[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TORONTO]

Preparation of the Epimeric 3,4-Dimethylpyrrolidines

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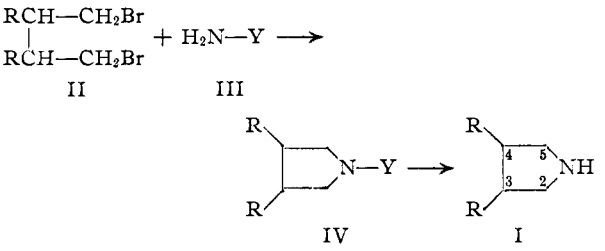
meso-3,4-Dimethylpyrrolidine has been obtained by hydrolysis of its N-tosyl derivative, prepared from *meso*-2,3-dimethyl-1,4-dibromobutane and *p*-toluenesulfonamide. DL-3,4-dimethylpyrrolidine has been obtained by reduction of dimethylsuccinimide with lithium aluminum hydride. Crystalline tosylate and picrate salts and N-tosyl derivatives of both the liquid dimethylpyrrolidines were prepared.

The 2,5-disubstituted derivatives of pyrrolidine, and of its oxygen and sulfur analogs, have been extensively studied, but relatively little work has been done on the 3,4-derivatives.



It appeared that a convenient process for preparing *meso*-3,4-dimethylpyrrolidine would be the reaction of the recently reported[3] *meso*-1,4-dibromo-2,3-dimethylbutane (II, R = $-CH_3$) with a suitable aminoid reagent (III).[4] Ammonia itself is not a suitable reagent, because the initially formed pyrrolidine would react further with dibromide to form tertiary amines and spiro quaternary salts. This can be avoided by choosing a reagent (III) with a suitable protective group (–Y). An alkyl or aryl protective group would be too difficult to remove after the reaction, and an ordinary acyl group (–OCR) would be unsuitable because carboxylic amides resist alkylation.

The solution was found in a method which had been reported by Müller and Sauerwald[5] in 1927 for preparing pyrrolidine itself. By their method a 1,4-dibromide II is allowed to react with an aromatic sulfonamide such as *p*-toluenesulfonamide (III, Y = $CH_3C_6H_4SO_2^-$). Since sulfonamides, because of their activated amino hydrogen atoms, are easily alkylated under mild conditions, N-tosylpyrrolidines (IV, Y = $CH_3C_6H_4SO_2^-$) can readily be prepared by this procedure.

Although N-tosyl derivatives have the reputation of being "hard" to hydrolyze, the hydrolysis to a free pyrrolidine is not actually difficult in practise if a suitable reaction time and temperature are employed. The traditional cleavage of sulfonamides with hydrochloric acid was found more satisfactory in this instance than the recently reported reductive procedures[6] using hydrobromic acid and phenol.

It is surprising that this elegant method[7] for the preparation of pyrrolidine derivatives from 1,4-dibromides (or at least from diprimary dibromides) has not been more widely employed.

The most convenient method for preparing DL-3,4-dimethylpyrrolidine was found to be the reduction of DL-2,3-dimethylsuccinimide with lithium aluminum hydride.[8] This DL-imide is easily prepared[9] from either DL or *meso*-dimethylsuccinic acid, but its *meso* epimer, although known, is not so readily available.

Both pyrrolidine epimers were characterized by conversion to their picrate and tosylate salts, and also to N-tosyl derivatives; the DL N-benzenesulfonyl derivative was also prepared. The identity of the DL N-tosyl derivative (m.p. 80°) was confirmed by an independent preparation using the reaction of DL-1,4-dibromo-2,3-dimethylbutane[3] with *p*-toluenesulfonamide.

In order to prove that the pyrrolidine prepared from the imide had a *trans* configuration a sample was resolved by treatment with *dx*-tartaric acid[10] to give the dextrorotatory pyrrolidine. Details will be given in a subsequent communication.

We find that non-aqueous titration[11] is useful for analyzing the salts of pyrrolidines. For example, the dimethylpyrrolidine tosylates were conveniently titrated in anhydrous dimethylformamide solvent with sodium methoxide. Titration of any such salt (*i.e.*, a salt of a strong acid and a moderately strong base) in aqueous solution usually fails because no sharp end-point can be obtained.[12]

Experimental[10]

All melting and boiling points have been corrected. Melting points were taken on the Köfler micro-block unless

(1) From a Ph.D. Thesis to be submitted by Stephen Proskow to the Graduate School, University of Toronto.

(2) National Research Council Fellow, 1954–1955; Nadine Phillips Fellow, 1953–1954.

(3) G. E. McCasland and S. Proskow, THIS JOURNAL, **76**, 3486 (1954).

(4) The preparation of dimethylpyrrolidines by reducing 3,4-dimethylpyrrole was also considered. This pyrrole is known (*Ann.*, **450**, 128 (1926)); however, it was obtained by a method not suitable for preparative purposes.

(5) A. Müller and A. Sauerwald, *Monatsh.*, **48**, 158 (1927).

(6) (a) D. I. Weisblat, *et al.*, THIS JOURNAL, **75**, 3630 (1953); (b) H. R. Snyder and R. E. Heckert, *ibid.*, **74**, 2006 (1952).

