mg. of Adams catalyst, at 23.3° and 627 mm. required 0.00103 mole (103%) of hydrogen and produced 60 mg. of alloisoleucine. The formation of alloisoleucine on hydrogenation was established by a comparison of the product with an authentic sample of alloisoleucine by paper chromatography and by a comparison of its infrared spectrum with those of isoleucine and alloisoleucine.

2-Benzamido-3-methyl-4-pentynoic Acid.—2-Amino-3-methylpentynoic acid was benzoylated according to the method of Steiger[14] to give the benzoyl derivative, m.p. 127°.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.63. Found: C, 67.50; H, 5.63.

Microbiological Tests.—Propargylglycine and 2-amino-3-methyl-4-pentynoic acid were tested for their ability to inhibit the growth of *E. coli*, ATCC 9723, and *S. cerevisiae*, strain 139, according to the method previously described.[6]

By these tests 2–3 μg. of propargylglycine per 7.5 ml. of medium inhibited the growth of yeast to 50% of normal; 14 μg. of 2-amino-3-methyl-4-pentynoic acid was required to give 50% inhibition of yeast growth. The growth of *E. coli* was inhibited to 50% of normal by 130 mg./7.2 ml. of propargylglycine and 50 μg./7.2 ml. of 2-amino-3-methyl-4-pentynoic acid. The acetylenic analogs of amino acids were more potent yeast growth inhibitors than the ethylenic analogs, allylglycine and methallylglycine. In the inhibition of the growth of *E. coli*, the ethylenic analogs were more potent than the acetylenic amino acids. Propargylglycine is the most potent yeast growth inhibitor so far prepared in our laboratory.

The relationship of the acetylenic amino acids to amino acid metabolism in these microörganisms will be reported elsewhere.

Acknowledgment.—The authors wish to thank Mrs. Ann E. Johnson and Miss Virginia Peck for the microbiological determinations.

Tallahassee, Florida

[Contribution from the Department of Chemistry, University of Toronto]

Preparation and Properties of the Epimeric 2,3-Dimethylbutane-1,4-diols and Some Derivatives

By G. E. McCasland and Stephen Proskow[1,2]

Received February 12, 1954

DL- and *meso*-2,3-dimethylbutane-1,4-diol were prepared by the lithium aluminum hydride reduction of the corresponding dimethylsuccinic acid diethyl esters. The diols are colorless, viscous oils and were characterized by conversion to their crystalline di-*p*-nitrobenzoates and ditrityl ethers. The diols were also converted to the corresponding dibromides. The colorless, liquid dibromides were characterized by conversion to their di-*p*-nitrophenyl ethers, and also by reaction with pyrrolidine to give the dimethylspirobipyrrolidinium bromides, picrates and chloroaurates.

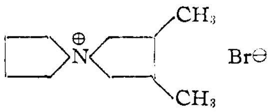
To facilitate the solution of a more fundamental problem, still in progress, we have prepared *meso*- and DL-2,3-dimethylbutane-1,4-diol and the corresponding dibromides. Each diol and dibromide has been characterized by the preparation of a number of solid derivatives.

Synthetic Route.—The key intermediate needed for preparation of the *meso*-diol was *meso*-2,3-dimethylsuccinic acid.[3] Since direct reduction of the *meso*-diacid with lithium aluminum hydride[4] gave us a poor yield of diol, the *meso* diethyl ester[5] was prepared; on reduction it gave a 56% yield of *meso*-diol. The diol obtained was a colorless viscous liquid, readily soluble in water and miscible with ether, whose molecular refraction was in agreement with the theoretical value.

The *meso*-diol was characterized by conversion to its di-*p*-nitrobenzoate and ditrityl ether,[6] both sharp-melting crystalline derivatives.

On treatment with anhydrous hydrogen bromide, the *meso*-diol gave the colorless, liquid *meso*-dibromide. The dibromide differs from the diol by its much higher density (1.6 *vs.* 1.0), by its lower viscosity and boiling point, and by its much lower solubility in water. The molecular refraction of the dibromide was in agreement with theory.

The *meso*-dibromide was first characterized by reaction with sodium nitrophenoxide to give the crystalline *meso*-di-*p*-nitrophenyl ether.[7] Since the yield of this reaction was only 25%, and the conditions somewhat drastic, the dibromide was characterized also by reaction with pyrrolidine, to give the *meso*-spiroquaternaryammonium bromide, A. This reaction which proceeds under mild conditions gave a 60% yield. This spirane bromide was further characterized by converting it to its picrate and chloroaurate.[8]



A

The work on the racemic diol and dibromide and their derivatives (see Experimental Section) was closely parallel to that on the *meso* epimers.

