oic acid (see below) melted and decomposed at 182–183°, and a mixture of the two melted and decomposed over the range 150–155°.

2-Hydroxy-6-methyl-3-pyrazinoic Acid.—A solution of 3.5 g. (0.023 mole) of 2-amino-6-methyl-3-pyrazinoic acid[8] in 100 ml. of 1.00 *N* hydrochloric acid was cooled to 10° and with stirring 4.5 g. (0.065 mole) of solid sodium nitrite was added in small portions. The solution stood at room temperature for one hour, and then it was heated at 70° for one-half hour. With stirring 3.0 g. (0.035 mole) of sodium bicarbonate was added, and the solution was evaporated to dryness in vacuum. The residue was extracted with 150 ml. of hot absolute alcohol, the alcohol solution was evaporated to 25 ml., and 200 ml. of dry ether was added. The resulting brown hygroscopic precipitate was recrystallized from 20 ml. of water to give 1.2 g. of tan powder. This was recrystallized from 4 ml. of water using carbon to decolorize, and 0.8 g. of light tan crystals were obtained; m. p. 183–184° (dec.).

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.75; H, 3.92; N, 18.18. Found: C, 47.04; H, 4.23; N, 18.65.

Summary

A new pyrazine synthesis has been evolved in which 1,2-dicarbonyl compounds are caused to condense with α-amino acid amides to yield substituted hydroxypyrazines.

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[CONTRIBUTION NO. 59 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Catalytic Hydrogenation of the Benzene Nucleus. IV. The Hydrogenation of Methyl-substituted Benzoic Acids

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Introduction

In an earlier paper[1] it was demonstrated that for the polymethylbenzenes the rate of catalytic hydrogenation of the benzene nucleus was governed not only by the number of substituents but also by their position. Those compounds which were symmetrically substituted reacted much faster than did others with the same number of substituents. Evidence that this was a question of symmetrical substitution and not of symmetry in the molecule itself was found in the fact that *p*-cymene hydrogenated more rapidly than did isopropylbenzene.

In order to study this matter further, a number of compounds have now been prepared which have both methyl groups and carboxyl groups attached to a benzene ring. With such compounds it should be possible to confirm the evidence that symmetrical substitution rather than molecular symmetry is the important factor.

Experimental

Benzoic, ortho-, meta- and para-toluic acids were all obtained from the Eastman Kodak Company and were Eastman best grade materials.

2,3-Dimethylbenzoic acid was prepared from 3-nitro-1,2-dimethylbenzene. The nitro group was reduced with iron and hydrochloric acid[2] to form the amino compound, which was then converted to 3-iodo-1,2-dimethylbenzene.[3] This was then converted to 2,3-dimethylbenzoic acid using an adaptation of the Grignard reaction.[4]

2,4-Dimethylbenzoic acid was prepared by diazotization of the corresponding amino compound followed by treatment of the diazonium salt with potassium iodide.[5] The iodo compound was converted to the acid by treatment of the corresponding Grignard reagent with carbon dioxide.

2,5-Dimethylbenzoic acid was prepared by bromination of *p*-xylene[6] which was then converted to the acid by carbonation of the corresponding Grignard reagent.

2,6-Dimethylbenzoic acid was prepared from 2-amino-1,3-dimethylbenzene using the same general procedure as that employed in the preparation of the 2,3-dimethylbenzoic acid.

3,4-Dimethylbenzoic acid was prepared from *o*-xylene in a manner analogous to that used for the 2,5-dimethylbenzoic acid.

3,5-Dimethylbenzoic acid was prepared from mesitylene by oxidation with dilute nitric acid.[7]

2,3,4-Trimethylbenzoic acid was prepared; 3-iodo-1,2-dimethylbenzene was treated with magnesium and dimethyl sulfate to form hemimellitene in the same manner as that used in the preparation of isodurene.[8] The hydrocarbon was converted to 2,3,4-trimethylbenzaldehyde through the action of zinc cyanide in the presence of hydrogen chloride gas and aluminum chloride.[9] The aldehyde was then oxidized to the desired acid by means of a 20% permanganate solution.

2,4,5-Trimethylbenzoic acid was prepared by bromination of pseudocumene[10] followed by a Grignard reaction similar to that used in the preparation of 2,3-dimethylbenzoic acid.

2,4,6-Trimethylbenzoic acid was prepared from bromomesitylene by means of a Grignard synthesis.

