can be done by a simple application of Kirkwood's optical rotation theory,[22a] analogous to his comparison[22a] of (+)-epoxypropane XXIV with (+)-epoxybutane XXIII. As a first rough approximation one may add Kirkwood's value (+17°) for the methyl–methyl interaction to twice the predicted methyl–ring interaction, taking the methyl–ring interaction as equal to the observed specific rotation (+33°) of the monomethyl anhydride XXII. If the (+)-dimethyl anhydride actually has the configuration XXI, its predicted specific rotation will then be +17 + 2(33°) = +83°, in fair agreement[22a,b] with the observed value[19b] of $[\alpha]^{20}D$ +105° (dioxane, *c* 8).

This leads us to conclude that (+)-2,3-dimethylsuccinic acid does in fact have the assumed absolute configuration XX. The absolute configurations of nearly all of the active compounds mentioned in this article are thereby established.

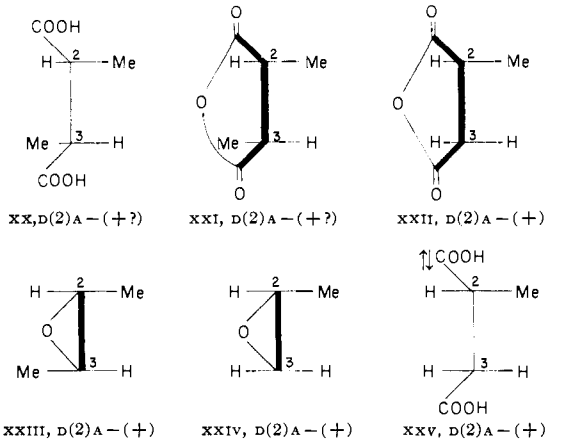
Application of the rather complicated Kirkwood theory was unusually simple in this instance because the dimethyl anhydride molecule is limited essentially to a single conformation and because information on the reference substances mentioned was already available.

In the course of work on the since discontinued pentaerythritol approach[5] the previously unreported pentaerythritol tetracarbanilate was prepared and characterized.

Acknowledgment.—We are indebted to the following persons for helpful consultation or suggestions: Drs. C. R. Noller, K. Mislow, M. L. Wolfrom, J. G. Kirkwood, R. Adams, R. L. Shriner and N. J. Leonard. Our interest in the alternating axis problem was first aroused by the comments of Drs. Adams and Shriner in Gilman's "Treatise." We have found the writings by Dr. G. W. Wheland on this and related topics exceedingly valuable and stimulating. Responsibility for any error of fact or interpretation is, of course, exclusively our own. Generous financial assistance was provided by the National Research Council.

CHART II

PREDICTION OF THE ABSOLUTE CONFIGURATION OF (+)-2,3-DIMETHYLSUCCINIC ACID



Experimental

All melting and boiling points have been corrected. Melting points were taken on the Köfler hot-stage unless otherwise noted. Microanalyses by Micro-Tech Laboratories, Skokie, Ill., by the Clark Microanalytical Laboratory, Urbana, Ill., and by Mr. Charles K. Cross, Toronto. Rotations are indicated by the usual prefixed symbols (+) and (−). Absolute configurations are indicated by prefixed symbols such as "D(2)A" (see above).

I. The Active Dimethylbutanediols and Derivatives

D(2)A-(+)-2,3-Dimethylsuccinic Acid.—Racemic diacid[18,19] of m.p. 128–130° (24 g., 0.165 mole) and 99 g. (0.25 mole) of anhydrous *l*-brucine ($[\alpha]D$ −127°, chloroform) were dissolved in 1300 ml. of boiling methanol. The filtered solution on cooling deposited 81.9 g. of crystals, m.p. 123–126°, $[\alpha]^{21}D$ −40.0° (chloroform, *c* 2). After repeated recrystallization from methanol, 50 g. (65%) of the di-(−)-brucine (+)-dimethylsuccinate of constant rotation $[\alpha]^{21}D$ −37.5° was obtained, m.p. 125–130°. The neutral brucine salt (1B)$_2$dA must have been obtained, since the yield calculated for the acid salt (1B)HdA would be 113%.

