[Contribution from the Chemical Laboratory of Northwestern University]

THE METALATION OF SOME ALKYL ANISOLES

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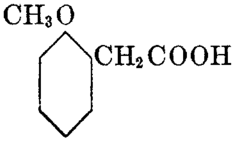
Some experiments concerning the metalation of methylanisole and ethylanisole are reported in this paper. Both amylsodium and butyllithium were used as metalating agents, and in all cases, the products were treated with carbon dioxide in order to convert the organometallic compounds to the corresponding carboxylic acid salts. The acids which were isolated from these reactions are listed in Table I. Amylsodium proved to be more satisfactory for the formation of the substituted acetic acids, while butyllithium was better for the preparation of the substituted benzoic acids.



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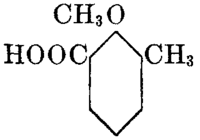

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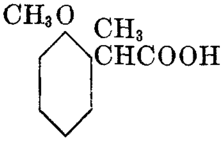

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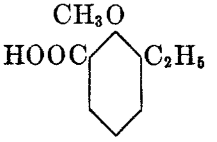

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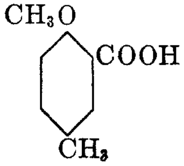
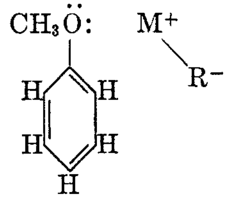


V

The identification of the acids from the metalation of methylanisole presented no problem since all the possible isomeric acids had been described. One of the products, IV, from the *o*-ethylanisole reactions, was previously unknown; however, the mode of its formation and the fact that it yielded 2-methoxyisophthalic acid on oxidation permitted the assignment of an unequivocal structure, 2-methoxy-3-ethylbenzoic acid. The other product, III, had been reported as a degradation product of a pentenylanisole (1). For confirmatory evidence concerning the structure of this acid, we synthesized α-(*o*-methoxyphenyl)propionic acid from *o*-methoxyacetophenone *via* the cyanohydrin and *o*-methoxyatropic acid. The acid thus obtained was identical (mixture melting point) with the product from the metalation reaction, and corresponded in melting point to the compound previously reported.

The reaction of butyllithium with *p*-methylanisole led to the isolation of products corresponding to metalation *ortho* to the methoxyl group. Furthermore, it has been reported that amylsodium metalated *p*-methylanisole in the ring rather than in the side chain (2). The evidence therefore indicates that a side chain *ortho* to a methoxyl group is more readily metalated than one *para* to it. In order to account for the *ortho* orientation observed in the metalation of anisole and similar compounds, it has been assumed that the reaction proceeds from an intermediate coordination complex (VI) (3). It seems very likely that the greater tendency for an *ortho* methyl group, as compared to a *para* methyl side chain, to undergo metalation is also due to the prior complexing of the alkyl anisole and the metal compound.



VI

EXPERIMENTAL

The substituted anisoles were prepared by methylation of the corresponding phenols with methyl sulfate. Amylsodium was prepared as previously described (4) from finely divided sodium (0.2 g.-atom) and amyl chloride (0.1 g.-atom). Butyllithium was prepared (5) and analyzed (6) by the method of Gilman and co-workers. In the amylsodium reactions, the anisole was added to the suspension of amylsodium in petroleum ether (b.p. 60–70°) and stirred vigorously at about 45° until carboxylated. The butyllithium metalations, which were homogeneous reactions, were carried out with milder stirring at the reflux temperature of the ether solutions. A nitrogen atmosphere was employed in all reactions, and carbonation was effected by forcing the contents of the flasks onto powdered Dry Ice. Further details are listed in Table I.

TABLE I

METALATION OF ALKYL ANISOLES

EXPT	REAGENT (moles)	ANISOLE (moles)	TIME (hours)	RECOVERED ANISOLE (moles)	ACID
A	$C_5H_{11}Na$ (0.14)[a]	*o*-CH_3 (0.3)	6	0.164	I
B	C_4H_9Li (0.22)	*o*-CH_3 (0.4)	93	.322	I + II
C	C_4H_9Li (0.22)	*o*-C_2H_5 (0.2)	60	.091	IV
D	$C_5H_{11}Na$ (0.07)[a]	*o*-C_2H_5 (0.25)	4	.175	III + IV
E	C_4H_9Li (0.34)	*p*-CH_3 (0.5)	40	.129	V

[a] The moles of $C_5H_{11}Na$ are based on the assumption of a 70% conversion of amyl chloride to $C_5H_{11}Na$.

