[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MISSOURI]

METHOXY (AND HYDROXY) PHENOXYBENZOIC ACIDS[1]

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It was observed some time ago that certain methoxyphenoxybenzoic acids show abnormal behavior on demethylation with hydriodic acid, and sodium hydroxide in ethylene glycol, respectively (1). The present investigation of all nineteen possible methoxy acids was undertaken in order to study their behavior on demethylation, to correlate this with the structures of the substances, and to characterize the hydroxy acids by their physical properties.

The methoxy acids were synthesized through four general methods: the oxidation of the methylmethoxydiphenyl ethers (A), Ullmann's chlorobenzoic acid synthesis (B) (2), the condensation of hydroxybenzoic esters with aryl halides (C), and by methylation of hydroxy acids which were obtained by the Kolbe synthesis.

Demethylation was effected by three standardized methods: with hydriodic acid in acetic acid containing sufficient acetic anhydride to form a homogeneous solution, with aluminum chloride in benzene, and with alkali in boiling ethylene glycol.

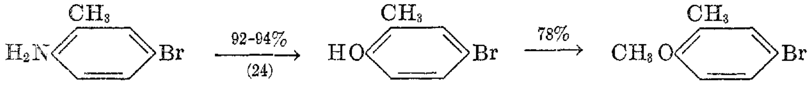
EXPERIMENTAL[4]

All temperatures uncorrected.

Analyses by Karl Zilch.

Methylmethoxydiphenyl ethers. The condensation of potassium phenoxides with aryl halides was carried out essentially as described previously (3). The solid products were crystallized and the liquid ones were distilled. The starting materials, yields, properties, and analyses of the compounds are listed in Table I.

4-Bromo-2-methylanisole was prepared from 4-bromo-2-methylaniline by the following sequence of reactions:



The pure material boiled at 124–125° (25 mm.), f.p. 65.8° (from the cooling curve).

Methylhydroxydiphenyl ethers. A few of the above methoxydiphenyl ethers were demethylated with hydriodic acid in acetic acid to the corresponding hydroxy compounds. The constants of the compounds and other pertinent data are given in Table II.

Methoxy acids. A. Methylmethoxydiphenyl ethers have been oxidized with chromic acid (6) and with permanganate (5). A modified procedure using aqueous pyridine as solvent has been described by one of us (4). It was employed successfully with a number of the methyl compounds but failed in the case of 6-methyl-2-methoxydiphenyl ether which was recovered unchanged (Table III). Chromic acid oxidation of the same compound lead to

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[4] The authors are indebted to students in the synthesis courses at the University of Missouri who prepared a number of the starting materials.

complete destruction [*cf.* Brewster (6) and Cook (7)]. The yields in the oxidation reaction varied from 23 to 88% and there was no apparent simple relationship between yield and the structure of the methyl compound. *m*- And *p*-phenoxytoluene gave yields of 63 and 75% of the corresponding phenoxy acids.

TABLE I

PREPARATION OF METHYLMETHOXYDIPHENYL ETHERS[a]

ME	MEO	PHENOL	PHENYL BR	YIELD, %	M.P., °C.	B.P., °C.	MM.	ANALYSES[b]	
								C	H
3	2[c]	Phenol	2-MeO 3-Me	39.6	55.5–56[d]	—	—	78.47	6.70
4	2	2-MeO 4-Me	C_6H_5	24	74–75[e]	—	—	78.65	6.78
5	2	2-MeO 5-Me	C_6H_5	60	38.5–39[d]	—	—	(1, 3)	
6	2	2-MeO 6-Me	C_6H_5	15	68–69[d]	—	—	78.53	6.48
3′	2	2-MeO	3-Me	63	liq.	85–90	0.1	78.3	6.84
4′	2	2-MeO	4-Me	54	50–51[d]	—	—	(3, 4)	
4	3	Phenol	3-MeO 4-Me[g]	10	liq.	275–276	740	(1)	
5	3	3-MeO 5-Me	C_6H_5	27.6	liq.	145–147	18[h]	78.40	6.62
3′	3	3-MeO	3-Me	16	liq.	178–180	20	78.52	6.64
4′	3	3-MeO	4-Me	10	liq.	179–181	20	78.48	6.59
3	4	Phenol	4-MeO 3-Me	37	44–45[d]	—	—	78.48	6.82
3′	4	4-MeO	3-Me	12.5	liq.	177–180	20	78.56	6.71
4	4′	4-MeO	4-Me	15	47–48[f]	—	—	(5)	

