172. *Polycyclic Aromatic Amines. Part II.*

By G. M. BADGER and A. R. M. GIBB.

Further work on the synthesis of compounds analogous to the cancer-producing amines is reported. 1 : 2-Benzanthraquinone has been brominated in the 4′-position, and the product converted into 4′-*amino*-1 : 2-*benzanthracene*, which has also been obtained from 4′-nitro-1 : 2-benzanthraquinone. 1′ : 9-*Imino*-1 : 2-*benzanthracene* has been prepared from 1′-nitro-1 : 2-benzanthraquinone. 1 : 2-Benzanthracene-10-carboxylic acid has been converted into the 10-amino-compound by the Schmidt reaction, which, however, failed with 1 : 2-benzanthracene-4′-carboxylic acid and also with 1 : 2-benzanthracene-4-carboxylic acid. The latter has been prepared in satisfactory yield from 4 : 10-oxalyl-1 : 2-benzanthracene.

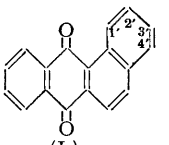
It has also been found that 1 : 2-benz-10-anthranylglyoxylic acid chloride is readily degraded to 1 : 2-benzanthracene-10-carboxylic acid by hydrolysis with sodium hydroxide. This finding is discussed in relation to the mechanism of the formation of carboxylic acid derivatives in Friedel–Crafts reactions with oxalyl chloride.

As it is important to determine the relationship, if any, between the carcinogens of the polycyclic aromatic hydrocarbon type and the cancer-producing amines such as 2-aminofluorene, the synthesis of certain aminobenzanthracenes has been undertaken. In Part I of this series, Badger (*J.*, 1948, 1756) has described the preparation of 2′-amino-1 : 2-benzanthracene, and the present paper describes further work in this field.

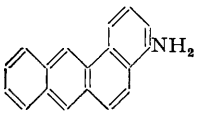
1 : 2-Benzanthraquinone (I) is known to undergo substitution in a variety of positions depending on the reagent and the experimental conditions. It has been sulphonated in the 4′-position at ordinary temperatures (Sempronj, *Gazzetta*, 1939, **69**, 448; Cason and Fieser, *J. Amer. Chem. Soc.*, 1940, **62**, 2681), and in the 2′-position at elevated temperatures (Joffe and Fedorova, *J. Gen. Chem. Russia*, 1941, **11**, 619; Badger, *J.*, 1947, 940). Furthermore, from the products of the nitration of benzanthraquinone, Scholl (*Ber.*, 1911, **44**, 2370) isolated 1′-nitro-1 : 2-benzanthraquinone and an isomeric nitrobenzanthraquinone which he regarded as the 4′-derivative.

It has now been found that benzanthraquinone is readily brominated in the 4′-position, the product being identical with a specimen of 4′-bromo-1 : 2-benzanthraquinone, of established constitution, prepared by the method of Johnson, Weinmayr, and Adams (*J. Amer. Chem. Soc.*, 1932, **54**, 3289) by cyclisation of *o*-(5′-bromo-1′-naphthoyl)benzoic acid. With ammonium hydroxide under pressure, this bromobenzanthraquinone has been converted into 4′-*amino*-1 : 2-*benzanthraquinone*, which, on reduction in the usual manner, gave 4′-*amino*-1 : 2-*benzanthracene* (II). The aminobenzanthraquinone, m. p. 255—257°, seemed not to be identical with the aminobenzanthraquinone, m. p. 215°, which Scholl (*loc. cit.*) obtained on reduction of his supposed 4′-nitro-1 : 2-benzanthraquinone, and in view of this discrepancy, the nitration of benzanthraquinone has been re-investigated. In agreement with Scholl, a mixture of nitrobenzanthraquinones was obtained, and 1′-nitro-1 : 2-benzanthraquinone was readily isolated in a pure condition. This product has been reduced to 1′ : 9-*imino*-1 : 2-*benzanthracene* (III) by the two-stage process frequently used for the reduction of benzanthraquinones (Badger and Cook, *J.*, 1939, 802), and the isolation of this compound confirms the orientation of the 1′-nitro-

derivative. In spite of repeated attempts, a completely pure specimen of the isomeric nitrobenzanthraquinone could not be obtained. Reduction of the partly purified material, however, with sodium sulphide, gave 4′-amino-1 : 2-benzanthraquinone, identical with the specimen obtained as above from the bromo-compound. The identity of the two specimens



(I.)