A solution of 49 g. of the brucine salt in 500 ml. of chloroform was extracted thrice with 1 *M* sodium carbonate and once with water. The combined, filtered aqueous phases were strongly acidified with 5 *M* hydrochloric acid, saturated with sodium chloride and continuously extracted with ether for 20 hr. The (not dried) ether extract was evaporated to near-dryness, benzene added, and the mixture distilled to a small volume and filtered, giving 7.2 g. of cotton-like crys-

(22) (a) J. G. Kirkwood, *et al.*, *J. Chem. Phys.*, **20**, 561 (1952); (b) according to a personal communication of December 19, 1955, from Professor Kirkwood, he believes that our assignment of absolute configuration to (+)-2,3-dimethylsuccinic anhydride is "reliable." He also suggests that his previous "estimate of the anisotropy of the methyl group is perhaps too small." This would cause each predicted rotation here mentioned to be low in magnitude but still correct in sign; (c) J. M. Bijvoet, *et al.*, *Nature*, **168**, 271 (1951); **173**, 888 (1954); *Proc. Roy. Acad. Amsterdam*, **B57**, 364 (1954).

(23) (a) J. W. Cornforth, *et al.*, *Nature*, **173**, 536 (1954); (b) A. Fredga, "T. Svedberg Memorial Volume," University, Uppsala, Sweden, 1944, pp. 261–273; (c) J. V. Braun, *Ber.*, **59**, 1447 (1926); (d) K. Freudenberg, *et al.*, *Ann.*, **594**, 76 (1955); (e) E. Fischer and E. Flateau, *ibid.*, **365**, 13 (1909).

tals, m.p. 128–133°. The product was recrystallized thrice from benzene, giving 5.7 g. (75% based on brucine salt) of pure (+)-diacid, m.p. 134–135° (preheat to 128°), $[\alpha]^{21}D$ +8.42° (water, *c* 4); reported[19b] m.p. 134–135°, $[\alpha]^{20}D$ +8.02° (water, *c* 4).

L(2)A-(−)-2,3-Dimethylsuccinic Acid.—The original methanolic mother liquor and first recrystallization filtrate from the above resolution were evaporated and the oily residue regenerated by the above procedure. This gave 12.5 g. (52%) of crude (−)-diacid, m.p. 122–130°, $[\alpha]^{23}D$ −4.24° (abs. ethanol, *c* 8); estimated aqueous rotation $[\alpha]^{23}D$ −7.50° (*c* 4). This crude product appears to contain about 11% of DL-impurity but would probably be satisfactory for preparation of the pure (+)-diol (see below).

Berner and Leonardsen reported[19b] that DL-impurity can be eliminated by a strychnine treatment, because the strychnine salt of the DL-diacid is relatively insoluble, but gave few details. Since the reported strychnine/diacid molar ratio of 1:2 failed to give a precipitate, we changed it to 3:2; actually this represents a large excess of strychnine with respect to the DL-diacid present. To 28 g. of the above crude (−)-diacid in 1100 ml. of hot *n*-butyl alcohol was added 96 g. of (−)-strychnine. On cooling, a crystalline precipitate with $[\alpha]^{23}D$ −138° (chloroform, *c* 2) was obtained, but appeared to consist largely of strychnine itself ($[\alpha]^{18}D$ −139°, chloroform, *c* 1). The yield including a second crop was 37 g.

The combined filtrates were evaporated, leaving an oil which was regenerated by the above brucine salt procedure, giving 14 g. of (−)-diacid with m.p. 122–125° and $[\alpha]^{23}D$ −4.31° (abs. ethanol, *c* 9) or −7.62° (water, *c* 4).

The strychnine treatment thus appeared nearly useless; however, when a filtered solution of this purified product in 28 ml. of warm water was treated with 14 ml. of 12 *M* hydrochloric acid and the mixture cooled, 8.7 g. of product melting at 132–134° (softens 126°) and having $[\alpha]^{25}D$ −8.06° (water, *c* 4) was obtained.

Dimethyl D(2)A-(+)-2,3-Dimethylsuccinate and Dimethyl L(2)A-(−)-2,3-Dimethylsuccinate. Levorotatory Diester from *d*-Diacid.—The diacid (5.3 g., $[\alpha]^{21}D$ +8.42°) in 150 ml. of ether was esterified with ethereal diazomethane, giving 5.42 g. (86%) of colorless liquid product, b.p. 88° (12 mm.), d_{20} 1.047, $n^{20}D$ 1.4219, M_D 42.6 (theor. 42.5), $[\alpha]^{21}D$ −9.42° (no solvent); reported[19b] d_{20} 1.053, $[\alpha]^{20}D$ −9.32°.

Dextrorotatory Diester from *l*-Diacid.—Using the diacid of $[\alpha]^{25}D$ −8.06° and the same procedure, a product of b.p. 87–88° (12 mm.), d_{20} 1.055, was obtained in 87% yield, $[\alpha]^{25}D$ +8.55° (no solvent). This product (not previously reported) apparently contained some impurity but gave an optically pure diol (see below).

