123. *Methoxylated* o-*Benzoylbenzoic Acids.*

By Ch. Weizmann and Ernst Bergmann.

For the synthesis of substituted *o*-benzoylbenzoic acids from phthalic anhydrides, two methods are available, *viz.*, the Friedel–Crafts reaction and the reaction with Grignard compounds (Weizmann and co-workers, J., 1935, 1367). Our interest in the synthesis of methoxylated *o*-benzoylbenzoic acids was their relation to hydroxylated anthraquinones and the extent, if any, to which demethylation occurs in the Friedel–Crafts reaction.

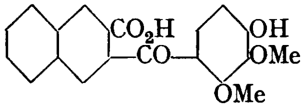
(1) According to the literature α-naphthyl methyl ether condenses with phthalic anhydride in presence of aluminium chloride to give *o*-(4′-hydroxy-1′-naphthoyl)benzoic acid (Fieser and Dietz, *J. Amer. Chem. Soc.*, 1929, **51**, 3141), and β-naphthyl methyl ether yields *o*-(2′-methoxy-1′-naphthoyl)benzoic acid (Knapp, *Monatsh.*, 1934, **60**, 189; Fieser, *J. Amer. Chem. Soc.*, 1931, **53**, 3546) or the demethylated compound (compare also Cohn, *Pharm. Zentr.*, 1914, **55**, 744). We obtained, at room temperature, the methoxylated acids in both cases. The structure of the keto-acid obtained from β-naphthyl methyl ether was proved by its synthesis from phthalic anhydride and the magnesium derivative of 1-bromo-2-naphthyl methyl ether. Condensation between 1 : 5-dimethoxynaphthalene and phthalic anhydride gave *o*-(1′ : 5′-dimethoxy-4′-naphthoyl)benzoic acid, reaction being assumed to take place in the 4′-position (compare the reaction with diazotised aniline and similar substances; Fischer and Bauer, *J. pr. Chem.*, 1916, **94**, 22; 1916, **95**, 261) : the product readily gave the 8′-acetyl compound on treatment with acetic anhydride.

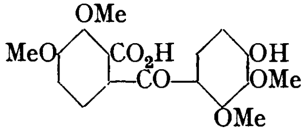
If the interaction between the components is smooth, aluminium chloride obviously combines with the formed carbonyl group before it can exert its demethylating action. Where reaction is rather slow, demethylation occurs; *e.g.*, pyrogallol trimethyl ether reacts with naphthalene-2 : 3-dicarboxylic anhydride and with hemipinic anhydride to produce (I) and (II), respectively, the positions of the acyl groups again being assumed. Undemethylated products are obtainable by means of 4-lithio-1 : 2 : 3-trimethoxybenzene (method of Ziegler and Colonius, *Annalen*, 1930, **479**, 135), which, *e.g.*, gives *o*-(2′ : 3′ : 4′-trimethoxybenzoyl)benzoic acid on reaction with phthalic anhydride. 4-Iodo-1 : 2 : 3-trimethoxybenzene does not react with magnesium.

(2) From hemipinic anhydride and phenylmagnesium bromide, an acid was obtained which was apparently identical with the dimethoxybenzoylbenzoic acid produced by oxidation of phenyldihydroberberine (Faltis, *Monatsh.*, 1910, **31**, 563). Since the latter acid can only be (III), the opening of the anhydride ring in our case (and in analogous ones) takes place in the neighbourhood of the methoxy-groups : the acid is converted into alizarin dimethyl ether by concentrated sulphuric acid at 30°. The analogous condensation

of hemipinic anhydride and benzene under the influence of aluminium chloride gives a hydroxymethoxybenzoylbenzoic acid (Lagodzinski, *Ber.*, 1895, **28**, 1427).

