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The Preparation of Substituted Mandelic Acids and their Bacteriological Effects. III

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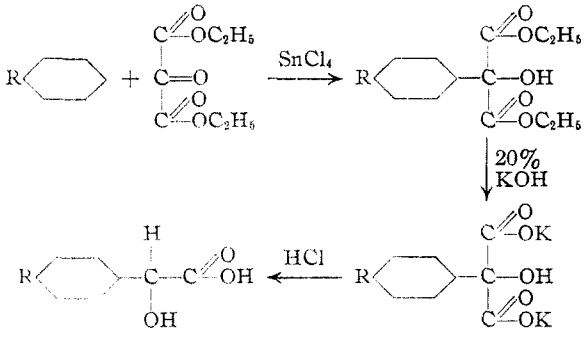
Up to the present publication in this series,[1,2] we have confined our attention essentially to the preparation of halogen and alkyl substituted mandelic acids in which substitution has been on the benzene ring. This paper not only extends the series of ring substituted compounds but also describes eight compounds in which the hydroxy groups of certain mandelic acids have been changed to acetyl or propionyl. This type of compound was considered of interest because its efficacy as a bacteriocide might give some indication concerning the bacteriological significance of the hydroxyl group in the original molecule.

The Ando synthesis which may be summarized as follows



was used with a number of aromatic compounds such as diphenylmethane, diphenyl, β-methylnaphthalene, α-methylnaphthalene, triphenylmethane, fluorene, acenaphthene and anthracene, hoping to prepare the corresponding hydroxy acetic acids. While the acids prepared from these more complex hydrocarbons may require a stretch of the rules of nomenclature to regard them as derivatives of mandelic acid, yet it seems appropriate to consider them here. Of the eight hydrocarbons listed above, only the first two of the series reacted as expected.

Experimental

The method used for the preparation of the nuclear substituted mandelic acids was the same as previously described.[1,2] The same method was used for β-methylnaphthalene and the other more complex hydrocarbons except that a solvent (usually chloroform) was used either to make a suspension or solution of the solid hydrocarbons.

To prepare the acetyl or propionyl derivatives the appropriate mandelic acid and twice the theoretical amount of acid chloride were refluxed gently for ten to twelve hours. The resulting mixture was cooled and poured into cracked ice. In most cases a solid separated at once. The solid was filtered, dried and crystallized from benzene or benzene–petroleum ether mixtures. Table I summarizes the properties, yields, analyses and bacteriological data for the substituted mandelic acids. The bacteriological activity of each acid is compared with mandelic acid as unity. These tests were made *in vitro* on *B. coli*.

The intermediates for the *p*-benzyl, 2,4-, 3,4- and 2,5-dimethyl mandelic acids boiled under a pressure of 4–5 mm. at 225–230, 150–155, 157–160, and 154–156°, and were obtained in yields of 51, 47, 51, and 47%, respectively. The intermediate from the *p*-phenyl derivative was not distilled, so its yield could not be ascertained.

It will be noticed that no mention is made in Table I of derivatives from α-methylnaphthalene, β-methylnaphthalene, acenaphthene, fluorene, anthracene or triphenylmethane. When α-methylnaphthalene was subjected to the usual reaction conditions, the mixture turned almost black. Upon washing with water and distilling, 7 g. of a viscous oil was produced, b. p. 180–230° at 2 mm. pressure, which apparently was the expected intermediate, but upon saponification and subsequent acidification only a thick oil was formed from which no crystals could be obtained. Essentially the same observations were made with acenaphthene. β-Methylnaphthalene gave a very low yield of an acid, m. p. 146.5–147.5°, neutralization equivalent 217.8, and a carbon–hydrogen analysis which corresponded with a β-methylnaphthylhydroxyacetic acid. We were unable to prove the identity of this product.

In the cases of fluorene and anthracene the mixtures became deep purple in color when stannic chloride was added but none of the expected

(1) Riebsomer, Irvine and Andrews, THIS JOURNAL, **60**, 1015 (1938).

