

a mixture of diethyl *cis*- and *trans*-hexahydroisophthalate (II) dissolved in 600 ml. of dry ether. After the mixture had been heated under reflux for 48 hr., the excess hydride was decomposed by the addition of 50 ml. of water. The complex was dissolved by the addition of 500 ml. of 10% hydrochloric acid to form a cloudy solution. The aqueous layer was extracted with ether for 11 days in an exhaustive ether extractor. The combined extracts and original ether layer were dried over magnesium sulfate. After the ether had been removed by distillation under reduced pressure, the residue was fractionated through a 10-inch Vigreux column to yield 58.6 g. (94%) of a mixture of *cis*- and *trans*-hexahydroisophthalyl alcohol, b.p. 139° (0.8 mm.), n_D^{25} 1.4879. [Since this work was completed, the preparations of the pure *cis*-hexahydroisophthalyl alcohol, m.p. 55°, and the pure *trans*-hexahydroisophthalyl alcohol, b.p. 112–114° (0.1 mm.), n_D^{24} 1.4941, have been reported²² starting from the corresponding pure acid in each case.]

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.67; H, 11.11. Found: C, 66.54; H, 10.90

B. From dimethyl hexahydroisophthalate. To a slurry of 105 g. (2.76 moles) of lithium aluminum hydride in 2500 ml. of ether was added dropwise 400 g. (2.0 moles) of a mixture of dimethyl *cis*- and *trans*-hexahydroisophthalate dissolved in 1000 ml. of dry ether. After the reaction mixture had been heated under reflux for 18 hr., the excess hydride was decomposed with 60 ml. of glacial acetic acid and the complex was dissolved with a minimum amount of 10% hydrochloric acid. The aqueous layer was extracted with ether in an exhaustive ether extractor for 6 days. After the combined extracts and original organic layer had been dried over magnesium sulfate, the ether was removed by distillation and the residue was fractionated through a 10-inch Vigreux column to yield 215 g. (75%) of a mixture of *cis*- and *trans*-hexahydroisophthalyl alcohol, b.p. 137–139° (0.8 mm.), n_D^{25} 1.4877.

Hexahydroisophthalyl diacetate (IV). After a mixture of 30 g. (0.21 mole) of a mixture of *cis*- and *trans*-hexahydroisophthalyl alcohol and 1500 ml. of acetic anhydride had been heated under reflux for 48 hr., the excess acetic anhydride and acetic acid were removed by distillation under reduced pressure. The residue was diluted with 100 ml. of ether and

the resulting solution was extracted consecutively with water, a saturated solution of sodium carbonate, and a saturated solution of sodium chloride. After the solution had been dried over potassium carbonate, the ether was removed by distillation, and the residue was fractionated through a 10-inch Vigreux column to yield 44 g. (95%) of a mixture of *cis*- and *trans*-hexahydroisophthalyl diacetate (IV), b.p. 94° (0.3 mm.), n_D^{25} 1.4634. [The pure *cis*-hexahydroisophthalyl diacetate, b.p. 105–107° (0.5 mm.), n_D^{25} 1.4598, was recently prepared by a series of involved reactions proceeding through a bicyclic ether.²²]

Pyrolysis of hexahydroisophthalyl diacetate (IV). At the rate of 36 drops per minute, 166 g. (0.55 mole) of hexahydroisophthalyl diacetate (IV) was added dropwise to a vertical Vycor combustion tube packed with 1/16-inch Pyrex helices and heated externally at 555° as described previously.²³ The apparatus was continuously flushed with a slow stream of oxygen-free nitrogen in order to prevent charring. The pyrolyzate, which was collected in a side-inlet flask cooled in a Dry Ice-acetone bath, was extracted with four 100-ml. portions of water. (Titration of an aliquot of the aqueous extracts indicated that 75% of two molar equivalents of acetic acid had been liberated.) After the organic layer had been dried over potassium carbonate, it was fractionated through a 6-inch, helix-packed column to yield 35.8 g. (61%) of 1,3-dimethylenecyclohexane (I), b.p. 122°, n_D^{25} 1.4697; 22 g. (24%) of 1-methylene-2-acetoxymethylcyclohexane (V), b.p. 62° (2.1 mm.), n_D^{25} 1.4600; and 13.9 g. (11% recovery) of unchanged starting ester IV. The yield of the diene I, based on unrecovered IV and V, was 94%.

