an electrophilic solvating agent such as phenol accelerates the reaction in proportion to its concentration. Methanol will perform the same function, but less effectively than the more electrophilic phenol; the reagent most effective in solvating the incipient bromide ion, and thereby diffusing the negative charge over a particle appreciably larger than the bromide ion, is the most effective in increasing the rate of reaction. Solvation of the large cation seems to be relatively unimportant, since the quaternization reaction in non-polar solvents has never been observed to have other than a first-order dependence on the concentration of the base, the component which would be capable of solvating a cation.

The phenacyl halide–base system is so constituted that one of the reactants can act as an electrophilic solvating agent. When the second-order process, with solvation performed by the solvent, is sufficiently slow, the third-order process can make an appreciable contribution to the over-all rate. This cannot occur in the quaternization reaction of alkyl halides in benzene, since neither reactant can function as an electrophilic solvating agent. For this reason, the reaction exhibits second-order kinetics if it is homogeneous.

From the data of Table II, the activation energy and entropy of activation of the *m*-nitrophenacyl bromide–4-picoline reaction can be calculated; they are shown in Table IV.

The heat of activation 12.4 kcal. and the entropy of activation −34 e.u. for the second-order process

TABLE IV

m-NITROPHENACYL BROMIDE AND 4-PICOLINE, BENZENE SOLUTION

	E_a, kcal./mole	$\Delta S^{\pm}$, e.u.
Second-order reaction	12.4 ± 0.5	−34 ± 1.5
Third-order reaction	15.6 ± 0.5	−20.6 ± 1.5

are about the same as those generally observed for a second-order quaternization reaction in benzene solution.[2a,7]

For quaternization reactions or in general reactions where ions are produced two generalizations are possible: First, heats of activation do not vary greatly with the solvent; they are if anything greater for the more polar solvents. Second, the entropies of activation are always negative and vary considerably with solvent, becoming more negative as the polarity of the solvent is decreased.[2a,7,8] On the basis of these generalizations the increase in heat of activation and the increase in $\Delta H^{\pm}$ listed for the third-order process as compared to a second-order process are about as expected if the third-order process involves solvation by a ketone, Fig. 9.

Acknowledgment.—We are indebted to the Abbott Fund of Northwestern University for a grant during the course of this work.

(7) F. Ozog, V. Comte and L. C. King, THIS JOURNAL, **74**, 6225 (1952).

(8) Recently R. J. Pearson has discussed a theoretical basis for these generalizations, *J. Chem. Phys.*, **20**, 1478 (1952).

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND CO.]

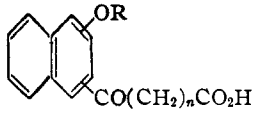
Synthetic Choleretics. II. Phenol Derivatives[1]

BY ROBERT R. BURTNER AND JOHN M. BROWN

RECEIVED AUGUST 13, 1952

A series of cycloalkyl, aryl and aralkyl phenol derivatives bearing the β-carboxypropionyl side chain, as well as some closely related types, were prepared and screened for choleretic activity in the dog. Under experimental conditions several of these compounds were two to four times as active as dehydrocholic acid.

In the first paper[2] of this series it was shown that certain keto acid derivatives of α- or β-naphthol having the general formula

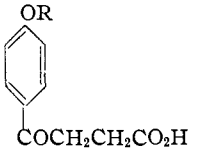


R = H or CH_3
n = 2-8

will increase the volume output of bile in dogs. Among the twenty-four compounds reported at that time, those bearing the β-carboxypropionyl side chain ($-COCH_2CH_2CO_2H$) were found to be especially effective choleretics. The most potent compound tested was β-(1-methoxy-4-naphthoyl)-propionic acid. This material not only produced a greater acute response than any other member of the series, but also manifested a longevity of action quite singular at that time.

In view of the foregoing results, it seemed advisable to extend the evaluation of choleretic activity to other phenolic, binuclear ketoalkanoic acids, particularly those closely related to β-(1-methoxy-4-naphthoyl)-propionic acid. Furthermore, a comparison of the activities of the free phenolic compounds with those of the corresponding methyl ethers was indicated.

Although β-(*p*-methoxybenzoyl)-propionic acid and β-(*p*-hydroxybenzoyl)-propionic acid themselves exhibit relatively feeble choleretic properties,[3] their structural relationship to the more