2,3,6-Trimethylbenzoic acid was prepared from pseudocumene.[10] The pseudocumene was first sulfonated to form pseudocumenesulfonic acid-5[11] which was then brominated. This bromination to form a mixture of 5-bromopseudocumene and 3-bromopseudocumenesulfonic acid-5 has been previously carried out by Smith and Kiess[12] but the procedure was sufficiently modified to warrant description: 136 grams of pseudocumenesulfonic acid-5 ($C_6H_2(CH_3)_3$-$SO_3H \cdot 1.5H_2O$) was suspended in 300 ml. of 20% hydrochloric acid solution; 122 g. of bromine suspended in 56

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[1] Smith and Pennekamp, THIS JOURNAL, **67**, 279 (1945).

[2] Mahood and Shaffner, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1944, p. 160.

[3] Lucas and Kennedy, *ibid.*, p. 351.

[4] Fuson and Kelton, *ibid*, **63**, 1500 (1941).

[5] Smith and Lund, *ibid.*, **52**, 4144 (1930).

[6] Smith, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1944, p. 95.

[7] Fittig, *Ann.*, **141**, 144 (1867); Snyder, Adams and McIntosh, THIS JOURNAL, **63**, 3280 (1941).

[8] *Cf.* Smith, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 360.

[9] *Cf.* Fuson, Horning, Rowland and Ward, "Organic Syntheses," **23**, 57 (1947).

[10] This was prepared by Mr. Comer Shacklett of this Laboratory by chloromethylation of mixed xylenes followed by a Grignard reaction.

[11] Smith and Cass, THIS JOURNAL, **54**, 1603 (1932).

[12] Smith and Kiess, *ibid.*, **61**, 284 (1939).

ml. of 20% hydrochloric acid was added to the cooled sulfonic acid suspension. The resulting jelly-like mass was stirred for several hours, and then allowed to stand overnight. The 5-bromopseudocumene together with some of the sulfonated material was removed by extraction with ether. The extract was washed with sodium bicarbonate until all acidic materials were removed. The ether was then removed by evaporation and the solid bromopseudocumene recrystallized from ethanol; 60 g. (50%) of white crystals, melting at 71–72° was obtained. In addition, 56 g. (33%) of 3-bromopseudocumenesulfonic acid-5 was recovered.

TABLE I

PHYSICAL CONSTANTS OF ACIDS HYDROGENATED

Acid	Corr.[a] M. p., °C.	Neutral equivalent Found	Neutral equivalent Theoretical
Benzoic	121.6–121.8	122.2	122.0
o-Toluic	106.0–107.0	136.2	136.1
m-Toluic	114.4–115.0	135.8	136.1
p-Toluic	182.0–183.0	136.3	136.1
2,3-Dimethylbenzoic	144.5–144.8	150.7	150.2
2,4-Dimethylbenzoic	125.4–125.8	150.3	150.2
2,5-Dimethylbenzoic	133.8–134.1	150.4	150.2
2,6-Dimethylbenzoic	115.8–116.2	150.0	150.2
3,4-Dimethylbenzoic	167.4–168.2	149.7	150.2
3,5-Dimethylbenzoic	171.6–172.0	150.2	150.2
2,3,4-Trimethylbenzoic	166.6–167.4	164.5	164.2
2,3,6-Trimethylbenzoic	102.4–102.8	164.4	164.2
2,4,5-Trimethylbenzoic	150.8–151.2	164.6	164.2
2,4,6-Trimethylbenzoic	157.0–158.0	164.4	164.2
2,3,4,6-Tetramethylbenzoic	169.4–170.0	178.5	178.2
2,3,5,6-Tetramethylbenzoic	179.4–180.0	178.3	178.2
2,3,4,5,6-Pentamethylbenzoic	211.0–211.6	192.0	192.2

[a] All melting points have been corrected for emergent thermometer stem.

The 5-bromopseudocumene was converted to 3-bromopseudocumenesulfonic acid-5 by the action of fuming sulfuric acid,[13] and subsequently hydrolyzed to form 3-bromopseudocumene. 2,3,6-Trimethylbenzoic acid was prepared from this bromide by a Grignard synthesis.

2,3,4,6-Tetramethylbenzoic acid was prepared using bromomesitylene as a starting material. This was converted to isodurene by the action of dimethyl sulfate on the corresponding Grignard reagent.[3] The isodurene was then brominated to form 4-bromo-1,2,3,5-tetramethylbenzene, which was then converted to 2,3,4,6-tetramethylbenzoic acid by the usual Grignard procedure.