[a] Procedure (3). [b] Calc'd for $C_{14}H_{14}O_2$: C, 78.5; H, 6.74. [c] Prepared by E. Klein. [d] Crystallized from petroleum ether. [e] Crystallized from aqueous methanol. [f] Crystallized from aqueous ethanol. [g] The aryl chloride was used in this case. [h] Japanese Patent 161,433 (1944) reports b.p. 130–135° (3 mm.).

TABLE II

PREPARATION OF METHYLHYDROXYDIPHENYL ETHERS[a]

ME	OH	YIELD, %	M.P., °C.	SOLVENT	ANALYSES[b]	
					C	H
4	2	89	78–79[c]	Aq. MeOH	77.80	6.16
5	2	92	68.7–70	Pet. ether	(1)	
6	2	98	121.5–122.6	Aq. EtOH	77.73	6.15
3′	2	96	68.5–69	Aq. EtOH	77.75	6.24
4′	2	87	63–63.8	Pet. ether	(4)	
4′	4	—	56–57, 72–73	Pet. ether	(5)	

[a] Procedure (4). [b] Calc'd for $C_{13}H_{12}O_2$: C, 78.00; H, 6.00. [c] Prepared by Karl Zilch.

B. Ullmann's chlorobenzoic acid synthesis was used with *o*-chlorobenzoic acids and suitable aryl halides. Attempts to use the *p*-chloro acids were unsuccessful. The yields in the reactions amounted to 30–61% (Table III) and the yield was no higher for the unsubstituted *o*-phenoxybenzoic acid (55%). An improved method has been described by Koelsch (14) since the completion of this work.

Starting materials: *o*-Chlorobenzoic acid (15), 2-chloro-6-methoxybenzoic acid (16), 2-chloro-4-methoxybenzoic acid (9), and 2-chloro-5-methoxybenzoic acid (8).

C. Hydroxybenzoic esters have been used previously in the Ullmann reaction by a number of workers (4, 12, 17, 18). In the present investigation this method provided the only successful synthesis for 2-phenoxy-3-methoxybenzoic acid. 2-Hydroxy-3-methoxybenzoic acid was prepared by silver oxide oxidation (19) of the corresponding aldehyde in 48.8% yield. The partial demethylation of 2,3-dimethoxybenzoic acid with aluminum chloride in benzene gave only a 27% yield of the same acid. Esterification of 2-hydroxy-3-methoxybenzoic acid (18 g.) with ethanolic hydrogen chloride furnished 13.9 g. (66.3%) of the ethyl ester, b.p. 119–122° (1 mm.).

TABLE III

THE PREPARATION OF THE METHOXYPHENOXYBENZOIC ACIDS

COOH	OMe	METHOD[a]	YIELD, %	M.P., °C.	CRYSTALLIZED FROM	ANALYSES[b]	
						C	H
3	2[c]	A	44	117.5–118	Pet. ether	69.16	5.11
4	2	A	30	174–175	Benzene	68.81	5.13
5	2	A	45	186–186.5	Pet. ether	(1, 22)	
6	2	C	14[d]	130–131	Ligroin	68.76	5.25
2′	2	B	30	110–111	Benzene	(8)	
3′	2	A	79	148–149	Benzene-ligroin	69.08	5.17
4′	2	A	88	159–160	Benzene-ligroin	(4)	
2	3	B	58	125–125.8	Benzene-ligroin	68.71	4.99
4	3	A	49	79–81	Ligroin	69.11	5.21
5	3	A	61	140–142	Benzene	68.77	4.98
6	3	B	61	174–175	Benzene	(9)	
2′	3	B	35	131–132	Benzene-ligroin	(10)	
3′	3	A	23	96.5–97.5	Benzene-pet. ether	69.03	5.10
4′	3	A	77	116.5–117.5	Ligroin	68.50	4.90
2	4	B	59	154–156	Benzene	(8)	
3	4	A	30	109–110	Ligroin	(11, 12)	
2′	4 (13)	B	57	144–145	Benzene	68.65	5.04
3′	4	A	56	139–140	Ligroin	68.65	4.98
4′	4	C	38	175–176	Benzene	(5, 11)	

[a] A: $ArCH_3 \rightarrow ArCOOH$; B: o-$Cl$-$C_6H_4COOK$ + $KOAr$; C: ArX + potassium hydroxybenzoate. [b] Calc'd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.92. [c] Prepared by E. Klein. [d] Ethyl ester, yield 16.5%, m.p. 108.5–110°. *Anal.* Calc'd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.87; H, 5.94.