The products of the reactions were worked up by conventional procedures of extraction and distillation. Amounts of recovered anisoles are listed in Table I. The characterization of the reaction products is discussed separately below for each reaction.

Reaction A (I). The acid fraction was extracted from the acidified aqueous layer with ether, dried, and the ether evaporated. The residual oil (16.1 g.) completely solidified on cooling to room temperature. After several recrystallizations from water, a sample (4.8 g.) was obtained which melted at 122.5–123.5° [Reported for *o*-methoxyphenylacetic acid, m.p. 123–124° (7)]. This is sufficiently different from those of other possible products so that no ambiguity exists; 2-methoxy-3-methylbenzoic acid, m.p. 83° (8); 3-methoxy-2-methylbenzoic acid, m.p. 145–146° (9); 3-methoxy-4-methylbenzoic acid, m.p. 156° (10); and 4-methoxy-3-methylbenzoic acid, m.p. 192° (11).

Anal.[1] Calc'd for $C_9H_{10}O_3$: C, 65.05; H, 6.07; Neut. equiv., 166.1.
Found: C, 64.83; H, 6.07; Neut. equiv., 163.

Reaction B (I + II). In addition to the recovery of *o*-methylanisole, 3.6 g. of *o*-cresol was isolated from the reaction. Acidification and extraction of the carboxylic acid portion yielded 4.72 g. of an oil which solidified completely on standing. After recrystallization from hexane it melted at 63–75°. Slow recrystallization from water gave two distinguishable crystalline forms in about equal amounts. One form, small white prisms m.p. 122–123°, showed no depression in melting point when mixed with *o*-methoxyphenylacetic acid from reaction A. The other form, fine needles m.p. 83.0–83.5°, was 2-methoxy-3-methylbenzoic acid (8) (see data under Reaction A).

Reaction C (IV). The acid (11.9 g.) crystallized after the ether used for its extraction had been removed, and distillation for purification was unnecessary. After several recrystallizations from ligroin (b.p. 80–120°), the acid (5.4 g.) melted at 58.5–59.0°. No α-(*o*-methoxyphenyl)propionic acid was found.

Anal. Calc'd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71; Neut. equiv., 180.2.
Found: C, 66.02; H, 6.53; Neut. equiv., 181.0.

Oxidation of 2.70 g. of this acid with 13.9 g. of potassium permanganate in 200 ml. of water gave on filtration, acidification, and cooling, 2.15 g. of an acid (73%) m.p. 216–218°; neutral equivalent, 99.8, which did not depress the melting point of 2-methoxyisophthalic acid (m.p. 216–218°) prepared by the oxidation of 2,6-dimethylanisole with potassium permanganate.

Anal. Calc'd for $C_9H_8O_5$: C, 55.11; H, 4.11; Neut. equiv., 98.08.
Found: C, 55.31; H, 4.12; Neut. equiv., 99.8.

Demethylation of 1.00 g. of 2-methoxy-3-ethylbenzoic acid (from the metalation reaction) with 25 ml. of 48% hydrobromic acid (two hours at reflux) gave 0.94 g. of 3-ethylsalicylic acid, m.p. 112.0–112.5°. This value agrees, incidentally, with the melting point of a compound prepared by the Kolbe reaction on ethylphenol and listed in Beilstein (X, p. 263) as x-ethylsalicylic acid.

Anal. Calc'd for $C_9H_{10}O_3$: C, 65.05; H, 6.07; Neut. equiv., 166.1.
Found: C, 64.80; H, 6.07; Neut. equiv., 165.7.

Reaction D (III + IV). Isolation of the acid fraction from this reaction yielded 1.82 g. of a yellow oil, b.p. 115–120° (0.18 mm.). It solidified on standing and gave on recrystallization from ligroin (b.p. 80–120°) colorless prisms, m.p. 101–102°. This compound was shown to be α-(*o*-methoxyphenyl)propionic acid by a mixture melting point determination with a sample of this acid prepared as described later. No solid acid could be obtained when this compound was treated with hydrobromic acid in an attempt to bring about demethylation.

The mother liquor from the recrystallization of acid III was evaporated, and the residue was demethylated by refluxing for one hour with 25 ml. of 48% hydrobromic acid, giving 0.39 g. of a white crystalline acid, m.p. 111–112°. This was 3-ethylsalicylic acid as it gave no depression when melted with an authentic sample obtained from the butyllithium reaction (C).