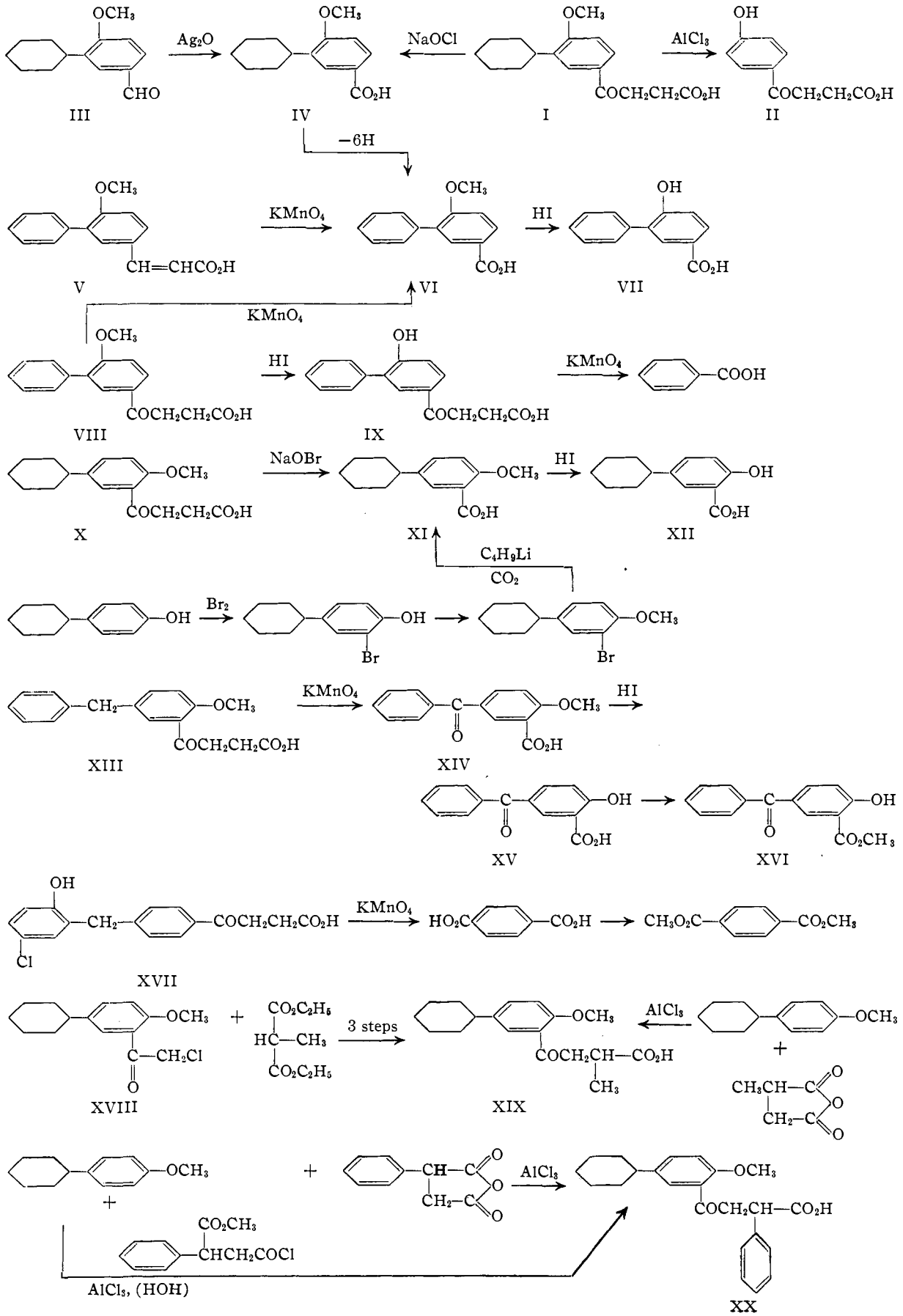


R = CH_3 or H

(1) Presented before the Division of Medicinal Chemistry of the American Chemical Society in September, 1950, at Chicago, Illinois.

(2) R. R. Burtner and J. M. Brown, THIS JOURNAL, **73**, 897 (1951).

(3) M. J. Gunter, K. S. Kim, D. F. Magee, H. Ralston and A. C. Ivy, *J. Pharmacol.*, **99**, 465 (1950).

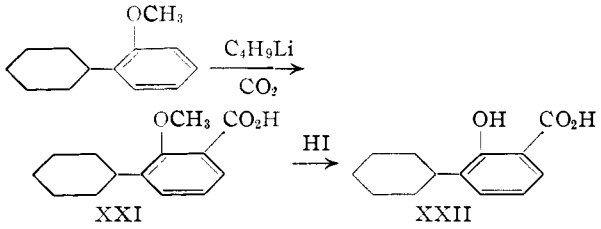

OCH3
Ag2O
NaOCl
AlCl3
OH
CHO
CO2H
COCH2CH2CO2H
III
IV
I
II
−6H
KMnO4
HI
CH=CHCO2H
V
VI
VII
KMnO4
VIII
IX
COOH
NaOBr
X
XI
XII
C4H9Li
CO2
Br2
Br
XIII
XIV
XV
XVI
CH2
Cl
XVII
HO2C
CH3O2C
CO2CH3
CO2C2H5
HC—CH3
3 steps
XVIII
XIX
CH3CH—C
CH2—C
AlCl3, (HOH)
XX

active naphthol derivatives, particularly when modified by the introduction of a second benzene or cycloalkyl nucleus, commends them for further attention. Accordingly, a number of cycloalkyl, aryl and aralkyl phenol derivatives bearing the β-carboxypropionyl side chain, as well as some closely related types, were prepared and screened as choleretics, forty-seven of which are reported in this paper.

The pharmacological evaluation of these compounds was carried out by Drs. Cook and Hambourger of these laboratories.[4] Assays were conducted on the acute biliary fistula dog, using dehydrocholic acid as the reference standard. Activities are reported on the basis of equimolar doses according to the following scheme, where the potency of the standard is arbitrarily designated as 1.0: potency 0–1.4 = +, 1.5–2.9 = ++, 3.0–4.9 = +++ and 5.0 or greater = ++++.

The structures of representative examples of the compounds listed in the table were determined by degradation to known compounds or to those which could be prepared in a reliable manner, or by synthesis using established methods.

Bruson[5] condensed salicylic acid and cyclohexene to obtain an acid melting at 102–103° which he described as 2-hydroxy-5-cyclohexylbenzoic acid. Since this compound (XII) as prepared by us melted at 151°, the possibility existed that Bruson had obtained the isomeric 3-cyclohexyl derivative (XXII). However, when the latter was synthesized as shown below, it was found to melt at 159–160°. Consequently, it is probable that the



XXI XXII

product melting at 102–103° is actually a mixture of the 3- and 5-isomers, an expected result of such a condensation.

Experimental Part

Intermediates. *p*-Cyclohexylanisole.—The following procedure furnishes better yields than those of existing methods. A stirred solution of 176 g. (1.0 mole) of *p*-cyclohexylphenol in 1200 ml. of 10% potassium hydroxide (2.0 moles) was treated during a 30-minute period with 190 g. (1.5 moles) of methyl sulfate. No attempt was made to control the temperature which rose to 55°. After a lapse of 15 minutes the mixture was heated and stirred at 75° for one hour. A solution of 56 g. (1.0 mole) of potassium hydroxide in 100 ml. of water was added at one time, followed by the addition of 63 g. (0.5 mole) of methyl sulfate during 15 minutes at 65°. The oily suspension was then heated with stirring at 75° for one hour, chilled, filtered and the crystalline product washed well with water. Distillation of the dried, crude ether gave 180.6 g. of colorless liquid, b.p. 100° at 0.4 mm., which crystallized on cooling (m.p. 57–58°).