Anal. Calc'd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17.
Found: C, 61.15; H, 6.29.

The customary procedure for the Ullmann reaction (17) failed to give any product with ethyl 2-hydroxy-3-methoxybenzoate, which was recovered.

Ethyl 2-phenoxy-3-methoxybenzoate was prepared as follows: Ethyl 2-hydroxy-3-methoxybenzoate (6.5 g.) was added to potassium methoxide in methanol (from 1.3 g. of potassium). The solvent was removed by distillation, the last traces *in vacuo* at 150°. The dry salt mixed with 0.1 g. of copper powder and bromobenzene (10 g.) was heated in a Carius tube at 220–240° for six hours. The reaction products were taken up in water and ether. The ether solution contained unchanged bromobenzene and a pale yellow oil, b.p. 170–180° (1 mm.), yield 1.49 g., which crystallized from alcohol (Table III). The ester was hydrolyzed to the acid in 83.5% yield by refluxing with alcohol and aqueous potassium hydroxide.

Kolbe synthesis. The carbonation of o-phenoxyphenol according to Rittler (sodium salt) (20) or Harris and Pierce (potassium salt) (21) took place at 200–230° (100–200 atm.) to give a single monocarboxylic acid, 2-hydroxy-3-phenoxybenzoic acid, in yields of 24 and 69%, m.p. 139–140.2°. Claims that the isomeric 4-hydroxy-3-phenoxybenzoic acid can be formed in the Kolbe reaction at high temperatures (23) could not be substantiated.[5]

The Kolbe synthesis with *p*-phenoxyphenol has been described previously (20) and gave the expected 3-acid.

While three possible isomers could be formed from *m*-phenoxyphenol on carbonation, only the 4-acid was isolated in yields of 50% from the reaction of the potassium salt at 230° m.p. 180–182°. No carboxylic acid was obtained at low temperature (160°).

TABLE IV

THE PREPARATION OF THE HYDROXYPHENOXYBENZOIC ACIDS

COOH	OH	METHOD[a]	YIELD, %	M.P., °C.	CRYSTALLIZED FROM	ANALYSES[b]	
						C	H
3	2	A	88	137–138.5	Benzene-ligroin	67.61	4.25 (20)
4	2	A	99	146–147	Benzene-ligroin	67.90	4.50
5	2	B	81	187.6–188	Benzene-ligroin	—	— (1)
6	2	B	75	152–153.5	Ligroin	67.73	4.41
2′	2	A	50	111–114[c] 121–122[c]	Benzene-ligroin	67.78	4.58
3′	2	C	80	121–123[c] 138–140[c]	Benzene-ligroin	67.69	4.42
4′	2	B	72	138.2–139	Benzene-ligroin	—	— (4)
2	3	B	62.5	124–125	Ligroin	67.83	4.42
4	3	B	76	182.4–183	Benzene-ligroin	—	— (1)
5	3	A	98	216–217	Benzene	67.80	4.46
6	3	C	71.5	164–165	Water	—	— (1)
2′	3	C	57	119–120	Ligroin	67.70	4.41
3′	3	A	55.5	130–132	Benzene-ligroin	67.88	4.47
4′	3	A	89	163.5–165	Benzene	67.91	4.44
2	4	A	62.5	167–168.5	Ligroin-chloroform	67.90	4.58
3	4	A	88	132–133	Ligroin	—	— (20)
2′	4	A	99	158–159.5	Benzene-ligroin	—	— (25)
3′	4	A	89	169.5–170.5	Benzene	67.76	4.51
4′	4	C	84	190–191	Benzene	—	— (5)

[a] A: Demethylation with HI; B: $AlCl_3$; C: KOH. [b] Calc'd for $C_{13}H_{10}O_4$: C, 67.84; H, 4.27. [c] Dimorphic forms.