Anal. Calcd. for C_8H_{12} : C, 88.89; H, 11.11. Found: C, 89.10; H, 11.06.

Calcd. for $C_{10}H_{16}O_2$: C, 71.43; H, 9.52. Found: C, 71.45; H, 9.38.

A sample of the diene I immediately decolorized a solution of bromine in carbon tetrachloride and a dilute potassium permanganate solution. Failure to obtain a precipitate from the attempted reaction with the diene I and maleic anhydride would indicate the absence of any product formed by the rearrangement of both double bonds into conjugation within the ring.

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(22) G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 399 (1953).

(23) W. J. Bailey and J. J. Hewitt, *J. Org. Chem.*, 21, 543 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Acid-Catalyzed Condensation of Phenols and Keto Acids

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Phenol, *o*-cresol, and 2,6-xyleneol were condensed with various keto acids or their methyl esters, in the presence of acid catalysts, to form *gem*-bis(*p*-hydroxyphenyl) substituted carboxylic acids.

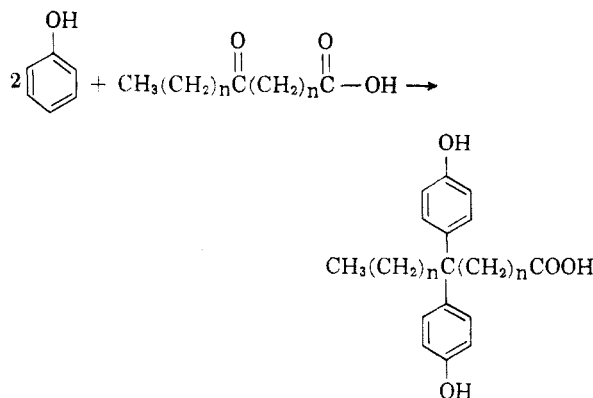
Extensive investigation of phenol has shown that it acts as a non-specific bactericide and fungicide by denaturing the proteins of the microorganisms. The phenols are often used in conjunction with a wetting agent in order that they may permeate freely, spread evenly, and gain ready access to the infected area. We have undertaken a program to

incorporate phenolic groups into aliphatic acids of varying chain length with the hope that germicidal and fungicidal activity may be combined with surface-activating properties.

Phenol, *o*-cresol, and 2,6-xyleneol have been condensed with a number of keto acids or their methyl esters to form di-*p*-hydroxyphenyl substituted carboxylic acids.

Concentrated sulfuric acid, 70 per cent sulfuric acid, and hydrogen chloride-acetic acid were the

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acid catalysts used for these condensations. The selection of the catalyst depends largely on its compatibility with the mixture of phenol and keto acid. Other factors were involved occasionally. For example, hydrogen chloride in acetic acid, phenol, and ethyl acetoacetate gave 3,3-bis(*p*-hydroxyphenyl)butanoic acid instead of undergoing a von Pechmann reaction to form a coumarin.² In some cases it was noted that sulfuric acid caused the formation of more polymeric material than did hydrogen chloride-acetic acid.

That the condensation occurred at the *p*-position rather than the *o*-position to the hydroxyl group was indicated by the infrared spectra which had a band at 12.0 μ and no band at 13.2 μ . The condensations were sensitive to steric hindrance. When the carbonyl group of the keto acid was flanked on both sides by relatively long chains, as in methyl 4-ketodecanoate and methyl 6-ketodecanoate, no condensation products were obtained.

The phenol moiety of the condensation products was readily nitrated with nitric acid in glacial acetic acid. Only the *o*-cresol-keto ester condensation products were nitrated in the present investigation. One compound, ethyl 3,3-bis(*p*-hydroxyphenyl)pentanoate, was chlorinated with sulfuryl chloride to form ethyl 3,3-bis(3-chloro-4-hydroxyphenyl)pentanoate.