***p*-Cyclopentylanisole.**—One hundred and eight grams (1.5 moles) of cyclopentanone was added during 30 minutes at about 30° (ice-bath cooling) to a vigorously stirred solution of the Grignard reagent prepared from 187 g. (1.0 mole) of *p*-bromoanisole and 24.3 g. (1.0 atom) of magnesium. After being stirred for two hours at room temperature, the lumpy mixture was refluxed for three hours. Subsequent to hydrolysis with ammonium chloride the aqueous phase was extracted once with ether, and the combined ether solutions were washed well with water. Upon removal of solvent the crude carbinol was distilled with the loss of water to yield 111 g. of *p*-cyclopentenylanisole which boiled at 96–98° (0.4 mm.) and crystallized on cooling (m.p. 88°). Crystallization from methanol afforded colorless plates, m.p. 91–92°.[6] Twenty grams of cyclopentanone was recovered in the distillation forerun.

A solution of 40.7 g. (0.23 mole) of *p*-cyclopentenylanisole in 250 ml. of hot absolute ethanol was cooled to room temperature until crystallization had ceased, and the resulting suspension was reduced in the presence of 0.3 g. of Adams catalyst under hydrogen pressure of about fifty pounds. The theoretical amount of hydrogen was absorbed in 75 minutes. After filtration and removal of the solvent the residue was distilled, collecting 36.6 g. of a colorless oil, b.p. 78–79° (0.35 mm.), $n^{24}D$ 1.5273.[7]

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.78; H, 9.12.

***p*-(Cyclohexylethyl)-anisole.**—To a stirred solution of 43.2 g. (0.4 mole) of anisole and 48 g. (0.3 mole) of cyclohexylacetyl chloride in 400 ml. of nitrobenzene was added 53.6 g. (0.4 mole) of aluminum chloride during a 30-minute period at 0–5°. The mixture was stirred for an additional two hours at about 0° and then allowed to stand overnight at room temperature. After hydrolysis and steam distillation of the solvent, the dark oily product was taken up in ether and washed well with water. Removal of solvent and distillation yielded 62 g. of *p*-(cyclohexylacetyl)-anisole as a pale yellow oil, b.p. 135–136° (0.3 mm.), $n^{25}D$ 1.5465.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.32; H, 8.66.

Sixty-two grams of the above ketone was reduced by refluxing for 48 hours with a suspension of 120 g. of amalgamated zinc in 75 ml. of water, 175 ml. of 12 *M* hydrochloric acid, 100 ml. of toluene and 10 ml. of acetic acid. Four 25-ml. portions of hydrochloric acid were added at 10-hour intervals. The toluene layer was separated, the solvent distilled and the residue refluxed with stirring for one hour with 30 ml. of 50% sodium hydroxide and 35 g. of methyl sulfate in 150 ml. of acetone. After removal of the solvent and addition of water, the mixture was extracted with ether and the extract distilled, yielding 30 g. of the desired product as a colorless oil, b.p. 128–130° (0.8 mm.), $n^{25}D$ 1.5183. There was a considerable amount of a viscous residue which decomposed upon attempted distillation.

Anal. Calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.78; H, 10.24.

3-Cyclohexyl-4-methoxybenzaldehyde (III).—A stirred suspension of 72 g. (0.38 mole) of *o*-cyclohexylanisole and 94 g. (0.8 mole) of zinc cyanide in 250 ml. of benzene was chilled in an ice-bath and saturated with hydrogen chloride. Then 80.4 g. (0.6 mole) of aluminum chloride was added during a 10-minute period, after which the stirred mixture was permitted to warm up to 40–45°. A slow stream of hydrogen chloride was introduced during the next 3.5 hours while the temperature was maintained at 40–45° by occasional cooling. After hydrolysis the curdy, yellow zinc complex of the aldimine was filtered and then refluxed with vigorous stirring with 200 ml. of 6 *N* hydrochloric acid for 20 minutes. The chilled mixture was extracted with benzene, the extract washed thrice with water and distilled, collecting 61.5 g. of a colorless oil, b.p. 145–146° (0.3 mm.), $n^{25}D$ 1.5640.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.90; H, 8.23.

The phenylhydrazone formed colorless crystals, m.p. 125–126°, upon crystallization from methanol.

Anal. Calcd. for $C_{20}H_{20}ON_2$: N, 9.09; CH_3O, 10.06. Found: N, 8.98; CH_3O, 10.06.

3-Phenyl-4-methoxybenzaldehyde.—Colorless, viscous oil, b.p. 149–150° (0.3 mm.).

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.35; H, 5.62.

(4) D. L. Cook and W. E. Hambourger, *ibid.*, **100**, 421 (1950).

(5) H. Bruson, U. S. Patent 1,998,750; *C. A.*, **29**, 3783 (1935).

(6) J. von Braun, *et al.*, *Ann.*, **472**, 1 (1929), prepared this compound by a different method and reported m.p. 90°.

(7) P. Cagniant, *et al.*, *Compt. rend.*, **224**, 1064 (1947), report $n^{20}D$ 1.5355; b.p. 143° (12 mm.) according to von Braun, ref. 6.

