pounds were prepared, are identical with those described in detail in paper II[2] of this series.

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Summary

1. Seven morpholinyl tertiary alcohols were prepared by the addition of various Grignard reagents to β-(4-morpholinyl)-propiophenone. All showed greater antispasmodic activity than the parent ketone, but none showed the maximum rating of the testing method.

2. Seventeen homologous piperidyl tertiary alcohols were prepared similarly from β-(1-piperidyl)-propiophenone. Nine of these showed the maximum antispasmodic activity-rating of the testing method.

3. Some, if not all, of these nine highly active piperidyl alcohols appear to warrant more extensive study as antispasmodic agents.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Preparation of Gentisic Acid and its Fatty Alcohol Esters[1]

BY STEWARD G. MORRIS

It is well known that 3,4,5-trihydroxybenzoic acid (gallic acid) and its alkyl esters are effective antioxidants for fats and oils. Comparatively little work has been done on other hydroxybenzoic acids and their esters. For the purpose of extending our information on the antioxidant properties of this class of compounds, 2,5-dihydroxybenzoic acid (gentisic acid) and its normal octyl, dodecyl, tetradecyl, hexadecyl and octadecyl esters were synthesized. This paper is restricted to the preparation of these compounds.

Gentisic acid was early prepared from 5-iodosalicylic acid by fusion with potassium hydroxide.[2,3] Similarly it was prepared by fusing gentisicaldehyde with potassium hydroxide.[4] Senhofer and Sarlay[5] obtained gentisic acid by heating hydroquinone, potassium carbonate and water in a sealed tube at 130°. More recently Mauthner,[6] prepared gentisic acid in 31–36% yields by treating an alkaline solution of salicyclic acid with potassium persulfate in the presence of a small amount of ferrous sulfate.

In the work described here, hydroquinone was used as starting material in the preparation of gentisic acid. Hydroquinone diacetate was prepared in practically quantitative yields by the method of Chattaway.[7] Acetylhydroquinone was then made from the hydroquinone diacetate by the Fries isomerization reaction, according to a modification of the method of Rosenmund and Lohfert.[8] The acetylhydroquinone was benzylated.[9] The resulting 2,5-dibenzyloxyacetophenone was oxidized to 2,5-dibenzyloxybenzoic acid by means of the haloform reaction, and the product was debenzylated by catalytic hydrogenolysis, forming gentisic acid. The esters of gentisic acid were obtained by the reactions of the acid chloride of 2,5-dibenzyloxybenzoic acid with various alcohols, followed by debenzylations.

Experimental

Acetylhydroquinone.—Into a 3-liter, 3-neck experimental flask equipped for stirring of the contents and disposing of hydrogen chloride fumes was introduced 293 g. (2.2 moles) of anhydrous aluminum chloride and 850 cc. of *o*-dichlorobenzene. The mixture was heated to 130° in an oil-bath. A mixture of 55 g. (0.5 mole) of hydroquinone and 97 g. (0.5 mole) of hydroquinone diacetate[7] was added in small portions to the *o*-dichlorobenzene solution in one hour. The reaction mixture was then heated for three additional hours at 140–150°. The acetylhydroquinone obtained on hydrolysis of the reaction product in ice and hydrochloric acid was crystallized from 50% alcohol solution. The yield was 61 g. (40%); m. p., 204–205.5°[10]; previously reported,[8] 202°.

Dibenzyl Ether Acetylhydroquinone.—Seventy-three grams of acetylhydroquinone (0.48 mole) was dissolved in 250 cc. of acetophenone and benzylated by means of 130 g. of benzyl chloride and 142 g. of anhydrous potassium carbonate.[9] For this reaction it was necessary to alter the original purification procedure. After the steam distillation the residue was cooled and the water poured off. The residue was then extracted four times with 375-cc. portions of 80% alcohol solution heated to about 60°. The alcoholic extracts were centrifuged to separate some suspended globules of tarlike material. The clear alcoholic solutions when cooled to 2° yielded 82 g. of white crystalline dibenzyl ether acetylhydroquinone. The yield was 51%. When it was recrystallized from benzene–petro-

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[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted. Presented at the Fall Meeting of the American Chemical Society, held at Washington, D. C., August 30–September 3, 1948.

