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

Synthesis of 3,4-Dimethyl Spirobipyrrolidinium Salts by Cyclization of Pyrrolidinealkanols

G. E. McCASLAND[1] AND STEPHEN PROSKOW[2]

Received July 25, 1956

(1,1′)-Spirobipyrrolidinium bromide and its 3,4-dimethyl or 3,4,3′,4′-tetramethyl derivatives are readily prepared by cyclization of appropriate derivatives of 1-bromo-4-(1-pyrrolidinyl)-butane prepared from the corresponding pyrrolidinealkanols. The pyrrolidinealkanols are prepared in turn by reduction of the corresponding 4-oxo-4-(1-pyrrolidinyl)-butyric acid esters, derived from appropriately methylated pyrrolidine and succinic anhydride starting materials. Stereoisomerism of the products and intermediates is discussed.

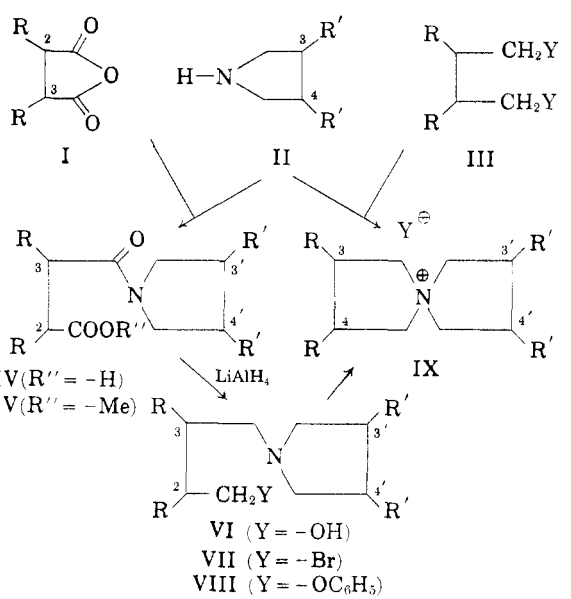
In recent communications[3] we have reported the synthesis of the four diastereomers of the tetramethylspirobipyrrolidinium *p*-toluenesulfonate, IX (R = R′ = Me). This set of diastereomers was of unusual interest because the molecule of one of them is superposable on its mirror image but possesses no plane or center of symmetry. The synthetic route utilized for the preparation of these spiranes was based on the cyclization of a suitable difunctional intermediate, III (Y = —Br or —$OSO_2C_6H_4CH_3$), caused by reaction with a suitable pyrrolidine derivative, II (R′ = Me).

During the course of these investigations we also explored an alternative route for the synthesis of such spiroquaternary salts, namely, the cyclization of a suitable *N*-alkylpyrrolidine derivative, VII, through the interaction of a side chain terminal functional group with the tertiary nitrogen atom.

The needed bromoalkyl pyrrolidine, VII, was prepared from the corresponding pyrrolidine alkanol, VI. The use of intermediates such as VII for spirane preparations has been known for many years,[4,5] but it is only recently that the convenient lithium aluminum hydride reduction procedure for preparing an alkanol VI from an amidic acid, IV (or ester V), has been available. The needed amidic acid is easily obtained by reaction of a heterocyclic secondary amine with a dicarboxylic acid anhydride.[6]

Nonmethylated spiranes. The reaction of pyrrolidine with succinic anhydride gave the amidic acid (IV, R = R′ = H). The crude liquid methyl ester of this amidic acid was reduced to give the known[7] liquid pyrrolidinebutanol (VI, R = R′ = H).

CHART I. SYNTHETIC ROUTES FOR THE PREPARATION OF SPIROBIPYRROLIDINIUM SALTS (R,R′ = —H or —Me)



The pyrrolidinebutanol was converted by hydrobromic acid to the bromobutyl hydrobromide (VII. HBr, R = R′ = H). This bromobutyl hydrobromide had been previously prepared by von Braun[4] in 1924 from the corresponding phenyl ether (VIII) derived from 4-phenoxybutyronitrile. The free bromobutylpyrrolidine liberated from its hydrobromide rapidly cyclized to give the hygroscopic[8] spirane bromide.[4]

cis- and trans-Dimethyl spiranes. When two methyl groups are introduced at positions 3 and 4 in one of the spirane rings (formula IX), the sub-

(1) Department of Chemistry, The Ohio State University, Columbus 10, Ohio, to whom any correspondence regarding this article should be sent.

(2) Taken in part from a Ph. D. Thesis submitted by Stephen Proskow to the Graduate School, University of Toronto, 1956. Fellow of the National Research Council, 1954–1955. Present address: Department of Chemistry, University of Illinois, Urbana, Ill.