Substituted β-benzoylpropionic acid	M.p., °C.	Crystn. solvent, ml./g.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Activity[a]
2-Methoxy-5-cyclohexyl	159–160	10 CH_3OH	$C_{17}H_{22}O_4$	70.32	70.12	7.64	7.70	++
[b]	126	5 CH_3OH	$C_{16}H_{20}O_4$	69.54	69.60	7.30	7.38	++
2-Methoxy-5-(β-cyclohexylethyl)	103	10 Cyclohexane	$C_{19}H_{26}O_4$	71.67	71.71	8.23	8.26	++
[b]	105.5	8 70% AcOH	$C_{18}H_{24}O_4$	71.02	71.21	7.95	8.04	++
2-Hydroxy-5-phenyl[c]	136–137	20 50% AcOH	$C_{16}H_{16}O_4$	71.10	70.90	5.22	5.20	+
2-Methoxy-5-benzyl	121	4 CH_3OH	$C_{18}H_{18}O_4$	72.46	72.45	6.08	6.19	++
[b]	161	8 EtOAc	$C_{17}H_{16}O_4$	71.81	71.92	5.67	5.72	+
2-Methoxy-5-cyclopentyl	147	4 CH_3OH	$C_{16}H_{20}O_4$	69.54	69.80	7.30	7.26	++
[b]	109	8 70% AcOH	$C_{15}H_{18}O_4$	68.68	68.47	6.92	7.02	+
β-(2-Methoxy-5-cyclohexylbenzoyl)-acrylic acid	139	4 CH_3OH	$C_{17}H_{20}O_4$	70.81	70.60	6.99	7.06	++
2-Methoxy-5-(α-phenethyl)	104	1 Benzene 5 Cyclohexane	$C_{19}H_{20}O_4$	73.06	72.89	6.45	6.45	+
ω-(2-Methoxy-5-cyclohexylbenzoyl)-valeric acid	95	4 CH_3OH	$C_{19}H_{26}O_4$	71.67	71.70	8.23	8.30	+
[b]	98	9 Cyclohexane	$C_{18}H_{24}O_4$	71.02	70.80	7.95	8.03	+++
α-Phenyl-2-methoxy-5-cyclohexyl	174	15 CH_3OH	$C_{23}H_{26}O_4$	75.38	75.32	7.15	7.26	+
[b]	165–166	6 CH_3OH	$C_{22}H_{24}O_4$	74.97	75.09	6.86	6.97	+
α-Methyl-2-methoxy-5-cyclohexyl	151	4 CH_3OH	$C_{18}H_{24}O_4$	71.02	71.06	7.95	7.98	+
[b]	126	4 80% CH_3OH	$C_{17}H_{22}O_4$	70.32	70.17	7.64	7.56	+
3-Cyclohexyl-4-methoxy	161	8 Toluene	$C_{17}H_{22}O_4$	70.32	70.30	7.64	7.60	++
[b]	194	12 EtOAc	$C_{16}H_{20}O_4$	69.54	69.60	7.30	7.12	+
3-Phenyl-4-methoxy	131–132	16 50% AcOH	$C_{17}H_{16}O_4$	71.82	71.60	5.67	5.59	+++
[b]	169–170	20 50% CH_3OH	$C_{16}H_{14}O_4$	70.83	70.70	5.57	5.47	+
3-Benzyl-4-methoxy	133	3 CH_3OH	$C_{18}H_{18}O_4$	72.46	72.41	6.08	6.06	+
[b]	185.5	9 EtOAc	$C_{17}H_{16}O_4$	71.81	71.81	5.67	5.61	+
3-Phenoxy-4-methoxy	158	10 EtOAc	$C_{17}H_{16}O_5$	67.99	67.80	5.37	5.55	+
[b]	143	15 Benzene[d]	$C_{16}H_{14}O_5$	67.12	67.00	4.93	5.10	+
3-(o-Methoxyphenethyl)-4-methoxy	143	5 EtOAc	$C_{20}H_{22}O_5$	70.16	69.98	6.48	6.52	[e]
[b]	147–148	10 Benzene[d]	$C_{18}H_{18}O_5$	68.77	68.68	5.77	5.86	+
2,2′-Dimethoxy-5,5′-bis-(β-carboxypropionyl)-bibenzyl	250	100 AcOH	$C_{24}H_{26}O_8$	65.14	65.00	5.92	6.03	[e]
[b]	227	15 AcOH	$C_{22}H_{22}O_8$	63.76	63.29	5.39	5.64	+
3-(α-Phenethyl)-4-methoxy	150	10 CH_3OH	$C_{19}H_{20}O_4$	73.06	73.20	6.45	6.41	+
β-(3-Cyclohexyl-4-methoxybenzoyl)-acrylic acid	180	10 CH_3OH	$C_{17}H_{20}O_4$	70.81	70.70	6.99	7.02	+
[f]	206 dec.	10 70% AcOH	$C_{16}H_{18}O_4$	70.07	69.89	6.56	6.54	+
β-(3-Phenyl-4-methoxybenzoyl)-acrylic acid	161	5 EtOAc	$C_{17}H_{14}O_4$	72.33	72.68	5.00	5.33	+
[f]	201 dec.	5 70% AcOH	$C_{16}H_{12}O_4$	71.63	71.59	4.51	4.53	+
β-(3-Benzyl-4-methoxybenzoyl)-acrylic acid	156	3 EtOAc	$C_{18}H_{16}O_4$	72.95	72.91	5.44	5.51	+
ω-(3-Cyclohexyl-4-methoxybenzoyl)-valeric acid	96	5 Toluene	$C_{19}H_{26}O_4$	71.67	71.58	8.23	8.21	[g]
[b]	137	4 70% AcOH	$C_{18}H_{24}O_4$	71.02	71.19	7.95	7.98	[g]
2-Hydroxy-3-cyclohexyl-5-chloro[h]	174	18 Toluene	$C_{16}H_{19}O_4Cl$	11.42[i]	11.42[i]			+
p-(2-Methoxy-5-chlorobenzyl)	144–145	8 CH_3OH	$C_{18}H_{17}O_4Cl$	10.66[i]	10.65[i]			+
[b]	200–201	5 AcOH	$C_{17}H_{15}O_4Cl$	11.12[i]	11.19[i]			+
β-[p-(2-Methoxy-5-chlorobenzyl)-benzoyl]-acrylic acid	162	20 Benzene	$C_{18}H_{15}O_4Cl$	10.72[i]	10.63[i]			+
p-(4-Hydroxyphenyl)[c]	218–220	10 C_2H_5OH	$C_{16}H_{14}O_4$	71.10	71.00	5.22	5.23	+
2-Methoxy-5-cyclohexylcinnamic acid	147	4 CH_3OH	$C_{16}H_{20}O_3$	73.82	73.58	7.74	7.66	+
3-Cyclohexyl-4-methoxycinnamic acid	203	15 CH_3OH	$C_{16}H_{20}O_3$	73.82	73.80	7.74	7.84	+
3-Phenyl-4-methoxycinnamic acid	227–228	7 AcOH	$C_{16}H_{14}O_3$	75.57	75.37	5.55	5.60	+
3-Benzyl-4-methoxycinnamic acid	181	20 CH_3OH	$C_{17}H_{16}O_3$	76.09	76.08	6.01	5.98	++
β-(3-Cyclohexyl-4-methoxyphenyl)-propionic acid	126–127	10 Cyclohexane	$C_{16}H_{22}O_3$	11.83[j]	11.96[j]			+
β-(3-Phenyl-4-methoxyphenyl)-propionic acid	135	5 CH_3OH	$C_{16}H_{16}O_3$	12.11[j]	12.12[j]			+
2-Hydroxy-5-cyclohexylbenzoic acid	151	8 Cyclohexane	$C_{13}H_{16}O_3$	70.88	70.91	7.32	7.32	++

[a] Dehydrocholic acid = +. [b] Phenolic compound prepared by demethylation of above methyl ether. [c] Obtained by demethylation of the corresponding methoxy compound which was prepared according to Fieser and Bradsher, THIS JOURNAL, **58**, 1738 (1938). [d] Too insoluble in common solvents to crystallize; washed with boiling solvent. [e] Not tested. [f] Cannot be prepared by demethylation of parent compound; see text. [g] Tested on cats; data to be reported elsewhere. [h] Obtained by demethylation *in situ* in 5% yield as the only product from the acylation of 2-cyclohexyl-4-chloroanisole. The position of the β-carboxypropionyl side chain has not been definitely established. [i] Chlorine. [j] CH_3O.