Reaction E (V). This reaction gave 17.8 g. of crude acid, m.p. 58–62°. After recrystallization from benzene-petroleum ether and from water, it melted at 63.5–64.5°. 2-Methoxy-5-methylbenzoic acid has been reported to melt at 67°, 69°, and 70° (12). The melting points of *p*-methoxyphenylacetic acid and 2-methyl-5-methoxybenzoic acid are 85–86° (13) and 146° (14), respectively.

Anal. Calc'd for $C_9H_{10}O_3$: C, 65.05; H, 6.07; Neut. equiv., 166.1.
Found: C, 64.91; H, 5.91; Neut. equiv., 164.5.

Oxidation of 2.00 g. of this acid with 4.2 g. of potassium permanganate, 1 g. of potassium hydroxide, and 100 ml. of water gave 1.70 g. (72%) of 4-methoxyisophthalic acid; m.p. 279–280°; reported m.p. 275–276° (15). *p*-Anisic acid melts at 185° (16).

Demethylation of 2.0 g. of the 2-methoxy-5-methylbenzoic acid with hydrobromic acid

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[1] The carbon-hydrogen analyses were made by J. Sorenson, C. Brauer, and M. Hines.

gave (after one recrystallization from water) 1.35 g. (74%) of 2-hydroxy-5-methylbenzoic acid; m.p. 151.0–151.5°; reported m.p. 148°, 149–150°, 151°, and 153° (17).

The neutral fraction from the metalation reaction gave, in addition to unreacted *p*-methylanisole, 23.4 g. of a ketone, b.p. 156–160° (0.17 mm.) and m.p. 65–70°. After several recrystallizations from hexane it melted at 82.0–82.5° [Reported for 2,2′-dimethoxy-5,5′-dimethyldiphenyl ketone, m.p. 82° (18)].

Anal. Calc'd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71.

Found: C, 75.49; H, 6.95.

The 2,4-dinitrophenylhydrazone melted at 166.0–166.5°.

Anal. Calc'd: N, 12.44. Found: N, 12.59.

In addition to these products, 0.90 g. of *p*-cresol was also obtained.

o-Methoxyatropic acid was prepared after the method of McKenzie and Wood (19) for atropic acid. Concentrated hydrochloric acid (75 ml.) was added in 1-ml. portions, with shaking, at five minute intervals to a mixture of potassium cyanide (60 g. 0.92 mole) and *o*-methoxyacetophenone (62.4 g., 0.415 mole). The flask was kept cool by an ice-bath throughout this operation. The organic layer was separated, washed with water, and then added to 100 ml. of concentrated hydrochloric acid. After this mixture had stood for 40 hours, it was neutralized with a 15% sodium hydroxide solution. An additional 50 g. of sodium hydroxide was added, and the basic solution then steam-distilled until ammonia was no longer detectable (litmus paper) in the distillate. From the distillate was recovered 35.6 g. of unreacted ketone. The non-volatile portion was freed of a brown oil by benzene extraction and then acidified. The *o*-methoxyatrolactinic acid, which separated as a viscous oil, was removed and dehydrated by distillation. *o*-Methoxyatropic acid distilled at 135–140° (0.5–1 mm.). It solidified in the condenser and was removed with hot methanol. The crystals which separated when the solution cooled melted at 98–125°. One recrystallization from water raised the melting point to 138–142°; yield, 5.3 g. (16% on basis of converted ketone). Further recrystallization gave an analytical sample, m.p. 144–145°.

Anal. Calc'd for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66; Neut. equiv., 178.

Found: C, 67.63; H, 5.62; Neut. equiv., 174.

α-(o-Methoxyphenyl)propionic acid. A sample (1.55 g.) of *o*-methoxyatropic acid was dissolved in 150 ml. of methanol and reduced with hydrogen (2 atmospheres) over a palladium-charcoal catalyst. The reduced acid was recrystallized several times from petroleum ether (b.p. 80–120°) to give 1.05 g. (68%), m.p. 101–102° [Reported m.p. 100–101° (1)].

Anal. Calc'd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71; Neut. equiv., 180.2.

Found: C, 66.76; H, 6.91; Neut. equiv., 180.5.

SUMMARY

o-Methylanisole and *o*-ethylanisole were metalated with amylsodium and butyllithium. *p*-Methylanisole was metalated with butyllithium. The acids isolated after carbonation of these metalated products are described.

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