(3) G. E. McCasland and Stephen Proskow, *J. Am. Chem. Soc.*, (a) **77**, 4688 (1955); (b) **78**, 5646 (1956); (c) **76**, 6087 (1954); (d) **76**, 3486 (1954).

(4) J. von Braun *et al.*, *Ber.* **57**, 187 (1924); **56**, 1994 (1923); **49**, 970 (1916).

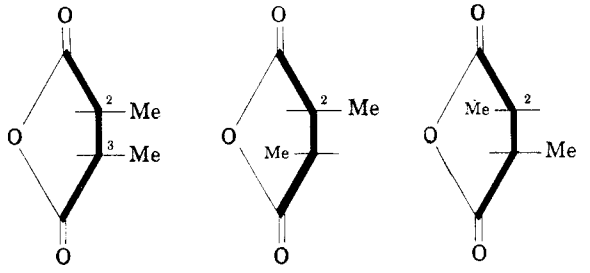
(5) A. Albert, *Ber.* **41**, 545 (1909).

(6) D. Pressman, J. H. Bryden, and L. Pauling, *J. Am. Chem. Soc.*, **70**, 1352 (1948), carried out a similar reaction with piperidine in place of pyrrolidine.

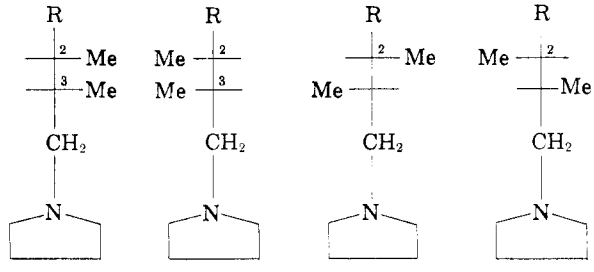
(7) R. B. Moffet, *J. Org. Chem.*, **14**, 862 (1949) prepared this pyrrolidinebutanol from pyrrolidine and 4-chlorobutanol-1.

(8) It is of interest that the tetramethyl spirane shows no hygroscopic properties, perhaps because it lacks the extreme water-solubility of its dimethyl and unmethylated homologs.

CHART II. CONFIGURATIONAL FORMULAS OF INTERMEDIATES AND PRODUCTS.[9,11-14] (R = —COOH, —COOMe, —CH_2OH, —OR —CH_2Br. FOR PYRROLIDINE DERIVATIVES REPLACE THREE O ATOMS IN FORMULAS X, XI, XII WITH —NH— AND H, H)

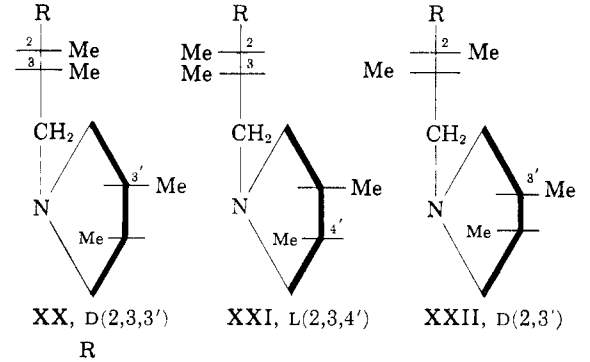


X, *meso* XI, D(2) XII, L(2)

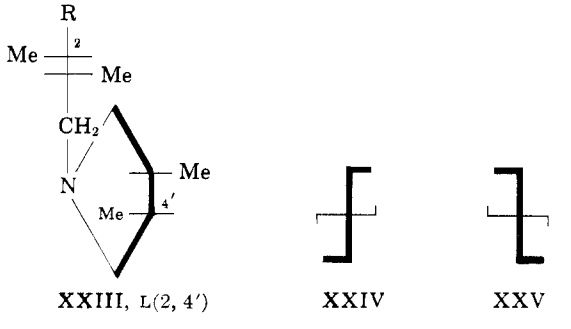


XIII, D(2,3) XIV, L(2,3) XV, D(2) XVI, L(2)

XVII XVIII XIX



XX, D(2,3,3′) XXI, L(2,3,4′) XXII, D(2,3′)



XXIII, L(2, 4′) XXIV XXV

stituted spirane can exist in two diastereomeric forms. The *meso-cis* diastereomer is conveniently depicted by the swastika-type projection formula,[9] XVII (Chart II), and the DL-*trans* diastereomer by the pair of formulas (XVIII, XIX). In order to prepare the *meso-cis* spirane, pyrrolidine was treated with *meso*-2,3-dimethylsuccinic anhydride,[10] X (Chart I). The preparation of the DL-*trans* spirane followed a parallel course.