The semicarbazone melted at 167° after crystallization from methanol.

Anal. Calcd. for $C_{15}H_{15}O_2N_3$: N, 15.60. Found: N, 15.52.

3-Benzyl-4-methoxybenzaldehyde.—Colorless, viscous oil, b.p. 152–155° (0.3 mm.), which on cooling formed a white solid melting at 59–60°.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.6; H, 6.24. Found: C, 79.53; H, 6.26.

The semicarbazone crystallized from methanol as white needles melting at 173°.

Anal. Calcd. for $C_{16}H_{17}O_2N_3$: N, 14.83. Found: N, 14.76.

2-Methoxy-5-cyclohexylbenzaldehyde.—This compound was obtained in a very crude state, b.p. 140–160° (0.6 mm.), in 15% yield. It was converted to the corresponding cinnamic acid without further treatment.

2-Cyclohexyl-4-chloroanisole.—To a stirred solution of 155 g. (0.81 mole) of *o*-cyclohexylanisole in 450 ml. of chlorobenzene heated on a steam-bath was added 121.5 g. (0.9 mole) of sulfuryl chloride during a 30-minute period. Heating was continued for 15 hours by which time hydrogen chloride evolution had virtually ceased. After the cooled solution had been thoroughly washed with a saturated solution of sodium bicarbonate, the solvent was stripped and the residue distilled through a 30-cm. Vigreux column, collecting 166 g. of a colorless liquid, b.p. 120° (0.3 mm.), $n^{25}D$ 1.5470.

Anal. Calcd. for $C_{13}H_{17}OCl$: C, 69.47; H, 7.63; Cl, 15.78. Found: C, 69.01; H, 7.40; Cl, 17.04.

As evidenced by the analysis this product contains a small amount of over-chlorinated material which a second fractionation failed to remove.

o-(α-Phenethyl)-anisole and *p*-(α-phenethyl)-anisole were obtained in excellent yields by methylation of the corresponding phenols[8] in the manner described above. 2,2′-Dimethoxybibenzyl[9] and *o*-methoxydiphenyl ether[10] were prepared by known methods.

Methoxyaroylalkanoic Acids.—With the exception of the two valeric acid derivatives all of the methoxyaroylalkanoic acids were prepared by the reaction of the appropriate phenolic ether with the required anhydride in the presence of aluminum chloride. In the case of the substituted valeric acids carbomethoxyvaleryl chloride was employed with great advantage instead of adipic anhydride. The yields varied from 40 to 80%, no attempt being made to secure optimum conditions in each instance. The following two examples served to illustrate the two methods.

A. **β-(3-Cyclohexyl-4-methoxybenzoyl)-propionic Acid (I).**—One hundred and thirty-four grams (1.0 mole) of aluminum chloride was added portionwise during a 30-minute period at 0–5° to a stirred suspension of 95 g. (0.5 mole) of *o*-cyclohexylanisole and 50 g. (0.5 mole) of succinic anhydride in 500 ml. of nitrobenzene. The mixture was stirred for two hours longer at 0–5° and then let stand overnight permitting the ice-bath to melt. After hydrolysis and steam distillation of the solvent, the crude acid was filtered, rinsed well with water and then dissolved in an excess of 2% sodium hydroxide at about 60°. Treatment with Darco and acidification of the cooled filtrate yielded 126 g. of fine white crystals, m.p. 160°. Crystallization from one liter of toluene gave 121 g. of pure acid melting at 161°.

B. **δ-(3-Cyclohexyl-4-methoxybenzoyl)-valeric Acid.**—A stirred solution of 47.5 g. (0.25 mole) of *o*-cyclohexylanisole and 44.6 g. (0.25 mole) of δ-carbomethoxyvaleryl chloride in 250 ml. of benzene was treated portionwise at 3–8° with 33.5 g. (0.25 mole)[11] of aluminum chloride. The mixture was stirred for four hours longer in the ice-bath and then at room temperature for 18 hours. After hydrolysis the benzene solution was washed with water, stripped of solvent, and the residual crude methyl ester was saponified by refluxing for 30 minutes with 16 g. of sodium hydroxide and 160 ml. of methanol. After removal of the solvent and acidification of the diluted sodium salt, the coarse, granular acid was collected and dried (58.6 g.). Crystallization from 200 ml. of toluene afforded 38.3 g. of colorless crystals melting at 96°.

Acylation of 2,2′-Dimethoxybibenzyl.—The interaction of 53.8 g. (0.22 mole) of 2,2′-dimethoxybibenzyl and 22 g. (0.22 mole) of succinic anhydride with 59 g. (0.44) mole of aluminum chloride in 220 ml. of nitrobenzene was carried out in the prescribed manner. After removal of the neutral products through solution in hot dilute sodium hydroxide and precipitation by acidification, the crude acid (71.5 g.) was extracted twice with 500-ml. portions of boiling methanol. Concentration of the methanolic extract to a volume of 150 ml. and dilution with one liter of water yielded 33.5 g. of a product which, upon crystallization from five volumes of ethyl acetate (Darco), weighed 17 g. and melted at 143°. This proved to be β-[3-(*o*-methoxyphenethyl)-4-methoxybenzoyl]-propionic acid.

The methanol insoluble acid from the above extraction (24.6 g.) was crystallized from one hundred volumes of acetic acid (Darco) to give 21 g. of 2,2′-dimethoxy-5,5′-bis-(β-carboxypropionyl)-bibenzyl as colorless prisms melting at 250° with decomposition.

