[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DEPAUW UNIVERSITY]

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

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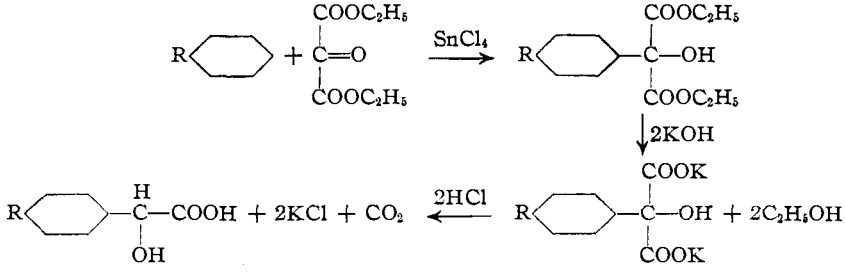
In 1935, Rosenheim[3] published an article in which he reported a study of the successful use of mandelic acid as a urinary antiseptic. Since that time several such studies have been made,[4] and the treatment is successful in most of the cases reported. There seems to be, however, one objection to it: namely, that the dosage required is larger than desirable, and that in consequence the treatment is in some cases accompanied by considerable unpleasantness.

Consequently, we have undertaken the preparation of a number of substituted mandelic acids with the hope that we might find a compound with the desired bacteriological effects when administered in smaller dosages. In this paper eight of these compounds have been prepared and examined.

All the alkyl derivatives were prepared by the method suggested by Ando.[5] This author showed that benzene and alkylbenzenes reacted with ethyl oxomalonate in the presence of anhydrous stannic chloride to produce an intermediate condensation product which upon hydrolysis and subsequent treatment with hydrochloric acid produced alkyl substituted mandelic acids. The essence of the process may be represented by the equations



Ando demonstrated that the reaction proceeded satisfactorily with benzene, toluene, *o*-xylene and *m*-xylene. We have corroborated this work except for the facts that 2,4-dimethylmandelic acid was the main product obtained from *m*-xylene instead of the 2,6-dimethyl derivative, and 3,4-dimethylmandelic acid was produced from *o*-xylene instead of the 2,3-dimethyl derivative. We have made a careful study of the optimum conditions of time, temperature and concentrations of reagents for the reaction. The reaction takes place in various solvents such as chloroform or carbon disulfide and various condensing agents other than stannic chloride have been used with some success.[6]

Furthermore, we have used the method to date to prepare ten alkylmandelic acids in addition to the four reported by Ando, and have shown that naphthalene can be used as the hydrocarbon to produce naphthylhydroxyacetic acids. Preliminary experiments indicate that the process may not be limited strictly to the alkylbenzenes. Hence the method appears to be sufficiently general to be of value. Further work is in progress in this Laboratory on various ramifications of this reaction.

Experimental

Preparation of alkyl substituted mandelic acids. The method for the preparation of these compounds was essentially that described by the authors previously.[6] The hydrocarbon (usually 0.25 mole) and ethyl oxomalonate (usually 0.05 mole) were mixed in a dry 3-necked flask, fitted with a stirrer and condenser, and anhydrous stannic chloride added with stirring over a period of two to three hours, while the temperature was kept from 0 to 10°. This product was added to cold water containing hydrochloric acid, stirred, extracted with ether, the ether solution washed with water until chloride free, and the resulting mixture fractionally distilled, collecting the condensation product at the proper temperature. This product was hydrolyzed in each case by warming it over a steam-bath for four to five hours with five times its weight of 20% aqueous potassium hydroxide solution, and the alkaline solution was then extracted with ether to remove impurities. The aqueous solution of the potassium salts was then acidified with hydrochloric acid and warmed over a steam-bath for four to five hours to expel carbon

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(3) Rosenheim, *Lancet*, **1**, 1032–37 (1935).

(4) Alexander, *ibid.*, **1**, 391 (1936); Cubitt, *ibid.*, **1**, 922 (1936); Holling and Platt, *ibid.*, **1**, 769–771 (1936); Lyon and Dunlop, *British Med. J.*, 1096–97 (1935).