The keto esters prepared in the course of this work were synthesized by the methods reported by Cason^{2a} and Cason and Prout.^{2b}

EXPERIMENTAL

Preparation of the methyl esters of keto acids. These compounds were made by previously described procedures.² Listed in Table I are the keto acids prepared in this work and their physical constants.

3,3-Bis(p-hydroxyphenyl)butanoic acid (I). Phenol (47 g. 0.05 mole) was dissolved in a mixture of 50 ml. of glacial acetic acid and 13 g. (0.1 mole) of ethyl acetoacetate. Anhydrous hydrogen chloride was passed through the solution for 4 hr. and it was allowed to stand for 7 days. The solution was poured into 400 ml. of water. The precipitated oil was

(2) von Pechmann and Duisberg, *Ber.*, 16, 2119 (1883).

2(a) Cason, *Org. Syntheses*, Coll. Vol. III, 169 (1955);

(b) Cason and Prout, *Org. Syntheses*, Coll. Vol. III, 601 (1955).

TABLE I
PHYSICAL CONSTANTS OF KETO ESTERS

Compound	Yield, %	B.P.	n_D^{25}
Methyl 4-ketohexanoate	71	63°/3 m.m.	1.4258
Methyl 6-ketoheptanoate	77	83–85°/3.5 m.m.	1.4320
Methyl 4-ketooctanoate	71	72°/0.5 m.m.	1.4288
Methyl 6-ketooctanoate	86	76–77°/0.5 m.m.	1.4316
Methyl 4-ketodecanoate	55	104–105°/1.2 m.m.	1.4350

washed twice with water and steam distilled to remove phenol. Sodium hydroxide pellets were dissolved in the solution to make it a 10% sodium hydroxide solution. It was heated to saponify the ester and then acidified. The product separated as an oil. The latter was dissolved in benzene, heated with decolorizing carbon, and dried over magnesium sulfate. The product was obtained as colorless crystals by partial removal of the solvent. It was recrystallized from benzene; yield 56%, m.p. 150°. All attempts to obtain a solvent-free sample failed.

Anal. Calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_4 \cdot 2\text{C}_6\text{H}_6$: C, 78.48; H, 6.58. Found: C, 78.37; H, 6.73.

The ethyl ester was prepared by heating the acid with excess ethanol in the presence of a small amount of concentrated sulfuric acid. The crude product was obtained by removing the excess ethanol. It was recrystallized from benzene. The yield was 80%, m.p. 127°.

Anal. Calcd. for $\text{C}_{18}\text{H}_{20}\text{O}_4 \cdot 2\text{C}_6\text{H}_6$: C, 78.91; H, 7.06. Found: C, 78.72; H, 6.99.

3,3-bis(3-Methyl-4-hydroxyphenyl)butanoic acid (II). This compound was prepared from 13 g. (0.1 mole) of ethyl acetoacetate and 43 g. (0.4 mole) of *o*-cresol by the method used for making I. The yield was 49%, m.p. 123° dec.

Anal. Calcd. for $\text{C}_{18}\text{H}_{20}\text{O}_4 \cdot 2\text{C}_6\text{H}_6$: C, 76.16; H, 6.92. Found: C, 75.96; H, 7.04.

3,3-bis(3,5-Dimethyl-4-hydroxyphenyl)butanoic acid (III) was prepared from ethyl acetoacetate and 2,6-xylenol by the same procedure that was used for making II. It was recrystallized from ethanol-water. The yield was 34%, m.p. 196°.

Anal. Calcd. for $\text{C}_{20}\text{H}_{24}\text{O}_4$: C, 73.14; H, 7.37. Found: C, 72.92; H, 7.37. The ethyl ester was obtained by direct esterification using sulfuric acid as the catalyst. The yield was 82%, m.p. 149–150°.

