61. *Polymethylbenzoylnaphthoic Acids.*

By Richard H. Martin.

Naphthalene-1 : 2-dicarboxylic anhydride has been condensed by the Friedel–Crafts reaction with 1 : 2 : 3 : 4-tetramethylbenzene and with hemimellithene. The latter has also been condensed with 2-methyl-1-naphthoyl chloride. 1-(3′ : 4′ : 5′-*Trimethylbenzoyl*)-2-*methylnaphthalene* has been oxidised by selenium dioxide to 1-(3′ : 4′ : 5′-*trimethylbenzoyl*)-2-*naphthoic acid.*

Many polymethyl-1 : 2-benzanthracenes have powerful carcinogenic activity (see Badger *et al.*, *Proc. Roy. Soc.*, 1940, *B*, **129**, 439). The most favourable positions of substitution in the 1 : 2-benzanthracene molecule are 5, 9, 10, and, to a less extent, 6. Simultaneous substitution at two or three of these positions gives rise to the most potent carcinogenic hydrocarbons known (*e.g.*, 9 : 10-dimethyl-1 : 2-benzanthracene). It was, therefore, considered of interest to investigate the effect of the simultaneous introduction of methyl groups into " favourable " and " less favourable " positions of the 1 : 2-benzanthracene molecule (*e.g.*, 5 : 6 : 7-, 6 : 7 : 8-, 5 : 6 : 7 : 8-). The work here described is preliminary and it is recorded because circumstances have prevented its completion (see also Bachmann and Chemerda, *J. Org. Chem.*, 1941, **6**, 36).

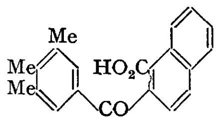
The results may be summarised as follows : 1. The Friedel–Crafts reaction between hemimellithene and naphthalene-1 : 2-dicarboxylic anhydride (in an excess of hemimellithene) gives a mixture of 2-(3′ : 4′ : 5′-*trimethylbenzoyl*)-1-*naphthoic acid* (I) and 1-(3′ : 4′ : 5′-*trimethylbenzoyl*)-2-*naphthoic acid* (II), the former preponderating. The above constitutions of the two acids were assigned on the basis of the results of potash fusions. This potash fusion method is not conclusive (cf. Huntress *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 2845), but the oxidation of 1-(3′ : 4′ : 5′-*trimethylbenzoyl*)-2-*methylnaphthalene* with selenium dioxide (see below) affords complete proof of the correctness of the constitutions given.

2. The condensation between the magnesium derivative of 4-bromohemimellithene (preparation improved) and naphthalene-1 : 2-dicarboxylic anhydride gives a mixture of acids difficult to separate.

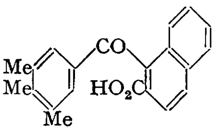
3. The Friedel–Crafts reaction between hemimellithene and 2-methyl-1-naphthoyl chloride (in carbon disulphide) gives a mixture of 1-(2′ : 3′ : 4′-*trimethylbenzoyl*)-2-*methylnaphthalene* and 1-(3′ : 4′ : 5′-trimethylbenzoyl)-2-methylnaphthalene. The latter on oxidation with selenium dioxide in a sealed tube furnishes 1-(3′ : 4′ : 5′-trimethylbenzoyl)-2-naphthoic acid (II), which was identified as its *acetoxy-lactone*. It is identical with the acetoxy-lactone of the acid obtained as described under (1). This acid was accompanied by other acids which were not further examined.

Preliminary attempts to cyclise 2-(3′ : 4′ : 5′-trimethylbenzoyl)-1-naphthoic acid (I) with benzoyl chloride and a few drops of concentrated sulphuric acid (Waldmann, *J. pr. Chem.*, 1938, **150**, 121) were unsuccessful.

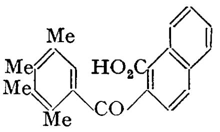
4. The Friedel–Crafts reaction between 1 : 2 : 3 : 4-tetramethylbenzene (Smith and Cass, *J. Amer. Chem. Soc.*, 1932, **54**, 1614) and naphthalene-1 : 2-dicarboxylic anhydride (in nitrobenzene) gives 2-(2′ : 3′ : 4′ : 5′-*tetramethylbenzoyl*)-1-*naphthoic acid* (III) or less probably 1-(2′ : 3′ : 4′ : 5′-*tetramethylbenzoyl*)-2-*naphthoic acid*. The choice between the two formulæ was made on account of the colour reaction with concentrated sulphuric acid (cf. Cook, J., 1932, 454, and the above cases). A yellow crystalline compound, the analysis of which agrees with the formula of 5 : 6 : 7 : 8-*tetramethyl*-1 : 2-*benzanthraquinone*, is produced when the above substituted naphthoic acid is treated with benzoyl chloride and a few drops of concentrated sulphuric acid.