D(2)A-(+) and L(2)A-(−)-2,3-Dimethylbutane-1,4-diol. *d*-Diol from *l*-Diester.—The dimethyl ester (9.6 g., $[\alpha]^{21}D$ −9.42°) of (+)-2,3-dimethylsuccinic acid was reduced with lithium aluminum hydride by the procedure described[2c] for *meso*-diol. The crude viscous liquid product (5.9 g.) was recrystallized from benzene–petroleum ether (1:1), giving colorless hygroscopic silk-like needles, m.p. 44–45.5°, $[\alpha]^{23}D$ +5.38° (dry ether, *c* 5). The total pure yield (including a second crop) was 3.2 g. (50%).

***l*-Diol from *d*-diester.**—Slightly impure dimethyl ester (3.4 g., $[\alpha]^{25}D$ +8.55°) was reduced by similar procedure, giving 1.1 g. (50%) of colorless hygroscopic silk-like needles, m.p. 44.5–45.5°, $[\alpha]^{25}D$ −5.42° (dry ether, *c* 5).

Admixture of equal weights of the above solid enantiomeric diols immediately gave the colorless liquid DL-diol.[2c]

D(2)A-(−) and L(2)A-(+)-1,4-Dibromo-2,3-dimethylbutane. *d*-Dibromide from *l*-Diol.—The diol (2.1 g.) was dissolved in a small amount of chloroform and treated with 1.7 ml. of phosphorus tribromide at 0°. The procedure was like that of Noller and Pannell.[11] The product weighed 1.3 g. (31%). It was a colorless liquid, b.p. 88–89° (10 mm.), d_{20} 1.622, $[\alpha]^{27}D$ +2.25° (ether, *c* 6). The product is levorotatory if no solvent is used, $[\alpha]^{27}D$ −1.08°.

***l*-Dibromide from *d*-Diol.**—The *d*-diol (1.8 g.) was treated by the same procedure, giving 1.1 g. (29%) of colorless liquid product, b.p. 100–101° (16 mm.), D_{20} 1.627, $[\alpha]^{25}D$ −2.35 (ether, *c* 14). Without a solvent the product is dextrorotatory, $[\alpha]^{26}D$ +0.44°.

If the *d*-diol was treated with anhydrous hydrogen bromide,[2c] the product, b.p. 101–102° (17 mm.), was obtained in 60% yield but had a rotation of only $[\alpha]^{21}D$ −1.48° (ether, *c* 38).

***meso*-2,3-Dimethylbutane-1,4-diol Di-*p*-toluenesulfonate.**—To 3.0 g. of the dry *meso*-diol[2c] in 20 ml. of anhydrous pyridine, 10.1 g. of tosyl chloride was gradually added with vigorous stirring at 5–10° (0.5 hr.). After stirring 1 hr. more at 10° the crude product (8.5 g.) was isolated in the usual manner,[20] m.p. 104–108°. The product recrystallized twice from ethanol weighed 7.5 g. (69%) and melted at 108–109°.

Anal. Calcd. for $C_{20}H_{26}O_6S_2$: C, 56.32; H, 6.15; S, 15.03. Found: C, 56.06; H, 6.21; S, 14.56.

L(2)A-(+)-, D(2)A-(−)- and DL-2,3-Dimethylbutane-1,4-diol Di-*p*-toluenesulfonate. *d*-Ditosylate from *l*-Diol.—The above *l*-diol (3.8 g.) when esterified by the above *meso*-diol procedure gave 11.5 g. of crude product, m.p. 84–88°. After two recrystallizations from ethanol, the product was obtained as 9.1 g. (67%) of long silk-like needles, m.p. 90.5–91.5°, $[\alpha]^{20}D$ +7.75° (benzene, *c* 5).

***l*-Ditosylate from *d*-Diol.**—From 5.0 g. of the above *d*-diol by a similar procedure there was obtained 13.6 g. (75%) of once-recrystallized product as long silk-like needles, m.p. 90.5–91.5°, $[\alpha]^{21}D$ −7.67° (benzene, *c* 5).

Racemic Ditosylate from Mixed Enantiomers.—A mixture of 10 mg. each of the above dextro and levo products was recrystallized from absolute ethanol, giving the DL-ditosylate in the form of colorless broad plates, m.p. 107–108°. A mixed m.p. with the *meso*-ditosylate was depressed.

Anal. Calcd. for $C_{20}H_{26}O_6S_2$: C, 56.32; H, 6.15; S, 15.03. Found: C, 56.43; H, 6.35; S, 14.71.