(7) A similar principle is involved in the preparation of N-methylaminoacids by the methylation and desulfonation of benzenesulfonylaminoacids, *e.g.*, see *J. Chem. Soc.*, 1894 (1931).

(8) *Cf.* the reduction of N-phenylsuccinimide in "Organic Reactions," Vol. 6, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 492.

(9) (a) W. Huckel and H. Müller, *Ber.*, **64**, 1981 (1931); (b) E. Ott, *Ber.*, **61**, 2131 (1928); (c) C. A. Bischoff and E. Voit, *Ber.*, **23**, 642 (1890).

(10) The nomenclature of stereoisomers here used is in conformity with rules proposed in the pamphlet "A New General System for the Naming of Stereoisomers," 1953, available from Chemical Abstracts, c/o Ohio State University, Columbus 10, Ohio; rules 15, 21, 27, 52, 53 and 54 are especially relevant.

(11) For a general discussion, see the 45-page pamphlet by James S. Fritz, "Acid-Base Titrations in Non-Aqueous Solvents," published by G. Frederick Smith Chemical Co., Columbus, Ohio, 1952.

(12) In a basic solvent, such as dimethylformamide, dimethylpyrrolidine tosylate behaves like the salt of a weak base and a very strong acid, and thus is easily titrated with a strong base, such as methoxide ion.

otherwise noted. Microanalyses by Micro-Tech Laboratories, Skokie, Illinois, and by Mr. Charles K. Cross, Toronto.

Meso Series

***meso*-3,4-Dimethyl-1-*p*-toluenesulfonylpyrrolidine.**—A mechanically stirred solution of 24.4 g. of *meso*-1,4-dibromo-2,3-dimethylbutane[3] and 17.2 g. of *p*-toluenesulfonamide in 65 ml. of 95% ethanol was kept at the boiling point under reflux while a solution of 11.2 g. of potassium hydroxide in 123 ml. of 87% (v./v.) ethanol was added gradually. The potassium hydroxide solution was added in 15-ml. portions at intervals of several hours so as to keep the reaction mixture somewhat basic. After the last addition, at 64 hours, the mixture was refluxed six hours longer, then cooled to 0°, and the precipitate (mainly potassium bromide) which had separated was removed by filtration.

The filtrate was vacuum-distilled to dryness and the combined solid residues were triturated with 2.8 *M* sodium hydroxide solution, filtered and washed with water. After drying, the crude product weighed 19.3 g., m.p. 35–61°. It was recrystallized twice from petroleum ether of b.p. 40–60° to give 11.2 g. of the pure tosyldimethylpyrrolidine, m.p. 62–64°. A second crop, 3.4 g., showed the same m.p.; total yield 14.6 g. (58%).

Anal. Calcd. for $C_{13}H_{19}NO_2S$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.73; H, 7.35; N, 5.44.

***meso*-3,4-Dimethylpyrrolidine.**—A mixture of 23.0 g. of the *meso* tosyl derivative with 48 ml. of 12 *M* hydrochloric acid was heated in a sealed tube at 160° for 8.5 hours. After cooling, the tube contents were removed with the aid of 50–75 ml. of water and a little ether, and the aqueous solution was extracted with ether to remove toluene (presumably formed by desulfonation of toluenesulfonic acid). The aqueous phase was vacuum-distilled down to a small oily residue. When this residue was treated with 7 *M* potassium hydroxide the product separated as a second liquid phase. The product (isolated by ether extraction) was fractionated, giving 5.00 g. (56%) of the colorless liquid dimethylpyrrolidine, which had a strong amine odor, b.p. 126–128° (749 mm.), d_{20} 0.858.

The identity of the product was confirmed by converting it (see below) to crystalline derivatives.

Reconversion of the Dimethylpyrrolidine to its N-Toluenesulfonyl Derivative.—A 0.25-g. portion of the above *meso*-dimethylpyrrolidine was treated with 0.57 g. of *p*-toluenesulfonyl chloride in 5 ml. of pyridine, giving 0.58 g. (92%) of product, m.p. 60.5–64°. On recrystallization of the product from petroleum ether (b.p. 40–60°), 0.28 g. of material melting at 62–64° was obtained, plus a second crop (0.16 g.) of the same m.p.

***meso*-3,4-Dimethylpyrrolidinium *p*-Toluenesulfonate.**—A 0.5-g. sample of the dimethylpyrrolidine in 5 ml. of ether was added to a solution of 0.97 g. of *p*-toluenesulfonic acid monohydrate in 100 ml. of ether. The crystals were collected, giving 1.26 g. (93%) of colorless needles, m.p. 105–110°. The product was recrystallized once from benzene, giving 0.70 g. of the pure tosylate, m.p. 109–111.5°.

For analysis, a *non-aqueous titration*[11] was employed. A sample was dissolved in dimethylformamide and titrated with standard 0.1 *M* sodium methoxide in absolute methanol–benzene (1:6), using thymol blue indicator.