(I.)



(II.)



(III.)

Experimental.

2-(3′ : 4′ : 5′-*Trimethylbenzoyl*)-1-*naphthoic Acid* (I) *and* 1-(3′ : 4′ : 5′-*trimethylbenzoyl*)-2-*naphthoic Acid* (II).—Powdered aluminium chloride (18 g.) is added in small portions to an ice-cold, finely divided suspension of naphthalene-1 : 2-dicarboxylic anhydride (12 g.) in hemimellithene (40 c.c.). The mixture is left for 6 hours at room temperature and then decomposed with ice and hydrochloric acid. The solid is extracted with 2N-sodium hydroxide and filtered from some neutral material (6·9 g.). This neutral fraction is unaffected by refluxing for 1 hour with 20% alcoholic potassium hydroxide. It has not been further investigated. The acids are precipitated from the alkaline solution with hydrochloric acid.

(*a*) 1-(3′ : 4′ : 5′-*Trimethylbenzoyl*)-2-*naphthoic acid* (II) is isolated through its insoluble ammonium salt and purified by crystallisation of its sodium salt. The free acid is then recrystallised successively from acetic acid and benzene–ethyl alcohol. It forms a colourless microcrystalline powder (1·6 g.), m. p. 273—274°, which gives a green colour with concentrated sulphuric acid (Found : C, 78·7; H, 5·7. $C_{21}H_{18}O_3$ requires C, 78·9; H, 5·7%).

Acetoxy-lactone. A solution of the acid (1 g.) in anhydrous pyridine (5 c.c.) and acetic anhydride (1·5 c.c.) is heated on the water-bath for 2 hours. The solid separating after dilution with water is recrystallised from benzene, separating as a white microcrystalline powder, m. p. 231—232° (Found : C, 76·8; H, 5·7. $C_{23}H_{20}O_4$ requires C, 76·6; H, 5·6%). By hydrolysis (alcoholic potash) the acid, m. p. 273—274°, is recovered.

(*b*) 2-(3′ : 4′ : 5′-*Trimethylbenzoyl*)-1-*naphthoic acid* (I), obtained by acidification of the ammonia solution after separation of the insoluble salt of (II), is purified through its sparingly soluble sodium salt. The free acid is recrystallised from acetic acid and then xylene. It forms small white needles (5·4 g.), m. p. 191—192°. This acid gives a reddish-brown colour with concentrated sulphuric acid (Found : C, 78·9; H, 5·4. $C_{21}H_{18}O_3$ requires C, 78·9; H, 5·7%).

The *acetoxy-lactone* (prepared as above) separates from ethyl alcohol as a white microcrystalline powder, m. p. 161·5—162·5° (Found : C, 76·6; H, 5·6. $C_{23}H_{20}O_4$ requires C, 76·6; H, 5·6%). By hydrolysis it regenerates the acid, m. p. 191—192°.

The *benzoyloxy-lactone* is prepared by means of benzoyl chloride in pyridine as for the acetoxy-lactone. The oily product is obtained crystalline by treatment with methyl alcohol and recrystallised from benzene–ethyl alcohol. It forms white microscopic needles, m. p. 191·5—192·5° (Found : C, 78·7; H, 5·4. $C_{28}H_{22}O_4$ requires C, 78·9; H, 5·3%).

Degradation of Acids (I) *and* (II) (cf. Cook, *loc. cit.*).—(*a*) The acid (II) (0·5 g.) is added in small portions to potassium hydroxide (4 g.) at 280°. After ½ hour at 340° the mass is cooled and extracted with hot water (charcoal) and the acids are precipitated with hydrochloric acid. After three recrystallisations from ethyl alcohol, 3 : 4 : 5-trimethylbenzoic acid separates in transparent prisms, m. p. 215·5—216° (Jacobson, *Ber.*, 1882, **15**, 1853). From the mother-liquor, 2-naphthoic acid is isolated with difficulty, m. p. 172—174° (not depressed by an authentic specimen, m. p. 182°).

(*b*) The acid (I) is added to potassium hydroxide as above, but the whole reaction is carried out between 260—280°; 3 : 4 : 5-trimethylbenzoic acid, m. p. 215·5—216·5°, and 1-naphthoic acid, m. p. 154°, are isolated in the same way as under (*a*).

4-*Bromo*-1 : 2 : 3-*trimethylbenzene*. This compound was prepared according to Smith and Moyle (*J. Amer. Chem. Soc.*, 1936, **58**, 1) but the reaction mixture was kept for 18 hours at 0° and then 2 hours at room temperature. Yield, 89%; b. p. 128°/25 mm. (Smith and Moyle, *loc. cit.*, claim 47% yield, b. p. 103—103·5°/12 mm.).