[2] Miller, *Ann.*, **220**, 113 (1883).

[3] Rakowski and Leppert, *Ber.*, **8**, 788 (1875).

[4] Tiemann and Müller, *ibid.*, **14**, 1985 (1881).

[5] Senhofer and Sarlay, *Monatsh.*, **2**, 448 (1881).

[6] Mauthner, *J. prakt. Chem.*, **156**, 150 (1940).

[7] Chattaway, *J. Chem. Soc.*, 2495 (1931).

[8] Rosenmund and Lohfert, *Ber.*, **61**, 2601 (1928).

[9] Clinton and Geissman, THIS JOURNAL, **65**, 85 (1943).

[10] The 76-mm. immersion thermometer used for all melting point determinations was calibrated against a 76-mm. immersion thermometer which had been certified by the National Bureau of Standards.

TABLE I

	ALKYL ESTERS OF 2,5-DIBENZYLOXYBENZOIC ACID						ESTERS OF 2,5-DIHYDROXYBENZOIC ACID					
			Analyses, %						Analyses, %			
			Carbon		Hydrogen				Carbon		Hydrogen	
Alkyl	M. p., °C.	Empirical formula	Calcd.	Found	Calcd.	Found	M. p., °C.	Empirical formula	Calcd.	Found	Calcd.	Found
n-Octyl	27.5–28.5	$C_{29}H_{34}O_4$	77.98	77.92	7.67	7.75	32.5–33	$C_{15}H_{22}O_4$	67.65	67.30	8.33	8.30
n-Dodecyl	24–25	$C_{33}H_{42}O_4$	78.85	78.71	8.42	8.36	53.5–55.5	$C_{19}H_{30}O_4$	70.77	71.33	9.37	9.59
n-Tetradecyl	34–35	$C_{35}H_{46}O_4$	79.21	78.96	8.74	8.75	60.2–61.5	$C_{21}H_{34}O_4$	71.99	71.82	9.79	9.97
n-Hexadecyl	39.5–40.5	$C_{37}H_{50}O_4$	79.52	79.42	9.02	8.96	73.5–74.5	$C_{23}H_{38}O_4$	72.96	73.00	10.13	10.40
n-Octadecyl	51.5–53	$C_{39}H_{54}O_4$	79.83	79.56	9.27	9.18	80.5–81.5	$C_{25}H_{42}O_4$	73.84	73.58	10.41	10.59

leum ether, the melting point was 80.0–81.0°. Calcd. for $C_{22}H_{20}O_3$: C, 79.48; H, 6.06. Found: C, 79.53; H, 6.17.

Purification of Dioxane for Use in Haloform Reaction.—The following modification of the method of Hess and Frahm[11] yielded dioxane of satisfactory purity for these reactions.[12] One liter of practical dioxane, 13 cc. of concentrated hydrochloric acid and 100 cc. of water were refluxed for four hours. The solution was cooled somewhat, 30 g. of sodium hydroxide dissolved in 150 cc. of water was added, and the mixture was refluxed for two more hours. The dioxane was decanted from the darkened sodium hydroxide solution. An excess of sodium hydroxide pellets was added, and the dioxane was distilled. The purified dioxane was free of aldehydes and peroxides.