II. The Active Dimethylpyrrolidines

D(3)A-(+)-3,4-Dimethylpyrrolidine.—To 11.8 g. (1 mole) of the racemic dimethylpyrrolidine[2b] in 166 ml. of water was added 5 ml. (0.5 mole) of 12 *M* hydrochloric acid and 8.9 g. (0.5 mole) of (+)-tartaric acid ($[\alpha]^{20}D$ +12.0°). The oily crystalline residue obtained upon vacuum distillation was redissolved in 150 ml. of boiling 95% ethanol and the hot solution filtered. On cooling, the solution deposited 9.8 g. of crude product, glistening transparent plates, m.p. 174–178°, $[\alpha]^{20}D$ +20° (methanol, *c* 2). After seven recrystallizations from 95% ethanol, 2.0 g. of the mono-(+)-pyrrolidinium (+)-tartrate, m.p. 187–191°, $[\alpha]^{24}D$ +32.8° (water, *c* 2) were obtained. This product if pure should have a rotation of about +36° (see below); probably some (−, +) impurity is present.

Three grams of the above nearly pure (+, +) salt in 25 ml. of water was basified with 9 ml. of 7 *M* potassium hydroxide. The liberated pyrrolidine was extracted with ether and the dried ethereal extract vacuum distilled. The product collected at about 55° (115 mm.) was a colorless, fuming liquid, $[\alpha]^{21}D$ +20.1° (dry ether, *c* 5). It was characterized by conversion to the *p*-toluenesulfonate.

The racemic pyrrolidine gave a crystalline (+)-camphor-10-sulfonate of constant rotation and m.p.; however, the regenerated free base showed no optical activity. An attempted resolution with malic acid failed because the (−)-malate was hygroscopic and difficult to crystallize. (−)-Quinic acid gave only oils.

D(3)A-(+)-3,4-Dimethylpyrrolidinium *p*-Toluenesulfonate.—To a small sample of the above dextro free base in ether was added ethereal *p*-toluenesulfonic acid monohydrate. The crystals which separated, m.p. 146–149.5°, were recrystallized twice from benzene, giving long cotton-like needles, m.p. 148–150°, $[\alpha]^{21}D$ +17.5° (methanol, *c* 2).

In subsequent experiments the crude undistilled residue from the ether evaporation (see above regeneration) was treated in the same manner. From 9.5 g. of (+, +) salt, 6.5 g. of thrice-recrystallized tosylate, m.p. 148–150°, $[\alpha]^{21}D$ +17.5° (water, *c* 10) was obtained. This product appears to contain about 13% of racemic impurity.

The (+)-tosylate gave a (+)-picrate of m.p. about 144° which was difficult to purify and was not further characterized.

Mono-(−)-3,4-dimethylpyrrolidinium (−)-Tartrate.—The original ethanolic mother liquor plus the first filtrate from the above resolution of 22 g. of racemic pyrrolidine were evaporated, giving about 14 g. of oily residue, rich in the (−, +) salt. The crude levo-rich free base was regenerated by the above procedure and found to have $[\alpha]^{21}D$ about −11° (no solvent) indicating a composition of about 75% levo, 25% dextro. It was dissolved in 81 ml. of water, and 2.4 ml. of 12 *M* hydrochloric acid and 17.0 g. of (−)-tartaric acid (Aldrich Chemical Co.) were added. After recrystallization from 95% ethanol, 19.4 g. of crude (−, −) salt was

obtained. After five more crystallizations 8.5 g. (30% based on DL-pyrrolidine) of nearly pure (−)-3,4-dimethylpyrrolidinium hydrogen (−)-tartrate was obtained as glistening transparent plates, m.p. 187–191°, $[\alpha]^{21}D$ −32.8° (water, *c* 2).

Anal. Calcd. for $C_6H_{13}N \cdot C_4H_6O_6$: N, 5.62. Found: N, 5.68.

This product appeared still to contain some (+, −) impurity, since when the number of recrystallizations was increased to 12, the rotation decreased to −36.2° (m.p. not improved).

L(3)A-(−)-3,4-Dimethylpyrrolidinium *p*-Toluenesulfonate.—The (−)-pyrrolidine regenerated from the purest (−)-tartrate (2.2 g., $[\alpha]D$ −36.2°) was converted by the above procedure to a crude *p*-toluenesulfonate of m.p. 147–151°, yield 2.0 g. This product was twice recrystallized from benzene, giving cotton-like needles of constant m.p. 150–153° (softens at 148°), $[\alpha]^{21}D$ −20.2° (water, *c* 10).

