Anal. Calcd. for $C_{11}H_{15}NO_4$: C, 58.64; H, 6.72; N, 6.22. Found: C, 58.91; H, 6.60; N, 6.36.

1,2-Dimethoxy-3-isopropyl-5-aminobenzene (VI).—The corresponding nitro compound was reduced in absolute ethanol solution at 2–3 atm. with Raney nickel as catalyst. The product was purified by sublimation, white crystals, m. p. 75° (corr.). The yield was 0.055 g. from 0.1 g. of nitro compound.

Anal. Calcd. for $C_{11}H_{17}O_2N$: C, 67.70; H, 8.72; N, 7.18. Found: C, 67.55; H, 8.77; N, 7.14.

This substance gave no depression in melting point when mixed with the compound assumed to have this structure and prepared from apogossypolic acid.[3]

1,2-Dimethoxy-3-isopropyl-5-diacetaminobenzene.—The amine was acetylated with acetic anhydride and sodium acetate in an 81% yield. The product was purified by washing the ether solution with 5% hydrochloric acid, evaporation of the solvent and sublimation. It formed white crystals, m. p. 86° (corr.).

Anal. Calcd. for $C_{15}H_{21}O_4N$: C, 64.52; H, 7.53; N, 5.02. Found: C, 64.57; H, 7.41; N, 5.01.

A mixed melting point of this product with the diacetyl derivative of the amine obtained by degradation of apogossypolic acid gave no depression.[3]

1,2-Dimethoxy-3-isopropyldinitrobenzene.—By nitrating 1,2-dimethoxy-3-isopropylbenzene as previously described except that excess nitric acid was used, a dinitro derivative was obtained. It was purified from methanol in yellow crystals, m. p. 106° (corr.).

Anal. Calcd. for $C_{11}H_{14}N_2O_6$: N, 10.31. Found: N, 10.10.

Whether the two nitro groups are both in the benzene ring or one in the ring and the other replacing the tertiary hydrogen of the isopropyl group was not determined. By analogy to the dinitro derivative of 1,2-dimethoxy-3-methylbenzene, it is probable that the two nitro groups occupy the 5-, 6-positions.[4b]

1,2-Dimethoxy-3-isopropyldiaminobenzene.—The reduction of the dinitro compound in absolute ethanol with Raney nickel as catalyst gave a diamine which was purified by sublimation to white crystals, m. p. 75° (corr.). This product was very unstable to atmospheric oxygen and turned brown rapidly.

Anal. Calcd. for $C_{11}H_{18}O_4N_2$: N, 13.13. Found, N, 13.14.

Summary

The synthesis of 1,2-dimethoxy-3-isopropyl-5-aminobenzene has been accomplished. It proved to be identical with the compound prepared from apogossypolic acid by nitration, subsequent reduction and sublimation.

This synthesis confirms the character of the functional groups in the 1-, 5-, 6-, 7- and 8-positions of the naphthalene nuclei in the previously postulated formula for gossypol.

URBANA, ILLINOIS RECEIVED OCTOBER 17, 1938

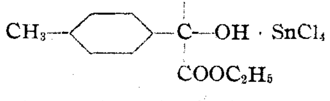
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DEPAUW UNIVERSITY]

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

BY J. L. RIEBSOMER, ROBERT BALDWIN, JACK BUCHANAN AND HOWARD BURKETT

It has been shown previously by work in this Laboratory[1,2] that alkyl substituted mandelic acids can be prepared readily from alkyl benzenes and ethyl oxomalonate when treated in the presence of anhydrous stannic chloride or certain other condensing agents. The intermediate condensation products are hydrolyzed and decarboxylated to form the corresponding mandelic acids. The purpose of the present work was to extend the studies reported in the first paper of this series[2] and to point out certain additional observations made on the general reaction mentioned above.

In nearly every case when anhydrous stannic chloride is added to an alkyl benzene–ethyl oxomalonate mixture a thick sticky solid separates out. With the hope that a knowledge of the composition of such a typical solid might contribute to an understanding of the mechanism of the general reaction, the solid which separated when toluene, ethyl oxomalonate and stannic chloride were mixed was purified and analyzed. This solid was very hygroscopic and immediately decomposed when added to water with the production of an oily layer. The aqueous solution gave qualitative tests for tin and chloride. The oily layers when hydrolyzed produced *p*-methylmandelic acid. A quantitative analysis for chloride indicated the compound to be an addition product as follows



This result is what would be expected from a consideration of the work of Voskresenskaya[3] who showed that the esters of several dibasic acids react with stannic chloride to form similar addition

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(1) Riebsomer, Irvine and Andrews, *Ind. Acad. Sci.*, **47**, in press (1937).

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

(3) Voskresenskaya, *C. A.*, **32**, 2551 (1938).