---

[1] Nadine Phillips Fellow, 1953–1954.

[2] From a Ph.D. Thesis to be submitted by Stephen Proskow to the Graduate School, University of Toronto.

[3] W. A. Bone and C. H. G. Sprankling, *J. Chem. Soc.*, **75**, 839 (1899). In this reference the *meso*-diacid (m.p. 209°) is incorrectly called "*trans*."

[4] (a) "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, Chap. 10; (b) R. F. Nystrom and W. G. Brown, This Journal, **69**, 2548 (1947).

[5] N. Zelinsky and S. Krapivin, *Ber.*, **22**, 646 (1889). In this reference the DL-diacid (m.p. 129°) is incorrectly called "maleinoid." These authors claim that the esterification of either pure isomer of dimethylsuccinic acid with ethanol and mineral acid causes partial isomerization and that the silver salt method does not.

[6] (a) "Advances in Carbohydrate Chemistry," Vol. 3, Academic Press, Inc., New York, N. Y., 1948, Chap. IV; (b) F. Valentin, *Chem. Zentr.*, **103**, I, 2160 (1932); (c) B. Helferich, *et al.*, *Ber.*, **56**, 766 (1923).

[7] Similar preparations of diaryl ethers from dibromides have been described by (a) A. Müller, *Monatsh.*, **49**, 27 (1928); (b) A. Wedige, *J. prakt. Chem.*, [2] **24**, 246 (1881); (c) E. Wagner, *ibid.*, [2] **27**, 201 (1883).

[8] In order to prove that our synthetic route did not cause any structural rearrangement, the spirane derivatives (both *meso* and DL) also were prepared by an independent route, namely: the substituted succinamic acid obtained by reaction of 2,3-dimethylsuccinic anhydride with pyrrolidine was reduced and cyclized. Details of the spirane work will be given in a subsequent communication.

Epimerization and Epimeric Purity.—It is believed that all of the crystalline derivatives here reported consist of a single pure diastereomer, since the melting points are reasonably sharp and the DL and *meso* epimers have decidedly different melting points. It is much more difficult, however, to detect epimeric impurity in the liquid diethyl esters, diols or dibromides, since in each case the pure DL and *meso* epimers would have the same calculated analysis, and very nearly the same boiling point, density and refractive index.

It is known[3] that *meso*-(or DL)-2,3-dimethylsuccinic acid is rather easily epimerized, to give an equilibrium mixture of *meso* and DL compounds; the *meso*-diacid seems to be more stable than DL. The corresponding anhydrides undergo epimerization even more easily[3]; in this case the DL epimer has the greater stability. Probably most other carbonyl derivatives of these compounds, including the diethyl esters, show some steric instability.

For these reasons we have devoted most of our efforts to the preparation of crystalline derivatives from which it should be possible to prepare sterically pure, stable diols (and from them the dibromides) when needed. Nevertheless, it is evident from the yields of pure derivatives obtained (60–80%) that even our non-regenerated *meso*- and DL-diols contained less than 40% of epimeric impurity, and probably much less. The dibromides prepared from *non*-regenerated diols also gave pure derivatives in about 60% yield, and thus were no doubt of comparable purity. Samples of the *meso*- and DL-diols prepared by regeneration from their di-*p*-nitrobenzoates showed no important differences in properties from the crude products.

The DL-dibromide gave a small amount of *meso*-di-*p*-nitrophenyl ether along with the DL derivative. This might be due to epimeric impurity in the sample of dibromide used; however, the conditions of this reaction are rather drastic (140°, five hours) and may have caused some isomerization.

It is interesting to note that all of the solid acyclic *meso* derivatives here reported have decidedly higher melting points than the corresponding racemic derivatives, perhaps because of the ease with which the *meso* molecules can assume centrosymmetric, or almost centrosymmetric, conformations.

Experimental

All melting and boiling points are corrected. Melting points were taken on the Köfler microblock unless noted otherwise; microanalyses for carbon and hydrogen by Micro-Tech Laboratories, Skokie, Illinois.

meso Series

***meso*-2,3-Dimethylbutane-1,4-diol.** (A) **From Diester.**—Finely powdered lithium aluminum hydride (6.1 g.) was stirred for four hours with 150 ml. of boiling absolute ether under reflux. To this vigorously stirred mixture at 25° was then slowly added a solution of 21.2 g. of diethyl *meso*-2,3-dimethylsuccinate[3,5] in 100 ml. of absolute ether. After the addition, the mixture was boiled with mechanical stirring for five hours longer.

