MANDELIC ACID AND ITS SALTS

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MANDELIC ACID

Mandelic acid so-called from the German word "mandel" meaning almond was discovered by F. L. Winckler (1) in 1831.

Winckler (1), (2), (3) first prepared the mandelic acid from bitter almond oil which was obtained by distilling eighty ounces of bitter almond paste with ninety pounds of water until one hundred and sixty ounces of distillate had passed over. Eighty ounces of this liquid was then taken, shaken up with the bitter almond oil, mixed with four ounces of hydrochloric acid sp. gr. 1.12, and evaporated to dryness over the water bath. The yellowish crystalline residue was treated with cold ether leaving behind sal-ammoniac. The etheral solution yielded by spontaneous evaporation a slightly yellow crystalline mass, which when treated with water, left a resinous flocculent body having the odor of bitter almonds. The aqueous solution was transparent and colorless, and contained pure mandelic acid which crystallized upon evaporation.

Other early methods of preparation of mandelic acid were Laurent's (4) method which consisted of the action of fuming sulfuric acid on bitter almond oil, and Wöhler's (5) method which was by heating amygdalin with fuming hydrochloric acid.

Mandelic acid is now prepared synthetically (6) by allowing sodium cyanide to react with the sodium bisulfite addition compound of benzaldehyde. The mandelonitrile thus formed is isolated and hydrolyized to give the impure acid, which is separated and purified.

Mandelic acid is a white, crystalline compound which gives a colorless, clear solution in water, alcohol, and alkali. It has a faint odor and possesses a sharp, salty taste. The solubility is 16 Gm. in 100 cc. of water at 20° C; 53.6 Gm. dissolve in 100 cc. of ethyl alcohol at 16.5° C. The melting point of the substance is 118 - 120°C.

Mandelic acid is slightly unstable, slowly turning yellow when exposed to light. It reacts with alkalis and basic substances. A saturated aqueous solution reacts strongly acid to Congo red test paper and slightly acid to Cresol red paper.

Not until recent years has the chemotheraputic usefulness of mandelic acid been recognized in the treatment of urinary tract infection. As early as 1883 Schotten (7) determined that the drug when fed to dogs could be almost entirely recover from the urine. However, its bactericidal value was only recognized when Rosenheim (8) of England in 1935, searching for a drug similar to betahydroxybutyric acid, which when given by mouth would resist oxidation and be eliminated in the urine, discovered the theraputic usefulness of mandelic acid. Betahydroxybutyric acid had been proved by A. T. Fuller (9) in 1933 to be responsible for the bacteriological effect of the ketogenic diet. Unfortunately, betahydroxybutyric acid in addition to being difficult to obtain is completely oxidized in the body. Rosenheim found that mandelic acid could be recovered unchanged in the urine, and that in sufficient dosage, it would kill bacteria provided the urine was highly acid.

Actions and Uses: - Mandelic acid is a non-metabolizable substance which when administered by mouth is excreted unchanged in the urine, and if the pH of the urine is kept at 5.5 or less it is rendered bactericidal or bacteriostatic against Escherichia coli, Aerobacter aerogenes, Streptococcus jaecalis and organisms of the Proteus, Pseudomonas, Alcaligenes, Salmonella and Shigella groups. The acidity should be controlled by frequent determination of the pH. In cases in which the acidity is not reduced to pH 5.5 or less, other acidifying agents such as ammonium chloride, ammonium nitrate or nitrohydrochloric acid may be administered concurrently providing there are no contra indications; the ketogenic diet may also be employed. Fluid intake should be restricted to an amount not exceeding 1200 cc. daily. It is usually neither necessary nor advisable to continue mandelic acid therapy longer than from twelve to fourteen days, as renal irritation may ensue. Nausea, diarrhea, dysuria and hematuria may also occur occasionally, requiring reduction in dosage or interruption of therapy. Mandelic acid should not be administered in the presence of renal insufficiency, as an inadequate concentration is obtained in the urine; renal irritation may result, and serious acidosis may occur from retention of the acid.

The usual dosage is 3 Gm. four time a day either as the free acid or in the form of the sodium or ammonium salt. An additional acidifying agent is usually required when the sodium salt is employed. (6)

Mandelic acid is rendered palatable by the addition of syrup of orange in such a formula as the following, (10)

R_x	Mandelic acid	gr. xxxxv
	Sodium bi-carbonate	gr. xxiv
	Syrup of Orange	1 dram
	Water q.s.	1 fl. oz.