TABLE I

Mandelic acid derivative	Benzene derivative or hydrocarbon used	B. p. intermediate 4–5 mm. °C.	Yield, %		M. p. acid, °C.	Neut. equiv.		Combustion analyses, %			
			Intermediate	Acid		Calcd.	Found	Calcd. C	Calcd. H	Found C	Found H
p-*n*-Propyl	*n*-Propylbenzene	170–175	40	20	126–126.5	194.1	191.7	68.08	7.22	67.77	7.20
p-*n*-Butyl	*n*-Butylbenzene	176–177	59	25	116.5–117	208.1	208.5	69.19	7.75	69.11	7.73
p-*n*-Amyl	*n*-Amylbenzene	199–204	51	8	112.5	222.1	223.6	69.92	7.92	70.11	8.14
p-Isoamyl	Isoamylbenzene			16	87–87.5	222.1	219.8	69.92	7.92	69.85	7.98
p-*t*-Amyl	*p*-*t*-Amylbenzene	178–179	95	53	73–74	222.1	220.5	69.92	7.92	69.95	8.07
p-Pentamethyl	Pentamethylbenzene			9	180–181	222.1	222.8	69.92	7.92	70.10	8.06
2,3,5,6-Tetramethyl	1,2,4,5-Tetramethylbenzene	195–210	27	1.3	163	208.1	212.0	69.19	7.75	68.68	7.60
p-Bromo	Bromobenzene			8.8	117.5	232.1	233.8				
p-Iodo	Iodobenzene		29	7.2	135–136	277.9	274.3				

products in a mole to mole ratio. Unfortunately, however, this discovery lends only little to an understanding of the mechanism of the condensation reaction. In fact it seems probable that the formation of this precipitate hinders rather than promotes the reaction because after its formation mixing is less efficient. This probably would help to account for the fact that the yields in these reactions are seldom greater than 60% of the theoretical and usually less.

When stannic chloride was mixed with ethyl oxomalonate a solid was produced which was probably another ester–stannic chloride addition product. It proved to be so unstable that an analysis was impossible. It would be difficult to explain how the formation of this product could promote the condensations.

Another condensing agent, boron trifluoride, was tried in the place of anhydrous stannic chloride. In general the yields of mandelic acids were low.

It was found that chloro-, bromo- and iodobenzene would each condense with ethyl oxomalonate by following the usual procedure. These condensation products hydrolyzed to form the corresponding *p*-halogen substituted mandelic acids. The yields in all cases were discouragingly low. But preliminary experiments indicate that benzene derivatives containing both a halogen and an alkyl substituent condense with ethyl oxomalonate to give respectable yields.

Experimental

Analysis of the Precipitate Formed when Stannic Chloride Was Added to a Mixture of Toluene and Ethyl Oxomalonate.—In a 200-cc. round-bottomed flask was placed 25 g. of toluene and 8.7 g. of ethyl oxomalonate. Ten cc. of anhydrous stannic chloride was added with stirring at a temperature of 0°. A white precipitate was formed which after two hours' stirring was filtered using a suction filter. The precipitate was washed with toluene several times and finally with petroleum ether (b. p. 30–40°). The product was transferred immediately to a vacuum desiccator and dried thoroughly under vacuum. Approximately 0.2-g. samples were weighed, water added to them and the solution titrated with standard silver nitrate. Calcd. % Cl for $CH_3C_6H_4C(OH)(CO_2C_2H_5)_2 \cdot SnCl_4$: 26.93; found, 26.83, 26.75.

Another portion of this solid was hydrolyzed with 20% aqueous potassium hydroxide, the product acidified and warmed as in the usual procedure, extracted with ether, the ether distilled off and the solid recrystallized from benzene, m. p. 145°. A mixed melting point with *p*-methylmandelic acid showed no depression.[4]

The method of preparation of these compounds was with minor alterations the same as reported in the first paper of this series.[2] Since pentamethylbenzene and tetramethylbenzene are solids, the preparation of the intermediates in these cases was carried out in chloroform solution. Chloroform had previously been shown to be satisfactory for this purpose.

Boron trifluoride instead of anhydrous stannic chloride was used to prepare the *p*-bromomandelic acid. In a typical experiment 45 g. of bromobenzene and 8.7 g. of ethyl oxomalonate were mixed in a flask and 2.5 g. of boron trifluoride was added under anhydrous conditions and at 0°. The resulting mixture was allowed to stand overnight and the product isolated in the usual way. The yield was about 9%. Similar experiments were made with chloro- and iodobenzene which resulted in even poorer yields. When stannic chloride was used in the place of boron trifluoride to produce *p*-bromomandelic acid a yield of 4% was obtained. Correspondingly low yields of *p*-chloro- and *p*-iodomandelic acids were obtained when anhydrous stannic chloride was used as the condensing agent.