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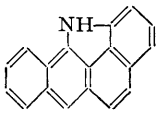
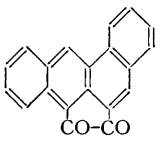


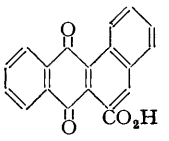
(III.)

was also confirmed by a comparison of the *acetyl* derivatives. It must be concluded, therefore, that although Scholl's orientation for the aminobenzanthraquinone is correct, his m. p. is in error.

1 : 2-Benzanthracene-10-carboxylic acid is readily available (Dansi, *Gazzetta*, 1937, **67**, 85; Badger and Cook, *J.*, 1940, 409; this paper), and it has been converted into the known 10-amino-1 : 2-benzanthracene (Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1938, **60**, 1893; Fieser and Creech, *ibid.*, 1939, **61**, 3502) by the Schmidt reaction. In view of this success, it was thought that the 4-amino-compound might become available through 1 : 2-benzanthracene-4-carboxylic acid. This acid had been obtained as a by-product by Cook (*J.*, 1931, 2524) and a more convenient synthesis was therefore desirable. 4 : 10-Oxalyl-1 : 2-benzanthracene (IV) (cf. Dansi, *loc. cit.*) was prepared by an improved method from benzanthracene and oxalyl chloride, and this was oxidised with sodium dichromate to 1 : 2-benzanthraquinone-4-carboxylic acid (V) and reduced to the desired 1 : 2-benzanthracene-4-carboxylic acid (VI), in reasonable yield. Both acids have been identified by comparison with authentic specimens, and it will be noted that this work confirms the structure of the 4 : 10-oxalyl-1 : 2-benzanthracene. The Schmidt reaction failed with 1 : 2-benzanthracene-4-carboxylic acid, however, and although several other attempts had been made to degrade this acid to the amino-compound, no success has yet been achieved. The Schmidt reaction also failed with 1 : 2-*benzanthracene-4′-carboxylic acid*, which has been prepared from 4′-bromo-1 : 2-benzanthraquinone through 4′-*cyano*-1 : 2-*benzanthraquinone* and 1 : 2-*benzanthraquinone-4′-carboxylic acid*.



(IV.)



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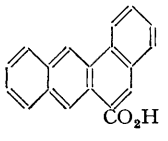

(VI.)

The Friedel–Crafts reaction with oxalyl chloride is of peculiar interest. Depending on the compound attacked, and on the experimental conditions, the product may be a ketone, a diketone, a carboxylic acid, or a mixture of two or more of these products. Furthermore, in particular cases, the ketones and diketones may be either uni- or bi-molecular. With certain compounds, oxalyl chloride provides the best method for the introduction of a carboxylic acid grouping. It is significant that glyoxylic acids seem never to be obtained, although these compounds are often readily available if " chloro-oxalic ester " is used in place of oxalyl chloride.

Oxalyl chloride is not a stable substance, and in the presence of aluminium chloride it is slowly decomposed into carbon monoxide and carbonyl chloride (Staudinger, *Ber.*, 1908, **41**, 3558). It has long been supposed (see Thomas, " Anhydrous Aluminium Chloride in Organic Chemistry," 1941) that the formation of monoketones, and of carboxylic acids, in Friedel–Crafts reactions with oxalyl chloride is due to this decomposition into carbonyl chloride which subsequently reacts with the aromatic component. As is well known, this substance does react with a variety of aromatic compounds to give monoketones and carboxylic acids. According to Staudinger (*Ber.*, 1912, **45**, 1594), whether Friedel–Crafts reactions with oxalyl chloride give rise to mono- or to di-ketones depends on the velocity of individual reactions: if the aromatic component is reactive, it combines with oxalyl chloride more rapidly than the latter is decomposed into carbon monoxide and carbonyl chloride, and a diketone is formed. This conclusion is illustrated by the fact that, although benzene reacts with oxalyl chloride to give benzoic acid and benzophenone (Staudinger, 1908, *loc. cit.*), yet anisole reacts rapidly to give anisil, in good yield (Staudinger, Goldstein, and Schlenker, *Helv. Chim. Acta*, 1921, **4**, 342).

Furthermore, oxalyl bromide, which is more stable than oxalyl chloride, reacts with benzene to give benzophenone and some benzil (Staudinger, 1912, *loc. cit.*).

