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MESO-α,β-DIAMINOSUCCINIC ACID

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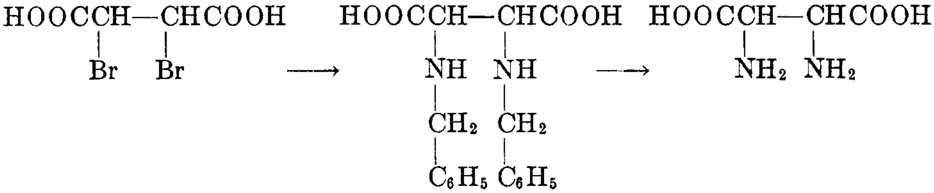
For the purpose of synthesizing biotin, meso-α,β-diaminosuccinic acid appears to be a convenient starting material. Since the methods described for its preparation (4, 11, 13, 15, 16, 18) have drawbacks, which become especially serious if considerable amounts of the acid are needed, a new synthesis was devised.

It consists in the following sequence of reactions: meso-α,β-Dibromosuccinic acid (I) is reacted with benzylamine to meso-α,β-bis(benzylamino)succinic acid II, which was first isolated by Frankland (5, 6). The preparation of this acid was considerably improved, affording yields of 80% and higher. As an intermediate in the reaction between meso-α,β-dibromosuccinic acid and benzylamine the dibenzylamine salt of meso-α,β-bis(benzylamino)succinic acid was isolated.



$$HOOCCH(Br)\text{—}CH(Br)COOH \longrightarrow HOOCCH(NHCH_2C_6H_5)\text{—}CH(NHCH_2C_6H_5)COOH \longrightarrow HOOCCH(NH_2)\text{—}CH(NH_2)COOH$$

I II III

meso-α,β-Bis(benzylamino)succinic acid is debenzylated by catalytic hydrogenation in the presence of at least one equivalent of hydrochloric or hydrobromic acid. This is an extension of the well known method of catalytic debenzylation (1, 2, 3, 7) to a compound containing two benzylamino groups in the same molecule. The free acid or its alkali salts cannot be debenzylated. Palladium on charcoal as catalyst is superior to platinum oxide.

The yield of meso-α,β-diaminosuccinic acid (III) is about 90% of the theoretical. The method is suitable for large scale manufacture, making meso-α,β-diaminosuccinic acid an easily accessible compound (17).

When instead of the meso- the *dl*-α,β-dibromosuccinic acid (8, 12) is reacted with benzylamine, an α,β-bis(benzylamino)succinic acid m.p. 210–212° is obtained in considerably lower yield, obviously because *dl*-α,β-dibromosuccinic acid is by far less stable than the meso acid (6, page 2880) and is split to a large extent into bromomaleic acid.

Hydrogenation of this *dl*-bis(benzylamino)succinic acid does not yield the expected *dl*-α,β-diaminosuccinic acid, but the meso acid. The *dl*-α,β-diaminosuccinic is probably formed originally but isomerizes into the meso acid under the influence of the mineral acid. Such a conversion has been observed previously by Kuhn and Zumstein (10). Obviously this rearrangement is facilitated during the cleavage of the benzyl groups. The identity of the meso-α,β-diaminosuccinic acid was established by conversion into the dibenzoyl derivative which melted at 208–210° in agreement with the results of Kuhn and Zumstein (9) who reported m.p. 212–213° for the dibenzoyl derivative of the meso acid. The dibenzoyl derivative of the racemic acid melts at 164°.

The debenzylation procedure allows the correlation between the structure of the α,β-bis(benzylamino)succinic acids and the α,β-diaminosuccinic acids which was hitherto impossible. The direct interconversion of meso-α,β-bis(benzylamino)succinic acid into meso-α,β-diaminosuccinic acid confirms Frankland's assumption that substitution of the bromo atoms by benzylamino groups in meso-α,β-dibromosuccinic acid occurs without change in the steric arrangement.

EXPERIMENTAL

The melting points are uncorrected.

1. meso-α,β-Bis(benzylamino)succinic acid. A. *Without solvent.* Fifty grams of meso-α,β-dibromosuccinic acid (14) is added in portions to 150 g. of benzylamine with stirring at 80°. After complete addition, the mixture is heated for two hours to 90–100°, then cooled to room temperature and 500 cc. of water added. The solution is treated with charcoal and filtered. The filtrate is made Congo acid by addition of dilute hydrochloric acid. meso-α,β-Bis(benzylamino)succinic acid separates as a colorless microcrystalline powder. It is filtered and washed with water; yield 50–55 g. (84–92%). The crude acid is dissolved in dilute sodium hydroxide solution, treated with charcoal, filtered, and the filtrate acidified with acetic acid. Thus prepared, meso-α,β-bis(benzylamino)succinic acid melts at 218–219°. If the acid is repeatedly precipitated from alkaline solution the melting point rises to 230°.

