[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Friedel–Crafts Synthesis of ω-Aroyl Aliphatic Acids[1]

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ω-Aroyl-aliphatic acids have been prepared almost exclusively by Friedel–Crafts reactions between aromatic nuclei and derivatives or anhydrides of dibasic acids. The first general method for the synthesis of these keto acids employed the chlorides of dibasic acids[2] as shown in equation I. The desired ω-aroyl aliphatic acids

$$3RH + ClOC(CH_2)_nCOCl \longrightarrow RCO(CH_2)_nCOOH\ (a) + RCO(CH_2)_nOCR\ (b) \quad (I)$$

I(a), however, are formed only as by-products in low and uncertain yields, along with the diaroyl hydrocarbons I(b), the principal products of the reaction. The latter substances, fortunately, are readily separated from the keto acids I(a).

An alternate synthesis for the keto acids I(a) utilizes anhydrides of α,ω-aliphatic dibasic acids. This type of reaction using succinic anhydride[3] has been applied extensively for the preparation of many β-aroylpropionic acids, and, in general, the yields have been most satisfactory. With the next higher homolog, glutaric anhydride, the γ-aroylbutyric acids have been obtained, but in somewhat poorer yields. In contrast, dicarboxylic acids of the general formula $HOOC(CH_2)_n$-COOH (n is greater than 3) form polymeric anhydrides,[4] which, in a Friedel–Crafts reaction with aromatic nuclei, give not only the desired ω-aroyl aliphatic acids, but also the corresponding diaroyl hydrocarbons and regenerated acids.[5,6,7] The maximum yield of ω-aroyl aliphatic acids obtainable by the polyanhydride synthesis is 50% of theory.[8]

As part of other investigations requiring large quantities of ω-aroyl aliphatic acids, we have studied in detail a third method for the synthesis of these compounds. Although this method has been known for a long time, it, unfortunately, has not been studied by other workers in this field. It consists of the Friedel–Crafts reaction between an aromatic nucleus and the ester-acid chloride of a dibasic acid. Ethyl aryl glyoxylates[9] and ethyl aroyl acetates[10] have been obtained in good yields by treating an aromatic hydrocarbon with ethyl oxalyl chloride and ethyl malonoyl chloride, respectively. Aromatic ester-acid chlorides likewise have been used, ethyl phthaloyl chloride and benzene giving *o*-carbethoxybenzophenone in good yield.[11] In a publication dealing primarily with the *in vivo* oxidation of ω-phenyl aliphatic acids, Raper and Wayne[12] applied the ester-acid chloride synthesis to the preparation of ω-benzoyl valeric, caprylic and pelargonic acids. These three keto acids presumably were obtained in fair yields, the authors only reporting that ethyl ω-benzoylvalerate was obtained in 53% yield. In the recent literature, only isolated instances[13] of the use of this synthesis can be found.

This study has established that under the proper experimental conditions the ester-acid chloride synthesis affords in most cases ω-aroyl aliphatic acids in 85–95% yields. Undoubtedly, the reaction is applicable to any ester-acid chloride of dicarboxylic acids and any aromatic hydrocarbon. Typical aryl nuclei that have been studied include benzene (Table I), its alkoxy, alkyl-alkoxy and alkyl substitution products (Table II), thiophene (Table III) and naphthalene. The ester-acid chlorides are of the general formula: $C_2H_5OOC(CH_2)_nCOCl$, where n varies from 2–8.

TABLE I

$C_6H_5CO(CH_2)_nCOOH$

n	Yield, g.	Yield, %	Melting point, °C.	Lit., °C.
2	75	84	113–114	114–115[a]
4	80	78	70–71	70–71[5]
8	104	80	78–79	77–78[5]

[a] "Org. Syn.," Coll. Vol. II, p. 83.

The half esters of dicarboxylic acids are readily accessible by the exchange reaction between the dicarboxylic acids and the corresponding diesters in the presence of alcohol and hydrochloric acid.[14] The ester acid chlorides have been obtained in excellent yields by the action of thionyl chloride on the half esters.

(1) Presented in abstract before the Division of Organic Chemistry at the Atlantic City Meeting of the American Chemical Society, April 15, 1947.

(2) Auger, *Ann. chim.*, [6] **22**, 360 (1891); Etaix, *ibid.*, [7] **9**, 391 (1896).

