The reaction was repeated twice with 2 g. of II-A, but only unchanged starting material was recovered.

Compound II-A (0.5 g.) was added to 2.5 ml. of 47% hydrobromic acid and 10 ml. of glacial acetic acid. The mixture was warmed to 50° for fifteen minutes, then poured into iced water. The separated solid was unchanged starting material.

Acylation of *o*-Xylene. Method B.—Aluminum chloride (3.9 g., 0.03 mole) was added to 2.7 g. (0.01 mole) of diphenoyl chloride dissolved in 10 ml. of nitrobenzene, and 3.5 ml. of *o*-xylene was added, as described above. The product, 4-(3,4-dimethylbenzoyl)-fluorenone, melted at 145–145.4°, the recorded value.[4]

Preparation of 2-Bromo-3',4'-dimethylbenzophenone.—The ketone was obtained by the usual Friedel–Crafts procedure from 20 g. of *o*-bromobenzoyl chloride, 18.3 g. of aluminum chloride and 35 ml. of *o*-xylene in 51% yield; m. p. 40–41°.

Anal. Calcd. for $C_{15}H_{13}BrO$: C, 62.28; H, 4.77. Found: C, 62.28; H, 4.89.

Preparation of II by the Ullmann Reaction.—A mixture of 2 g. of 2-bromo-3',4'-dimethylbenzophenone and 5 g. of copper powder was heated at 250–260° for one hour. The reaction mixture was extracted with alcohol. The diketone melted at 122.5–123° after recrystallization from alcohol.

Preparation of 7,7-Diphenyldiphenide from Diphenic Anhydride and Phenyllithium.—Solid diphenic anhydride (3.5 g.) was added to 0.056 mole of phenyllithium in 100 ml. of dry ether, in an atmosphere of nitrogen. The reaction mixture was stirred and refluxed for about two hours, then decomposed with iced hydrochloric acid. The sticky yellowish solid was recrystallized from glacial acetic acid and melted at 189–190°, the recorded value.[7]

The 7,7-diphenyldiphenide was also prepared according to Sergeev's procedure,[7] from diphenic anhydride and phenylmagnesium bromide, and a mixture of the two compounds melted at 189–190°. A better yield was obtained from the phenyllithium reaction.

Reaction of 2,2'-Bis-(2,4-dimethylbenzoyl)-biphenyl and 2,2'-Bis-(2,4,6-trimethylbenzoyl)-biphenyl with Concd. Sulfuric Acid.—The diketone (0.3 g.) was warmed with 1 ml. of concd. sulfuric acid at 110–120° for fifteen minutes. The cooled mixture was poured into water and the yellow solid which separated was recrystallized from alcohol. Both diketones yielded fluorenone-4-carboxylic acid, m. p. and mixed m. p. 225–227°.

Summary

2,2'-Diphenoyl chloride reacted as the symmetrical diacid chloride with toluene, the xylenes, mesitylene and anisole in the presence of aluminum chloride to form the 2,2'-diarylbiphenyls.

In nitrobenzene solution, 2,2'-diphenoyl chloride reacted with the methylbenzenes to yield 4-aroylfluorenones.

2,2'-Diphenoyl chloride and benzene reacted in benzene solution to yield 4-benzoylfluorenone. In nitrobenzene solution the fluorenone-4-carboxylic acid was the only product isolated.

COLUMBIA, MISSOURI RECEIVED NOVEMBER 28, 1949

[FROM THE CHEMISTRY LABORATORY OF THE STATE UNIVERSITY OF IOWA]

The Synthesis of Substituted β-Arylglutaric Acids

BY WALTER T. SMITH, JR., AND PAUL G. KORT

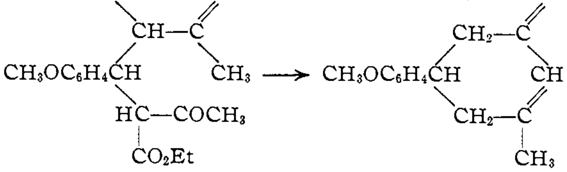
β-Arylglutaric acids have been prepared frequently by saponification and decarboxylation of the tri-ester obtained by the addition of malonic ester to cinnamic esters or to substituted cinnamic esters.[1] This method has the disadvantage of being rather long and requiring carefully dried reagents and anhydrous conditions.

Knoevenagel[2] reported that β-(*m*-nitrophenyl)- and β-(*p*-nitrophenyl)-glutaric acids were formed by cleavage of the corresponding ethyl nitrobenzal-bis-acetoacetates but no yields were given. The principal products of the reactions were the nitrophenylcyclohexenones. The substituted ethyl benzal-bis-acetoacetates are usually readily prepared by the piperidine-catalyzed condensation of an aromatic aldehyde with two moles of ethyl acetoacetate.

It was the purpose of the present work to determine if cleavage of substituted benzal-bis-acetoacetic esters might not be a convenient method for the preparation of substituted β-arylglutaric acids, and at the same time to prepare some β-arylglutaric acids in which the aryl groups are derived from vanillin. These acids are of interest because of their possible toxicity toward aerobic microörganisms which attack foods, particularly in view of the recent reports concerning the high toxicity of certain esters of vanillic acid and related compounds toward representative microörganisms.[3]

Ten aromatic aldehydes were successfully condensed with ethyl acetoacetate by means of piperidine to give the corresponding ethyl benzal-bis-acetoacetates in yields ranging from 34–80%. The data for these products are summarized in Table I.