Anal. Calc'd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53.
Found: C, 65.90; H, 6.27; N, 8.71.

B. *In alcohol.* To a stirred solution of 250 g. of meso-α,β-dibromosuccinic acid in 2 liters of alcohol, 855 g. of benzylamine are added slowly. After complete addition the mixture is heated on the steam-bath for 5–6 hours. A heavy precipitate of the dibenzylamine salt of meso-α,β-bis(benzylamino)succinic acid appears (see C). After cooling to about 40–50° about 1 liter of water is added, then conc'd hydrochloric acid in small portions until *p*H 1–2 is reached (about 250–270 cc.). The *p*H is then adjusted with conc'd sodium acetate solution to *p*H 4–5. The mixture is filtered by suction. The crystals are washed with water and alcohol until colorless. meso-α,β-bis(benzylamino)succinic acid is obtained in a yield varying from 320 to 380 g. (80–91%). The acid melts generally at 213–217°. Recrystallization from acetic acid with addition of water raises the m.p. to 225°.

Anal. Calc'd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53.
Found: C, 66.13, 65.62; H, 6.29, 5.94; N, 8.65, 8.54.

Instead of alcohol, methanol can be used as solvent.

From the original mother liquor the excess benzylamine is recovered by addition of potassium hydroxide and distillation.

C. *Dibenzylamine salt of meso-α,β-bis(benzylamino)succinic acid.* If the reaction mixture from B above after heating is diluted with about three volumes of water, the dibenzylamine salt crystallizes. It is filtered and washed with cold water. Recrystallization from water yields colorless prisms of m.p. 211–222°.

Anal. Calc'd for $C_{32}H_{38}N_4O_4$: C, 70.82; H, 7.06; N, 10.33.
Found: C, 70.11; H, 6.73; N, 10.40.

D. *Monohydrochloride.* One gram of meso-α,β-bis(benzylamino)succinic acid is dissolved in 6 cc. of conc'd hydrochloric acid and 10 cc. of water at 90–100°. Upon cooling, the hydrochloride crystallizes. It is filtered and dried without washing in order to prevent hydrolysis.

Anal. Calc'd for $C_{18}H_{20}N_2O_4 \cdot HCl$: Cl, 9.95. Found: Cl, 10.37.

E. *Dihydrobromide.* Ten grams meso-α,β-bis(benzylamino)succinic acid is dissolved in 20 cc. of 48% hydrobromic acid by warming on the steam-bath. The solution is cooled in a refrigerator for several hours. The dihydrobromide is filtered, washed with some conc'd hydrobromic acid, and dried in a desiccator; yield 18–19 g., m.p. 155° (dec.).

Anal. Calc'd for $C_{18}H_{20}N_2O_4 \cdot 2HBr$ (490.22): C, 44.10; H, 4.52; N, 5.71.
Found: C, 44.20; H, 4.81; N, 5.55.

F. *Separation of mixtures of meso-α,β-bis(benzylamino)succinic acid and meso-α,β-diaminosuccinic acid.* One-half gram of meso-α,β-bis(benzylamino)succinic acid and 0.5 g. of meso-α,β-diaminosuccinic acid are mixed and suspended in 50 cc. of absolute alcohol. Two cc. of aqueous hydrochloric acid (35%) is added. The mixture is shaken for one hour at room temperature, and is then filtered. The undissolved material is pure meso-α,β-diaminosuccinic acid of m.p. 303°; yield 0.48 g.

Anal. Calc'd for $C_4H_8N_2O_4$: C, 32.43; H, 5.44; N, 18.91.
Found: C, 31.84; H, 5.74; N, 18.63.

The filtrate is concentrated to a small volume. Upon addition of water, crystallization starts immediately. Filtration gives 0.4 g. of meso-α,β-bis(benzylamino)succinic acid of m.p. 230°.