(3) C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1941, p. 583–592.

(4) (a) Hill, THIS JOURNAL, **52**, 4110 (1930); (b) Hill and Carothers, *ibid.*, **54**, 1569 (1932).

(5) Hill, *ibid.*, **54**, 4105 (1932).

(6) Plant and Tomlinson, *J. Chem. Soc.*, 1092 (1935).

(7) Billman and Travis, *Proc. Indiana Acad. Sci.*, **54**, 101 (1945); *C. A.*, **40**, 1826 (1946).

(8) In the reaction between aniline and polymeric adipic anhydride, it has been demonstrated theoretically and verified experimentally that the three possible reaction products, namely, the dianilide, the monoanilide and the regenerated acid are formed in the molecular ratio of 1:2:1, respectively.[5a] On the basis of the data, it was inferred[5] that the Friedel–Crafts synthesis should yield the three possible products in the same proportions.

(9) C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publishing Corporation, 1941, pp. 252–253, 329, 372.

(10) Marguery, *Bull. soc. chim.*, [3] **33**, 549 (1905).

(11) Smith, THIS JOURNAL, **43**, 1920 (1921).

(12) Raper and Wayne, *Biochem. J.*, **22**, 193 (1928); compare Grateau, *Compt. rend.*, **191**, 947 (1930).

(13) (a) Strain, Plati and Warren, THIS JOURNAL, **64**, 1436 (1942); (b) Blicke, *ibid.*, **66**, 1646 (1944); (c) Cogniant and Deluzarcke, *Compt. rend.*, **222**, 1301–1302 (1946); *C. A.*, **40**, 5428 (1946).

(14) Swann, "Organic Syntheses," **19**, 45 (1940).

TABLE II

$RR'C_6H_3CO(CH_2)_nCOOH$

R	R'	n	Yield G.	Yield %	Melting point[a] °C.	Lit., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
p-OCH_3	H	2	94	90	147–148	146[b]					
p-OCH_3[c]	H	3	104	93.5	138–139	137[d]					
p-OCH_3[c]	H	4	112	95	128–129	127[e]					
p-OCH_3[c]	H	8	140	96	101.5–102		$C_{17}H_{24}O_4$	69.82	8.28	69.64	8.30
p-OC_2H_5	H	2	98	88	138–139	138–139[f]					
p-OC_2H_5	H	8	136	90	101–101.5		$C_{18}H_{26}O_4$	70.54	8.56	70.86	8.79
p-i-C_3H_7	H	2	97	88	141–142	142[g]					
p-i-C_3H_7	H	8	144	95	76.5–77		$C_{19}H_{28}O_3$	75.22	9.26	74.65	9.22
2-CH_3[h]	5-CH_3	8	138	95	57–58		$C_{18}H_{26}O_3$	74.44	9.26	74.25	9.33
2-CH_3	4-OCH_3	2	100	90	136–137		$C_{12}H_{14}O_4$	64.84	6.35	64.79	6.48

[a] The melting points are for recrystallized products. [b] Haworth and Sheldrick, *J. Chem. Soc.*, 1951 (1934). [c] In addition to acetylene tetrachloride, carbon disulfide and nitrobenzene have been used as solvents for these reactions. Although the latter solvent gave yields equal to those obtained with acetylene tetrachloride, carbon disulfide was found unsatisfactory in yield and quality of keto acid. [d] Plant and Tomlinson, *J. Chem. Soc.*, 856 (1935). [e] Plant and Tomlinson, *J. Chem. Soc.*, 1092 (1935). [f] Gabriel and Colman, *Ber.*, **32**, 404 (1899); G. P. Rice, THIS JOURNAL, **46**, 2320 (1924), reports a 59% yield using succinic anhydride. [g] Barnett and Sanders, *J. Chem. Soc.*, 434 (1933). [h] Reaction mixture decomposed after forty-eight hours at room temperature. [i] This compound has been prepared by Desar and Wali, *Proc. Ind. Chem. Soc.*, **6A**, 144 (1937), who report no m. p. for the compound. However, its reduction to γ-(2-methyl-4-methoxyphenyl)-butyric acid, m. p. 92°, and its oxidation with alkaline hypobromite to 2-methyl-4-methoxybenzoic acid are described. Rosenmund and Shapiro, *Arch. Pharm.*, **272**, 313 (1934), *C. A.*, **28**, 4046 (1934), report m. p. 138° for this compound. The reaction of *m*-cresyl methyl ether and succinic anhydride as described by Rosenmund and Shapiro was repeated and gave in addition to the methoxy compound about an equal amount of the corresponding hydroxy compound which melted after recrystallization from water at 179.5–180.5°. *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.42; H, 5.82. Found: C, 63.28; H, 5.93.