Anal. Calcd. for $C_{13}H_{21}NO_3S$: mol. wt., 271.4. Found: mol. wt., 269.3.

***meso*-3,4-Dimethylpyrrolidinium Picrate.**—By treating 0.3 g. of the pyrrolidine with 0.71 g. of picric acid in ethanol, 0.64 g. (66%) of long, bright yellow needles, m.p. 163–167° (softened and partially sublimed at 150°), was obtained. After recrystallization from 95% ethanol 0.44 g. of pure product, m.p. 165–168° (partial sublimation at 155°) resulted. The melting behavior remained unchanged after further recrystallizations.

Anal. Calcd. for $C_{12}H_{16}N_4O_7$ (328.28): N, 17.06. Found: N, 17.20.

Racemic Series

DL-3,4-Dimethylpyrrolidine.—The DL-imide (47.8 g.) in a Soxhlet thimble was extracted (about 3 hours) into a solution of 32.7 g. of the hydride in 500 ml. of anhydrous ether, and the resulting mixture refluxed overnight. The apparatus must include an adequate outlet for the periodic sudden emissions of hydrogen.

After destruction of excess hydride with water, the crystalline inorganic precipitate was removed by filtration and washed repeatedly with ether. The combined ethereal filtrate was extracted four times with 75-ml. portions of 3.3 *M* hydrochloric acid, then once with 50 ml. of water. The combined aqueous phases were then vacuum-distilled to a small volume, and excess 7 *M* potassium hydroxide was added with cooling.

The product was extracted with five 75-ml. portions of ether. After removal of ether the product was distilled (fractionating column), giving finally 20.3 g. (55%) of dimethylpyrrolidine boiling at 118–122° (756 mm.), d_{20} 0.835.

For analysis, the liquid product was converted to its crystalline picrate (see below).

DL-3,4-Dimethylpyrrolidinium Picrate.—Ethanolic picric acid was added to the dimethylpyrrolidine, giving bright yellow needles, m.p. 140–142° (sintered at 131°). For analysis, a sample was recrystallized several times more from ethanol. The melting behavior remained unchanged.

Anal. Calcd. for $C_{12}H_{16}N_4O_7$ (328.28): C, 43.89; H, 4.91. Found: C, 43.86; H, 5.07.

Regeneration of DL-3,4-Dimethylpyrrolidine from its Picrate.—The picrate (26.8 g.) was treated with hydrochloric acid in the usual manner, giving 5.31 g. (65%) of the regenerated dimethylpyrrolidine, b.p. 115–118° (743 mm.), d_{20} 0.836.

DL-3,4-Dimethylpyrrolidinium *p*-Toluenesulfonate.—Five grams of the crude DL-dimethylpyrrolidine was added to 11.4 g. of *p*-toluenesulfonic acid monohydrate in ether, giving 11.0 g. (81%) of product, m.p. 136.5–142°. After three recrystallizations from benzene, 8.0 g. of colorless needles, m.p. 139.5–142.5°, was obtained. The DL-tosylate was analyzed by non-aqueous titration as for the *meso* isomer (see above).

Anal. Calcd. for $C_{13}H_{21}NO_3S$: mol. wt., 271.4. Found: mol. wt., 269.6.

Regeneration of DL-3,4-Dimethylpyrrolidine from its Tosylate.—A 41.5-g. portion of the DL-tosylate was treated with potassium hydroxide, and the liberated pyrrolidine extracted with ether. The regenerated liquid product was fractionated, giving 10.5 g. (71%) of colorless dimethylpyrrolidine, b.p. 119–122° (752 mm.), d_{20} 0.835.

DL-3,4-Dimethyl-1-*p*-toluenesulfonylpyrrolidine. (A) **From Dimethylpyrrolidine.**—A 0.5-g. sample of the DL-dimethylpyrrolidine (regenerated from tosylate) was treated with 1.14 g. of *p*-toluenesulfonyl chloride, giving 1.12 g. (88%) of crude product, m.p. 75–78.5°. The product was recrystallized from petroleum ether (b.p. 60–80°), giving 0.86 g. (68%) of colorless needles, m.p. 78–80°.

The product was shown by mixed m.p. to be identical with that derived from the DL-dibromide (see below).

(B) **From Dibromodimethylbutane.**—A 1.0-g. portion of DL-1,4-dibromo-2,3-dimethylbutane[3] was treated with *p*-toluenesulfonamide as for the *meso* dibromide (see above). However, the reaction time was shortened to eight hours, and the potassium hydroxide added in hourly portions. A yield of 0.25 g. (24%) of product, m.p. 79–80°, was obtained.

Anal. Calcd. for $C_{13}H_{19}NO_2S$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.67; H, 7.62; N, 5.26.

DL-1-Benzenesulfonyl-3,4-dimethylpyrrolidine.—A small sample of the DL-pyrrolidine (regenerated from picrate) was treated with benzenesulfonyl chloride and sodium hydroxide. The product was recrystallized successively from ethanol–water and from methanol, giving colorless crystals, m.p. 59–61°.

Anal. Calcd. for $C_{12}H_{17}NO_2S$ (239.26): N, 5.85. Found: N, 5.62.

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