In the first synthesis each of the monocyclic intermediates IV, V, VI, and VII had the DL-*erythro* configuration[11-13] (XIII, XIV). In the second synthesis each had the diastereomeric DL-*threo* configuration (XV, XVI).

The structure of the *trans* dimethylspirane bromide was confirmed by an independent preparation from pyrrolidine and DL-1,4-dibromo-2,3-dimethylbutane,[3d] and that of the *cis* isomer by a preparation from pyrrolidine and *meso*-1,4-dibromo-2,3-dimethylbutane.[3d]

trans/trans Tetramethyl spirane. The tetramethylspirane, IX (R = R′ = Me), can exist in four diastereomeric forms. All four have previously[3a,3b] been prepared. We have now demonstrated that the alternative synthesis described in our present article can be applied at least to preparation of the DL-*trans/trans* diastereomer[3a,3b,9] (XXIV, XXV).

By reaction of the racemic form of 3,4-dimethylpyrrolidine,[3c] (XI, XII) and of 2,3-dimethylsuccinic anhydride, we obtained an amidic acid, IV (R = R′ = Me), which is presumably a mixture of the

(9) For an explanation of the swastika-type projection formulas for spiranes, and of the double configurational prefixes such as "*trans/trans.*" See Ref. 3b.

(10) (a) W. A. Bone and C. H. G. Sprankling, *J. Chem. Soc.*, **75**, 839 (1899). For correction, see Ref. 3(b), footnotes 18 and 19. (b) P. E. Verkade and H. Hartman, *Rec. trav. chim.*, **52**, 945 (1933).

(11) The side chains in formulas XIII–XVI and XX–XXIII are depicted by the usual projection-formula conventions, *i. e.*, lateral groups in front of plane of depiction, and lower-numbered end of chain at top. The rings in formulas XX–XXIII are twisted so that they can be depicted by vertical perspective-formulas, with ring regarded as perpendicular to paper, and shaded edge to front. (*Note:* To produce formulas XX–XXIII, each ring may be twisted *either* clockwise or counterclockwise. Formulas for *cis*-ring stereoisomers would require additional orientation conventions, which need not be considered here, but are proposed in Ref. 13.)

(12) Each of the monocyclic dimethyl intermediates in this article can exist in four stereoisomeric forms (2 racemic pairs), as shown in formulas XIII–XVI. Although no official rules for naming such stereoisomers are available, they can conveniently be designated by systematic configurational prefixes, as indicated in Chart II. For example, the prefix "D(2,3)" for stereoisomer XIII signifies that the methyl groups at positions 2 and 3 are both to the *right* of the properly oriented projection-formula. The corresponding racemic form (XIII, XIV) would be "DL(2,3)". For further explanation, see Ref. 13. However, when only racemic forms need be considered, the more familiar *erythro*, *threo* terminology is adequate, and it has been employed for the dimethyl intermediates in the present article.

(13) For an explanation of systematic configurational prefixes, see "A New General System for the Naming of Stereoisomers", 1953, a pamphlet available from Chemical Abstracts Service, Ohio State University, Columbus 10, Ohio. The capital letter "A" when included in a systematic configurational prefix signifies *absolute* configuration.

two *threo/trans* diastereomers,[14] DL-XXII and DL-XXIII. This diastereomeric mixture without separation was carried through the methyl ester (V) and alkanol (VI) stages. The picrate of the alkanol appears to consist of a single pure diastereomer, DL-XXII.

The pure alkanol (regenerated from picrate) was converted in the usual manner to the bromobutyl hydrobromide (VII. HBr). This product on cyclization gave a single diastereomerically pure spirane bromide. This product was found to be identical with the previously reported[3a,3b] DL-*trans/trans* tetramethylspirane derivative (XXIV, XXV). The corresponding picrates were also identical.

In a partially completed attempt to prepare the optically active (+)-*trans/trans* spirane,[3a,3b] XXIV, the above synthesis was repeated using dextrorotatory dimethylpyrrolidine,[15] XI, in place of racemic. After several steps, the apparently homogeneous picrate of a dextrorotatory pyrrolidinealkanol (XXII or XXIII) was obtained.

Using *meso* dimethylsuccinic anhydride and racemic dimethylpyrrolidine, we have also prepared an *erythro/trans* diastereomer (presumably a mixture of DL-XX and DL-XXI) of the above *threo/trans* amidic acid, but have not examined the further reactions of this intermediate.

EXPERIMENTAL

All melting and boiling points have been corrected. Melting points were taken on the Köfler micro hot-stage unless otherwise noted. Microanalyses by the Micro-Tech Laboratories, Skokie, Ill., and by Mr. Charles K. Cross, Toronto.