TABLE III

$C_4H_3SCO(CH_2)_nCOOH$

n	Yield G.	Yield %	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
2	138[a]	75	120–120.5[17]					
4	148	70	76–77[b,c]	$C_{10}H_{12}O_3S$	56.58	5.71	56.59	5.83
8	176	66	53.5–54.4[b,d]	$C_{14}H_{20}O_3S$	62.65	7.52	62.84	7.26

[a] The yield and melting point represent the product obtained directly from the hydrolysis. In one experiment, the ester group was hydrolyzed during the steam distillation and the free acid was isolated from the steam distillation residue. [b] Recrystallized from benzene–petroleum ether. Using aluminum chloride, these two acids were obtained in yields of 30–40%, the recrystallized products retaining colored impurities. [c] Literature[7] m. p., 76.5–77°. [d] Literature[7] m. p., 54.5–55°.

Almost without exception, previous investigators have used carbon disulfide as solvent in this synthesis. From the standpoint of both yield and quality of keto acid this solvent has been found unsatisfactory. In the synthesis of ω-(*p*-methoxybenzoyl)-butyric, valeric and pelargonic acids, a comparative study was made using carbon disulfide, nitrobenzene and acetylene tetrachloride as solvent. From the standpoint of ease of operation, yield and purity of keto acid, acetylene tetrachloride was the solvent of choice. However, in these three cases, nitrobenzene gave yields comparable to those obtained with acetylene tetrachloride.

For the preparation of ω-benzoyl- and ω-(α-thenoyl)-aliphatic acids, benzene was used as solvent. The yields in these instances were somewhat lower than those reported for acetylene tetrachloride.

It is well established that alkoxy substituted aromatic hydrocarbons undergo, in a great majority of cases, demethylation in the presence of aluminum chloride,[15] especially at temperatures exceeding 50°. In the reactions with phenolic ethers reported in Table II, demethylation has not been observed. At the low temperature of the ester-acid chloride synthesis, one would expect little, if any, hydrolysis to occur.

Although benzene and its substitution products may be combined with ester-acid chlorides in the presence of aluminum chloride, it has been shown that anhydrous stannic chloride[16] is a superior catalyst for acylations of thiophene. For example, thiophene and succinic anhydride in the presence of aluminum chloride gives a 54% yield of β-(α-thenoyl)-propionic acid along with considerable tar[17]; whereas thiophene and β-carbethoxypropionyl chloride with stannic chloride gives a 75% yield of pure product. From the appropriate ester-acid chlorides, ω-(α-thenoyl)-

(15) G. Baddeley, *J. Chem. Soc.*, 330 (1944); compare Holmes and Trevoy, *Can. J. Research*, **22B**, 109 (1944).

(16) Ref. 3, p. 875–876.

(17) Fieser and Kennelly, THIS JOURNAL, **57**, 1615 (1935).

TABLE IV

$RR'C_6H_3(CH_2)_nCOOH$

R	R'	n	M. p., °C.	Yield, %	Analyses, % Calcd. Formula	C	H	Found C	H
H	H	5	B. p. 167–169 (1 mm.)	72					
H[a,b]	H	9	41–42[c]	60					
p-OCH_3	H	4	116–118[d]	74	$C_{12}H_{16}O_3$	69.19	7.75	69.35	7.61
p-OCH_3	H	5	46–47[e]	80					
p-OCH_3[b]	H	9	68–69[f,g]	78	$C_{17}H_{26}O_3$	73.33	9.42	72.94	9.36
p-OC_2H_5	H	9	60–60.5[f]	80	$C_{18}H_{28}O_3$	73.92	9.66	74.18	9.86
p-*i*-C_3H_7[a]	H	3	49–50[g]	76					
p-*i*-C_3H_7[b]	H	9	41.5–42[h]	64	$C_{19}H_{30}O_2$	78.55	10.42	78.14	10.78
2-CH_3	5 CH_3	9	67–67.5[i]	70	$C_{18}H_{28}O_2$	78.22	10.22	77.96	10.40