When (−)-tartrate of rotation −32.8° was used, a less pure product of m.p. 148–150°, $[\alpha]^{21}D$ −18.0° (water, *c* 10), was obtained after four recrystallizations from benzene; yield 46%.

This product when mixed with an equal weight of the above (+)-tosylate in boiling benzene gave crystals of the racemic pyrrolidine tosylate,[2b] m.p. 140.7–142.7°, optical rotation zero. A mixed m.p. with an authentic sample was not depressed.

III. *cis/cis*-Spirane Derivatives

DL-*cis/cis*-3,4,3′,4′-Tetramethylspiro-(1,1′)-bipyrrolidinium Bromide.—To a solution of 1.19 g. of the *meso*-pyrrolidine[2b] in 14.5 ml. of 0.834 *M* sodium hydroxide was added 3.0 g. of the *meso*-dibromide,[2c] and the mixture refluxed for 1.5 hr. To the resulting solution at 0° was added about 20 ml. of 10 *M* potassium hydroxide and the solution then extracted repeatedly with 1,2-dichloroethane. On adding dry ether to the dried dichloroethane extract, 2.5 g. (80%) of colorless, non-hygroscopic crystals, m.p. 314–316° (cap.-dec.) was obtained. By recrystallization from butanone the spirane bromide was obtained as transparent plates, m.p. 316–317°, yield (including second crop) 1.68 g.

Anal. Calcd. for $C_{12}H_{24}NBr$: C, 54.96; H, 9.22; N, 5.34. Found: C, 54.98; H, 8.93; N, 5.46.

The product was further characterized as the picrate and tosylate (see below). The chloride was crystalline and non-hygroscopic but was not further investigated. The gum-like yellow chloroaurate appeared unsuitable as a derivative.

DL-*cis/cis*-3,4,3′,4′-Tetramethylspiro-(1,1′)-bipyrrolidinium Picrate.—To a concentrated aqueous solution of the spirane bromide was added saturated aqueous picric acid (1 mole). The yellow precipitate was recrystallized once from 95% ethanol, giving bright yellow needles, m.p. 156–157.5°.

Anal. Calcd. for $C_{12}H_{24}N \cdot C_6H_3N_3O_7$: N, 13.66. Found: N, 13.87.

DL-*cis/cis*-3,4,3′,4′-Tetramethylspiro-(1,1′)-bipyrrolidinium *p*-Toluenesulfonate.—A solution of 0.26 g. of the spirane bromide in 10 ml. of water was stirred for 15 minutes with 0.28 g. of silver *p*-toluenesulfonate. The mixture was filtered and the filtrate vacuum-distilled to dryness. The residue was recrystallized six times from dioxane, giving 0.12 g. (34%) of the spirane tosylate, m.p. 185.5–187°.

Anal. Calcd. for $C_{12}H_{24}N.C_7H_8O_3S$: C, 64.55; H, 8.84; N, 3.96. Found: C, 64.27; H, 8.88; N, 3.57.

IV. *cis/trans*-Spirane Derivatives

DL-*cis/trans*-3,4,3′,4′-Tetramethylspiro-(1,1′)-bipyrrolidinium Bromide and Picrate.—The racemic pyrrolidine[2b] and *meso*-dibromide[2c] were treated by the procedure described above for the DL-*cis/cis*-spirane bromide. Extraction was conducted with many portions of chloroform; probably fewer portions of 1,2-dichloroethane would suffice. A 2.6 g. (83%) yield of crude product, colorless non-hygroscopic crystals, m.p. 334° (cap.-dec.), was obtained. A sample recrystallized from butanone for analysis gave transparent plates of unchanged m.p.

Anal. Calcd. for $C_{12}H_{24}NBr$: C, 54.96; H, 9.22; N, 5.34. Found: C, 55.22; H, 9.34; N, 5.24.

The bromide was converted to the picrate in the usual manner. The picrate was obtained as yellow needles, m.p. 146.5–148°.

Anal. Calcd. for $C_{12}H_{24}N \cdot C_6H_3N_3O_7$: N, 13.66. Found: N, 13.48.

DL-*cis/trans*-3,4,3′,4′-Tetramethylspiro-(1,1′)-bipyrrolidinium *p*-Toluenesulfonate. (A) From Ditosyl Diol.—The reaction of 0.85 g. of the above *meso*-ditosyl diol with 0.41 g. of the above racemic pyrrolidine (each in 7 ml. of dry dioxane) was carried out exactly as described for the (+)-*trans/trans*-spirane tosylate (see below). After reaction 0.11 g. of unreacted ditosyl diol was recovered. The crude tosylate precipitated from chloroform–ether weighed 0.62 g., m.p. 120–174°. The final product twice recrystallized from dioxane weighed 0.30 g., m.p. 180–181.5°.