2,5-Dibenzyloxybenzoic Acid.—A sodium hypochlorite solution was prepared by dissolving 40 g. of sodium hydroxide in 300 cc. of water, followed by the addition of 24 g. of chlorine. To the hypochlorite solution was added 14 g. of dibenzyl ether acetylhydroquinone dissolved in 150 cc. of dioxane. The reaction mixture was stirred for two and one-half hours at 35–40°. The solution was then heated to 70° to ensure hydrolysis of the chlorinated compound. The solution was cooled, and the excess hypochlorite was decomposed by the addition of a few cc. of acetone. The solution was diluted with one volume of water and then acidified with hydrochloric acid to precipitate the 2,5-dibenzyloxybenzoic acid. The product, crystallized from 95% alcohol, was obtained in a yield of 13.2 g. (94%), m. p. 109–110°. *Anal.* Calcd. for $C_{21}H_{18}O_4$: C, 75.44; H, 5.43. Found: C, 75.47; H, 5.53.

Gentisic Acid (2,5-Dihydroxybenzoic Acid).—Gentisic acid was prepared from 2,5-dibenzyloxybenzoic acid by catalytic hydrogenolysis.[13] After carbon treatment, it was crystallized from benzene–ethyl ether. The yield was 84%; m. p., 204.5–205.5°; previously reported,[2] 196–197°; 199–200°.

Acid Chloride of 2,5-Dibenzyloxybenzoic Acid.—Ten grams of the acid was dissolved in 40 g. of thionyl chloride (purified by use of quinoline and linseed oil)[14] and heated at 60° for one hour. The excess thionyl chloride was recovered, and the residue was further freed of thionyl chloride by dissolving it in benzene and again taking to dryness. The acid chloride was dissolved in benzene–petroleum ether, carbon treated and allowed to crystallize at 2°. The yield was 8.9 g. (84%); m. p. 89–90°. The pure acid chloride of 2,5-dibenzyloxybenzoic acid is odorless, and fairly stable and can be dried in air without appreciable decomposition. However, on standing for three or four days in a closed container, the acid chloride gave off an odor of hydrochloric acid when the container was opened. If the thionyl chloride is not highly purified, the acid chloride formed decomposes so rapidly that the pure acid chloride cannot be obtained by crystallization. *Anal.* Calcd. for $C_{21}H_{17}O_3Cl$: C, 71.49; H, 4.85; Cl, 10.05. Found: C, 71.39; H, 4.73; Cl, 9.41.

Esters of 2,5-Dibenzyloxybenzoic Acid.—The general procedure was as follows: Ten grams of the acid chloride of 2,5-dibenzyloxybenzoic acid and an equivalent amount of the alcohol was placed in a 100-cc. round-bottom flask and heated for one hour on a steam-bath. The esters were crystallized from petroleum ether at −20°, followed by crystallization from methanol at 0°. The yield at this stage was about 75%. Although the esters were sufficiently pure for use in the next step of the preparation, three or four additional crystallizations from methanol were required in order to obtain the pure esters. The esters, their melting points, and the carbon and hydrogen analyses are shown in Table I.

Esters of 2,5-Dihydroxybenzoic Acid.—The esters of 2,5-dibenzyloxybenzoic acids were debenzylated by catalytic hydrogenation.[13] The resulting dihydroxybenzoic esters, except the octyl ester, were crystallized from benzene–petroleum ether. The octyl ester was crystallized from petroleum ether. The yields for these esters were 80 ± 2%. The esters are listed in Table I.

Acknowledgments.—The author is indebted to Jane Dixon and Mary J. Welsh for the carbon and hydrogen microanalyses.

Summary

Gentisic acid was synthesized from hydroquinone as starting material. The normal octyl, dodecyl, tetradecyl, hexadecyl and octadecyl esters of gentisic acid were prepared and described.

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[11] Hess and Frahm, *Ber.*, **71B**, 2627 (1938); Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, 1941, p. 369.

[12] Blank runs with the untreated dioxane caused vigorous reactions with the hypochlorite solution.

[13] Morris and Riemenschneider, THIS JOURNAL, **68**, 500 (1946).

[14] Meyer and Schlegl, *Monatsh.*, **34**, 561 (1913); Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, 1941, p. 381.