[a] Also obtained by reduction with Raney alloy and aqueous alkali. In the case of ω-phenylcapric acid, the yield was somewhat lower than that obtained by the Clemmensen method, whereas ω-phenylhexoic acid and γ-(*p*-isopropyl phenyl)-butyric acid were obtained in 85% yields. [b] Also obtained by modified Wolff–Kishner reduction. [c] B. p. 202–205° (5 mm.); literature 228–230° (18 mm.); m. p. 41°, Borsch, *Ber.*, **52**, 2085 (1919). [d] Recrystallized from dilute alcohol. Fourneau and Baranger, *Bull. soc. chim.*, **49**, 1161 (1931), who prepared the compound from diethyl allyl malonate and anisole *via* the Friedel–Crafts reaction, followed by hydrolysis and decarboxylation, reported m. p. 65°. [e] M. p., 47–49°; ref. 6. [f] A reaction time of approximately one hundred hours was necessary for complete reduction of one mole of the keto acid. Stirring during the reduction decreased considerably the reaction time. However, a much lower yield was obtained, the reduction product being contaminated with a viscous gum which was not investigated, but very likely was the pinacol. [g] Barnett and Sanders, *J. Chem. Soc.*, 434 (1933). [h] Xylene was used in place of toluene[20] and for one mole of compound complete reduction required seventy to eighty hours. After cooling, the xylene layer was separated, the aqueous acid layer diluted with four volumes of water and extracted twice with ether. The ether extracts and xylene layer were combined, washed with water and the solvents removed. The residue was esterified with ethyl alcohol and the resulting ester fractionated. After a fore-run of 46 g., b. p. 120–160° (2 mm.), the ethyl ω-(2,5-dimethyl phenyl)-caprate was obtained in a yield of 213 g. (70%), b. p. 168–172° (1 mm.), n^{24} 1.4822. Analytical sample, b. p. 172° (1 mm.), n^{24} 1.4889. *Anal.* Calcd. for $C_{20}H_{32}O_2$: C, 78.88; H, 10.60. Found: C, 78.49; H, 10.46. Hydrolysis of the ester gave the ω-(2,5-dimethylphenyl)-capric acid which was recrystallized from petroleum ether. [i] Proceeded as described under [h], forerun 30 g., b. p. 160–180° (2 mm.) and ethyl ω-(*p*-isopropylphenyl)-caprate, yield 203 g. (64%), b. p. 185–187° (2 mm.). Analytical sample, b. p. 186° (2 mm.), n^{20} 1.4868. *Anal.* Calcd. for $C_{21}H_{34}O_2$: C, 79.18; H, 10.77. Found: C, 78.78; H, 10.53. A residue of 43 g. was not further investigated. Hydrolysis of the ester gave ω-(*p*-isopropylphenyl)-capric acid which was recrystallized from petroleum ether.

valeric and pelargonic acids have also been prepared with stannic chloride.[18]

It seemed of interest to investigate the applicability of the ester-acid chloride synthesis to polycyclic hydrocarbons in view of the poor yields and number of isomers generally encountered with other preparative methods. The succinic anhydride synthesis has been applied extensively to the synthesis of β-naphthoyl and β-phenanthroyl propionic acids and their substitution products; and, in a number of instances, the isolation and/or purification of the desired product has been indeed difficult, if not impossible. The rather simple reaction between naphthalene and succinic anhydride gives a mixture of the β-1- and 2-naphthoylpropionic acids in a yield of 35 and 29%, respectively.[19] Separation of the two isomers is achieved by the fractional crystallization from acetic acid.

Using the general procedure described for the monocyclic compounds, naphthalene and β-carbethoxypropionyl chloride gave in nitrobenzene a 75% yield of almost pure β-(1-naphthoyl)-propionic acid purified by recrystallizations from acetic acid and then methyl alcohol. In acetylene tetrachloride, both isomeric acids were obtained in an over-all yield of 80%, the larger part of which (55%) was the β-(2-naphthoyl)-propionic acid.