Hemipinic anhydride reacted with the Grignard derivatives of α-bromonaphthalene and of 2-bromo-6-methoxynaphthalene to give 2-α-naphthoyl- and 2-(6′-methoxy-2′-naphthoyl)-3 : 4-dimethoxybenzoic acid respectively. The former was converted by concentrated sulphuric acid into 1 : 2-dimethoxy-7 : 8-benzanthraquinone.


(I.)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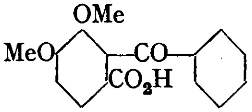
(III.)

EXPERIMENTAL.

Phthalic Anhydride and Naphthyl Methyl Ethers.—The anhydride (1 mol.) and the ether (1 mol.) were kept in benzene solution in presence of anhydrous aluminium chloride for 24 hours at room temperature. The product from the α-compound was *o*-(4′-methoxy-1′-naphthoyl)-benzoic acid, m. p. 194° (Cohn, *loc. cit.*; Schulenberg, *Ber.*, 1920, **53**, 1445; Fieser and Dietz, *loc. cit.*). β-Naphthyl methyl ether gave a greenish powder, which crystallised from butyl acetate in quartz-like crystals, m. p. 198°, of *o*-(2′-methoxy-1′-naphthoyl)benzoic acid (Found : OMe, 10·4. Calc. : OMe, 10·1%).

Phthalic Anhydride and 1 : 5-*Dimethoxynaphthalene.*—The same procedure as above gave *o*-(1′ : 5′-dimethoxy-4′-naphthoyl)benzoic acid as a brown powder, which crystallised from glacial acetic acid and from xylene in small prisms, m. p. 263° [Found : C, 71·2; H, 4·8; OMe, 19·2. Calc. for $C_{18}H_{10}O_3(OMe)_2$: C, 71·4; H, 4·8; OMe, 18·6%]. On crystallisation from acetic anhydride, it gave yellow prismatic plates, m. p. 185°, of the 8′-acetyl compound (Found : C, 69·8; H, 5·1. Calc. for $C_{22}H_{18}O_6$: C, 70·0; H, 4·5%).

2-*Methoxy*-1-*naphthylmagnesium Bromide and Phthalic Anhydride.*—The reagent prepared from magnesium turnings (1·4 g.; 2 mols.), a few drops of methyl iodide, and 1-bromo-β-naphthyl methyl ether (6·8 g.) in ether reacted violently with phthalic anhydride (3·5 g.) in boiling benzene. After 2 hours' boiling, the product was treated with ice and dilute sulphuric acid, the ethereal layer extracted with sodium hydroxide solution, and the extract acidified. The oily acid solidified after some hours and then separated from butyl acetate in crystals, m.p. 198°, undepressed by *o*-(2′-methoxy-1′-naphthoyl)benzoic acid (above). Concentrated sulphuric acid produced a red-brown solution, changing to violet.

Naphthalene-2 : 3-*dicarboxylic Anhydride and Pyrogallol Trimethyl Ether.*—The anhydride (4 g.), the ether (3·4 g.), and aluminium chloride (2·7 g.) were kept in carbon disulphide (50 c.c.) at room temperature for 24 hours, and then boiled for 2 hours. The acid product was dissolved in hot 90% acetic acid; naphthalene-2 : 3-dicarboxylic acid, m.p. 241° (decomp.), separated on cooling, followed, after dilution with water, by 3-(4′-hydroxy-2′ : 3′-dimethoxybenzoyl)-2-naphthoic acid (I), which crystallised from 50% acetic acid in needles, m.p. 245°, in poor yield (Found : C, 68·2; H, 4·8; OMe, 17·5. Calc. for $C_{20}H_{16}O_6$: C, 68·2; H, 4·5; OMe, 17·6%). The sulphuric acid colour reaction is reddish-violet.

6-(4′-Hydroxy-2′ : 3′-dimethoxybenzoyl)-2 : 3-dimethoxybenzoic acid (II), obtained similarly from hemipinic anhydride and pyrogallol trimethyl ether, formed prisms, m. p. 194—195°, from 50% acetic acid (Found : C, 59·6; H, 5·3; OMe, 34·9. Calc. for $C_{18}H_{18}O_8$: C, 59·7; H, 5·0; OMe, 34·3%).