Aroylacrylic Acids.—All of the methoxyaroylacrylic acids were obtained by the interaction of the proper phenolic ether and maleic anhydride with aluminum chloride. The yields were generally somewhat lower than those of the analogous saturated compounds, conceivably due to the formation of secondary addition products.[12] The two hydroxyaroylacrylic acids (footnote *e* in the table), which, because of the susceptible α,β-unsaturated ketone group, cannot be obtained by demethylation of the corresponding methyl ethers, were prepared by dehydrohalogenation of the brominated hydroxyaroylpropionic acids.

A. **β-(3-Phenyl-4-methoxybenzoyl)-acrylic Acid.**—One hundred and thirty-four grams (1.0 mole) of aluminum chloride was added portionwise at 0–3° to a stirred solution of 92 g. (0.5 mole) of *o*-methoxydiphenyl and 49 g. (0.5 mole) of maleic anhydride in 500 ml. of nitrobenzene. The mixture was stirred for two hours at 0°, stored overnight at room temperature and then hydrolyzed. After steam distillation of the solvent the crude acid was taken up in two liters of 3% sodium carbonate at *room temperature*, and the solution was filtered with Celite to remove a small amount of neutral material. Acidification precipitated a viscous yellow acid which granulated after standing for two hours (129 g., m.p. 145°). Crystallization from 650 ml. of ethyl acetate (Darco) yielded 52.5 g. of bright yellow needles, m.p. 161°. A solution of this acid in 5% sodium hydroxide decomposed immediately upon heating to form the expected methyl ketone.

B. **β-(3-Phenyl-4-hydroxybenzoyl)-acrylic Acid.**—A solution of 26.4 g. (0.16 mole) of bromine in 60 ml. of acetic acid was added dropwise at 60° during a 30-minute period to a stirred solution of 45.5 g. (0.16 mole) of β-(3-phenyl-4-hydroxybenzoyl)-propionic acid (IX) (subsequently described) in 455 ml. of acetic acid. The bromine was promptly absorbed with no formation of hydrogen bromide. Heating was continued for 45 minutes, after which the solvent was stripped, and the viscous residue was suspended in 300 ml. of Skellysolve B. The bromo acid, which soon crystallized, was filtered, rinsed with fresh solvent and dried at room temperature (42.5 g., m.p. 141–142° dec.). Crystallization of a sample from twelve volumes of toluene gave almost colorless crystals melting at 146° with decomposition.

Anal. Calcd. for $C_{16}H_{13}O_4Br$: Br, 22.89. Found: Br, 23.11.

A solution of the above acid and 18.8 g. of fused sodium acetate was stirred and refluxed for 30 minutes with simultaneous precipitation of sodium bromide. Dilution of the hot mixture with one liter of ice water produced a viscous green acid which soon crystallized. The dried acid, which weighed 27.5 g. and melted at 195° dec., was crystallized from 125 ml. of 70% acetic acid (Darco) to yield 18 g. of bright yellow crystals, m.p. 201° with decomposition.

Subsequent experiments have shown that this method offers no definite advantage over that of direct acylation for the preparation of these methoxyaroylacrylic acids.

Hydroxyaroylalkanoic Acids.—Previous studies[2] have demonstrated the facile demethylation of various methoxy-

(8) Kindly supplied by the Koppers Company. Two crystallizations of the crude *p*-isomer from four volumes of Skellysolve C raised the melting point to 57–58°, which agrees exactly with that reported by R. C. Huston, *et al.*, THIS JOURNAL, **49**, 1366 (1927).

(9) A. Schönberg and W. Malchow, *Ber.*, **55**, 3751 (1922).

(10) *Org. Syntheses*, **26**, 50 (1946).

(11) No significant improvement in yield resulted from the use of two molecular equivalents of aluminum chloride.

(12) Consult *Org. Reactions*, **5**, 250 (1949).

naphthoylalkanoic acids by means of aluminum chloride in chlorobenzene solution. In attempting to apply this method to the present series of compounds, we were surprised to find that internuclear cleavage occurred to a marked degree (about 50%) in several cases. Thus, in the treatment of β-(3-cyclohexyl-4-methoxybenzoyl)-propionic acid (I) with aluminum chloride in the prescribed manner, the principal product was β-(*p*-hydroxybenzoyl)-propionic acid (II). The desired β-(3-cyclohexyl-4-hydroxybenzoyl)-propionic acid was obtained in less than 5% yield. In view of this situation it was necessary to employ an entirely different demethylation method (illustrated below), which proved to be very satisfactory for compounds of the type under consideration.[13] As was expected those compounds containing a carbonyl group attached to the nucleus in a position ortho to the phenolic hydroxyl group produced intense color with ferric chloride.

β-(3-Phenyl-4-hydroxybenzoyl)-propionic Acid (IX).—A suspension of 10 g. of β-(3-phenyl-4-methoxybenzoyl)-propionic acid (VIII) in 25 ml. of acetic anhydride and 60 ml. of hydriodic acid (sp. gr. 1.7) was refluxed in a 300-ml. flask fitted with a short, vertical air-cooled condenser which in turn was attached to a water-cooled condenser set for distillation. When the distillation of methyl iodide had ceased (about 20 minutes), the red solution was diluted with 200 ml. of ice-water and filtered. The crude acid (8 g., m.p. 165–167°) was crystallized from 160 ml. of 50% methanol to give 7.2 g. of white crystals melting at 169–170°.

Substituted Cinnamic Acids.—These acids were readily obtained by the Doebner modification of the Knoevenagel condensation as in the following example.

3-Phenyl-4-methoxycinnamic Acid (V).—A solution of 21.2 g. (0.1 mole) of 3-phenyl-4-methoxybenzaldehyde in 50 ml. of pyridine and 1 ml. of piperidine was heated on the steam-bath for four hours. Dilution of the chilled mixture with 200 ml. of ice-cold 20% sulfuric acid precipitated the crude acid, which, after crystallization from 175 ml. of acetic acid, weighed 20 g. and melted at 227–228°.

Hydrogenation of this acid in fifty volumes of acetic acid at 60° under three atmospheres pressure with Adams catalyst afforded an excellent yield of the corresponding propionic acid.