The ω-aroyl aliphatic acids were reduced to the ω-aryl aliphatic acids by the Clemmensen method as modified by Martin[20] (Table IV). The modified–Wolff Kishner method using hydrazine hydrate and sodium in ethylene glycol[21] was studied in the case of ω-benzoylpelargonic acid and the *p*-isopropyl and *p*-methoxy derivatives. Only in the latter case was the yield unsatisfactory, appreciable demethylation occurring in the course of the reduction. Reduction with Raney alloy and aqueous alkali[22] was also applied and found satisfactory for unsubstituted or alkyl substituted benzene compounds. A *p*-alkoxy substituted compound, namely, ω-(*p*-methoxybenzoyl)-valeric acid on treatment with Raney alloy and aqueous alkali underwent hydrogenolysis of the ether group in accordance with previous observations.[23]

In the course of this work, there has been pre-

(18) In a recent publication,[7] the polymeric anhydrides of adipic, suberic, azelaic and sebacic acids have been condensed with thiophene in the presence of stannic chloride to give the corresponding ω-(α-thenoyl)-valeric, heptanoic, caprylic and pelargonic acids in very poor yield. Except for polymeric adipic anhydride, the remaining anhydrides also gave the expected di-(α-thenoyl)-hydrocarbons. The synthesis of γ-(α-thenoyl)-butyric acid by the reaction of thiophene with either glutaric anhydride or γ-carbethoxybutyroyl chloride has also been recently published.[13c] The anhydride was reported to react unsatisfactorily, whereas the ester-acid chloride gave good yields of the γ-(α-thenoyl)-butyric acid.

(19) Haworth, *J. Chem. Soc.*, 1129 (1932).

(20) Martin, THIS JOURNAL, **58**, 1438 (1936).

(21) Soffer, Soffer and Sherk, *ibid.*, **67**, 1435 (1945); Herr, Whitmore and Schiessler, *ibid.*, **67**, 2061 (1945); compare Huang-Minlon *ibid.*, **68**, 2487 (1946).

(22) Papa, Schwenk and Whitman, *J. Org. Chem.*, **7**, 587 (1942).

(23) Schwenk, Papa, Whitman and Ginsberg, *ibid.*, **9**, 1 (1944).

pared the yet unknown ω-(*p*-methoxybenzoyl)-, ω-(*p*-ethoxybenzoyl)-, ω-(*p*-isopropylbenzoyl)- and ω-(2,5-dimethylbenzoyl)-pelargonic acids. The corresponding ω-aryl aliphatic acids, namely, ω-(*p*-methoxyphenyl)-, ω-(*p*-ethoxyphenyl)-, ω-(2,5-dimethylphenyl)- and ω-(*p*-isopropylphenyl)-capric acids are also reported. Demethylation of the corresponding alkoxy compounds with hydrobromic and acetic acids afforded the new ω-(*p*-hydroxyphenyl)-butyric, caproic and capric acids[24] (Table V).

TABLE V

p-HOC$_6$H$_4$(CH$_2$)$_n$COOH

n	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
3	110–111	$C_{10}H_{12}O_3$	66.62	6.72	67.05	6.77
5	107–108	$C_{12}H_{16}O_3$	69.19	7.75	69.06	7.82
9	99–100	$C_{16}H_{24}O_3$	72.67	9.16	72.41	8.95

Experimental

All melting points have been corrected for stem exposure. The Friedel-Crafts reactions were carried out in 1,000 cc., three-necked flasks equipped with thermometer, ground-glass stirrer, and adapter with condenser and opening for introducing the aluminum chloride under anhydrous conditions.[25]

ω-Carbethoxy Aliphatic Acid Chlorides

β-Carbethoxypropionyl chloride was secured from succinic anhydride by the action of ethyl alcohol followed by treatment of the β-carbethoxypropionic acid with thionyl chloride, b. p. 75–77° (8 mm.).[26]

γ-Carbethoxybutyroyl chloride was obtained from ethyl hydrogen glutarate[27] and thionyl chloride, yield 92%, b. p. 98–100° (2 mm.), literature b. p. 108–110° (15 mm.).