NONMETHYLATED SERIES

4-Oxo-4-(1-pyrrolidinyl)-butyric acid. To a vigorously stirred solution of 25.0 g. of succinic anhydride in 200 ml. of absolute ether was gradually added a solution of 17.8 g. of pyrrolidine in 50 ml. of ether. After addition, the mixture was boiled for 1 hr.

The ethereal solution was decanted and the oily solid residue was dried, and recrystallized from ethyl acetate (charcoal), giving 29.2 g. of product, m.p. 105–108°. A second crop (2.3 g.) of the same m.p. was obtained. The combined product was again recrystallized, giving 25.8 g. (60%) of the nearly pure amidic acid, m.p. 106.5–108°.

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.18. Found: C, 55.44; H, 7.59; N, 7.93.

The compound is readily soluble in cold water, and causes sodium carbonate solution to effervesce. When excess pyrrolidine was used in the original reaction, the pyrrolidine salt of the amidic acid was obtained; it was an oil, and on acidification the above free amidic acid was liberated.

4-(1-Pyrrolidinyl)-butanol-1 and its picrate. The above amidic acid (26.3 g.) was esterified with diazomethane in the usual manner, giving 17.5 g. of a colorless liquid product, b.p. 161°/8 mm., d_{20} 1.120, n_D^{20} 1.4798, M_D 47.0 (theoretical 47.0). The ester was soluble in about 10 parts of water and gave no effervescence with sodium carbonate.

The methyl ester (17.0 g.) in 100 ml. of absolute ether was slowly added at 25° with stirring to a mixture of 8.0 g. of lithium aluminum hydride and 150 ml. of absolute ether (prestirred 4 hr. under reflux). After addition, the mixture was boiled 2 hr. more with stirring.

To destroy excess hydride a minimum volume of water was cautiously added at 0°. The inorganic precipitate was removed and the ethereal filtrate extracted with a small volume of dilute hydrochloric acid. The acidic extract was basified with sodium hydroxide, saturated with sodium chloride, and extracted throughly with ether. The dried ethereal extract on evaporation yielded 10.6 g. (81%) of the colorless, liquid pyrrolidinebutanol, b.p. 103–104°/7 mm., d_{20} 0.943, n_D^{20} 1.4705, M_D 42.4 (theor. 42.4); reported[7] b.p. 113°/12 mm.

The picrate was obtained by treatment with ethereal picric acid, and was recrystallized three times from butanol-1, giving long yellow needles of m.p. 97–98°.

Anal. Calcd. for $C_8H_{17}NO \cdot C_6H_3N_3O_7$: N, 15.05. Found: N, 14.97.

1-(4-Triphenylmethoxybutyl)-pyrrolidinium chloride. The above free pyrrolidinebutanol (0.47 g.) was treated with 0.92 g. of triphenylchloromethane in 5 ml. of anhydrous pyridine for 15–20 hr. at 25°. Ten drops of water were added and after 30 min. the solution was vacuum-distilled to dryness. The residue was triturated with 15 ml. of ether, giving 1.10 g. of product m.p. 170–184°, which after 2 recrystallizations from benzene showed a constant m.p. of 194.5–195.5°. The trityl group content was determined by the method of Valentin.[16]

Anal. Calcd. trityl groups per molecule: 1.00. Found: 0.85.

The compound was readily soluble in ethanol or butanone but sparingly soluble in water; it gave a positive test for chloride ion.

1-(4-Bromobutyl)-pyrrolidinium bromide and chloroplatinate. To 1.9 g. of the pyrrolidinebutanol in a borosilicate glass tube was added 4.7 ml. of aqueous hydrogen bromide (saturated at 0°), and the tube sealed and heated at 150° for 3 hr. The tube content was vacuum-distilled, giving a dark brown oil which was dried over potassium hydroxide *in vacuo*, giving 3.8 g. of crude, hygroscopic solid hydrobromide.

A sample of the hydrobromide in water was treated with warm aqueous ammonium chloroplatinate, giving a bright red crystalline precipitate, which after two recrystallizations from water melted at 132.5–135°; reported[4] m.p. 133–134°.

When the above bromobutyl bromide was treated with sodium carbonate in an attempt to prepare the free bromobutylpyrrolidine, spontaneous cyclization to the spirane bromide took place; the spirane bromide was identified by conversion to the picrate (see below).