(2) Riebsomer, Baldwin, Buchanan and Burkett, *ibid.*, **60**, 2974 (1938).

TABLE I

Mandelic acid derivative	Bacteriological activity (mandelic acid = 1)	Yield of acid, %	M. p. of acid, °C.	Neut. equiv. Calcd.	Neut. equiv. Found	Combustion analyses, % Calcd. Carbon	Calcd. Hydrogen	Found Carbon	Found Hydrogen
2,4-Dimethyl	3.5	44	113–115	180.1	180.6	66.6	6.7	67.1	6.8
3,4-Dimethyl	3.5	37	135	180.1	179.3	66.6	6.7	66.4	6.8
2,5-Dimethyl	3.5	37	116.5–117	180.1	180.0	66.6	6.7	66.4	6.8
p-Phenyl	0	63	192	228.1	229.3	73.7	5.3	73.7	5.6
p-Benzyl	< 1	26	133.5–134.5	242.1	238.6	74.4	5.8	74.3	6.4
Acetyl	1	94	76–76.5	194.1	192.6	61.8	5.2	61.5	5.3
Acetyl-2,4-dimethyl	0.5	74	92	222.2	222.0	64.8	6.4	65.3	6.4
Acetyl-2,5-dimethyl	< 1	72	112–113	222.2	221.2	64.8	6.4	64.5	6.4
Acetyl-*p*-phenyl	< 1	63	133	270.2	269.9	71.1	5.2	70.6	5.1
Acetyl-*p*-methyl	0.5	71	104–105	208.2	207.0	63.5	5.8	63.2	5.9
Propionyl	2	55	58	208.2	208.0	63.5	5.8	63.9	5.9
Propionyl-2,5-dimethyl	< 1	89	86	236.2	236.2	66.1	6.8	66.0	6.7
Propionyl-*p*-phenyl	0	64	107	284.2	284.0	71.8	5.6	72.3	5.6

products were obtained. The appearance of this purple color is typical of many of these reactions which do proceed as desired.

When triphenylmethane was run through the usual reaction routine, an acidic compound which crystallized from benzene (m. p. 90–95°) was formed but we were unable to get a product with a sharp melting point upon further crystallizations. The neutral equivalent was 335.5; calculated for the expected compound, 318.2, This material discolored upon standing. Its identity was not established.

The structures of the three dimethylmandelic acids described in Table I were determined previously[3] by careful permanganate oxidation to the corresponding dimethylbenzoic acids. The 2,4- and 3,4-dimethylmandelic acids were previously prepared by Ando but not tested bacteriologically.

The mandelic acid prepared from diphenyl was oxidized with dilute permanganate and produced diphenyl-4-carboxylic acid, m. p. 228°, thus indicating this product to be *p*-phenylmandelic acid. The compound prepared from diphenylmethane was shown to be *p*-benzylmandelic acid by permanganate oxidation to *p*-benzylbenzoic acid, m. p. 154–155°.

Discussion

The mixture of isomeric dimethylmandelic acids, which may be obtained using a commercial xylene mixture in the Ando synthesis, shows the same bacteriological activity as the pure isomers (3.5). This mixture would therefore appear to be better than mandelic acid in treating urinary tract infections, especially since its cost of production could be relatively low. Unfortunately, when the mixture of isomers was injected intravenously into rabbits it proved to be somewhat more toxic than mandelic acid. Accordingly its use in medicine is prohibited.

It was hoped that converting the hydroxy group of some of these mandelic acids to the acetyl or propionyl group would throw some light on the significance of the hydroxy group in the bacteriological activity of mandelic acids. It is obvious from the results shown in Table I that the data are conflicting and that no conclusions are justifiable.

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Summary

1. The synthesis and bacteriological activity of thirteen mandelic acids are reported.

2. Only the dimethyl derivatives show markedly greater activity than mandelic acid, but they proved to be too toxic to be used medicinally.

(3) Riebsomer and Burkett, *Indiana Acad. Sci.*, **48**, 75 (1939).

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