Anal. Calcd. for $\text{C}_{22}\text{H}_{28}\text{O}_4$: C, 74.13; H, 7.92. Found: C, 74.27; H, 7.86.

3,3-bis(3-Methyl-4-hydroxyphenyl)pentanoic acid (IV). A mixture of 260 g. (2.5 mole) of *o*-cresol, and 116 g. (1 mole) of levulinic acid was cooled to 0°. To this mixture, 96 g. of concentrated sulfuric acid was added dropwise with stirring. After standing for 3 days, the viscous, red oil was washed with water and dissolved in 500 ml. of ethyl acetate. The ethyl acetate solution was thoroughly extracted with saturated sodium carbonate solution. Acidification of the carbonate extract gave a heavy oil which was dissolved in benzene, decolorized with Darco, and dried over sodium sulfate. A colorless product was obtained by partially removing the solvent. It was recrystallized from benzene. The yield was 37%, m.p. 96° dec.

Anal. Calcd. for $\text{C}_{18}\text{H}_{22}\text{O}_4 \cdot 2\text{C}_6\text{H}_6$: C, 74.59; H, 7.19. Found: C, 74.76; H, 7.13.

The ethyl ester, prepared as described under I, was obtained as an oil. The latter was dissolved in benzene, decolorized with Darco, and precipitated with petroleum ether. It was recrystallized from methanol-water, yield 50%, m.p. 144°.

Anal. Calcd. for $\text{C}_{21}\text{H}_{26}\text{O}_4$: C, 73.66; H, 7.65. Found: C, 73.62; H, 7.65.

TABLE II
 NITRO DERIVATIVES

Compound	Yield, %	M.P.	Analysis					
			Calcd.			Found		
			C	H	N	C	H	N
3,3-Bis(3-Me-4-OH-5-NO ₂ -phenyl)butanoic acid	76	230	55.38	4.64	7.17	55.51	4.61	7.43
4,4-Bis(3-Me-4-OH-5-NO ₂ -phenyl)pentanoic acid	81	234	56.43	4.99	6.93	56.29	5.16	6.80
4,4-Bis(3-Me-4-OH-5-NO ₂ -phenyl)hexanoic acid	71	224	57.41	5.30	6.70	57.43	5.25	6.44
6,6-Bis(3-Me-4-OH-5-NO ₂ -phenyl)heptanoic acid	67	204	58.32	5.60	6.48	58.35	5.65	6.31
6,6-Bis(3-Me-4-OH-5-NO ₂ -phenyl)octanoic acid	70	194	59.18	5.87	6.27	59.01	6.01	6.13

4,4-Bis(3,5-dimethyl-4-hydroxyphenyl)pentanoic acid (V). Levulinic acid (11.6 g., 0.1 mole) was dissolved in a mixture of 75 ml. of glacial acetic acid and 25 g. (0.2 mole) of 2,6-xylol. Dry hydrogen chloride was passed into the solution for 4 hrs. and it was then allowed to stand for 10 days. The solution was poured into 500 ml. of water and the red oil removed and dissolved in ethyl acetate. The ethyl acetate solution was extracted with saturated sodium carbonate solution. Acidification of the carbonate solution precipitated an oil which solidified on standing. It was recrystallized from ethanol-water, yield 25%, m.p. 198°.

Anal. Calcd. for C₂₁H₂₆O₄: C, 73.66; H, 7.65. Found: C, 73.46; H, 7.74.

4,4-Bis(p-hydroxyphenyl)hexanoic acid (VI). Phenol (47 g., 0.5 mole) was added to 14.5 g. (0.1 mole) of methyl 4-ketohexanoate. After warming to effect solution, it was cooled to 0° and 10 g. of concentrated sulfuric acid was added dropwise with stirring. After standing for 14 days the mixture was poured into water and the oil treated as in the preparation of I. It was finally recrystallized from toluene; yield 33%, m.p. 183–184°.

Anal. Calcd. for C₁₈H₂₀O₄: C, 71.98; H, 6.71. Found: C, 71.95; H, 6.52.

