

PREPARATION AND HAIR WAVING PROPERTIES OF 2,5-DIMERCAPTOADIPIC ACID

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VARIOUS MERCAPTANS have been utilized to wave human hair over the years, but few have achieved the commercial importance of thioglycolic acid. Despite the pre-eminence of this substance, new compounds continue to be sought which will provide an effective waving composition and conceivably possess novel and other unexpected properties in addition.

This paper describes work done with a new compound, 2,5-dimercaptoadipic acid (DMA), that is bifunctional in two senses: it is a dithiol as well as a dicarboxylic acid. Thus, it was thought useful to compare it with thioglycolic acid which is monofunctional in these respects. Furthermore, this compound has two asymmetric carbon atoms and is capable of forming a stable cyclic disulfide, leading to properties which might prove novel in use. This paper describes the synthesis, waving behavior and some toxicological properties of DMA.

EXPERIMENTAL

Synthesis

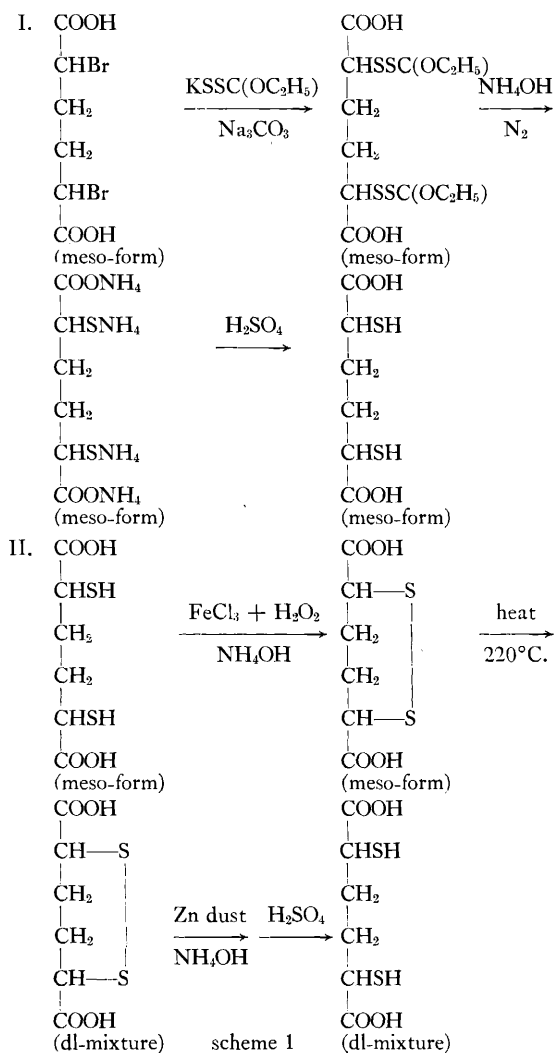
For this study, DMA was prepared according to scheme 1. The details of the various reactions are given below.

A. 2,5-Dibromadipic Acid. Adipic acid was converted into its acid chloride and brominated as described in Organic Syntheses (1).

The brominated acid chloride was slowly added to eight liters of cold water contained in a three-gallon enameled pail. During the addition, good agitation was maintained, and the reaction vessel was cooled externally. Stirring was continued for several hours during which time the crude dibromadipic acid separated as a pale yellow solid. It was removed by suction filtration, well washed with cold water, and, finally, air dried. The yield of crude product was 65-75 per cent.

The crude acid was purified by recrystallization from glacial acetic acid.

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The recovery was approximately 80 per cent. A further amount could be obtained by concentrating the mother liquors. The acid had a melting point of 191–193°C., corresponding to the literature value for the melting point of the meso-form (7).

B. 2,5-Xanthogenoadipic Acid (meso-form). Dibromoadipic acid (304 gm.; 1 mole) was added to two liters of water contained in a four liter beaker. To the well-stirred mixture, solid sodium carbonate (106 gm.; 1 mole) was added in small portions. In order to minimize foaming, approximately 1 ml. of octyl alcohol was added. After addition of the

sodium carbonate was complete, stirring was continued until solution was complete. The reaction mixture was neutral at this time. Potassium ethyl xanthate (320 gm.; 2 moles), which had been previously recrystallized from alcohol, was added over a period of ten minutes. Stirring was continued until solution was complete. This required approximately one hour. The reaction mixture after standing at room temperature for twenty-four hours was acidified with 50 per cent sulfuric acid to Congo Red. The dixanthogenoadipic acid separated as an oil, which soon solidified. By maintaining good agitation during this time, a granular solid was obtained, which was removed by suction filtration and washed with water until free of mineral acid as indicated by Congo Red paper.