ω-Carbethoxyvaleroyl chloride resulted from ethyl hydrogen adipate[14] and thionyl chloride, yield 88%, b. p. 127–128° (20 mm.); literature b. p. 128° (17 mm.), 117–118° (9 mm.).[28]

ω-Carbethoxypelargonoyl chloride was obtained from ethyl hydrogen sebacate[14] and thionyl chloride, yield 86%, b. p. 143–145° (5 mm.); literature b. p. 168–170° (18 mm.).[29]

I. **C$_6$H$_5$CO(CH$_2$)$_n$COOH.**—To a mixture of 200 cc. of anhydrous benzene and 0.5 mole of the appropriate ω-carbethoxy acid chloride there was added at 5–10° with stirring 133 g. (1.0 mole) of granular anhydrous aluminum chloride. The reaction mixture was then allowed to come to room temperature, heated on the steam-bath for two and one-half to three hours and after standing overnight was decomposed with ice and 1:1 hydrochloric acid. The excess benzene was steam distilled, and the oily residue extracted with ether. The ether was removed and the crude ester[30] saponified with 350 cc. of 10% alcoholic sodium hydroxide. After diluting with water and removing the alcohol, the aqueous solution was filtered through Super-cel, cooled and acidified. The crude keto acids were recrystallized from benzene–petroleum ether.

II. **RR′C$_6$H$_3$CO(CH$_2$)$_n$COOH.**—To a mixture of 60 g. (0.55 mole) of anhydrous anisole and 200 cc. of anhydrous acetylene tetrachloride, there was added slowly with stirring, at or below 0°, 133 g. (1.0 mole) of granular anhydrous aluminum chloride, followed by the dropwise addition at 0° of 0.5 mole of the ω-carbethoxy acid chloride. The temperature must be controlled carefully when using phenolic ethers in order to avoid demethylation and contamination of the final products with phenolic keto acids. After the addition of the ester-acid chloride, the reaction mixture was stirred at 0° for approximately three to four hours and then allowed to come slowly to room temperature overnight. The acetylene tetrachloride and excess anisole were steam distilled off and the oily residue extracted twice with ether. The combined ether extracts were washed with water, evaporated and the residue saponified with 350 cc. of 10% alcoholic sodium hydroxide. After diluting with water and removing the alcohol, the hot alkaline solution was neutralized, treated with Norite and filtered. The pale yellow solution was cooled, acidified and the precipitated keto acid filtered. The products so obtained were quite pure. Analytical samples were recrystallized from either benzene–petroleum ether or aqueous alcohol.

III. **C$_4$H$_3$SCO(CH$_2$)$_n$COOH.**—To a mixture of 84 g. (1.0 mole) of thiophene, 1.0 mole of the ω-carbethoxy acid chloride and 1,000 cc. of anhydrous benzene, there was added slowly with stirring at 0° 165 cc. of freshly distilled anhydrous stannic chloride.[16] At the end of the addition, the ice-bath was removed and the reaction mixture was stirred for one hour. It was then decomposed in the usual manner and the benzene and unreacted thiophene removed by steam distillation. The steam distillation residue on cooling partially solidified and was extracted with ether. The ether was evaporated and the residual crude ester saponified with 600 cc. of 10% alcoholic sodium hydroxide. After diluting with water and removing the alcohol, the alkaline solution was filtered, cooled thoroughly and acidified. The precipitated α-thenoyl aliphatic acids were filtered and dried.

IV. **RR′C$_6$H$_3$(CH$_2$)$_n$COOH.**—Reduction of the keto acids was carried out by the Clemmensen method as modified by Martin.[20] The alkoxy compounds reported in Table IV were etherified following the reduction. Those compounds where $n = 9$ reduced slowly and for one mole of substance, a reaction time of approximately seventy-hundred hours was necessary for complete reduction, additional zinc amalgam and hydrochloric acid being added as required.

Reduction with Raney alloy and aqueous alkali was carried out as previously described.[22] For 10 g. of the keto acid, 500 cc. of 10% sodium hydroxide and 40 g. of alloy were used.