2,3,5,6-Tetramethylbenzoic acid was obtained by brominating durene to form 3-bromo-1,2,4,5-tetramethylbenzene which was then converted to the desired acid by a Grignard procedure.

2,3,4,5,6-Pentamethylbenzoic acid was prepared by bromination of pentamethylbenzene followed by a Grignard synthesis.[4] The latter was somewhat complicated by the insolubility of both the magnesium complex in ether and the sodium salt of the acid in water. However, good yields (60%) were obtained.

It was necessary that all of these acids be very pure before hydrogenation was attempted. They were recrystallized several times; the solvent for the final crystallization was usually Eastman best grade cyclohexane. Occasionally this solvent was shaken with Raney nickel before use. Neutral equivalents of all acids were determined by titration with standard base. Table I gives the melting points and neutral equivalents of the acids.

As in earlier work, the acetic acid solvent was prepared by fractionation in a five-foot helix-packed still, and the platinum catalyst was either prepared by standard methods[14] or was a commercial sample. The hydrogenations were carried out in a low pressure Parr catalytic reduction apparatus in the manner previously described.[15] For the slower runs, the standard hydrogen reservoir tank (4.02 l.) was replaced by a smaller one (0.875 l.); 50 ml. of glacial acetic acid was used as solvent for each run. This solvent was purified before use by fractionation.

After each hydrogenation was complete, the platinum catalyst was recovered from the solution by filtration. Most of the solvent was then removed by distillation. If the product was a liquid or low-melting solid, it was purified by distillation through a 10-inch Vigreux column. If the product was of sufficiently high melting point so that good crystals could be obtained, the warm liquid from which the excess solvent had been removed was poured into water, and the crystals removed by filtration. The physical constants of the products are given in Table II.

TABLE II

PRODUCTS ISOLATED FROM HYDROGENATION

Cyclohexanecarboxylic acid derivative	B. p. cor.[a] °C.	B. p. cor.[a] Mm.	M. p., cor.[a]	Neutral equivalent Found	Neutral equivalent Theory	$n^{20}D$	Per cent. recovery
2-Methyl-	241.7–241.9	760		141.9	142.1	....	91
3-Methyl-	143.5–143.8	21		142.4	142.1	1.4570	93
4-Methyl-	143.2	20.5		142.1	142.1	....	..
2,3-Dimethyl-[b]	138.2–138.3	13.5		156.6	156.2	1.4661	87
2,4-Dimethyl[b]	143.2–143.4	21		156.1	156.2	1.4590	95
2,5-Dimethyl-[b]	150.2	21		156.0	156.2	1.4590	90
2,6-Dimethyl-			87.6–88.0	155.9	156.2		91
3,4-Dimethyl-	155.5–155.8	20.5		156.7	156.2	1.4628	88
3,5-Dimethyl-	137.6–137.7	14		155.9	156.2		91
2,3,4-Trimethyl-[b]			63.5–64.4	170.4	170.2		88
2,3,6-Trimethyl-[b]			77.8–78.2	169.6	170.2		85
2,4,5-Trimethyl-[b]			57.5–58.0	170.8	170.2		87
2,4,6-Trimethyl-			103.5–104.3	169.7	170.2		96
2,3,4,6-Tetramethyl-[b]			43.8–44.8	184.0	184.2		85
2,3,5,6-Tetramethyl-[b]			137.6–138.6	184.7	184.2		87
2,3,4,5,6-Pentamethyl-[b]			129.1–130.2	198.4	198.2		78

[a] All melting and boiling points have been corrected for emergent thermometer stem. [b] New compounds.

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[13] Smith and Moyle, THIS JOURNAL, 58, 1 (1936).

[14] Adams, Voorhees and Shriner, "Organic Syntheses," 8, 92 (1928).

[15] Smith, Alderman and Nadig, THIS JOURNAL, 67, 272 (1945).

Experimental Calculations and Results

It was established, as in previous work, that the hydrogenation reaction was first order with respect to hydrogen pressure, zero order with respect to the hydrogen acceptor, and directly proportional to the amount of catalyst used. This is also true for the compounds studied here, as is shown by Table III. These rate constants are calculated from the equation

$$\log \frac{p^0_{H_2}}{p_{H_2}} = \frac{kt}{2.303\ V}$$

by plotting $\log p^0_{H_2}/p_{H_2}$ against t, and multiplying the slope of the line thus obtained by 2.303 V.[16] These constants all referred to one gram of standard catalyst at 30°[15,17] are given in Table IV. The table also includes constants for corresponding polymethylbenzenes.