4,4-Bis(3-methyl-4-hydroxyphenyl)hexanoic acid (VII). A mixture of 14 g. (0.1 mole) of methyl 4-ketohexanoate and 43 g. (0.4 mole) of *o*-cresol was cooled to 0° and 10 g. of concentrated sulfuric acid added dropwise with stirring. After standing for 7 days the red, viscous oil was worked up by the procedure used for I. The oily product which was obtained when the solution of the sodium salt was acidified was kept at 1–2 mm. at room temperature until it had solidified. The solid was washed with petroleum ether and recrystallized from benzene; yield 61%, m.p. 106° dec.

Anal. Calcd. for C₂₀H₂₄O₄·1/2C₆H₆: C, 75.17; H, 7.40. Found: C, 75.27; H, 7.60.

The formula showing 1/2 mole of benzene is not to be regarded as established just because it fits the analytical data. The fact that a number of compounds in this investigation had an attraction for benzene is of interest and a study of this behavior will be reported later.

6,6-Bis(3-methyl-4-hydroxyphenyl)heptanoic acid (VIII) was prepared from methyl 6-ketoheptanoate and *o*-cresol by the procedure used for making compound VI. It was recrystallized from benzene. The yield was 44%, m.p. 151–152°.

Anal. Calcd. for C₂₁H₂₆O₄: C, 73.66; H, 7.65. Found: C, 73.43; H, 7.67.

6,6-Bis(3,5-dimethyl-4-hydroxyphenyl)heptanoic acid (IX) was prepared from methyl 6-ketoheptanoate and 2,6-xylol by the method used for making compound I. It was recrystallized from benzene. The yield was 73%, m.p. 177°.

Anal. Calcd. for C₂₃H₃₀O₄: C, 74.55; H, 8.16. Found: C, 74.59; H, 8.20.

4,4-Bis(p-hydroxyphenyl)octanoic acid (X) was prepared from methyl 4-ketooctanoate and phenol by the method used for VI. It was recrystallized from xylene; yield 48%, m.p. 139–140°.

Anal. Calcd. for C₂₀H₂₄O₄: C, 73.14; H, 7.37. Found: C, 73.04; H, 7.36.

4,4-Bis(3-methyl-4-hydroxyphenyl)hexanoic acid and 6,6-bis(3-methyl-4-hydroxyphenyl)octanoic acid. These compounds were prepared by the procedure used for the condensation of *o*-cresol and the other keto esters. The products were obtained as gummy solids. All attempts to purify them failed. They were successfully nitrated, however, to the 5-nitro compounds.

Preparation of nitro derivatives. In this work only the condensation products from *o*-cresol and keto acids were nitrated. The nitro derivatives are listed in Table II. The general procedure was to suspend about 0.02 mole of the acid in 30 ml. of glacial acetic acid. To this suspension with stirring and cooling, a solution of 6.3 g. (0.1 mole) of nitric acid in 20 ml. of glacial acetic acid was added dropwise. After an induction period of about 1 min., the solution turned red, and fine yellow crystals began to separate. After 1 hr., the crystals were collected, washed with water, and recrystallized from an ethanol-water mixture.

Preparation of ethyl 4,4-bis(3-chloro-4-hydroxyphenyl)pentanoate. Eight grams (0.025 mole) of ethyl 4,4-bis(p-hydroxyphenyl)pentanoate was dissolved in 300 ml. of chloroform and 40 g. (0.3 mole) of freshly distilled sulfuryl chloride added. The solution was refluxed for 3 hr. and the excess sulfuryl chloride and chloroform were removed under reduced pressure. The oily residue was dissolved in benzene and decolorized with Darco. The filtrate was reduced to a small volume under reduced pressure and petroleum ether added until the solution almost remained turbid. After cooling overnight, the product was removed and recrystallized from methanol; yield 41%, m.p. 131°.

Anal. Calcd. for C₁₉H₂₀O₄Cl₂: C, 59.54; H, 5.26; Cl, 18.50. Found: C, 59.62; H, 5.41; Cl, 18.51.

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