The Wolff-Kishner reductions were carried out as follows: In typical experiments, 35 g. of sodium was dissolved in one liter of ethylene glycol, and after the addition of 45 g. of hydrazine, 0.1 mole of the keto acid was added. The reaction mixture was heated for thirty hours at 170–180°. On pouring into water and acidifying with concentrated hydrochloric acid, there was obtained 17 g. (70%) of ω-phenylcapric acid, m. p. 40–42°; 18 g. (62%) of ω-(*p*-isopropylphenyl)-capric acid, m. p. 40–41° and 14 g. of ω-(*p*-methoxyphenyl)-capric acid melting at 76–89°. The latter substance gave positive tests for a phenolic group, indicating that demethylation occurred during the reduction. On methylating the crude reduced acid and recrystallizing the product from benzene–petroleum ether, a yield of 12 g. (42%) of pure ω-(*p*-methoxyphenyl)-capric acid was obtained melting at 67–68.5°.

V. ***p*-HOC$_6$H$_5$(CH$_2$)$_n$COOH.**—A mixture of one mole of the ω-(alkoxyphenyl)-aliphatic acid, 200 cc. of 48% hydrobromic acid and 450 cc. of acetic acid was refluxed for six hours. The reaction mixture was poured into 1,000 cc. of water, cooled and filtered. The hydroxy compounds were recrystallized from dilute alcohol and were obtained in yields exceeding 90%.

(24) These three hydroxy acids are mentioned in U. S. Patent 2,400,433, May 14, 1946. However, no melting point or other data is reported for them.

(25) Fieser, "Experiments in Organic Chemistry," 2nd ed., 1941, D. C. Heath and Co., New York, N. Y., p. 311.

(26) Compare Cason, THIS JOURNAL, **64**, 1107 (1942).

(27) Bachmann, Kusher and Stevenson, *ibid.*, **64**, 974 (1942).

(28) Blaise and Koehler, *Bull. soc. chim. France*, [4] **7**, 219 (1910).

(29) Ruzicka and Stoll, *Helv. Chim. Acta*, **10**, 693 (1927).

(30) At this point, the residue, consisting mostly of the ethyl ester, may be reësterified with ethyl alcohol and sulfuric acid. After working up the esterification mixture, the ester so obtained may be distilled in good vacuum. For ethyl ω-benzoylvalerate, b. p. 152–155° (1 mm.); ethyl ω-benzoylpelargonate, b. p. 186–190° (1 mm.).

VI. $C_{10}H_7COCH_2CH_2COOH$.—(a) To a mixture of 200 cc. of anhydrous acetylene tetrachloride and 82 g. (0.5 mole) of β-carbethoxypropionyl chloride cooled to 0°, there was added 133 g. (1 mole) of granular anhydrous aluminum chloride. Keeping the temperature at 0°, 64 g. (0.5 mole) of naphthalene in 200 cc. of anhydrous acetylenetetrachloride was added dropwise. The resulting mixture was stirred for three to four hours at 0° and then allowed to come slowly to room temperature overnight. The reaction mixture was decomposed, the solvent and excess naphthalene steam distilled off and the residue extracted twice with ether. The ether extracts were evaporated and the crude ester saponified with 300 cc. of 10% alcoholic sodium hydroxide. The clear alcoholic solution was diluted with water, the alcohol removed *in vacuo*, and, after cooling, the aqueous solution was acidified; yield, 97 g. (85%), m. p. 151.5–156.5°. The crude product was recrystallized from 1,000 cc. of 50% alcohol and allowed to cool slowly at room temperature. The first crop yielded 63 g. (55%) of β-(2-naphthoyl)-propionic acid, m. p. 172.5–173°; literature, 171–173°,[19] 174°.[31] The filtrate on dilution with water yielded 28 g. (25%) of the β-(1-naphthoyl)-propionic acid which melted after recrystallization from dilute acetic acid and aqueous methanol at 129–130°; literature, 129–131°,[19] 131°.[31]

(b) The above described experiment was repeated substituting an equal volume of nitrobenzene for the acetylene tetrachloride. The crude β-(1-naphthoyl)-propionic acid was obtained in a yield of 85 g. (75%), melting at 120–122.5°; recrystallized from dilute acetic acid followed by recrystallization from aqueous methyl alcohol, m. p. 130–131°; mixed m. p. with product obtained under (a), 130–131°.

(31) Schroeter, Muller and Huang, *Ber.*, **62**, 645 (1929).