The product thus obtained was air dried. The yield of crude product was 80–85 per cent. Upon recrystallization of a small amount from ethyl acetate, it had a melting point of 163–164°C.

C. 2,5-Dimercaptoadipic Acid (meso-form). Crude 1,4-dixanthogenoadipic acid (386 gm.; 1 mole) was dissolved in 500 ml. of methanol contained in a two-liter round-bottom flask. While the solution was slowly stirred with a magnetic stirrer and externally cooled, concentrated aqua ammonia (500 ml.) was slowly added over a period of thirty minutes. An atmosphere of nitrogen was maintained during this time. The reaction vessel was stoppered and allowed to stand for forty-eight hours at room temperature.

At the end of this time, most of the methanol and ammonia were removed under reduced pressure. The residue was made distinctly alkaline with ammonia and extracted twice with 100 ml. portions of di-isopropyl ether in order to remove some ethyl thionocarbamate (xanthogenamide), which is formed during the reaction. The ether extracts were discarded. The aqueous phase was acidified with 50 per cent sulfuric acid to Congo Red. The dimercapto acid separated as a light brown solid. It was removed by suction filtration and washed free of mineral acid with water as indicated by Congo Red paper. The yield of crude product was 80–85 per cent.

The crude dimercaptoadipic acid was purified by dissolving it in hot glacial acetic acid, treating with decolorizing charcoal, and filtering through a hot funnel. The recovery was 80–90 per cent. The recrystallized product had a melting point of 186–188°C. (with moderate decomposition).

D. 2,5-Dimercaptoadipic Acid (dl-mixture). The dl-mixture of DMA was prepared from the meso cyclic disulfide by heating it at 220°C. for seven minutes, followed by reduction (2).

An aqueous slurry of meso-DMA (105 gm.; 0.5 moles) was adjusted to pH 8 with ammonium hydroxide. Fifteen drops of 1 per cent ferric chloride were added and the solution cooled in an ice bath, while 15 per cent hydrogen peroxide was added dropwise with stirring until the violet

color caused by the ferric chloride-DMA complex disappeared. The solution was acidified with 8*M* sulfuric acid to pH 2. The precipitate which formed was filtered and recrystallized twice from water. This disulfide had a melting point of 196–198°C.; the yield was 56 per cent.

In a Woods metal bath, this disulfide (20.8 gm.; 0.1 mole) was heated to 220°C. for seven minutes with stirring. Fusion and then solidification took place. The product was slurried with glacial acetic acid, filtered, washed and dried. The yield was 66 per cent, and melting point was 250–252°C. with decomposition. Recrystallization from glacial acetic acid raised this to 267–270°C.

The reduction of this disulfide was carried out with two equivalents excess of ammonia and excess zinc dust. The reaction mixture containing dl-disulfide (59 gm.; 0.284 moles) was stirred at room temperature overnight, then filtered, acidified to pH 3, and extracted with alcohol-free ether. Evaporation of the ether gave 49 gm. of product melting at 103–110°C. Recrystallization twice from ether-petroleum ether (30–60°C. b.p.) gave 29 gm. melting at 111–113°C., which titrated 94.8 per cent pure.

HAIR WAVING

The waving behavior of DMA was evaluated by waving tresses of virgin hair using two procedures simulating those utilized in commercial practice. These employ an oxidant such as hydrogen peroxide to terminate the waving action of the mercaptan after a brief period of processing, hereafter referred to as chemical neutralization (CN). Alternatively, the moist reduced hair is allowed to remain on the waving rods for a sufficiently long time to allow for aerial oxidation (AO). The details of the waving processes are as follows:

A. Chemical Neutralization

Tresses of hair five inches long, weighing about 1.4 gm., were glued to white vinylite plastic tabs ($2\frac{1}{8} \times 1\frac{3}{4} \times 0.02$ in.). The hair was wet with waving lotion and wrapped on a 0.20 in. diameter rod, using an end paper to start the wrap. After fifteen minutes, the hair was resaturated with more lotion and allowed to process for fifteen minutes. Then the hair was rinsed for thirty seconds with warm water (40°C.), blotted and allowed to remain on the rod for thirty minutes. Next, it was neutralized with 0.75*N* hydrogen peroxide. After five minutes, it was unwound gently and more hydrogen peroxide was poured through the tress. Finally, it was rinsed with tap water and shampooed.