The mixture was then cooled to 0° and excess hydride destroyed by cautious addition of a minimum volume of water. The crystalline inorganic precipitate was removed by filtration and washed repeatedly with ether. The combined ethereal filtrate was washed with 50 ml. of saturated sodium carbonate solution and then with 20 ml. of water. After drying, the separated ethereal phase was evaporated, and the liquid residue distilled *in vacuo*, giving 6.90 g. (56%) of the diol as a colorless, very viscous liquid, b.p. 127–128° (9 mm.), d_{20} 0.970, n^{20}_{D} 1.4539, n^{25}_{D} 1.4525, M_D 33.0 (theor. 33.0). For analysis the diol was converted to its di-*p*-nitrobenzoate and ditrityl ether (see below).

(B) **From Diacid.**—Reduction of the free diacid gives a lower yield of diol. A 10.0-g. portion of the *meso*-diacid[3] in a Soxhlet thimble was extracted (seven hours) into a solution of 8.0 g. of the hydride in 300 ml. of absolute ether (*cf.* procedure of Nystrom and Brown[4b]). The crude reduction product on distillation gave a 1.70 g. forerun boiling at 78–80° (752 mm.), d_{20} 0.828, presumably consisting of *meso*-3,4-dimethyltetrahydrofuran. The diol itself was then collected at 137–138° (17 mm.),[9] d_{20} 0.970, n^{20}_{D} 1.4541, n^{25}_{D} 1.4530, M_D 33.0 (theor. 33.0). The yield was 2.16 g. (27%).

(C) **From Di-*p*-nitrobenzoate.**—The diol regenerated from its nitrobenzoate (see below) had essentially the same properties given above.

***meso*-2,3-Dimethylbutane-1,4-diol Di-*p*-nitrobenzoate.** (A) **From Reduction Mixture.**—Ten grams of the *meso*-diacid was reduced as described above. After destruction of excess hydride with water, the inorganic precipitate was brought into solution by adding about 500 ml. of 15% cold sulfuric acid to the mixture. The separated ethereal phase was evaporated and the residue added to the aqueous phase.

The aqueous phase was then made slightly basic by addition of 10% sodium hydroxide, and the precipitate removed by filtration. After washing the precipitate with water, the combined filtrate was concentrated to about 300 ml. *in vacuo*. To this was added 55 g. of *p*-nitrobenzoyl chloride and 175 ml. of 10% sodium hydroxide, and the mixture shaken mechanically for five hours. The precipitate of crude di-*p*-nitrobenzoate was collected and dried; weight 8.5 g. (30%), m.p. 187–191°. The product was recrystallized once from benzene, giving 4.5 g. of pale yellow needles, m.p. 194–196°.

Anal. Calcd. for $C_{20}H_{20}N_2O_8$: C, 57.69; H, 4.84. Found: C, 58.02; H, 5.04.

(B) **From Purified Diol.**—A sample of purified *meso*-diol (3.5 g.) esterified as above gave 8.03 g. (65%) of product, m.p. 193.5–195.5°. After recrystallization from butanone the product melted at 195–196°.

(C) **By Pyridine Method.**—Finely powdered *p*-nitrobenzoyl chloride (0.70 g.) was added in portions, with vigorous shaking, to a solution of 0.2 g. of *meso*-diol in 2.5 ml. of dry pyridine. After the addition, the mixture was allowed to stand overnight. Ten drops of water were added and 0.5 hour later the paste was poured into 15 ml. of water. The precipitate was collected, washed, stirred one hour with 7 ml. of 5% sodium carbonate solution, filtered, washed and dried, giving 0.70 g. (99%) of crude product, m.p. 193.5–197°. This was recrystallized once from butanone, giving 0.58 g. of pure *meso*-di-*p*-nitrobenzoate, m.p. 195–196°.

Regeneration of the *meso*-Diol from Its Di-*p*-nitrobenzoate.—To a portion (4.87 g.) of the pure *meso*-di-*p*-nitrobenzoate was added 76 ml. of a 0.465 *M* solution of sodium hydroxide in 95% ethanol. The mixture was refluxed on the steam-bath for 0.5 hour, cooled to 0°, filtered, and the precipitate washed several times with small portions of ice-cooled absolute ethanol. The combined filtrate was evaporated to a small volume *in vacuo*, the residue dissolved in 25 ml. of water and the clear solution saturated with sodium chloride. It was then continuously extracted with ether for 20 hours, and the pale yellow ether extract dried. After evaporating the ether, the product was distilled *in vacuo*, giving 0.80 g. (58%) of regenerated diol as a colorless, very viscous liquid, b.p. 124–125° (8 mm.), d_{20} 0.970, n^{20}_{D} 1.4536, n^{25}_{D} 1.4519.