Spiro-(1,1')-bipyrrolidinium bromide and picrate. (*A*) *From the bromobutyl pyrrolidine.* The above bromobutyl bromide (0.8 g.) was dissolved in 41 ml. of 0.069*M* sodium hydroxide, and the solution heated at 90–100° for 30 min. The product was isolated by a procedure like that of von

(14) Each of the monocyclic tetramethyl intermediates in this article can exist in 12 stereoisomeric forms (6 racemic pairs). In Chart II only four of the six diastereomers are depicted (formulas XX–XXIII); each formula depicts one of two possible enantiomers. Since no official rules for naming such stereoisomers are available, we have in this article employed systematic configurational prefixes as indicated in Chart II. For example the prefix "D(2,3,3')" for stereoisomer XX signifies that the methyl groups at positions 2,3, and 3' are to the *right* of the properly oriented projection-perspective formula, and methyl group 4' to the left. The prefix "DL(2,3,3')" would represent the corresponding racemic form. For further explanation, see Ref. 13.

(15) The (+)-3,4-dimethylpyrrolidine has previously been shown to have the absolute configuration XI (see Ref. 3b). The absolute configurations of the optically active compounds now reported can be deduced from that of the dimethylpyrrolidine starting material.

(16) F. Valentin, *Chem. Zentr.*, 103, I, 2160 (1932).

Braun,[4] giving 0.56 g. (97%) of the hygroscopic spirane bromide.

To the spirane bromide (0.28 g.) in 5 ml. of water was added 1 mole of saturated aqueous picric acid, giving 0.16 g. (34% based on spirane bromide) of the spirane picrate, long bright yellow needles, m.p. 259–261°. The melting point was unchanged on recrystallization from 95% ethanol.

Anal. Calcd. for $C_8H_{16}N \cdot C_6H_2N_3O_7$: C, 47.45; H, 5.12; N, 15.81. Found: C, 48.17; H, 5.34; N, 15.69.

(*B*) *From dibromobutane.* To 10.0 g. of 1,4-dibromobutane was added 3.27 g. of pyrrolidine and 62 ml. of 0.74*M* sodium hydroxide, and the mixture refluxed for 1 hr. A 4.6 g. (49%) yield of the above spirane bromide was obtained. The spirane picrate obtained from this bromide was identical with that above; a mixed m.p. was not depressed.

ERYTHRO OR CIS-DIMETHYL SERIES

DL-*Erythro-2,3-dimethyl-4-oxo-4-(1-pyrrolidinyl)-butyric acid.* A well stirred mixture of 12.0 g. of *meso*-2,3-dimethylsuccinic anhydride[10] and 8.04 g. of pyrrolidine in 150 ml. of absolute ether was boiled under reflux for 2 hr. The total residue after vacuum-distillation was dissolved in sodium chloride-saturated 0.5*M* hydrochloric acid (300 ml.) and the product extracted with chloroform (4 × 100 ml.). The residue from evaporation of the chloroform extract was dried, giving 18.6 g. (99%) of product melting at 128–132°. Recrystallization from ethyl acetate (charcoal) gave 9.4 g. of colorless crystals, m.p. 130–132.5°—or 12.8 g. including the second and third crops which were nearly as pure. A sample recrystallized repeatedly from ethyl acetate and from benzene melted at 132–134°.

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 59.79; H, 8.59; N, 7.17.

The compound is soluble in butanone or water, and insoluble in hot petroleum ether.

DL-*Erythro-2,3-dimethyl-4-(1-pyrrolidinyl)-butanol-1.* The above oxobutyric acid (11.3 g.) on treatment with ethereal diazomethane gave 10.7 g. (90%) of the colorless, liquid methyl ester, b.p. 123–124°/1 mm., d_{20} 1.060, n_D^{20} 1.4728, M_D 56.5 (theoretical 56.2).

Reduction of the methyl ester (9.4 g) with lithium aluminum hydride by the above procedure gave 5.8 g. (78%) of the colorless liquid pyrrolidinebutanol, b.p. 81–83°/0.8 mm., d_{20} 0.923, n_D^{20} 1.4679, M_D 51.6 (theoretical 51.7). The product was characterized by conversion to the dimethylspirobipyrrolidinium picrate and to the bromobutyl chloroaurate (see below).

The pyrrolidinebutanol gave a picrate of m.p. 71.5–75° and a trityl ether hydrochloride of m.p. 169–173°, but these derivatives were not further characterized. The pyrrolidinebutanol hydrobromide was very hygroscopic.

DL-*Erythro-1-bromo-2,3-dimethyl-4-(1-pyrrolidinyl)-butane hydrobromide and chloroaurate.* The dimethylpyrrolidinebutanol (1.0 ml.) was treated with saturated aqueous hydrogen bromide in a sealed tube (100°, 4 hr.) in a manner similar to that described above.

The tube contents on evaporation in vacuo gave 1.79 g. of gray-brown solid residue, m.p. 130–148°. This material was recrystallized from 4-methylpentanone-2 (charcoal), giving (including second crop) 0.98 g. (57%) of colorless transparent plates, m.p. 138–144°. The melting behavior was not changed by further recrystallization.