Summary

1. ω-Aroyl aliphatic acids have been obtained in excellent yield by the Friedel–Crafts reaction of ester-acid chlorides of aliphatic dicarboxylic acids with aryl nuclei.

2. The reaction has been shown to be applicable to benzene, its alkyl, alkoxy and alkyl-alkoxy derivatives as well as to thiophene and to naphthalene.

3. The ω-aroyl aliphatic acids have been reduced to the ω-aryl fatty acids by the Clemmensen method. Reduction with Raney alloy and aqueous alkali and the Wolff–Kishner method were applied in a few cases.

4. Several new ω-aroyl and ω-aryl aliphatic acids are described.

BLOOMFIELD, N. J. RECEIVED JUNE 18, 1947

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

α-Aryloxy and α-Aryl Thiol Cinnamic Acids

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For studies on the hydrogenolysis of oxygen and thio ethers with Raney alloy and aqueous alkali,[1] several α-phenoxycinnamic acids and α-phenylmercaptocinnamic acids, as well as the corresponding hydrogenated derivatives, were required. The Perkin condensation of sodium phenoxyacetate and benzaldehyde[2] has been described long ago as a convenient preparative method for α-phenoxycinnamic acid and its halogen, alkyl, alkoxy and alkyl–alkoxy derivatives.[3] The corresponding α-phenylmercaptocinnamic acids, however, are not known.[4]

The Perkin condensation of *p*-hydroxybenzaldehyde and either anhydrous sodium or potassium phenoxyacetate yielded the α-phenoxy-*p*-hydroxycinnamic acid. Under similar conditions, benzaldehyde and *p*-hydroxybenzaldehyde and the alkali metal salts of phenyl thioglycolic acid gave the α-phenylmercaptocinnamic acid and α-phenylmercapto-*p*-hydroxycinnamic acid, respectively. Although the yields in these reactions were not entirely satisfactory, the accessibility of the starting materials and the simplicity of the procedure renders the method a useful synthetic tool for the preparation of these compounds.

In a previous publication,[5] it has been shown that cycloalkyl and cycloalkylidene acetic acids may be condensed with aromatic aldehydes in the presence of equimolecular amounts of metallic salts or organic amines. This modification of the Perkin reaction has been found applicable to aryloxy acetic acids as well as to the corresponding thio compounds. The yields of cinnamic acids obtained with either triethylamine or anhydrous potassium acetate are somewhat better than those obtained with the alkali metal salts.[6]

Reduction of the α-phenoxy-*p*-hydroxycinnamic acid and the α-phenylmercapto-*p*-hydroxycinnamic acid to the corresponding propionic acid derivatives was achieved in good yield by sodium amalgam in very dilute alkaline solution.

Experimental

1. α-Phenoxy-*p*-hydroxycinnamic Acid, A.—A mixture of 38 g. (0.25 mole) of phenoxyacetic acid, 30.5 g. (0.25 mole) of *p*-hydroxybenzaldehyde, 25 g. (0.25 mole) of triethylamine and 75 g. of acetic anhydride was heated with stirring at 105–110° for thirty-five to forty hours. The reaction mixture was cooled to 60°, the excess acetic anhydride cautiously decomposed with water, and then poured on ice. The semi-solid residue was extracted with

(1) A preliminary report of the hydrogenolysis of oxygen and thio ethers with Raney alloy and aqueous alkali was presented before the Division of Organic Chemistry at the New York Meeting of the American Chemical Society on September 11, 1944

(2) Oglialoro, *Gazz. chim. ital.*, **10**, 483 (1880).

(3) Oglialoro, *ibid.*, **20**, 505 (1890); Stoermer and Biesenbach, *Ber.*, **38**, 1966 (1905).

(4) β-Phenyl mercaptocinnamic acids, however, are readily accessible by the condensation of ethyl phenylpropiolate with sodium thiophenolate, Ruhemann and Stapleton, *J. Chem. Soc.*, **77**, 1181 (1900). The corresponding oxygen analogs are similarly prepared with sodium phenolate, Ruhemann and Beddow, *ibid.*, **77**, 985 (1900).

(5) Schwenk and Papa, THIS JOURNAL, **67**, 1432 (1945).

(6) Compare "Organic Reactions," Vol. I, John Wiley & Sons, Inc., 1942, p. 238–240.