2-Hydroxy-5-cyclohexylbenzoic Acid (XII).—To a solution of 33 g. of β-(2-methoxy-5-cyclohexylbenzoyl)-propionic acid (X) in 1320 ml. of water containing 93 g. of sodium hydroxide was added 93 g. of bromine during a 30-minute period at 10–15°. The mixture was stirred for three hours longer at 10° and then stored overnight at room temperature. After decomposing excess sodium hypobromite with sulfur dioxide, the solution was made strongly alkaline, washed thrice with ether and acidified. The oily acid was taken up in benzene, the solution washed with water and the solvent evaporated to yield 19 g. of a brown oil which resisted crystallization.

When the crude oxidation product was demethylated with hydriodic acid as described above, there was obtained 13.4 g. of crude acid, which after crystallization from 100 ml. of cyclohexane (Darco), weighed 6 g. and melted at 151° (XII).

The following procedure is more convenient for the preparation of larger amounts of this acid. One hundred and sixty grams (1.0 mole) of bromine was added to a hot, stirred suspension of 176 g. (1.0 mole) of *p*-cyclohexylphenol in 750 ml. of carbon disulfide at such a rate as to produce gentle refluxing. The resulting solution was refluxed for one hour and then vacuum evaporated, leaving 255 g. of 2-bromo-4-cyclohexylphenol as an oil which resisted crystallization.

Methylation of this crude product in the manner described above gave 246 g. of a yellow liquid, b.p. 128° (0.6 mm.), which solidified on cooling. A sample, after crystallization from five volumes of methanol, melted at 53°.

Anal. Calcd. for $C_{13}H_{17}OBr$: Br, 29.69. Found: Br, 29.50.

A solution of 134.5 g. (0.5 mole) of the bromo ether in 500 ml. of ether was added during a one-hour period to a stirred solution of butyllithium prepared from 69 g. (0.75 mole) of *n*-butyl chloride and 11.4 g. (1.65 atoms) of lithium. The mixture was refluxed for thirty minutes and then carbonated by pouring onto Dry Ice. After addition of one liter of 5% sodium hydroxide, the aqueous layer was separated, washed with ether and acidified. Extraction with ether and removal of solvent yielded the crude acid which was then distilled, collecting 64 g. of a colorless, viscous oil, b.p. 180° (0.7 mm.). Two crystallizations of a sample from a mixture of benzene and Skellysolve B produced white needles melting at 70–71° (XI).

Anal. Calcd. for $C_{14}H_{18}O_3$: CH_3O, 13.25. Found: CH_3O, 13.16.

Demethylation of 60.8 g. of this compound with hydriodic acid in the prescribed manner gave 56 g. of acid, m.p. 147–148°, which is identical with that obtained by the oxidation procedure.

Proof of Structures

3-Cyclohexyl-4-methoxybenzoic Acid (IV). (a) By Oxidation of I.—A solution of 5 g. of I, 10 g. of sodium hydroxide and 175 ml. of Clorox (5.25% sodium hypochlorite) in 325 ml. of water was heated at 60° for 0.5 hour and then refluxed for 0.5 hour. The cooled mixture was washed with ether and then treated with sulfur dioxide to decompose excess hypochlorite. Acidification precipitated an acid (1.0 g.), which, after crystallization from methanol, melted at 194–195°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74; CH_3O, 13.24. Found: C, 71.83; H, 7.77; CH_3O, 13.12.

(b) By Oxidation of III.—A stirred suspension of 1.0 g. of III and 5 g. of freshly precipitated silver oxide in 100 ml. of 1% sodium hydroxide was refluxed for one hour. After filtration the cooled solution was washed with ether, acidified, and the crude acid was collected. Crystallization from methanol gave white plates, m.p. 195°, which showed no depression in melting point when mixed with the acid obtained from I.

3-Phenyl-4-methoxybenzoic Acid (VI). (a) By Oxidation of V.—A solution of 4.5 g. of V, 29 g. of potassium permanganate and 15 g. of potassium hydroxide in 500 ml. of water was refluxed and stirred for four hours. The manganese dioxide was filtered, rinsed by suspension in 300 ml. of hot water, and the combined filtrates were acidified. The crude acid, which coagulated after brief boiling, weighed 1.5 g. and melted at 219°. Crystallization from methanol afforded lustrous plates, m.p. 221–222°.[14]

Anal. Calcd. for $C_{14}H_{12}O_2$: CH_3O, 13.60; neut. equiv., 228. Found: CH_3O, 13.54; neut. equiv., 228.

Demethylation of VI with hydriodic acid and acetic anhydride yielded an acid (VII) which melted at 148° and gave no color with ferric chloride.

(b) By Oxidation of VIII.—Five grams of VIII was oxidized with potassium permanganate in the same manner to yield an acid melting at 220–221° which was identical with that of (a).

A solution of 3 g. of IX, 15 g. of potassium hydroxide and 20 g. of potassium permanganate was refluxed for four hours. After saturating the cooled mixture with sulfur dioxide, the solution was extracted with ether and the extract evaporated to yield 1.1 g. of benzoic acid (m.m.p. 121°; anilide, m.m.p. 161–162°). Thus, acylation occurred in the oxygenated nucleus.

(c) By Dehydrogenation of IV.—One and seven-tenths grams of IV was esterified by refluxing overnight in 10 ml. of ethanol containing 0.5 ml. of sulfuric acid. Work-up in the customary manner yielded the crude ester as a crystalline solid. A mixture of this ester and 0.2 g. of 5% palladium-charcoal was heated at 270–280° (bath temp.) for three hours. After solution with 15 ml. of ethanol and filtration, the filtrate was mixed with 2 g. of sodium hydroxide and then refluxed for 0.5 hour. Removal of solvent and acidification gave 1.1 g. of crude acid which was washed by suspension with 60 ml. of boiling cyclohexane and crystallized twice from methanol. The resulting product

(13) δ-(3-Cyclohexyl-4-methoxybenzoyl)-valeric acid was exceptional, since it could not be demethylated with hydriodic acid. The desired phenolic derivative was obtained in 50% yield by refluxing for 0.5 hour with four parts of freshly distilled pyridine hydrochloride. Attempted cleavage of this methyl ether with aluminum chloride gave only δ-(*p*-hydroxybenzoyl)-valeric acid.