Tests for acidity of the urine are usually carried out in early morning specimens of the urine using a solution of methyl red as an indicator. Five drops of the indicator is added to 2 cc. of the urine in a test tube, when a pH 5.3 - 5.5 produces a reddish-orange color. If the color is yellow red, the urine is insufficient acid. This is overcome by administering one gram of ammonium chloride four times daily. A red color shows that the urine is too acid. This is overcome by administering sodium bi-carbonate. (10)

SODIUM MANDELATE

Sodium mandelate appeared on the market to obviate the necessity of preparing it extemporaneously. It is a white crystalline powder, soluble in water (1-3), and insoluble in alcohol. The dose is 3.4 Gm. (50 gr.) four times daily, equivalent to three grams of the mandelic acid. It was felt that the treatment had not yet attained prefection; very many patients requiring ammonium chloride and, while not being too unpleasant when taken for a short period, after a time caused nausea or even vomiting. Occasionally casts and albumin were found to be present in the urine, and Rosenheim (8) considered the chloride to be responsible for these complications. Investigations were, therefore, carried still further. (10)

AMMONIUM MANDELATE

Ammonium mandelate was tested clinically by Holling and Platt (11), excellent results being obtained. The pure substance is in the form of white hygroscopic crystals very soluble in alcohol and water. On account of its hygroscopic nature it is usually obtained commercially as a 50% aqueous solution. It may be prepared by neutralizing mandelic acid with ammonium carbonate, or a strong solution of ammonium hydroxide having the advantage of the excess being dispersed by heat generated during the reaction.

As 3.3 Gm. (52 gr.) of ammonium mandelate is equivalent to three grams of acid, this amount is given four times daily. Liquid extract of licorice masks its unpleasant taste, and the following formula in use at the Hospital for Sick Children is said to make a moderately palatable mixture.

R_x	Ammonium mandelate	26 gr.
	Liq. Ext. of Glycyrhiza	5 m.
	Elixir of Saccharin	1/5 m.
	Water q.s.	1 fl. dram

Usual daily dose for adults would be one ounce. Other flavoring agents in combination with Glycyrrhiza are in use, such as essential oils of anise, dill, and fennel. (10)

To disguise the taste of ammonium mandelate W. A. Knight (12) uses this formula:

R_x	Mandelic acid	9 drams
	Strong ammonia water	264 m.
	Liq. ext. Glycyrrhiza	240 m.
	Tinct. Capsium	20 m.
	Tinct. Ginger	20 m.
	Syrup	1 fl. oz.
	Mucilage Ceratonia	3 fl. oz.
	Chloroform water g.s.	12 fl. oz.

The dose of this mixture is one fluid ounce containing 3 Gm. of mandelic acid.

Fantus and Sison (13) gave the following formula:

Soluble saccharin	1.00	Gm.
Ammonium Chloride	50.0	Gm.
Ammonium Carbonate	80.0	Gm.
Mandelic Acid	200.0	Gm.
Sucrose	400.0	Gm.
Benzaldehyde	.04	cc.
Oil of Fennel	.10	cc.
Anethol	1.00	cc.
Fluid extract glycyrrhize	175.0	cc.
Water q.s.	1000	cc.

In a large vessel the mandelic acid and ammonium carbonate is mixed with 400 cc. of warm distilled water and allowed to stand until effervesence has ceased. The ammonium chloride, saccharin, and sucrose are dissolved in this solution by agitation. The fluid extract in which the oils have been dissolved is added, and finally sufficient quantity of water to make 1000 cc.

The average dose is 15 cc. Each dose represents three grams of mandelic acid and .75 Gm. of ammonium chloride. The mixture is prepared to be used in tablespoonful doses freely diluted with water and four times daily.

Ammonium chloride has been added to the formula to the limit of palatibility for the purpose of securing acidification of the urine with the use of a smaller quantity of the expensive mandelic acid. Saccharin was found necessary to make the product sufficiently sweet, in spite of the fact that sugar was used as well as fluid extract of glycyrrhiza, a combination which, after numerous experiments seemed to yield the best available disguising vehicle.

In the body ammonium mandelate is broken down into urea and mandelic acid. In the majority of cases the urine is sufficiently acid without the administration of ammonium chloride. (11)

At the Hospital for Sick Children, W. W. Payne (14) prescribes ammonium phosphate in place of the chloride when an acidifying agent is needed. It is by no means so nauseating, particularly when dispensed according to the formula:

R_x	Ammonium phosphate	7 1/2 gr.
	Liquid extract of glycyrrhiza	1 1/2 m.
	Citric acid	1/4 gr.
	Oil of lemon	1/120 m.
	Syrup	15 m.
	Water q.s.	1 fl. dr.