B. Aerial Oxidation

A tress of hair was wrapped with waving lotion as described in the neutralization process. After a fifteen minute wait, it was resaturated

with waving lotion and allowed to process for twenty minutes. Then it was rinsed with warm water (40°C.) for thirty seconds and blotted. Finally, it was allowed to air-oxidize at room temperature overnight and then shampooed after being unwrapped.

EXTENT OF REDUCTION

Measurement of the extent of reduction of the hair (i.e., sulfhydryl levels) was performed by reacting the keratin sulfhydryl groups with 2,3-dichloro-1,4-naphthoquinone (NQ). This reagent has been mentioned briefly in the literature by Whitman and Eckstrom (3).

DEGREE OF CURLINESS

In all waving experiments performed, a control tress was run using a thioglycolate lotion which was 0.6M and which was adjusted to pH 9.2 with ammonia. The standard CN process was used. In every case, the control tress was given a rating of 100 and the experimental tresses were rated by comparison with the control tress.

RESULTS

A. Use of Meso- and dl-Dimercaptoadipic Acid in Waving

The lotion composition and permanent wave results are given in Table 1. For comparison purposes, a thioglycolate lotion was used. No

TABLE 1—USE OF MESO- AND DL-DMA IN CN AND IN AO PROCESSES

| Experiment No. | Lotion Composition (NH ₄) ₂ DMA | Process | |
|----------------|---|--------------------------------------|-----|
| | | Curl Level† (After 1 Shampoo) CN* | AO* |
| 1 | 0.4M meso-DMA, NH ₃ to pH 9.28 | 60 | 100 |
| 2 | 0.4M dl-DMA, NH ₃ to pH 9.28 | 55 | 95 |
| 3 | Thioglycolate control | 100 | 110 |

* CN procedure and AO procedure described in text.

† Average of 2 tresses.

differences are apparent between meso- and dl-DMA, but both produce comparatively weak waves in the CN process. The AO process gives much stronger wave results, which strongly suggest that penetration of DMA into the fiber is much slower than with thioglycolate. (See also Figs. 1 and 2 referred to below.)

B. Use of Additives with Dimercaptoadipic Acid

To boost the wave level in the CN process, thioglycolate or dithiodi-glycolate was added to the DMA lotion. The compositions employed and

TABLE 2-A—EFFECT OF ADDITIVES ON THE WAVING PROPERTIES OF MESO- AND DL-DMA IN BOTH CN AND AO PROCESSES

| Experiment No. | Lotion Composition | | | NH ₃ to pH | Process—Curl Level (After 1 Shampoo) | |
|----------------|---|----------------------------------|---|-----------------------|--------------------------------------|-----|
| | (NH ₄) ₂ DMA <i>M</i> | NH ₄ TGA* <i>M</i> | (NH ₄) ₂ SS-TGA† <i>M</i> | | CN | AO |
| 1 | 0.4 meso | ... | ... | 9.28 | 60 | 100 |
| 2 | 0.4 meso | 0.1 | ... | 9.28 | 85 | 110 |
| 3 | 0.4 dl | ... | ... | 9.28 | 55 | 95 |
| 4 | 0.4 dl | 0.1 | ... | 9.28 | 85 | 110 |
| 5 | 0.4 meso | ... | 0.05 | 9.12 | 90 | ... |
| 6 | Thioglycolate control | ... | ... | ... | 100 | 110 |

* Ammonium thioglycolate.

† Diammonium dithiodiglycolate.

TABLE 2-B—EFFECT OF ADDITIVES ON WAVING PROPERTIES AND SULFHYDRYL LEVELS OF HAIR WAVED WITH DMA LOTIONS IN A CN PROCESS

| Experiment No. | Lotion Composition | | | Curl Level | SH Level,* Meq./G. Hair |
|----------------|---|---------------------------------|-----------------------|------------|----------------------------|
| | (NH ₄) ₂ DMA <i>M</i> | NH ₄ TGA <i>M</i> | NH ₃ to pH | | |
| 1 | 0.50 | ... | 9.30 | 65 | 0.27 |
| 2 | 0.45 | 0.1 | 9.25 | 95 | ... |
| 3 | 0.39 | 0.2 | 9.25 | 110 | 0.29 |
| 4 | Thioglycolate control | ... | ... | 100 | 0.22 |

* Measured just prior to chemical neutralization.

the results obtained are given in Table 2-A. Again, for comparison, a standard thioglycolate lotion was used.