4-*Lithio*-1 : 2 : 3-*trimethoxybenzene and Phthalic Anhydride.*—13·5 G. of 4-iodo-1 : 2 : 3-trimethoxybenzene and 0·8 g. of lithium were shaken with 200 c.c. of ether in a Schlenk tube for 8 days. The precipitated lithium compound was introduced (in a nitrogen atmosphere) into a boiling solution of 6·6 g. of phthalic anhydride in benzene. The reaction was rather violent and was completed by 2 hours' boiling. The usual treatment gave *o*-(2′ : 3′ : 4′-trimethoxybenzoyl)benzoic acid, which was triturated with glacial acetic acid and recrystallised from 25% acetic acid; it formed stout prisms, m. p. 196°, giving a brown-yellow colour reaction with concentrated sulphuric acid (Found : C, 64·5; H, 5·1. Calc. for $C_{17}H_{16}O_6$: C, 64·6; H, 5·1%). The product, m. p. 169°, obtained by Bentley and Weizmann (J., 1908, **93**, 436) in the analogous aluminium chloride condensation was certainly partly demethylated (compare the above-mentioned experiments).

Phenylmagnesium Bromide and Hemipinic Anhydride.—The Grignard solution (magnesium, 0·3 g.; bromobenzene, 1·1 c.c.) was introduced into a boiling suspension of hemipinic anhydride (2 g.) in benzene. The yellowish crystalline product was treated with cold sulphuric acid and extracted with alkali. The alkaline solution, which, as in all these experiments, exhibited a strong greenish-yellow fluorescence, was acidified, and the resinous 2-benzoyl-3 : 4-dimethoxybenzoic acid (III) triturated with and recrystallised from 50% acetic acid; it formed prisms, m. p. 192°, which gave a purple colour reaction with sulphuric acid. *Cyclisation.* 0·2 G. was treated with sulphuric acid (5 c.c.) at 30° for 24 hours. The mass was poured into water, and the yellow precipitate centrifuged off and freed from unchanged acid by washing with sodium carbonate solution. On crystallisation from butyl acetate, a small quantity of orange-red needles, m. p. 192°, was obtained, which gave a stable red colour with concentrated sulphuric acid and could not be identified; then silky yellow needles of alizarin 1 : 2-dimethyl ether, m. p. 209—210°, separated.

α-Naphthylmagnesium Bromide and Hemipinic Anhydride.—From α-bromonaphthalene (1·5 c.c.), 2-α-naphthoyl-3 : 4-dimethoxybenzoic acid was obtained. It separated from 60% acetic acid in lancet-shaped crystals, m. p. 223° (slight decomp.), giving a blue-green, then dark blue, colour with sulphuric acid (Found : C, 71·1; H, 5·0. Calc. for $C_{20}H_{16}O_5$: C, 71·4; H, 4·8%). When treated with concentrated sulphuric acid at 30° for 48 hours, it gave red needles, m. p. 240°, of 1 : 2-dimethoxy-7 : 8-benzanthraquinone, which were recrystallised from glacial acetic acid or butyl acetate (Found : C, 75·5; H, 4·7. Calc. for $C_{20}H_{14}O_4$: C, 75·5; H, 4·5%).

2-(6′-Methoxy-β-naphthoyl)-3 : 4-dimethoxybenzoic acid, similarly obtained from the magnesium derivative of 2-bromo-6-methoxynaphthalene (2·4 g.), was triturated with 50% acetic acid and recrystallised from butyl acetate. The acid, which gives a dark green, then dark blue colour reaction with sulphuric acid, is dimorphous, crystallising in octahedra, m. p. 237°, or needles, m. p. 240° (after sintering) (Found : C, 68·8; H, 5·2. Calc. for $C_{21}H_{18}O_6$: C, 68·8; H, 4·9%).

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