2. meso-α,β-Diaminosuccinic acid. A. *In water.* Three grams of meso-α,β-bis(benzylamino)succinic acid is dissolved in 50 cc. of hydrochloric acid (10%). The solution is hydrogenated with one gram of palladium charcoal (10% Pd) at 25° and 500 lbs. pressure for 20 hours. It is filtered and distilled to dryness *in vacuo*. The crystalline residue is dissolved in dilute sodium hydroxide and filtered. The clear filtrate is acidified with acetic acid. meso-α,β-Diaminosuccinic acid separates immediately. It is filtered, washed with water, and dried at 60°. The yield of material melting at 281–284° (dec.)[1] is 0.6 g.

Anal. Calc'd for $C_4H_8N_2O_4$: C, 32.43; H, 5.44.
Found: C, 32.47; H, 6.05.

B. *In methanol.* Five grams of meso-α,β-bis(benzylamino)succinic acid and 70 cc. of methanol are placed into the glass liner of a shaking autoclave. Five cc. of conc'd hydrochloric acid and 2 g. of palladium charcoal (20% Pd) are added. The mixture is hydrogenated at room temperature and 1000 lbs. pressure for 16 hours. The solution is filtered from the catalyst and distilled to dryness. The residue is dissolved in dilute sodium hydroxide and filtered. Addition of acetic acid to the filtrate precipitates meso-α,β-diaminosuccinic acid at once. It is filtered, dissolved cold in the minimum quantity of 10% hydrochloric acid, filtered, and diluted to five times its volume with water. On standing, the pure acid crystallizes slowly. It is filtered after 24 hours and dried; m.p. 303–305° (dec.).

Anal. Calc'd for $C_4H_8N_2O$: C, 32.43; H, 5.44.
Found: C, 32.24; H, 5.84.

C. *In acetic acid.* In a glass-lined autoclave 150 g. of meso-α,β-bis(benzylamino)succinic acid, 650 g. of acetic acid, 140 g. of hydrochloric acid (35%), and 25 g. of palladium charcoal (containing 2.5 g. of palladium) are hydrogenated at 800 lbs. The temperature is kept for 15 hours at 35°, for six hours at 50–60° and finally for 15 hours at 20°. The mixture is treated with 10% aqueous hydrochloric acid in order to dissolve the precipitated hydrochloride of meso-α,β-diaminosuccinic acid at 80°. The hot solution is filtered by suction from the catalyst. The latter is washed thoroughly with 10% hydrochloric acid. The combined filtrates are distilled to dryness in a vacuum. The residue is stirred with distilled water and cooled in a refrigerator for 20 hours. The colorless crystals are filtered, washed with water and dried; yield 59 g. (90%) of meso-α,β-diaminosuccinic acid of m.p. 305–306° (dec.).

3. dl-α,β-Bis(benzylamino)succinic acid. Thirty grams of *dl*-α,β-dibromosuccinic acid (8, 12) is stirred with 200 cc. of ethanol at room temperature. Ninety cc. of benzylamine is added slowly. The mixture is refluxed for five hours with stirring. The formed crystalline precipitate is filtered and washed with cold alcohol. It is stirred up with 100 cc. of

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[1] Kuhn and Zumstein (9, page 1430) claim that diaminosuccinic acids do not have definite melting or decomposition points. We find distinct decomposition points which, however, vary considerably depending upon the rate of heating.

water. Twenty cc. of acetic acid is added. The crystals which separate are filtered and dissolved in 40 cc. of 3 *N* sodium hydroxide and 90 cc. of water. The cold solution is treated with charcoal, filtered, and the filtrate is acidified with acetic acid. *dl*-α,β-Bis(benzylamino)succinic acid separates colorless. It is filtered, washed with water, and dried; yield 13 g., m.p. 210–212°. Reprecipitation from alkaline solution raises the m.p. to 215°.

Anal. Calc'd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53.
Found: C, 66.29; H, 6.31; N, 8.34.

Hydrochloride. One gram of the acid is warmed with 5 cc. of 3 *N* hydrochloric acid. The acid does not dissolve, but forms a voluminous hydrochloride. To isolate the hydrochloride, 1 g. of the acid is dissolved in 10 cc. of conc'd hydrochloric acid and 15 cc. of water at 80°. The solution is filtered immediately and diluted with 20 cc. of water. On standing at room temperature for 24 hours, 0.7 g. of the monohydrochloride separates, melting at 175–176° (dec.).

Anal. Calc'd for $C_{18}H_{20}N_2O_4 \cdot HCl$: C, 59.26; H, 5.80; N, 7.68; Cl, 9.73.
Found: C, 59.22; H, 5.69; N, 7.89; Cl, 9.62.