***meso*-2,3-Dimethylbutane-1,4-diol Bistriphenylmethyl Ether.**—The tritylation procedure of Helferich, *et al.*,[6c] was modified as follows. A clear solution of 3.0 g. of dry *meso*-diol and 17.6 g. of triphenylchloromethane in 50 ml. of dry pyridine was heated on the steam-bath for three hours. Benzene was used as extracting solvent. The benzene extract on vacuum distillation gave a pale yellow crystalline

---

[9] It is interesting to note that in 1952 H. J. Bernstein predicted from purely theoretical considerations that 2,3-dimethylbutane-1,4-diol (configuration not specified) would when discovered be found to have a b.p. of 258° (760 mm.): see THIS JOURNAL, **74**, 2675 (1952). We find that the actual b.p. of the *meso*-diol at 760 mm. is about 239°. The DL-isomer has almost the same b.p.

residue. This residue was recrystallized from ethanol-benzene (charcoal). Three crops of crystals were collected; combined weight 13.1 g.

The product was recrystallized twice from butanone, giving 9.2 g. (61%) of the *meso*-ditrityl ether, m.p. 177.5-179.5° (cap., cor.). The product is easily soluble in benzene or chloroform, very slightly soluble in hot absolute ethanol and insoluble in water or petroleum ether.

Analysis by the method of Valentin[6b] showed 2.02 trityl groups per molecule (theor. 2.00).

***meso*-1,4-Dibromo-2,3-dimethylbutane.** **(A) From Diol and Anhydrous Hydrogen Bromide.**—A stream of dry commercial hydrogen bromide was passed through a 16.4-g. portion of the *meso*-diol at 100° for five hours. To the resulting mixture water and ether (75 ml., 150 ml.) were added. The separated ether phase was washed successively with ice-cold 80% sulfuric acid, water, 10% sodium carbonate and twice with water. After drying, the ether phase was evaporated and the residue distilled *in vacuo*, giving 28.5 g. (84%) of the dibromide, a colorless liquid, b.p. 106-108° (22 mm.), d_{20} 1.620, n^{20}D 1.5128, n^{25}D 1.5101, MD 45.3 (theor. 45.4). For analysis, the dibromide was converted to its diaryl ether and spirobipyrrolidinium[8] derivatives.

(B) From Diol and Aqueous Hydrogen Bromide.—The *meso*-diol (9.0 g.) was heated with a mixture of 20.7 ml. of 8.7 M hydrobromic acid and 13.4 ml. of 18 M sulfuric acid. The product was isolated as described above. It was a colorless liquid, b.p. 94-96° (15 mm.), d_{20} 1.620, n^{20}D 1.5120, n^{25}D 1.5093, MD 45.2 (theor. 45.4). The yield was 8.5 g. (46%).

(C).—A sample of *meso*-dibromide prepared from diol regenerated from its di-*p*-nitrobenzoate had n^{20}D 1.5119, n^{25}D 1.5095, and thus was apparently identical with the product from procedures A and B.

***meso*-2,3-Dimethylbutane-1,4-diol Di-*p*-nitrophenyl Ether.**—Sodium metal (0.11 g.) was dissolved in 2 ml. of absolute ethanol contained in a Pyrex tube. A solution of 0.71 g. of *p*-nitrophenol in 8 ml. of absolute ethanol, and 0.50 g. of the *meso*-dibromide, were then added, and the sealed tube was heated at 140° for 5 hours.

After cooling, the tube contents were filtered, washed with cold 95% ethanol, thoroughly with water, and dried, giving 0.34 g. (47%) of crude product, m.p. 158-175°. After three recrystallizations from butanone (charcoal), pure pale yellow-brown crystals of m.p. 177-178° were obtained. The combined yield, after concentrating the combined mother liquors for additional pure product, was 0.18 g. (25%).

The compound is very slightly soluble in hot benzene or hot ethanol, and insoluble in water.

Anal. Calcd. for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.99; H, 5.46; N, 7.75.

Racemic Series

DL-2,3-Dimethylbutane-1,4-diol.—Diethyl DL-2,3-dimethylsuccinate[3,5] (42.5 g.) was reduced by the same procedure (see above) used for the *meso* diethyl ester, giving 12.8 g. (52%) of the DL-diol, a colorless, very viscous liquid, b.p. 124-125° (7 mm.), d_{20} 0.974, n^{20}D 1.4555, n^{25}D 1.4538, MD 33.0 (theor. 33.0). For analysis the diol was converted to its di-*p*-nitrobenzoate and its ditrityl ether.