Anal. Calcd. for $C_{19}H_{32}NO_3S$: C, 64.55; H, 8.84; N, 3.96. Found: C, 64.51; H, 8.97; N, 3.57.

B. From Spirane Bromide.—A small portion of the bromide was treated with silver tosylate by the above procedure used for the DL-*cis/cis* isomer. After successive recrystallizations from ethyl acetate and from dioxane, colorless crystals, m.p. 180–182°, identical with the above spirane tosylate were obtained.

A small sample of the spirane tosylate and sodium iodide were dissolved in chloroform–ethanol, and ether added to precipitate the DL-*cis/trans*-spirane iodide. This product was recrystallized from ethanol–butanone to give glistening transparent plates, m.p. 333–335° (cap.-dec.). Because of its inconveniently high m.p., the iodide was not further characterized.

L(A)-(−)-*cis/trans*-3,4,3′,4′-Tetramethylspiro-(1,1′)-bipyrrolidinium Bromide.—To 0.41 g. of the (−)-pyrrolidine ($[\alpha]^{21}D$ −21.7°) and 1.0 g. of the *meso*-dibromide[2c] was added 4.9 ml. of 0.834 *M* sodium hydroxide, and the mixture refluxed for 2 hr. The product was isolated by the DL-*cis/cis* procedure (see above), giving 0.33 g. of crude product, $[\alpha]^{21}D$ −15.8° (methanol, *c* 5). The colorless crystals (30 mg.) of (−)-*cis/trans*-spirane bromide obtained after two recrystallizations from butanone had $[\alpha]^{25}D$ −20.00 (water, *c* 2), m.p. 341–343° (cap.-dec.).

D(A)-(+)-*cis/trans*-3,4,3′,4′-Tetramethylspiro-(1,1′)-bipyrrolidinium *p*-Toluenesulfonate.—The above *meso*-ditosyldiol (0.64 g.) in dioxane and 1.0 g. of the (+)-pyrrolidine ($[\alpha]^{21}D$ +17.5°) were treated by the (+)-*trans/trans* procedure given below. After removal of 0.39 g. of unreacted ditosyldiol, 0.13 g. (65% based on reacted ditosyldiol) of crude product was obtained, m.p. 175–181°, $[\alpha]^{26}D$ +12.23° (water, *c* 5). After two recrystallizations from dioxane, the (+)-*cis/trans*-spirane tosylate was obtained as colorless needles m.p. 177.5–179°, rotation unchanged.

V. *trans/trans*-Spirane Derivatives

DL-*trans/trans*-3,4,3′,4′-Tetramethylspiro-(1,1′)-bipyrrolidinium Bromide and Picrate.—To 1.98 g. of the racemic pyrrolidine[2b] in 24.5 ml. of 0.834 *M* sodium hydroxide was added 4.88 g. of the racemic dibromide,[2c] and the mixture refluxed for 1.5 hr. The product was isolated by the above DL-*cis/cis*-spirane bromide procedure. The crude product consisted of 4.3 g. (82%) of non-hygroscopic colorless crystals, m.p. 320° (cap.-dec.) and was presumably a mixture of the *meso* and DL-*trans/trans* forms, richer in the latter.

After four recrystallizations from butanone–absolute ethanol (9:1), the pure or nearly pure DL-*trans/trans*-bromide, m.p. 323–324° (cap.-dec.), was obtained.

Anal. Calcd. for $C_{12}H_{24}BrN$: C, 54.96; H, 9.22; N, 5.34. Found: C, 54.61; H, 9.10; N, 5.20.

A portion of the analytical sample was dissolved in water and treated with excess aqueous triethanolamine picrate. Long yellow needles crystallized out, m.p. 131–134°. After three recrystallizations from 95% ethanol, the DL-*trans/trans*-spirane picrate, m.p. 134.5°–136°, was obtained. (The corresponding *meso*-picrate melts at 116°—see below.)

Anal. Calcd. for $C_{12}H_{24}N.C_6H_3N_3O_7$: N, 13.66. Found: N, 13.45.

The first butanone–ethanol mother liquor above after vacuum-concentration deposited a second crop, which was discarded. The filtrate from the second crop was taken to dryness, giving a crystalline residue of m.p. 316–318° (cap.-dec.). This material was converted to a picrate (crude m.p. 123.5–128.5°), which after repeated recrystallization melted at 130.5–133°, mixed m.p. with the above picrate not depressed. These last results suggest that very little *meso* isomer is present in the original mixture (m.p. 320°) of DL- and *meso-trans/trans*-bromides.