1-(2′ : 3′ : 4′-*Trimethylbenzoyl*)- *and* 1-(3′ : 4′ : 5′-*Trimethylbenzoyl*)-2-*methylnaphthalene*.—Powdered aluminium chloride (4 g.) is added in small portions to a solution of 2-methyl-1-naphthoyl chloride (prepared from 5 g. of the acid by refluxing with thionyl chloride, followed by distillation under reduced pressure) in carbon disulphide (35 c.c.) containing 4 c.c. of hemimellithene and cooled in ice. The mixture is kept for 40 hours at 0° and 24 hours at room temperature (with frequent shaking) and then decomposed with ice and hydrochloric acid and volatile products are steam-distilled. The non-volatile residue is extracted with ether and washed with aqueous sodium carbonate. The two ketones formed are separated by crystallisation from acetic acid.

The less soluble 1-(3′ : 4′ : 5′-*trimethylbenzoyl*)-2-*methylnaphthalene* is purified by sublimation at 170°/0·1 mm. and recrystallised from acetic acid and then from methyl alcohol. It forms microscopic transparent prisms (2·8 g.), m. p. 150—151° (Found : C, 87·2; H, 7·1. $C_{21}H_{20}O$ requires C, 87·4; H, 7·0%).

1-(2′ : 3′ : 4′-*Trimethylbenzoyl*)-2-*methylnaphthalene*, isolated from the acetic acid mother-liquor, is sublimed at 90°/0·2 mm. and then crystallised successively from acetic acid and methyl alcohol. It forms microscopic transparent prisms, m. p. 108—108·5° (Found : C, 87·1, H, 6·8%).

Oxidation of 1-(3′ : 4′ : 5′-*Trimethylbenzoyl*)-2-*methylnaphthalene with Selenium Dioxide* (cf. Cook, J., 1932, 1476).—The ketone (1·5 g.) is heated at 235° for 4 hours in a sealed tube with selenium dioxide (3 g.) and water (3 c.c.). The products are collected, washed with water, and extracted with aqueous sodium carbonate. The precipitated acids (1·1 g.) are heated on the water-bath for 1 hour with acetic anhydride in pyridine. The benzene solution of the reaction products is washed with aqueous sodium carbonate. By addition of hydrochloric acid to this solution an appreciable amount of acidic products is precipitated (formed possibly by oxidation of one or more of the methyl groups in the benzene ring). The neutral fraction gives after purification the acetoxy-lactone of 1-(3′ : 4′ : 5′-trimethylbenzoyl)-2-naphthoic acid (II), m. p. 231—232°, not depressed by the specimen obtained above. Attempts to reduce the amount of acids formed as by-product by altering the conditions of reaction were unsuccessful; *e.g.*, 3 hours at 235° gave the same result and 2 hours at 215° gave only a very small amount of total acids.

2-(2′ : 3′ : 4′ : 5′-*Tetramethylbenzoyl*)-1-*naphthoic Acid* (III).—Aluminium chloride (35 g.) is added in small portions to a well-stirred suspension of finely divided naphthalene-1 : 2-dicarboxylic anhydride (25 g.) in nitrobenzene (150 c.c.), the temperature being maintained at 10—15°. The mixture is then cooled to 0°, and 1 : 2 : 3 : 4-tetramethylbenzene (16·8 g.) added drop by drop. The reaction mixture is stirred for 12 hours at 0° and then 60 hours at room temperature. The complex is decomposed with ice and hydrochloric acid, the nitrobenzene steam-distilled, the residual aqueous solution decanted, and the steam-distillation carried on in the presence of 2N-sodium carbonate. The carbonate solution is heated with charcoal, filtered, and the acid is precipitated with hydrochloric acid. The acid is purified through its sparingly soluble sodium salt, followed by crystallisation from acetic acid. It forms a white powder, m. p. 241·5—242·5° (Found : C, 79·2; H, 5·8. $C_{22}H_{20}O_3$ requires C, 79·5; H, 6·1%). It gives a reddish-brown colour with concentrated sulphuric acid. Yield, 13 g. (m. p. 240°). Numerous alterations of the above procedure failed to improve the yield of this acid.

5 : 6 : 7 : 8-*Tetramethyl*-1 : 2-*benzanthraquinone* (?).—The acid (III) (1 g.) is heated on the water-bath with benzoyl chloride (2 c.c.) and concentrated sulphuric acid (2 drops) for 1 hour. The cold solution is poured into water, boiled, and the solid collected. This solid, after being boiled with 2N-sodium carbonate and then water, is sublimed at 200°/0·2 mm. and recrystallised from xylene. It separates as a microcrystalline yellow powder, m. p. 203—203·5° (Found : C, 83·9; H, 5·95. $C_{22}H_{18}O_2$ requires C, 84·1; H, 5·75%).

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THE CHESTER BEATTY RESEARCH INSTITUTE, THE ROYAL CANCER HOSPITAL (FREE),
LONDON, S.W.3.

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