To 0.15 g. of this hydrobromide was added aqueous chloroauric acid (1 mole), giving 0.29 g. of rust-colored precipitate (presumably a hydrate), m.p. 99–120°. The melting point of the product dropped to 78–80° on recrystallization from ethanol, and increased to 79.5–82° on 3 additional recrystallizations from ethanol. The resulting product was apparently not solvated.

Anal. Calcd. for $C_{10}H_{20}NBr \cdot HAuCl_4$: Au, 34.34. Found: Au, 34.41.

meso-cis-3,4-Dimethylspiro-(1,1')-bipyrrolidinium bromide. (*A*) *From dibromodimethylbutane.* A mixture of 3.0 g. of *meso*-1,4-dibromo-2,3-dimethylbutane,[3d] 1.0 ml. of pyrrolidine, and excess sodium hydroxide was refluxed for 90 min. The product was isolated by the procedure (*B*) below, giving 2.13 g. (76%) of spirane bromide melting at 295–297° (capillary, decomp.). After repeated recrystallization from acetone, hygroscopic crystals of constant m.p. 295–296.5° (sealed capillary tube, decomp.) were obtained, still not entirely pure.

Anal. Calcd. for $C_{10}H_{20}NBr$: C, 51.28; H, 8.61; N, 5.98. Found: C, 49.05; H, 9.10; N, 5.76.

(*B*) *From bromobutyl bromide.* To the bromobutyl bromide (0.57 g.) was added 7.2 ml. of 0.255*M* sodium hydroxide, and the two phase mixture refluxed until clear (1 hr.). The clear solution at 0° was treated with 10 ml. of 10*M* potassium hydroxide solution, and extracted with chloroform (3 × 10 ml.). Addition of ether to the separated, dried chloroform extract precipitated 0.19 g. (45%) of the hygroscopic spirane bromide, m.p. 294–298° (cap., decomp.), identical with the above product. The product was characterized as its chloroaurate and picrate (see below).

meso-cis-3,4-Dimethylspiro-(1,1')-bipyrrolidinium picrate. A concentrated aqueous solution of the spirane bromide (prepared from dibromodimethylbutane) was added to *M*/5 aqueous triethanolamine picrate, giving bright yellow needles, m.p. 124–125.5°.

Anal. Calcd. for $C_{10}H_{20}N \cdot C_6H_2N_3O_7$: C, 50.24; H, 5.80. Found: C, 50.66; H, 5.77.

When spirane bromide prepared from the bromobutyl bromide was used, the picrate melted at 122–125.5°, and after recrystallization from 95% ethanol, at 124.5–126°. A mixed melting point with the above picrate was not depressed.

meso-cis-3,4-Dimethylspiro(1,1')-bipyrrolidinium chloroaurate. The spirane bromide (100 mg. prepared from bromobutyl bromide) in water was stirred for 30 min. with excess freshly precipitated and washed silver chloride. After removal of silver salts by filtration, the filtrate was evaporated to give the crystalline, hygroscopic chloride. This chloride on treatment with aqueous chloroauric acid tetrahydrate gave a precipitate, which was recrystallized from 95% ethanol, giving broad, bright yellow plates, m.p. 68–69°.

Anal. Calcd. for $C_{10}H_{20}NAuCl_4$: Au, 39.97. Found: Au, 39.85.

The spirane bromide prepared from dibromodimethylbutane gave a chloroaurate which was shown by melting point and mixed melting point to be identical with the above.

THREO OR TRANS DIMETHYL SERIES

DL-*Threo-2,3-dimethyl-4-oxo-4-(1-pyrrolidinyl)-butyric acid.* Racemic 2,3-dimethylsuccinic anhydride[10] (11.2 g.) was treated as for the *meso* anhydride (see above). However, the ether extract residue was dissolved in 200 ml. of chloroform, and the solution extracted with 1*M* hydrochloric acid (2 × 50 ml.). The combined aqueous extract was then saturated with sodium chloride and extracted with chloroform (3 × 50 ml.). The combined chloroform solutions (350 ml.) on vacuum-distillation gave a solid residue which was recrystallized from ethyl acetate (charcoal), giving 12.0 g. (70%, including second and third crops) of product melting at 104–107°. The melting behavior was unchanged by further recrystallization from ethyl acetate or benzene-petroleum ether.

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.12; H, 8.55; N, 6.92.

DL-*Threo-2,3-dimethyl-4-(1-pyrrolidinyl)-butanol-1.* The above oxobutyric acid (7.7 g.) with ethereal diazomethane gave 6.8 g. (83%) of the colorless, liquid methyl ester, b.p. 174–175°/12 mm., d_{20} 1.058, n_D^{20} 1.4724, M_D 56.5 (theoretical 56.2).