Hydrobromide. Ten grams of *dl*-bis(benzylamino)succinic acid is stirred with 40 cc. of hydrobromic acid (48%). The acid dissolves with evolution of heat. After a few minutes the dihydrobromide starts to separate. The mixture becomes almost solid. It is filtered after two hours, the crystals are washed with some conc'd hydrobromic acid and dried in a desiccator; yield 16–18 g., m.p. 175° (dec.).

Anal. Calc'd for $C_{18}H_{20}N_2O_4 \cdot 2\,HBr$ (490.22): C, 44.10; H, 4.52; N, 5.71.
Found: C, 44.90; H, 4.30; N, 6.27.

4. Hydrogenation of dl-α,β-bis(benzylamino)succinic acid. Six grams of *dl*-α,β-bis(benzylamino)succinic acid, 26 cc. of acetic acid, 5 cc. of hydrochloric acid (35%), and 2 g. of palladium charcoal (10% Pd) are hydrogenated at 800 lbs. pressure. The temperature is kept for 17 hours at 35°, for 6 hours at 50–60° and finally for 15 hours at 20°. The solution smells of toluene and a precipitate has formed. It is dissolved by heating to about 60° and the solution is filtered. The catalyst is washed with dilute hydrochloric acid. The combined filtrates are distilled to dryness. The residue is an amorphous yellow material which crystallizes immediately upon addition of 70 cc. distilled water. It is filtered, washed with water and alcohol, and dried. The crystals melt at 324–326° (dec.).

Anal. Calc'd for $C_4H_8N_2O_4$: C, 32.43; H, 5.44; N, 18.91.
Found: C, 31.54; H, 5.53; N, 18.41.

Benzoyl derivative. Two hundred mg. of the acid is benzoylated by shaking with 1.2 cc. of benzoyl chloride in 10 cc. of 3 *N* sodium hydroxide and 5 cc. of water. The mixture is acidified after 4 hours. The crystals are filtered, dried, and extracted with hot ligroin to remove benzoic acid. The undissolved material is crystallized from dil. acetic acid (40%). The resulting dibenzoyl compound melts at 208–210°, which is the melting point of the dibenzoyl derivative of the meso compound (9).

Anal. Calc'd for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.52; N, 7.86.
Found: C, 60.51; H, 4.68; N, 8.26.

The hydrogenation of the *dl*-α,β-bis(benzylamino)succinic acid has therefore yielded meso-α,β-diaminosuccinic acid, indicating isomerization during the hydrogenation.

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SUMMARY

1. An improved method for the preparation of α,β-bis(benzylamino)succinic acids is described.

2. Catalytic debenzylation of α,β-bis(benzylamino)succinic acid is a convenient method for the preparation of meso-α,β-diaminosuccinic acid.

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REFERENCES

(1) Birkofer, *Ber.*, **75**, 429 (1942).
(2) Buck, Baltzly, *J. Am. Chem. Soc.*, **63**, 1964 (1941).
(3) Eisleb, *Ber.*, **74**, 1433 (1941).
(4) Farchy, Tafel, *Ber.*, **26**, 1980 (1893).
(5) Frankland, *J. Chem. Soc.*, **99**, 1775 (1911).
(6) Frankland, *J. Chem. Soc.*, **105**, 2879 (1914).
(7) I. G. Farbenindustrie, Germ. Pat. 550,762; *Frdl.*, **19**, 1422 (1934).
(8) Kuhn, Wagner-Jauregg, *Ber.*, **61**, 502 (1928).
(9) Kuhn, Zumstein, *Ber.*, **58**, 1429 (1925).
(10) Kuhn, Zumstein, *Ber.*, **59**, 479 (1926).
(11) Lehrfeld, *Ber.*, **14**, 1816 (1881).
(12) Michael, *J. prakt. Chem.*, (2) **52**, 292 (1895).
(13) Neuberg, Silbermann, *Z. physiol. Chem.*, **44**, 154 (1905).
(14) Rinesmith, *Org. Syntheses*, Coll. Vol. 2, John Wiley & Sons, New York, **1943**, 177.
(15) Tafel, *Ber.*, **20**, 244 (1887).
(16) Tafel, Stern, *Ber.*, **38**, 1589 (1905).
(17) Wenner, U.S.P. 2,389,099 (Nov. 13, 1945) to Hoffmann-La Roche, Inc.
(18) Ziegler, Locher, *Ber.*, **20**, 834 (1887).