Methylation. The hydroxy acid (1 mole), dissolved in 2 moles of 10% aqueous sodium hydroxide, was treated with 1.1 moles of methyl sulfate. The mixture was heated on a water-bath with stirring for one hour. The homogeneous mixture was acidified with hydrochloric acid. The solid acids were filtered and crystallized. 2-Methoxy-3-phenoxybenzoic acid melted at 116–117° (47%), and 2-methoxy-4-phenoxybenzoic acid melted at 79–81° (49%). Neither acid depressed the melting point of the compounds obtained by other methods.

Hydroxy acids. Each of the nineteen methoxy acids was treated with the three demethylating agents under identical conditions. The preferred method for preparative purposes, yields, and constants for the acids are listed in Table IV.

A. *Hydriodic acid.* The methoxy acid (100 mg.) was refluxed with 1 cc. of acetic acid, 1

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[5] The claimed 4-hydroxy-3-phenoxybenzoic acid, m.p. 152–154°, (23) very likely represents a mixture since the authentic acid has been shown to melt at 187.6–188° (1).

cc. of hydriodic acid (*d.* 1.5), and 0.5 cc. of acetic anhydride for 15 minutes. The mixture was poured into 10 ml. of water and worked up in the usual manner.

B. *Aluminum chloride.* Aluminum chloride (1.5 g.) was added to 170 mg. of the methoxy acid in 35 cc. of dry, thiophene-free benzene. The mixture was stirred and refluxed for two hours. After cooling it was poured into ice and hydrochloric acid. The benzene was removed by distillation and the aqueous residue was extracted with ether. The organic acid was taken up in 10% aqueous sodium carbonate, decolorized, and acidified with hydrochloric acid.

C. *Potassium hydroxide.* A mixture of 150 mg. of methoxy acid, 1.0 g. of potassium hydroxide, and 5.5 cc. of ethylene glycol was refluxed for four hours. The hot mixture was poured into 20 ml. of water, mixed well, and acidified with hydrochloric acid.

The results of the reactions are listed in Table V.

TABLE V

THE DEMETHYLATION OF THE METHOXYPHENOXYBENZOIC ACIDS

	COOH	OH	HYDRIODIC ACID	YIELD, %	ALUMINUM CHLORIDE	YIELD, %	POTASSIUM HYDROXIDE	YIELD, %	
I	3	2	HOA[a]	88	HOA	62	HOA	36	D 27
II	4	2	HOA	99	HOA	75	MeOA	72	
III	5	2	MeOA	90	HOA	81			D 75
IV	6	2	HOA[c]	40	HOA	75	MeOA	62	
V	2′	2	HOA	50	HOA	31	HOA[b]	71	
VI	3′	2	HOA	66	HOA	58	HOA	80	
VII	4′	2	HOA	72	HOA	65	HOA	53	
VIII	2	3	D	67	HOA	62.5	MeOA	78.5	
IX	4	3	HOA	68	HOA	76	MeOA	35	D 23
X	5	3	HOA	98	HOA	50	HOA	65	
XI	6	3	HOA	67	HOA	54	HOA	71.5	
XII	2′	3	HOA[c]	50	MeOA	40	HOA	57	
XIII	3′	3	HOA	55.5	MeOA	82	HOA	70	
XIV	4′	3	HOA	89	HOA	65	MeOA	66	
XV	2	4	HOA	55.5	HOA	62.5	HOA[c]	73	
XVI	3	4	HOA	88	HOA	62	HOA[c]	70	
XVII	2′	4	HOA	99	HOA	62.5	HOA[c]	60	
XVIII	3′	4	HOA	89	HOA	62.5	HOA[c]	60	
XIX	4′	4	HOA	54	HOA	63	HOA	84	

[a] HOA, hydroxy acid; MeOA, methoxy acid; D, decarboxylation. [b] The product was the lactone. [c] Partial demethylation.

The yields of demethylation products were based on purified crystalline compounds and were therefore subject to mechanical losses. The total yields in the reactions are undoubtedly larger than the reported values.