Ammonium mandelate has well fulfilled the expectations of the physicians who introduced it, and gives rise to complications less often than sodium mandelate. In an attempt to eliminate these entirely, still another salt of mandelic acid has come into use.

CALCIUM MANDELATE

Calcium mandelate is a white granular powder insoluble in water. It is prepared by double decomposition of sodium mandelate and calcium chloride. It was introduced as a urinary antiseptic by E. Schnohr (15). In the stomach it is changed into calcium chloride and mandelic acid. Calcium mandelate is tasteless and seldom causes dyspeptic discomfort (11) (16). Schnohr recommended the following formula dispensed in the form of granules:

R_x	Calcium mandelate	72.25
	Cocoa powder	7.50
	Sucrose	20.00
	Soluble saccharin	.02

One level desert spoonful is equivalent to two grams of mandelic acid. It is occasionally found necessary to supplement treatment by ammonium chloride or phosphate to produce the required acidity. (11)

CYCLOHEXYLAMMONIUM MANDELATE

The salt was first prepared by Stuart (10) in 1938 by reacting 50 Gms. of mandelic acid dissolved in 200 cc. of 95% ethyl alcohol with 35 cc. of cyclohexylamine dissolved in 65 cc. of 95% ethyl alcohol. The two solutions are mixed rapidly and the cyclohexylammonium mandelate separates out immediately. It is washed with alcohol and air dried at

130° F. Yield obtained equals 77 Gms.

Cyclohexylammonium mandelate is a non-hygroscopic, white crystalline powder, m.p. 208° c, soluble in water, slightly soluble in alcohol, and insoluble in ether. It may be administered as an elixir in dilute alcohol. It is preferably administered, however, in enteric coated tablets.

If the urinary infection is caused by B. coli, cyclohexylammonium mandelate is usually sufficient to produce adequate acid in the urine to enable the mandelic acid to be effective. However, if the infection is due to B. proteus, such infection causes fermentation in the bladder with a resultant production of such high alkalinity in the urine that the mandelate is unable to act effectively against the infection. In such cases it is desirable to administer with the mandelate a suitable amount of an acidifying agent, such as ammonium chloride or nitrate. Relatively small amounts are needed in comparison to the amount needed when sodium mandelate is administered.

Stuart found it advantageous to use about one gram of the acidifying agent to two to four grams of the mandelate for the production of enteric coated tablets.

Stuart claims as the advantages for his compound that it is easy to obtain in the crystalline form and, unlike sodium or ammonium mandelate is non-hygroscopic. It is free from any alkali which might make it more difficult to acidify the urine. In addition, it is a mandelate whose taste can be rather easily masked in the form of an elixir.

METHENAMINE MANDELATE

The dosages necessary to accomplish theraputic results with mandelic and its aforementioned salts is so large (12 Gms. daily) that a physician will resort to the use of it in desperate cases only. Further, it is necessary to administer simultaneously a large amount of ammonium chloride, or other agent, to acidify the urine. The gastric disturbances caused by this treatment makes their use undesirable.

Since the establishing of mandelic acid as a urinary antiseptic and knowing that methenamine is also a valuable urinary antiseptic, it is reasonable to assume that a combination of the two might yield a compound more satisfactory than either when used alone. E. T. Tiza (18) in 1938 set about to determine the advantages and disadvantages of the combination of these two salts, and has given several methods for the preparation of methenamine mandelate.

Methenamine itself shows very little bactericidal action when tested in vitro. However, the methenamine mandelate shows a decided bactericidal action when tested by the same method. Further, this bactericidal action is about three to five times higher than that of mandelic acid alone.

Following are some specific methods for preparing the new compound methenamine mandelate. (18)

Example 1. 14 Gms. methenamine (I) and 15.2 Gms. d.l. mandelic acid (II) are dissolved in 30 cc. of water, filtered and evaporated in a vacuum at 40° C. to dryness.

Example 2. 14 Gms. (I) and 15.2 Gms. (II) are dissolved in 50 cc. of hot methanol and boiled on a steam bath until the salt begins to crystallize, and then cooled in an ice bath. The crystals are collected in a filter, washed with ice cold methanol, and dried.

Example 3. 14 Gm.s (I) and 15.2 Gms. (II) are dissolved in 50 cc. of hot chloroform and boiled on the steam bath until crystallization. The solution is then cooled in ice and the crystals collected, washed with ice cold chloroform, and dried.