Boron trifluoride was also used in the place of anhydrous stannic chloride with benzene and toluene in the general reaction, but in each case with poor results.

Table I presents a summary of the properties of the compounds. The yields were all calculated on the basis of the ethyl oxomalonate used.

In order to prove the structure of the *p*-*n*-propyl, *p*-*n*-butyl, *p*-*n*-amyl, *p*-isoamyl and *p*-*t*-amyl mandelic acids each of these compounds was treated with excess alkaline permanganate solution.[5] The acids so produced were converted into the methyl esters. In each case the ester melted at 140°, indicating dimethyl terephthalate. This established the para position for each of the alkyl groups.

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[4] The authors are indebted to Mr. John Bishop for this analysis.

[5] Mulliken, "Identification of Pure Organic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1904, p. 85.

In the cases of the tetra- and pentamethyl derivatives, the method of synthesis was regarded as sufficient proof of their structures.

p-Bromo- and *p*-iodomandelic acids are well known, hence their melting points and neutral equivalents were considered to be sufficient to identify these compounds.

A summary of the bacteriological data is presented in Table II. These tests were made *in vitro* on three different organisms (*B. coli*). The activities are compared with mandelic acid as a standard.

TABLE II

Mandelic acid derivative	Activity
Mandelic	1
p-*n*-Propyl	1 or less
p-*n*-Butyl	1 or less
p-*n*-Amyl	1 or less
p-Isoamyl	1 or less
p-*t*-Amyl	1 or less
Pentamethyl	No activity
2,3,5,6-Tetramethyl	Less than 1
p-Bromo	2–4
p-Iodo	2–4

The first seven of the compounds listed in Table II are so costly to prepare and show so little activity that further experimentation with them would appear fruitless. The two halogen derivatives possess sufficient activity to warrant animal tests to determine their efficacy as urinary tract antiseptics.

The authors are glad to acknowledge the coöperation of Dr. Robert S. Shelton of the Wm. S. Merrell Co., of Cincinnati, Ohio, who performed the bacteriological work, and wish to thank Dean William M. Blanchard of this department who was instrumental in securing financial aid from The National Research Council and from Mr. J. K. Lilly of Indianapolis, Indiana.

Summary

1. Nine substituted mandelic acids have been prepared and compared with mandelic acid with regard to bacteriological activity. Only the *p*-bromo- and *p*-iodomandelic acids show any promise as medicinals.

2. Ando's method for the synthesis of substituted mandelic acids has been extended for alkyl derivatives and has been shown to work poorly for halogen derivatives.

3. Boron trifluoride is not satisfactory to use in the place of anhydrous stannic chloride as the condensing agent.

GREENCASTLE, INDIANA RECEIVED AUGUST 8, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF TRINITY COLLEGE]

Amide Hydrolysis with High Concentrations of Mineral Acids

BY VERNON K. KRIEBLE AND KARL AUGUST HOLST

The hydrolysis of amides in dilute acid solutions has been studied repeatedly. There are, however, few studies on record for acid concentrations greater than normal, and these have nearly all been made on acetamide.

Benrath[1] had some indications that the velocity of hydrolysis of acetamide reached a maximum by increasing the acid concentration. This was definitely shown by Taylor[2] for both hydrochloric and hydrobromic acids although he did not find such a maximum for sulfuric acid. As we have been interested in the hydrolysis of nitriles it seemed worth while to extend the study to amide hydrolysis.

Materials and Procedure

Amides.—These were bought from well-known manufacturers and further purified. We did not try to remove all the water from formamide. This was allowed for in weighing out samples of this particular amide.

Formaldehyde.—Merck U. S. P. grade was used.

Calcium Hypochlorite.—The grade marked "H. T. H." and manufactured by the Mathieson Alkali Works was used. All other chemicals were of the blue label or reagent grade.

Procedure.—Exactly 200 cc. of acid, carefully standardized in terms of molality, was delivered to a glass-stoppered flask which was placed in a thermostat for one-half hour before the experiment was started. Enough amide was weighed out to make the solution contain from 0.5 to 0.8 mole of amide if the formol method of analysis was to be used and 0.05 mole if the oxidation method was to be used to follow the hydrolysis. The acid was poured on the amide which quickly dissolved. The solution after thorough mixing was poured into a series of Pyrex tubes. These were closed with rubber stoppers, wired down, and then put back in the thermostat. When a sample was to be taken, a tube was removed and a definite quantity pipetted into a titration beaker containing enough water to dilute the solution sufficiently to stop the reaction. This

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(1) Benrath, *Z. anorg. allgem. Chem.*, **151**, 53 (1926).

(2) Taylor, *J. Chem. Soc.*, 2741 (1930).