(5) Ando, *J. Chem. Soc. Japan*, **56**, 745–756 (1935); *C. A.*, **29**, (1935).

(6) Riebsomer, Irvine and Andrews, *Proc. Indiana Acad. Sci.*, **47**, in press (1937).

TABLE I

Mandelic acid derivative	Hydrocarbon used	B. p. intermediate 4-5 mm., °C.	Yield intermediate, %	Yield acid, %	M. p. acid, °C.	Neutral equivalent Calcd.	Neutral equivalent Found	Combustion analyses, % Calcd. C	Calcd. H	Found C	Found H
p-Methyl	Toluene	150–155	60	58	145–145.5	166.1	166.1	65.03	6.06	65.04	6.25
p-Ethyl	Ethylbenzene	157–160	56	33	141–142	180.1	180.4	66.63	6.72	66.66	6.78
p-Isopropyl	Isopropylbenzene	170–174	46	36	159.2–160	194.1	194.2	68.08	7.22	68.01	7.18
p-*s*-Butyl	*p*-*s*-Butylbenzene	170–176	64	38	108–109	208.1	206.0	69.19	7.75	68.99	7.73
p-*t*-Butyl	*t*-Butylbenzene	183–185	56	40	149.5–150	208.1	208.7	69.19	7.75	69.75	7.81
2,4,6-Trimethyl	Mesitylene	164–168	59	47	148–148.5	194.1	195.5	68.08	7.22	67.83	7.22

dioxide. The resulting mandelic acid was extracted with ether and crystallized from the proper solvent. Benzene, petroleum ether, and chloroform or mixtures of these reagents served as solvents for purification.

The calculations of the yields which follow are based on the ethyl oxomalonate used.

Table I lists a summary of the properties, yields, and analyses of the alkyl substituted mandelic acids.

The *p*-methyl, *p*-ethyl, and *p*-*s*-butylmandelic acids were treated with alkaline potassium permanganate solution, and the acids thus produced were converted into the methyl esters. In each case the ester melted at 140°, which corresponds to dimethyl terephthalate, thus establishing the fact that the alkyl groups of these compounds are in the para position.[7]

The *p*-isopropylmandelic acid was oxidized with dilute chromic acid to *p*-isopropylbenzoic acid, and with concentrated chromic acid to terephthalic acid, thus indicating the isopropyl group to be in the para position.

The derivative from *t*-butylbenzene was oxidized with alkaline permanganate and *p*-*t*-butylbenzoic acid (m. p. 163–164°) was produced, which demonstrates that the tertiary butyl group is in the para position.

o-Chloro- and *p*-chloromandelic acids were prepared by the method suggested by Jenkins,[8] which consisted of converting the corresponding aldehydes to the nitriles, followed by hydrolysis to the mandelic acids. These compounds checked with known data in melting points, neutral equivalents, and halogen analyses.

Table II gives a summary of the bacteriological tests. These tests were carried out *in vitro* on three different organisms (*B. coli*). The activity of mandelic acid is regarded as unity for comparison.

TABLE II

Mandelic acid derivative	Activity
Mandelic	1
o-Chloro-	1
p-Chloro	2–4
p-Methyl	1–2
p-Ethyl	1–4
p-*s*-Butyl	1–2
p-*t*-Butyl	Less than 1
p-Isopropyl	1
2,4,6-Trimethyl	1–4

Since these compounds have not been administered to animals it is impossible to draw any conclusions regarding their merits as medicinals.

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Summary

1. Eight substituted mandelic acids have been prepared and their bacteriological activity compared with mandelic acid.

2. The method of Ando for the preparation of alkyl substituted mandelic acids has been corroborated and extended.

3. Some of these derivatives seem to be more active than mandelic acid as shown by the *in vitro* tests but no definite conclusions can be made concerning their medicinal value until animal tests have been performed.

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(7) Mulliken, "Identification of Pure Organic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1904, p. 85.

(8) Jenkins, THIS JOURNAL, **53**, 2341 (1931).