DL-2,3-Dimethylbutane-1,4-diol Di-*p*-nitrobenzoate.—The pure DL-diol (6.04 g.) was acylated by the pyridine method (see above) used for the *meso*-diol, giving 20.7 g. (98%) of the crude product, m.p. 142-146° (a small portion of the melt remained crystalline). This material was recrystallized thrice from benzene, giving 6.63 g. of DL-di-*p*-nitrobenzoate, pale yellow crystals, m.p. 143-146°. The combined yield, after concentrating the combined mother liquors for additional pure product, was 14.0 g. (66%). This product is much more soluble in benzene and butanone than the *meso* isomer.

Regeneration of the DL-Diol from Its Di-*p*-nitrobenzoate.—The DL-di-*p*-nitrobenzoate (6.63 g.) was saponified by the same procedure (see above) used for the *meso*-di-*p*-nitrobenzoate. The time of reflux was extended to 0.75 hour and there was obtained on distillation *in vacuo*, 1.11 g. (59%) of the regenerated diol as a colorless, very viscous liquid, b.p. 124-125° (10 mm.), d_{20} 0.974, n^{20}D 1.4548, n^{25}D 1.4525.

DL-2,3-Dimethylbutane-1,4-diol Bistriphenylmethyl Ether.—The DL-diol (3.0 g.) was tritylated by the same procedure (see above) used for the *meso*-diol. This time the residue from the benzene extract was an oil. This oil was crystallized by dissolving it in a minimum volume of boiling absolute ethanol (charcoal) and cooling the solution to 0°. The crystals after drying weighed 10.5 g. and melted at 124-130.5°. A second crop of 0.2 g. (same m.p.) was obtained.

The combined product was recrystallized thrice from ethanol, giving 6.7 g. (44%) of the pure DL-ditrityl ether, m.p. 135-136.5° (cap.).

The DL-ditrityl ether is more soluble in ethanol than the *meso*-diether, but otherwise shows similar solubilities. Analysis[6b] showed 2.01 trityl groups per molecule (theor. 2.00).

DL-1,4-Dibromo-2,3-dimethylbutane.—The DL-diol (9.1 g.) when treated by the same procedure A used for the *meso*-diol (see above), gave 16.1 g. (86%) of the DL-dibromide, a colorless liquid, b.p. 104-105° (21 mm.), d_{20} 1.624, n^{20}D 1.5080, n^{25}D 1.5076.

For analysis the dibromide was converted to crystalline diaryl ether and spirobipyrrolidinium[8] derivatives.

By reaction with silver *p*-nitrobenzoate the DL-dibromide gave a dinitrobenzoate identical with that prepared directly from the DL-diol.

DL-2,3-Dimethylbutane-1,4-diol Di-*p*-nitrophenyl Ether.—Sodium metal (0.71 g.) was dissolved in 12 ml. of absolute ethanol. A solution of 4.6 g. of *p*-nitrophenol in 8 ml. of absolute ethanol, and 3.25 g. of the DL-dibromide, were then added, and the mixture heated in a sealed tube at 140° for 2.5 hours.

After cooling, the tube contents were transferred to a flask with the aid of absolute ethanol (10 ml.) and water (15 ml.). The mixture was then acidified by dropwise addition of 1 ml. of 12 M hydrochloric acid at 0°, and shaken vigorously for one or two minutes. After recooling, the crude product was removed by filtration and washed with a little ice-cold 95% ethanol, then with water until the filtrate gave a negative bromide test. The dry crude DL-diaryl ether weighed 1.7 g. (36%) and melted at 77-85°.

This crude product was dissolved in boiling butanone (charcoal) and after cooling, the small amount of *meso* impurity which separated was removed by filtration, m.p. 168-177°. This insoluble *meso* residue was recrystallized from butanone (charcoal), giving a very small amount of pure *meso* product, pale yellow crystals, m.p. 175.5-177°, whose identity was confirmed by mixed m.p. and X-ray powder spectra.

The filtrate on evaporation to dryness *in vacuo* gave a solid residue which was recrystallized from benzene-petroleum ether (b.p. 60-80°), giving a DL product of m.p. 84-92°. After recrystallization from 95% ethanol the pure DL-di-*p*-nitrophenyl ether melted at 92-94°. The yield was poor.

Anal. Calcd. for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 60.31; H, 5.60; N, 7.68.

The DL-di-*p*-nitrophenyl ether is much more soluble than its *meso* isomer in benzene, butanone, or hot ethanol.

Acknowledgment.—We are indebted to the National Research Council and to the Advisory Committee on Scientific Research for generous financial support of this work.

TORONTO, CANADA