The organic material was separated into carboxylic acids and phenols. The acids were crystallized; the solid phenoxyphenols were compared with authentic specimens, and *m*-phenoxyphenol was identified as aryloxyacetic acid (1).

Partial demethylation was indicated by the melting behavior of the mixture. It was conclusively established by complete demethylation and identification of the end product.

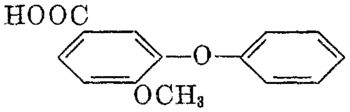
o-(2-Hydroxyphenoxy)benzoic acid lactone. The basic demethylation of *o*-(2-methoxyphenoxy)benzoic acid gave a good yield (70%) of the hitherto unknown lactone which represents the basic ring system in the depsidones (26). The water-insoluble substance was obtained by acidification of the demethylation mixture. It melted at 100–101° (from ligroin) and depressed the melting point of the hydroxy acid (m.p. 111–114° and 119–121°).

Anal. Calc'd for $C_{13}H_8O_3$: C, 68.41; H, 5.15.
Found: C, 68.23; H, 5.18.

The lactone was hydrolyzed by dissolving it in 5% aqueous sodium hydroxide and was reformed by acidifying the alkaline solution. It could be prepared from the hydroxy acid by acidification of the water solution of its sodium salt.

DISCUSSION

Demethylation with hydriodic acid took place in all but one of the 19 acids. The 2,5-acid (III) was recovered unchanged.



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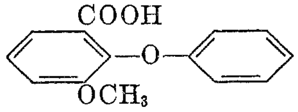
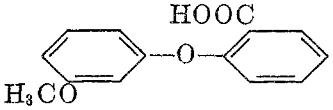


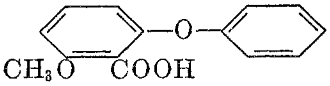
IV

Acids (IV) and (XII) were only partially demethylated under the conditions of the reaction and are therefore more resistant than the remaining acids which were completely demethylated under the same conditions. The demethylation of IV with hydriodic acid was completed by heating for 30 minutes.

2-Methoxy-6-phenoxybenzoic acid (VIII) was simultaneously demethylated and decarboxylated with hydriodic acid in acetic acid. The decarboxylation occurred also with the corresponding hydroxy acid under the same conditions. It is regarded as an example of proton attack on the ring carbon which carries the carboxyl group (27, 28) and which undoubtedly has a high electron density.

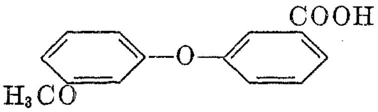


XII

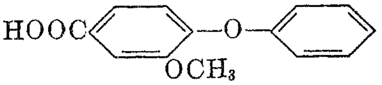


VIII

Aluminum chloride in benzene proved to be the most reliable of the demethylating agents. It gave hydroxy acids in good yield from 17 of the methoxy acids. Two acids, XII and XIII, were recovered unchanged. The method appears to be free from any appreciable side reactions and is therefore preferred for preparative purposes.

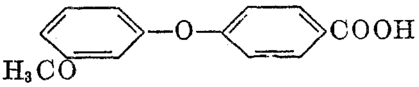


XIII

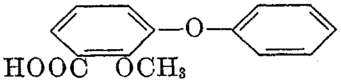


II

The basic demethylation procedure failed to affect acids II, IV, VIII, and XIV which were recovered unchanged. It caused decarboxylation and demeth-



VII



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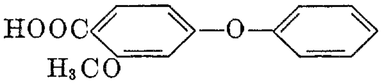
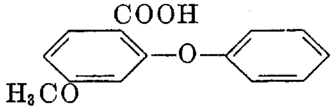
ylation in two acids having adjacent hydroxyl and carboxyl groups, the 2,3 acid (I) and the 3,4 acid (IX) but not in XVI. The carboxyl group was eliminated in the *p*-methoxybenzoic acid (III) but not the isomer XI, *i.e.*, decarboxylation in the *p*-methoxy acids failed to take place when the carboxyl group was adjacent to the phenoxyl group. The reason for this is not immediately apparent.



IX



XI

The demethylation reactions are undoubtedly subject to both electronic and steric effects. The combined effects, however, fail to give a clearcut explanation for all the abnormal cases.

SUMMARY

The nineteen possible methoxy acids of diphenyl ether have been prepared and demethylated by three standardized procedures.

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