The presence of a small amount (0.05 to 0.1*M*) of either thioglycolate or dithiodiglycolate in a 0.4*M* DMA solution boosts the wave level an average of 35 per cent. With these additives, a 0.4*M* DMA lotion is about equivalent to a thioglycolate lotion. This is true for both the meso- and the dl-DMA lotions.

The results of the sulfhydryl analysis of the hair in these experiments do not indicate less attack by DMA than by thioglycolate (Table 2-B). However, it was shown that the distribution of the sulfhydryl groups was confined mainly to the periphery of the fiber when DMA alone was used, whereas thioglycolate-treated hair showed a more uniform distribution of sulfhydryl groups (see Figs. 1 and 2). Thus, it appears that for adequate waving to occur it is necessary to reduce more than just the periphery of the fiber in order to allow it to creep to a new configuration.

C. Powdered Waving Compositions Containing DMA

In contrast to most other mercaptans, DMA has exceptionally high stability and low odor when kept as a dry solid or formulated in aqueous solutions. In Table 3 are given some stability data on typical powdered materials or solutions. The solutions are free of mercaptan odor before and after aging.

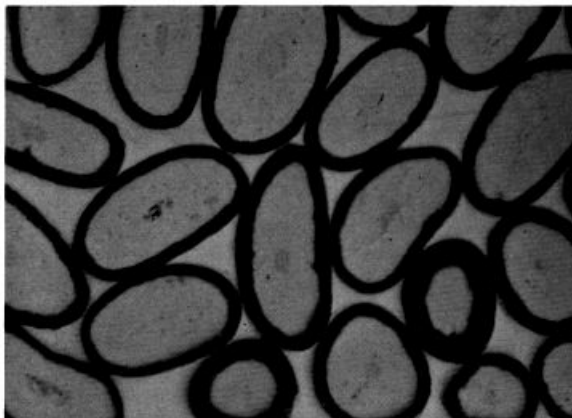


Figure 1.—Distribution of sulfhydryl groups in cross section of hair following exposure to DMA lotion but before chemical neutralization (stained with NQ reagent described in text).

Making use of these properties it is possible to formulate powdered DMA compositions with suitable booster additives which will give wave levels in a CN or AO process which are equivalent to thioglycolate waves. Table 4 lists some such compositions.

D. Waving End Papers Impregnated with Booster Additives for DMA Lotions

Because of the odor and stability advantages of DMA, it is desirable to formulate aqueous lotions based on this mercaptan for commercial use.

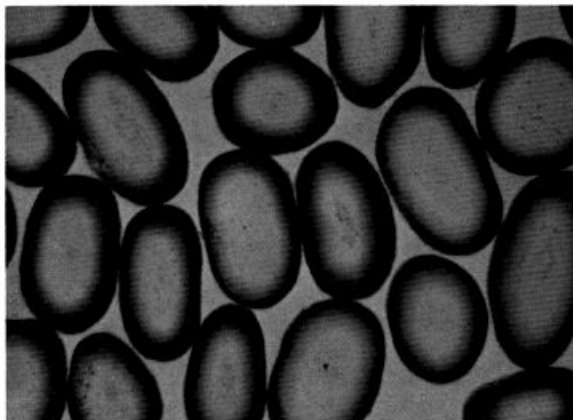


Figure 2.—Distribution of sulfhydryl groups in cross section of hair following exposure to thioglycolate lotion but before chemical neutralization (stained with NQ reagent described in text).

TABLE 3—STABILITY OF SOLID DMA AND DMA LOTIONS

| Sample No. | Samples* | Time Aged | —Before Aging— | | | —After Aging— | | |
|------------|--|------------------------|----------------|------|-------------|---------------|------|-------------|
| | | | Eq. Wt. | SH M | Free Alk. M | Eq. Wt. | SH M | Free Alk. M |
| 1 | DMA solid | 5 $\frac{1}{2}$ months | 105.0 | | | 105. | | |
| 2 | DMA solid | 4 $\frac{1}{2}$ years | 105.2 | | | 106.0 | | |
| 3 | (NH ₄) ₂ DMA solid | 5 $\frac{1}{2}$ months | 122.6 | | | 123.8 | | |
| 4 | Na ₂ DMA solid | 5 $\frac{1}{2}$ months | 128.6 | | | 129.2 | | |
| 5 | (NH ₄) ₂ DMA-NH ₃ lotion | 1 year | ... | 0.46 | 0.55 | ... | 0.46 | 0.54 |
| 6 | (NH ₄) ₂ DMA-MIPA† lotion | 1 year | ... | 0.47 | 0.69 | ... | 0.46 | 0.70 |
| 7 | (NH ₄) ₂ DMA-DIPA‡ lotion | 1 year | ... | 0.48 | 0.66 | ... | 0.48 | 0.66 |

* Samples were stored in closed bottles at room temperature.