Example 4. .92 Gm.s (I) and 1.0 Gm. d mandelic acid are dissolved in 10 cc. of chloroform, evaporated on the steam bath until crystallization, and then cooled in an ice bath. The crystals are collected on a filter and recrystallized from chloroform. M. P. 186-188° C with decomposition.

Example 5. 1.42 Gm. (I) and 1.5 Gm. l-mandelic acid are dissolved in 10 cc. of methanol and evaporated on a steam bath to crystallization and then cooled in ice. The crystals are collected on a filter and recrystallized from methanol. M. P. 217 - 219° C. with decomposition.

Example 6. (19) A solution of 79.2 Gm. of (I) and 86 Gm. of (II) in 100 cc. of water is concentrated to a volume of 85 cc. and allowed to crystallize in the cold. The crystalline material is filtered and recrystallized from 200 cc. of absolute alcohol from which the product was obtained as clumps of small, white, granular crystals (54 Gms). M. P. 130 - 132° C. The original mother liquor on further concentrating and cooling yielded 88 Gm. more of the salt melting at 129 - 131° C.

As there is no appreciable difference in the bactericidal action of d, l, or d.l. mandelic acid, either of the optical isomers or the inactive mandelic acid will serve the same purpose. For technical reasons the d.l. mandelate is the preferred compound.

As methenamine is monobasic, it combines with one molecule of mandelic acid. The white crystalline product formed has the formula $C_6H_{12}N_4 \cdot C_6H_5$ CH(OH) COOH. It is very soluble in water, alcohol, acetone, chloroform, slightly soluble in cold, more in hot benzene, insoluble in ligroine. The melting point of methenamine d.l. mandelate is 128 - 130° C.

The product shows a decided bactericidal action against cocci and bacilli. The increase in action over both methenamine and mandelic acid is shown in the following table. The test was made by the agar plate method. Those plates which did not show any growth after 48 hours incubation were subcultured.

Dilution	Methenamine		Man. Ac.		Meth. Mandelate	
	s.	c.	s.	c.	s.	c.
1:200	0-	+	0-	0-	0-	0-
1:400	+	+	0-	0-	0-	0-
1:600	+	+	0-	+	0-	0 +
1:800	+	+	+	+	0-	+
1:1000	+	+	+	+	0-	+
1:1500	+	+	+	+	0-	+
1:2000	+	+	+	+	+	+
Control	+	+	+	+	+	+

s = staphylococcus

c = Escherichia coli

0 = no growth on plate

- = no growth on subculture

+ = growth

This table clearly shows the improvement in bactericidal action. Considering the fact that methenamine mandelate contains only 50% mandelic acid, the bactericidalaction against Staphylococcus increased five times and against coli three times. (18)

EXPERIMENTAL

The object of the work was to prepare methenamine mandelate and to incorporate it into a palatable preparation.

Methenamine mandelate was prepared according to Example 6. In making the compound by this method, it was found necessary to concentrate the solution to a volume of 85 cc. by the use of a vacuum and moderate heat. The first yield obtained was 54.8 Gm. of the salt with a melting point of 115 - 118° C. After recrystallization from hot ethanol the melting point was 128-130° and the yield 33 Gms.

Eighty grains of the salt, equivalent to ten grains to a teaspoonful, was then made into one fluid ounce preparations using the different flavoring agents found in the laboratory. The aim was to find a vehicle usually present and commonly used in the prescription department. With one-half ounce syrup of orange and one-half ounce of water a not unpleasant, but salty preparation was obtained. When elixir of glycyrrhiza was used instead of syrup of orange, no improvement in palatibility was made, in fact it did not taste as well as the syrup of orange preparation. On standing the elixir of glycyrrhiza preparation forms a sediment which is a disadvantage. Syrup of sarsaparilla compound also yielded sediment on standing. When the salt was incorporated into the formula of W. A. Knight, given for disguising the taste of ammonium mandelate, a slight sediment also formed and the solution tasted no better than the others. Mucilage of ceratonia was left out of the formula as no method for its preparation could be found. Syrup of cinnamon yielded the most palatable preparation and did not form any sediment upon standing.

In conclusion it is suggested that methenamine mandelate be dispensed according to the formula:

R_x Methenamine mamdelate gr Lxxx
Water ʒ ii
Syrup of cinnamon q.s. ℥ i

This preparation was found to be the most palatable. Since syrup of cinnamon is in most cases on hand in the prescription room, the formula offers a simple and quick method of dispensing methenamine mandelate.

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