D(A)-(+)-*trans/trans*-**3,4,3′,4′-Tetramethylspiro-(1,1′)-bipyrrolidinium Bromide.**—To 0.38 g. of the above (+)-pyrrolidine, $[\alpha]^{21}D$ +20.1°, was added 0.94 g. of the above levo-in-ether dibromide ($[\alpha]^{21}D$ −1.48°) and 4.65 ml. of 0.834 *M* sodium hydroxide. The mixture was refluxed for 1.8 hr. The product isolated by the above DL-*cis/cis* procedure weighed 0.20 g., $[\alpha]^{21}D$ +27.7° (methanol, *c* 4). Recrystallization from butanone gave 0.09 g. of product with $[\alpha]^{21}D$ +29.8° (methanol, *c* 2). After a second recrystallization the specific rotation at 25° was +30.26° (water, *c* 2), $M^{25}D$ +79°, m.p. 346–348° (cap.-dec.).

D(A)-(+)-*trans/trans*-**3,4,3′,4′-Tetramethylspiro(1,1′)-bipyrrolidinium *p*-Toluenesulfonate.**—To 0.64 g. of the above (−)-ditosyl diol and 5 ml. of dry dioxane at 100° was added gradually (2 hr.) with stirring a solution in 5 ml. of dioxane of the (+)-pyrrolidine regenerated from 1.00 g. of its tosylate ($[\alpha]^{21}D$ +17.5°). (The regeneration was effected by the use of aqueous potassium hydroxide and ether.)

After stirring 3.5 hr. more, the hot solution was filtered and the filtrate vacuum distilled to dryness. The semi-crystalline residue was triturated with 27 ml. of 0.1 *M* sodium hydroxide and the residue washed (water, 25 ml.) and dried, giving 0.31 g. of unreacted ditosyldiol, m.p. 87–90°.

The combined aqueous filtrate was extracted with ether, neutralized with *p*-toluenesulfonic acid and vacuum distilled to dryness. To remove traces of water, the distillation was repeated after adding absolute ethanol. The crystalline residue was extracted with boiling chloroform and the residual sodium *p*-toluenesulfonate removed by filtration.

The chloroform filtrate was vacuum distilled, and the distillation repeated after adding benzene to the residue. The final semi-crystalline residue was washed with absolute ether (50 ml.). The residue was dissolved in 5 ml. of chloroform (filter). On adding 50 ml. of anhydrous ether, 0.175 g. (65% allowing for recovered starting material) of crude product precipitated, m.p. 147–150.5°, $[\alpha]^{27}D$ +18.80° (water, *c* 5). After three recrystallizations from dioxane, we obtained 0.052 g. of the (+)-*trans/trans*-tosylate as colorless crystals, m.p. 150–152.5°, $[\alpha]^{30}D$ +19.88° (water, *c* 5), $M^{30}D$ +70°.

Anal. Calcd. for $C_{19}H_{32}NO_3S$: C, 64.55; H, 8.84. Found: C, 61.54; H, 8.07.

From the analysis it appears that this product is still not entirely pure, but there can be little doubt of its identity.

L(A)-(−)-*trans/trans*-**3,4,3′,4′-Tetramethylspiro-(1,1′)-bipyrrolidinium *p*-Toluenesulfonate.**—The levorotatory pyrrolidine and dextrorotatory ditosyldiol were treated by the same procedure described for the (+)-*trans/trans*-spirane tosylate, giving a 28% yield of once-recrystallized product as colorless long silky needles, m.p. 149.5–151°, $[\alpha]^{19}D$ −20.2° (water, *c* 6).

DL-*trans/trans*-**3,4,3′,4′-Tetramethylspiro-(1,1′)-bipyrrolidinium *p*-Toluenesulfonate and Picrate.**—Equal 100-mg. portions of the two enantiomers (m.p. 149.5–151°, $[\alpha]^{19}D$ ±20.2°) were dissolved in boiling dioxane. The filtered solution on cooling deposited 110 mg. of glistening, colorless, rhombic leaflets, m.p. 150–151°. After recrystallization, the melting point was unchanged, and the rotation was zero.