Although the decomposition of oxalyl chloride into carbonyl chloride, and the subsequent condensation of this reagent with the aromatic component is without doubt the explanation for the formation of monoketones and, in some cases, for the formation of carboxylic acid, it seems that this is not the *only* mechanism by which carboxylic acids may be formed in this reaction. It had been observed (i) that the use of a large excess of aluminium chloride in the condensation of benzanthracene with oxalyl chloride does not result in an increased yield of carboxylic acid, as might be expected if the excess of aluminium chloride promoted the decomposition of oxalyl chloride into carbonyl chloride; and (ii) that an attempt to cyclise 1 : 2-benzanthranyl-10-glyoxylic acid chloride to 4 : 10-oxalyl-1 : 2-benzanthracene (IV) resulted in the isolation, in reasonable yield, of 1 : 2-benzanthracene-10-carboxylic acid. It therefore seemed likely that formation of carboxylic acids in Friedel–Crafts reactions with oxalyl chloride might, in some cases, be due to the degradation, by hydrolysis, of glyoxylic acid chloride formed as intermediate. This supposition is supported by the fact, mentioned above, that glyoxylic acids are never obtained in Friedel–Crafts reactions with oxalyl chloride, and it has been confirmed by the observation that 1 : 2-benz-10-anthranylglyoxylic acid chloride is hydrolysed and degraded to 1 : 2-benzanthracene-10-carboxylic acid by boiling for a few minutes with dilute sodium hydroxide. This observation is clearly related to the fact that oxalyl chloride is decomposed by water to hydrogen chloride, carbon monoxide, and carbon dioxide, and that no oxalic acid is formed under these conditions (Staudinger, 1908, *loc. cit.*).

It seems probable that this degradation of a glyoxylic acid chloride to a carboxylic acid, simply by hydrolysing with alkali, will prove to be of general application, and experiments to test this assumption are planned.

Badger and Cook (*J.*, 1940, 409) observed that when 1 : 2-benz-10-anthranylglyoxylic acid was submitted to the action of red phosphorus and hydriodic acid, some benzanthracene was formed as well as the desired acetic acid derivative. An attempt to carry out the reduction by the modified Kishner–Wolff method (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) resulted in only a trace of the desired acid, almost the whole of the material being converted into benzanthracene. Indeed, benzanthracene was obtained when the glyoxylic acid was heated with potassium hydroxide in glycol, alone.

Experimental.

4′-Bromo-1 : 2-benzanthraquinone.—A mixture of 1 : 2-benzanthraquinone (2·6 g.), acetic acid (30 c.c.), and bromine (2 c.c.) was boiled under reflux for 4 hours. After cooling, the crystalline product was collected, and recrystallised from acetic acid, in which it is sparingly soluble (yield, 2·6 g.). 4′-Bromo-1 : 2-benzanthraquinone formed long yellow needles, m. p. 230—232° (lit. 231—232°) (Found: C, 64·2; H, 2·7. Calc. for $C_{18}H_9O_2Br$: C, 64·1; H, 2·7%). The m. p. was not depressed by admixture with a specimen prepared by brominating naphthoylbenzoic acid, followed by cyclisation (Johnson, Weinmayr, and Adams, *loc. cit.*).

4′-Bromo-1 : 2-benzanthracene.—The above bromobenzanthraquinone (1·5 g.) was heated under reflux for 1 hour with acetic acid (150 c.c.), concentrated hydrochloric acid (15 c.c.), and stannous chloride (3 g.). The crude product obtained by the addition of water was immediately reduced further by 3 hours' boiling with zinc dust (10 g.) and 2N-sodium hydroxide (100 c.c.). *4′-Bromo-1 : 2-benzanthracene* (1·4 g.) formed colourless plates from acetic acid, m. p. 210—211° (Found: C, 70·2; H, 3·6. $C_{18}H_{11}Br$ requires C, 70·4; H, 3·6%).

4′-Cyano-1 : 2-benzanthraquinone.—A suspension of the above bromobenzanthraquinone (2 g.) and cuprous cyanide (2 g.) in benzyl cyanide (10 c.c.) was heated at 180—200° for 6 hours. The cooled mixture, after being warmed for ½ hour on the steam-bath with a little concentrated hydrochloric acid, was treated with a little benzene and, after cooling, collected. The solid so obtained was recrystallised from benzyl cyanide and then from tetrahydrofurfuryl alcohol. *4′-Cyano-1 : 2-benzanthraquinone* (1·1 g.) formed fluffy yellow needles, m. p. 297—299°, after darkening (Found: C, 80·5; H, 3·3. $C_{19}H_9O_2N$ requires C, 80·6; H, 3·2%).