On reduction of the ester (5.7 g.) as for the *erythro* diastereomer, 3.6 g. (79% based on ester) of the colorless, liquid pyrrolidinebutanol were obtained, b.p. 134–135°/12 mm., d_{20} 0.929, n_D^{20} 1.4712, M_D 51.5 (theoretical 51.7). The product

was characterized by conversion to the bromobutyl chloroaurate (see below). A picrate of m.p. 83–88° and a crude trityl ether hydrochloride of m.p. 130–148° were also obtained, but were not fully characterized.

DL-*Threo-1-bromo-2,3-dimethyl-4-(1-pyrrolidinyl)-butane hydrobromide and chloroaurate.* From 2.0 ml. of the pyrrolidinebutanol by the above (*erythro*) procedure there was obtained 3.33 g. of crude gray-brown product, m.p. 133–142°. This material was twice recrystallized from 4-methylpentanone-2 (charcoal), giving 1.2 g. (36%) of colorless flakes, m.p. 130–137°. The melting point was unchanged by further recrystallization. The crystals were readily soluble in ethanol, and insoluble in benzene.

The hydrobromide was converted to the chloroaurate by the above (*erythro*) procedure. The crude product (presumably hydrated) melted at 131–149°, but after recrystallization from ethanol, pure deep red crystals of m.p. 97–99° were obtained.

Anal. Calcd. for $C_{10}H_{20}NBr \cdot HAuCl_4$: Au, 34.34. Found: Au, 34.44.

DL-*Trans-3,4-dimethylspiro-(1,1')-bipyrrolidinium bromide.* (*A*) *From dibromodimethylbutane.* From DL-1,4-dibromo-2,3-dimethylbutane[3d] treated as for the *meso* epimer (see above) there was obtained 5.2 g. (68%) of crude product, m.p. 264–268°. After recrystallization from ethanol-butanone (1:8) there was obtained (including second crop) 4.1 g. of colorless crystals, m.p. 267–269° (sealed capillary). The product was hygroscopic, but less so than its *meso* epimer, and melted without decomposing.

Anal. Calcd. for $C_{10}H_{20}NBr$: C, 51.28; H, 8.61; N, 5.98; Br, 34.13. Found: C, 51.44; H, 8.60; N, 5.74; Br, 34.64.

A picrate of m.p. 113–114.5° was obtained, but was not fully characterized.

(*B*) *From the bromobutyl bromide.* The *threo* bromobutyl bromide (0.5 g.) was cyclized by the above (*erythro*) procedure, but using a reflux time of only 10 min. On isolation, 0.23 g. (63%) of product melting at 261–265° was obtained, and shown to be identical with the product (A) above.

DL-*Trans-3,4-dimethylspiro-(1,1')-bipyrrolidinium chloroaurate.* The spirane bromide (prepared from bromobutyl bromide) was treated successively with silver chloride and chloroauric acid (see above *erythro* procedure). From the hygroscopic chloride a crude chloroaurate of m.p. 94–97° was obtained, and after three recrystallizations from ethanol it gave bright yellow plates of m.p. 97–98°.

Anal. Calcd. for $C_{10}H_{20}NAuCl_4$: Au, 39.97. Found: Au, 39.78.

The spirane bromide prepared from dibromodimethylbutane gave a chloroaurate which was shown by melting point and mixed melting point to be identical with the above.

TETRAMETHYL SERIES

2,3-Dimethyl-4-oxo-4-(3',4'-dimethyl-1'-pyrrolidinyl)-butyric acid (mixture of DL*(2,3,3')diastereomer, XX, and* DL *(2,3,4') diastereomer, XXI).* Treatment of DL-3,4-dimethylpyrrolidine[3c] with *meso*-2,3-dimethylsuccinic anhydride[10] by the same procedure used for treatment of pyrrolidine itself (see above) gave 5.3 g. of crude mixed diastereomers, m.p. 115–122°. After several recrystallizations from benzene, crystals of m.p. 142–147° were obtained. Apparently the purified material still contains both of the *erythro/trans* diastereomers, but the ratio is not known.

Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.52; H, 8.72; N, 5.93.

2,3-Dimethyl-4-oxo-4-(3',4'-dimethyl-1'-pyrrolidinyl)-butyric acid (mixture of DL*(2,3')diastereomer, XXII, and* DL*(2,4')diastereomer, XXIII).* The DL-3,4-dimethylpyrrolidine[3c] (2.5 g.) by treatment with DL-2,3-dimethylsuccinic anhydride[10] (see above *erythro* dimethyl oxobutyric acid procedure) gave a residue from the ether evaporation which was dissolved in chloroform (100 ml.), and the solution extracted with 1*M* hydrochloric acid and then with water (15 ml.; 10 ml.). On evaporation of the dried chloroform phase, 5.4 g. (97%) of crystals melting at 92–105° was obtained.