This tosylate when treated with aqueous picric acid gave a picrate of m.p. 135–136.5°, identical with that prepared from the DL-*trans/trans*-bromide (see above).

meso-trans/trans-**3,4,3′,4′-Tetramethylspiro-(1,1′)-bipyrrolidinium *p*-Toluenesulfonate. (A). From Levorotatory Starting Materials.**—The procedure used was similar to that for the (+)-*trans/trans* diastereomer (see above). The above (−)-ditosyldiol (0.64 g., $[\alpha]^{21}D$ −7.67°) was treated with 1.25 g. of the (−)-pyrrolidine tosylate ($[\alpha]^{21}D$ −20.2°) in hot dioxane. After the reaction 0.17 g. of unreacted ditosyldiol, m.p. 86–89°, was reclaimed. The crude product, m.p. 153–160.5°, weighed 0.24 g. (60%, allowing for recovered starting material). It was optically inactive within experimental error, the observed rotation being $\alpha^{30}D$ +0.012° (water, *c* 5, *l* 0.5); a second, independent observer reported $\alpha^{30}D$ 0.003° for the same solution.

After recrystallization from dry tetrahydrofuran, colorless crystals, m.p. 160.5–162.5°, were obtained, the observed rotation was $\alpha^{30}D$ +0.010° (water, *c* 5, *l* 0.5). A second, independent observer reported for the same solution $\alpha^{30}D$ +0.005°.

The observed rotation in chloroform (*c* 1.6) using a 4-dm. tube was $\alpha^{29}D$ +0.021°.

The product was again recrystallized for analysis, m.p. 160–162°.

Anal. Calcd. for $C_{19}H_{32}NO_3S$: C, 64.55; H, 8.84; N, 3.96; S, 9.07. Found: C, 63.93; H, 8.92; N, 4.07; S, 8.94.

(B) From Dextrorotatory Starting Materials.—Using the (+)-ditosyldiol ($[\alpha]D$ +7.75°) and the (+)-pyrrolidine tosylate ($[\alpha]^{21}D$ +17.5°), a crude product of m.p. 158–161.5° and observed rotation $\alpha^{25}D$ 0.049 (water, *c* 5, *l* 0.5) was obtained. After three recrystallizations from dry dioxane nearly pure *meso-trans/trans*-spirane tosylate, m.p. 160–162°, was obtained; the observed rotation was $\alpha^{25}D$ −0.051 (water, *c* 5, *l* 0.5).

Since it later appeared that tetrahydrofuran is superior to dioxane, all of the above crystals and mother liquors were recombined and recrystallized thrice from this new solvent. The colorless crystals obtained had a m.p. of 160.5–162.5° and an observed rotation of $\alpha^{27}D$ −0.027° (water, *c* 5, *l* 0.5).

meso-trans/trans-**3,4,3′,4′-Tetramethylspiro-(1,1′)-bipyrrolidinium Bromide and Picrate. (A) From Dextrorotatory Starting Materials.**—The procedure was similar to that for the DL-*cis/cis*-bromide, except as noted. One mole each of the dextro-in-ether dibromide ($[\alpha]^{25}D$ +2.25°) and the (+)-pyrrolidine tosylate ($[\alpha]^{21}D$ +17.5°) was refluxed with two moles of sodium hydroxide.

The crude *meso-trans/trans*-spirane bromide was converted to the picrate, which was thrice recrystallized from benzene, giving canary-yellow needles, m.p. 116.5–118.5°.

Anal. Calcd. for $C_{12}H_{24}N{\cdot}C_6H_3N_3O_7$: N, 13.66. Found: N, 13.85.

This picrate appears still to contain levorotatory impurities, since spirane bromide regenerated from it had an observed rotation of $\alpha^{26}D$ −0.15° (water, *c* 7, *l* 0.5).

(B) From Levorotatory Starting Materials.—When the levo-in-ether dibromide ($[\alpha]^{25}D$ −2.35°) and the (−)-pyrrolidine tosylate ($[\alpha]^{23}D$ −18.0°) were employed, the *meso-trans/trans*-spirane picrate obtained had a m.p. of 115–117°. The regenerated spirane bromide showed an observed rotation of $\alpha^{25}D$ +0.044° (water, *c* 5, *l* 0.5).

Pentaerythritol Tetracarbanilate.—A mixture of 5.0 g. of finely powdered anhydrous pentaerythritol with 33 ml. of phenyl isocyanate was heated briefly with a free flame. A rapid reaction occurred and the mixture appeared to solidify. After cooling, the product was washed with petroleum ether and recrystallized twice from 95% ethanol. Colorless needles (5.6 g.) of constant m.p. 252–253° were obtained.

Anal. Calcd. for $C_5H_8O_4(C_8H_3NO)_4$: C, 64.69; H, 5.27; N, 9.15. Found: C, 64.87; H, 5.26; N, 9.65.

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