(14) K. H. Slotta and A. E. Nold, *Ber.*, **68**, 2226 (1935), obtained an acid, m.p. 217–218°, by oxidation of the product resulting from the acetylation of 2-methoxybiphenyl, to which they assigned this structure. Demethylation gave an acid melting at 148–149°. No conclusive evidence concerning the structures of these compounds was furnished.

melted at 220° and showed no depression in melting point when mixed with the acids from (a) or (b).

Oxidation of β-(2-Methoxy-5-benzylbenzoyl)-propionic Acid (XIII).—A solution of 4.5 g. of XIII, 15 g. of potassium hydroxide and 30 g. of potassium permanganate in 500 ml. of water was refluxed for four hours. The manganese dioxide was filtered, rinsed well with hot water, and the cooled filtrate was acidified. The precipitated acid was collected and then demethylated by refluxing with hydriodic acid, yielding 1.0 g. of XV as colorless needles, m.p. 215° after crystallization from 25% alcohol. The methyl ester melted at 94°.[15]

Oxidation of β-[p-(2-Hydroxy-4-chlorobenzylbenzoyl)]-propionic Acid (XVII).—A stirred solution of 3.8 g. of XVII, 15 g. of potassium hydroxide and 25 g. of potassium permanganate in 300 ml. of water was refluxed for four hours. After filtration of the manganese dioxide, the filtrate was saturated with sulfur dioxide, strongly acidified and finally boiled for 20 minutes. The resulting terephthalic acid (1.4 g.) was collected, dried and then converted to the dimethyl ester, m.m.p. 140°.

α-Methyl-β-(2-methoxy-5-cyclohexylbenzoyl)-propionic Acid (XIX).—A stirred solution of 76 g. (0.4 mole) of *p*-cyclohexylanisole and 45.2 g. (0.4 mole) of chloroacetyl chloride in 400 ml. of *s*-tetrachloroethane was treated portionwise at −5 to 0° with 56.3 g. (0.42 mole) of aluminum chloride. The mixture was stirred overnight, coming to room temperature as the coolant melted. After hydrolysis the solvent layer was washed first with sodium bicarbonate solution and then with water. Vacuum distillation of the solvent afforded 103 g. of crude product as a crystalline paste, which, upon crystallization from 500 ml. of Skellysolve B (Darco), yielded 39.3 g. of the ketone XVIII, m.p. 112–113°.

Anal. Calcd. for $C_{15}H_{19}O_2Cl$: Cl, 13.29; CH_3O, 11.63. Found: Cl, 12.97; CH_3O, 11.50.

A solution of sodiomalonic ester, prepared from 1.15 g. (0.05 mole) of sodium and 8.7 g. (0.05 mole) of ethyl malonate in 30 ml. of anhydrous alcohol, and 13.3 g. (0.05 mole) of the chloro ketone was refluxed for 14 hours. A solution of 8 g. of sodium hydroxide in 80 ml. of ethanol was added, and the mixture was refluxed for one hour to effect saponification. Subsequent to removal of the solvent and acidification, the crude acid was taken up in ether, which solution upon evaporation gave 9.4 g. of a dark, viscous oil. This was heated at 180–190° until evolution of carbon dioxide ceased (about one hour). A solution of the resulting product in 80 ml. of 5% sodium hydroxide was washed with ether and acidified to precipitate a viscous oil which crystallized after several hours. Two crystallizations from methanol (Darco) yielded 2 g. of the acid XIX, m.p. 149–150°, which was identical with that obtained by the interaction of *p*-cyclohexylanisole and methylsuccinic anhydride.

(15) H. Limpricht, *Ann.*, **290**, 167 (1896), reported m.p. 210° for 4-hydroxybenzophenone-3-carboxylic acid and m.p. 92° for its methyl ester.

α-Phenyl-β-(2-methoxy-5-cyclohexylbenzoyl)-propionic Acid (XX).—A solution of 7.5 g. (0.03 mole) of β-carbomethoxyhydrocinnamic acid[16] and 7.2 g. (0.06 mole) of thionyl chloride was heated at 50–60° for four hours. The excess thionyl chloride was removed by vacuum distillation and subsequent stripping with benzene.

Four grams (0.03 mole) of aluminum chloride was added in two portions at 5° to a stirred solution of the crude acid chloride and 5.7 g. (0.03 mole) of *p*-cyclohexylanisole in 30 ml. of benzene. The mixture was stirred for 14 hours at room temperature, hydrolyzed and extracted with ether. After removal of the solvent the crude methyl ester was saponified by refluxing for one hour with 3 g. of sodium hydroxide in 30 ml. of methanol. The resulting solution was diluted with 300 ml. of water, washed with ether, boiled briefly and acidified. The crude acid (12 g.) was collected, dried and crystallized from 60 ml. of methanol to give 4.5 g. of XX melting at 171–172°. Its identity with the acid derived from phenylsuccinic anhydride was established by a mixed melting point determination.

2-Hydroxy-3-cyclohexylbenzoic Acid (XXII).—Thirty-eight grams (0.02 mole) of *o*-cyclohexylanisole was added dropwise to a stirred solution of *n*-butyllithium, prepared in the usual manner from 6.1 g. (0.88 atom) of lithium and 37 g. (0.4 mole) of *n*-butyl chloride in 300 ml. of ether. After the mild exothermic reaction had subsided, the mixture was refluxed with stirring for 20 hours and then carbonated with Dry Ice. The product was taken up in 1 l. of 2% sodium hydroxide and washed twice with ether. Acidification of the alkaline solution followed by extraction with ether and evaporation of the solvent yielded an oily acid which partially crystallized after 15 hours. This crystalline product was separated by filtration and crystallized twice from cyclohexane, affording 4.5 g. of XXI melting at 113°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.78; H, 7.77.

A mixture of 4 g. of XXI, 30 ml. of 47% hydroiodic acid and 12.5 ml. of acetic anhydride was refluxed for 0.5 hour. After dilution with ice-water the crystalline product was collected, rinsed well and dried to give 3.7 g. of pure XXII, m.p. 159–160°. It produced a deep blue color with ferric chloride.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.74; H, 7.37.

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(16) R. Anschütz, *ibid.*, **354**, 129 (1907).