† MIPA—monoisopropanol amine.

‡ DIPA—diisopropanol amine.

TABLE 4—POWDERED WAVING COMPOSITIONS FORMULATED WITH DMA

| Experiment No. | Waving Compositions | pH | Curl Level (After 1 Shampoo) | |
|----------------|--|------|------------------------------|-----|
| | | | CN | AO |
| 1 | 0.50M (NH ₄) ₂ DMA, 0.65M Na ₂ CO ₃ | 9.05 | 90 | 120 |
| 2 | Thioglycolate control | | 100 | 115 |
| 3 | 0.4M (NH ₄) ₂ DMA, 0.2M MgTGA, 0.66M AMP* | 9.10 | 100 | |
| 4 | Thioglycolate control | | 100 | |
| 5 | 0.4M (NH ₄) ₂ DMA, 0.35M (NH ₄) ₂ SS-TGA, † 0.6M Na ₂ CO ₃ | 8.96 | 85 | |
| 6 | 0.35M Na ₂ DMA, 0.35M Na ₂ SS-TGA, 0.5M AMP | 9.30 | 90 | |
| 7 | 0.4M (NH ₄) ₂ DMA, 0.35M (NH ₄) ₂ SS-TGA, 0.65M AMP | 9.08 | 90 | |
| 8 | Thioglycolate control | | 100 | |

* 2-Amino-2-methyl-1,3-propanediol.

† SS-TGA = dithiodiglycolate.

TABLE 5—THE USE OF IMPREGNATED END PAPERS TOGETHER WITH DMA LOTIONS ON A CN PROCESS

| Experiment No. | Lotion Composition | End Paper (3 $\frac{1}{2}$ × 2 in.) | | Curl Level† (After 1 Shampoo) |
|----------------|--|-------------------------------------|--|-------------------------------|
| | | MgTGA* Meq. | (NH ₄) ₂ SS-TGA† Meq. | |
| 1 | 0.41M (NH ₄) ₂ DMA NH ₃ to pH 9.28 | 0.30 | ... | 115 |
| 2 | "do" | 0.59 | ... | 120 |
| 3 | "do" | ... | 0.40 | 115 |
| 4 | "do" | ... | 0.90 | 100 |
| 5 | "do" | Regular end paper | | 80 |
| 6 | Thioglycolate control | Regular end paper | | 100 |

* Magnesium thioglycolate.

† Ammonium dithiodiglycolate.

‡ Average of 2 tresses.

However, these advantages would be lost if it were necessary to employ booster additives which were odoriferous. A means of overcoming this drawback would be to impregnate the waving end paper with the booster. As is shown in Table 5, satisfactory wave levels could be achieved by using either a solid thioglycolate salt (magnesium thioglycolate) or diammonium dithiodiglycolate to impregnate the waving end papers.

SAFETY EVALUATION

A. Toxicity

The acute intraperitoneal toxicity (mice) of DMA indicates that it is even less toxic than thioglycolate (L.D.₅₀ equals 425 mg./kg. for DMA *vs.* 187 mg./kg. for thioglycolate).

B. Sensitization Potential

Human volunteers were used to evaluate the sensitization potential of 0.4M DMA solutions, such as those used in the waving experiments, by a procedure previously reported (4). Of a total of 33 subjects, none reacted to either the meso- or the dl-form.

C. Primary Irritancy

The irritancy of DMA waving lotion formulations was found to be low in the same range of irritancy as standard thioglycolate lotions. No untoward reactions were observed in over 100 subjects given waves with such compositions.

DISCUSSION

When compared to thioglycolate as an agent for waving hair, DMA has several advantages and certain disadvantages. The main disadvantages are higher cost and the need for a booster additive, such as thioglycolate, in small amounts. It has the advantages of excellent stability in the dry state or in lotion form (in the absence of oxygen, of course) and of very low odor. Most other mercaptans reported in the literature (5) seem to cause sensitization reactions in humans, but DMA, like thioglycolate, apparently does not.

Attempts were made to boost the waving activity of DMA by converting it to amide or ester derivatives (6). Although in general it is possible to boost the waving activity of mercapto acids by such modifications, this has not been successful with DMA. However, when used on hair which has been previously waved or bleached, DMA does not require any waving boost to produce satisfactory results.

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