TABLE III

EFFECT OF VARIABLES ON RATE OF HYDROGENATION OF METHYL-SUBSTITUTED BENZOIC ACIDS

Acid	Moles	Grams of catalyst	Initial pressure (p. s. i.)	$k^\circ_{30} \times 10^4$
o-Toluic	0.025	0.2000	64.7	312[a]
o-Toluic	.025	.2000	17.9	319
2,3,5,6-Tetramethylbenzoic	.05	.2000	64.7	35.6
2,3,5,6-Tetramethylbenzoic	.05	.1000	64.7	34.8
2,4-Dimethylbenzoic	.03	.2000	64.5	289
2,4-Dimethylbenzoic	.01	.2000	65.0	291

[a] The units of all rate constants are liters × grams^{-1} × min.$^{-1}$.

Discussion

An examination of Table IV shows at once that the same trend is found in the reaction rate constants for the methyl-substituted benzoic acids as was found in the polymethylbenzenes. In general, the greater the number of substituents found on the benzene ring, the slower is the rate constant. However, whenever the number of substituents is the same, the position of substitution becomes important. In all cases, the most symmetrically substituted molecules hydrogenate faster. This confirms the idea that symmetrical substitution rather than molecular symmetry is the important factor in influencing the rate.

In the last column of Table IV is given the ratio of the rate constants for the corresponding methyl-substituted benzoic acids and polymethylbenzenes. This ratio, which indicates the effect of substitution of a carboxyl group for a methyl group, is fairly constant, the only noteworthy exception being the ratio of the rate constants for pentamethylbenzoic acid and hexamethylbenzene. This acid hydrogenates somewhat more readily than was anticipated. No explanation for this fact can be offered at the present time.

TABLE IV

COMPARISON OF RATE CONSTANTS WITH PREVIOUS DATA

Methylbenzene	$k^\circ_{30} \times 10^4$ [b]	Corresponding methylbenzoic acid	$k^\circ_{30} \times 10^4$	Ratio of rate constants[a]
Toluene	1800	Benzoic	1120	1.6
o-Xylene	932	2-Methyl-	312	3.0
m-Xylene	1434	3-Methyl-	813	1.8
p-Xylene	1882	4-Methyl-	942	2.0
Hemimellitene	417	2,6-Dimethyl-	200	2.1
Hemimellitene	417	2,3-Dimethyl-	186	2.2
Pseudocumene	847	2,5-Dimethyl	404	2.1
Pseudocumene	847	2,4-Dimethyl-	289	2.9
Pseudocumene	847	3,4-Dimethyl	350	2.4
Mesitylene	1680	3,5-Dimethyl-	641	2.6
Prehnitene	282	2,3,4-Trimethyl-	83.6	3.3
Prehnitene	282	2,3,6-Trimethyl-	77.4	3.6
Isodurene	332	2,4,6-Trimethyl-	209	1.6
Durene	529	2,4,5-Trimethyl-	211	2.5
Pentamethylbenzene	103	2,3,4,6-Tetramethyl-	61.3	1.7
Pentamethylbenzene	103	2,3,5,6-Tetramethyl-	35.2	2.9
Hexamethylbenzene	18	2,3,4,5,6-Pentamethyl-	23.2	0.8
			Av.	2.3

[a] The ratio of the rate constants is obtained by dividing the constant of the second column by the constant of the fourth column. The units of all rate constants are liters × grams^{-1} × min.$^{-1}$. [b] Calculated from the data of Smith and Pennekamp (ref. 1) by multiplying the rate constants previously reported by 4.43. The value for hexamethylbenzene has been revised due to errors in previous calculation.

It is possible for the methyl-substituted cyclohexanecarboxylic acids to exist in various isomeric forms depending on the *cis* or *trans* configurations of the substituent groups. From the physical constants obtained, it appears that in all cases a single form predominates. No attempt was made to determine which form was present.

Summary

A study has been made of the kinetics of catalytic hydrogenation of a number of methyl-substituted benzoic acids. The reactions were carried out at low pressures, in acetic acid solution, using Adams platinum catalyst. First-order reaction rate constants, all referred to one gram of standard platinum oxide, are given.

It has been demonstrated that the substitution of a carboxyl group for a methyl group cuts the rate of hydrogenation approximately in half. It has also been demonstrated that compounds with symmetrical substitution generally hydrogenate more readily than corresponding unsymmetrically substituted compounds.

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[16] Fuzek and Smith, THIS JOURNAL, **70**, 3743 (1948).

[17] These constants, k°_{30}, differ from those previously published by a factor of 4.43.