Anal. Calcd. for $C_{12}H_{21}NO_3$: N, 6.16. Found: N, 6.12.

The product, presumably a mixture of the two possible *threo/trans* diastereomers, XXII and XXIII, was readily soluble in ether and slightly soluble in water.

2,3-Dimethyl-4-(3',4'-dimethyl-1'-pyrrolidinyl)-butanol-1 picrate (single pure diastereomer DL*(2,3'), XXII.* The above mixture of *threo/trans* diastereomeric acids (5.3 g.) with diazomethane gave 4.8 g. (85%) of colorless liquid ester (presumably a diastereomeric mixture), b.p. 133–135°/2 mm., d_{20} 1.033, n_D^{20} 1.4651, M_D 64.6 (theoretical 65.5).

This ester (4.4 g.) on lithium aluminum hydride reduction gave 3.1 g. (87%) of colorless liquid pyrrolidinealkanol (presumably a diastereomeric mixture), b.p. 101–102°/2 mm.

By treatment of 2.92 g. of this pyrrolidinealkanol with ethanolic picric acid (3.34 g.), a picrate was obtained, and recrystallized four times from benzene, giving 2.9 g. of pale yellow crystals, m.p. 115–117°.

Anal. Calcd. for $C_{12}H_{25}NO \cdot C_6H_3N_3O_7$: C, 50.48; H, 6.59; N, 13.08. Found: C, 51.21; H, 6.21; N, 12.89.

This picrate is believed to consist of a single pure diastereomer, DL-XXII.

A 2.8 g. portion of the picrate in dilute aqueous hydrogen chloride was extracted with benzene, and the aqueous phase basified, salt-saturated, and extracted with ether. From the ethereal extract was obtained 0.94 g. (74%) of regenerated free pyrrolidinealkanol, b.p. 110–112°/4 mm., d_{20} 0.905, n_D^{20} 1.4595, M_D 60.3 (theoretical 60.9).

Dextrorotatory 2,3-dimethyl-4-(3',4'-dimethyl-1'-pyrrolidinyl)-butanol-1 picrate (single pure diastereomer D*(2,3')A, XXII).* When the above amidic acid preparation was repeated with dextrorotatory dimethylpyrrolidine[3a,b] and racemic dimethylsuccinic anhydride,[10] an amidic acid mixture with $[\alpha]_D^{23}$ +16.3° (ether, *c* 1) was obtained. With diazomethane, a methyl ester mixture with $[\alpha]_D^{25}$ +8.7° (ether, *c* 1) resulted. On reduction, a pyrrolidinealkanol mixture with $[\alpha]_D^{26}$ 5.7° (benzene, *c* 1) resulted. The picrate of this product after repeated recrystallizations from benzene attained a constant m.p. of 114.5°–117°. A mixed melting point with the above racemic picrate was not depressed.

This picrate appears to consist of a single pure diastereomer and is probably one of the active forms of the above racemic picrate.

1-Bromo-2,3-dimethyl-4-(3',4'-dimethyl-1'-pyrrolidinyl)-butane hydrobromide (single pure diastereomer DL*(2,3'), XXII).* The pure liquid racemic pyrrolidinealkanol (regenerated from picrate) was treated by the above (*meso* dimethyl) procedure, giving 0.85 g. of a light-brown powder, m.p. 143–148° (sintered 125°). A sample recrystallized twice from 4-methylbutanone-2 (charcoal) gave colorless crystals of m.p. 152–165°. The product was characterized by conversion to the spirane bromide and picrate (see below).

DL-*trans/trans-3,4,3',4'-Tetramethylspiro-(1,1')-bipyrrolidinium bromide and picrate.* The above bromobutyl bromide (0.27 g., m.p. 143–148°) was mixed with 3.98 ml. of 0.205*M* sodium hydroxide, and the turbid mixture refluxed for 30 min. From the mixture was isolated by the above procedure 0.093 g. of product melting at 314° (cap., decomp.). Recrystallization from butanone gave the DL-*trans/trans* spirane bromide, m.p. 318° (cap., decomp.); reported[3a,b] m.p. 323–324° (cap., decomp.).

A sample was treated with triethanolamine picrate, giving after recrystallization from aqueous ethanol long yellow needles of the DL-*trans/trans* spirane picrate, m.p. 130–135.5°; reported[3a,b] m.p. 134.5–136°.

Acknowledgment. We are indebted to the National Research Council and to the Advisory Committee on Scientific Research for generous grants in support of this research.

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