Sodium ethoxide has been used to cleave disubstituted ethyl acetoacetates to disubstituted ethyl acetates.[4] Efforts to cleave ethyl anisal-bis-acetoacetate (I) by a similar procedure gave only the cyclic ketone, 5-anisyl-3-methyl-2-cyclohexen-1-one (II).



I II

However, cleavage of the condensation products

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[1] Michael, *Am. Chem. J.*, **9**, 114 (1887).

[2] Knoevenagel, *Ann.*, **303**, 223–257 (1898).

[3] Pearl and Beyer, THIS JOURNAL, **71**, 1066 (1949).

[4] Renfrow and Walker, *ibid.*, **70**, 3957 (1948).

TABLE I

SUBSTITUTED ETHYL BENZAL-BIS-ACETOACETATES

Aldehyde	Reaction time, hr.	Ml. alc. for recrystn.[a] 1	2	Yield, %	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Ethylvanillin	7	230	...	57	125–126	62.54	62.54	7.16	7.19
Ethylisovanillin	12	470	250	56	140.5–141.5	62.54	62.45	7.16	7.03
n-Butylvanillin	8	350	300	67	133–134	63.98	63.68	7.61	7.51
n-Propylisovanillin	12	500	350	64	139–140	63.28	62.90	7.39	7.30
Benzylvanillin	10	510	500	66	160–161	66.92	66.60	6.66	6.58
Benzylisovanillin	19	400	300	70	139–140	66.92	66.79	6.66	6.72
Benzoylvanillin	20	250	...	34	178–179	65.05	64.74	6.07	5.97
5-Bromovanillin	90	...	...	34	186–187	50.75	50.68	5.32	5.27
Anisaldehyde	5	300	...	80	138–139	[b]			
Benzaldehyde	3	400	350	60	156–157	[b]			

[a] A blank space indicates that the product was sufficiently pure to omit the recrystallization and merely wash the product with a little alc. to remove any yellow color. [b] These compounds have been previously reported: Knoevenagel, *Ann.*, **303**, 247 (1898), and Knoevenagel and Vieth, *Ann.*, 281, 76 (1894).

TABLE II

β-ARYLGLUTARIC ACIDS

Arylglutaric acid from	H₂O, ml. 1st recrystn.	2nd recrystn.	Yield, %	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Ethylvanillin	110	70	49	109.5–110.5	59.56	59.52	6.43	6.51
Ethylisovanillin	160[a]	150	62	127–128	59.56	59.63	6.43	6.59
n-Butylvanillin	100	100	81	109–110	61.92	61.45	7.15	7.13
n-Propylisovanillin	300[a]	300	83	152.5–153.5	60.80	60.87	6.80	6.77
Benzylvanillin	210[a]	200[a]	89	141–142	66.27	66.06	5.85	5.80
Benzylisovanillin	200[a]	150[a]	95	143–144	66.27	66.26	5.85	5.89
Anisaldehyde	150	..	40	160–161	[b]			
Benzaldehyde	80	40[a]	29	137–138	[b]			

[a] In these cases the acid was not completely soluble in the amount of water used so from 10–20% of 95% ethanol was added to effect complete solution without using excessively large volumes. [b] These compounds have been previously reported. Dixit, *J. Indian Chem. Soc.*, **8**, 787–800 (1931), and Michael, *Am. Chem. J.*, **9**, 114–116 (1887).

with boiling alcoholic sodium hydroxide solution was found to give the desired β-arylglutaric acids in yields of 29–95%. These data are given in Table II.

The results of the testing of these acids will be published elsewhere.

Experimental

Substituted Ethyl Benzal-*bis*-acetoacetates.—The preparation of these compounds is illustrated by the following preparation of ethyl anisal-bis-acetoacetate.

A mixture of 27.2 g. (0.2 mole) of anisaldehyde, 52.1 g. (0.4 mole) of ethyl acetoacetate and 4 ml. of piperidine in 10 ml. of 95% ethanol was placed in a stoppered flask and allowed to stand at room temperature until the mixture was solid (about four and one-half hours). This solid was recrystallized twice from 95% ethanol. Solid aldehydes were added as saturated ethanolic solutions.

β-Arylglutaric Acids.—The substituted ethyl benzal-bis-acetoacetate (20 g.) was dissolved in 250–300 ml. of 95% ethanol and mixed with 300 g. of 50% sodium hydroxide solution. The resulting mixture was refluxed vigorously for three hours and then poured into a beaker containing about 100 ml. of water. The alcohol was removed by evaporation on a steam-bath and the resulting mixture was acidified with concentrated hydrochloric acid. The mixture was cooled. The precipitated glutaric acid was removed by filtration and washed with cold water to remove sodium chloride. The β-arylglutaric acids were recrystallized from water. In some cases a little alcohol was added to the water to effect complete solution. The quantities of reagents used are given in Table II.

Summary

Substituted aromatic aldehydes can be conveniently condensed with ethyl acetoacetate in the presence of piperidine to give substituted ethyl benzal-bis-acetoacetates. These products are cleaved with alcoholic alkali to give substituted β-arylglutaric acids.

Eight new substituted ethyl benzal-bis-acetoacetates and six new substituted β-arylglutaric acids are reported.

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