1 : 2-Benzanthraquinone-4′-carboxylic Acid.—The above cyanobenzanthraquinone (1 g.) was hydrolysed by 20-hours' boiling with a solution of acetic acid (100 c.c.) and 65% sulphuric acid (25 c.c.) (cf. Newman and Orchin, *J. Amer. Chem. Soc.*, 1939, **61**, 244). *1 : 2-Benzanthraquinone-4′-carboxylic acid*, isolated by addition of water to the hot solution, and recrystallised from acetic acid, formed small yellow needles, m. p. 301—303° (decomp.) (0·75 g.) (Found: C, 75·7; H, 3·2. $C_{19}H_{11}O_3N$ requires C, 75·5; H, 3·3%).

1 : 2-Benzanthracene-4′-carboxylic acid.—The above carboxybenzanthraquinone was reduced in the usual manner with zinc dust and boiling dilute ammonia. *1 : 2-Benzanthracene-4′-carboxylic acid* formed small orange needles, m. p. 286° (Found: C, 83·8; H, 4·5. $C_{19}H_{12}O_2$ requires C, 83·8; H, 4·4%). No non-acidic material was obtained when this compound was submitted to the action of hydrazoic acid in the same way as for the 10-isomer (below).

Nitration of Benzanthraquinone.—Nitration of benzanthraquinone by Scholl's method (*loc. cit.*), and separation of the isomers with boiling chloroform, readily gave crude 1′- and 4′-nitro-1 : 2-benzanthra-

quinone. The former was obtained as glistening yellow blades, m. p. 286—288° (lit. 277—278°) after 12 recrystallisations from nitrobenzene. The 4′-isomer could not be obtained completely pure, but a crude product, m. p. 220—230°, was easily obtained, and was found suitable for further work.

*4′-Amino-*1 : 2-*benzanthraquinone.*—(i) A mixture of bromobenzanthraquinone (0·5 g.), cuprous chloride (0·5 g.), ammonium hydroxide (12 c.c.; *d* 0·880), and dioxan (3 c.c.) was heated in a sealed tube at 180—190° for 48 hours. The product, 4′-*amino*-1 : 2-*benzanthraquinone* (0·3 g.), was recrystallised from nitrobenzene, and then from toluene, and formed dark red prisms, m. p. 255—257° (Found: C, 79·3; H, 3·9. $C_{18}H_{11}O_2N$ requires C, 79·1; H, 4·0%). The *acetyl* derivative, prepared from the amine with acetic anhydride and sodium acetate, formed yellow needles, m. p. 289—290°, from acetic acid (Found: C, 76·0; H, 4·1. $C_{20}H_{13}O_3N$ requires C, 76·1; H, 4·2%).

(ii) 4′-Nitro-1 : 2-benzanthraquinone (2 g.) was made into a thin paste with sodium sulphide (10 g.) and water, and added to 200 c.c. of boiling water, and the whole boiled for a further ½ hour. The crude aminobenzanthraquinone (1·6 g.) was collected, and recrystallised from toluene. After 3 recrystallisations, it had m. p. 254°, not depressed by admixture with 4′-amino-1 : 2-benzanthraquinone prepared as described above. The acetyl derivatives were also shown to be identical by direct comparison.

*4′-Amino-*1 : 2-*benzanthracene.*—The above aminobenzanthraquinone was reduced with zinc dust and dilute ammonium hydroxide, in the usual way. 4′-*Amino*-1 : 2-*benzanthracene*, recrystallised from benzene, formed yellow plates, m. p. 199—201° (Found: C, 88·9; H, 5·4. $C_{18}H_{13}N$ requires C, 88·9; H, 5·35%). The acetyl derivative proved to be unstable: each recrystallisation gave some insoluble material, and a pure specimen could not be obtained. The *benzoyl* derivative formed colourless silky needles, m. p. 276—277°, from acetone (Found: C, 86·5; H, 5·05. $C_{25}H_{17}ON$ requires C, 86·4; H, 4·9%).

1′ : 9-*Imino*-1 : 2-*benzanthracene.*—1′-Nitro-1 : 2-benzanthraquinone (1 g.) was boiled for 1 hour with acetic acid (50 c.c.), hydrochloric acid (10 c.c.), and stannous chloride (5 g.). Water was added, and after standing for 1 hour, the solid was collected and immediately boiled with zinc dust (5 g.) and 2N-sodium hydroxide (50 c.c.) for 3 hours. The solid was dried, extracted with benzene, and the solvent removed. The product, after sublimation at 200°/0·1 mm., was recrystallised from benzene. The dilute solution had an intense blue fluorescence in daylight. 1′ : 9-*Imino*-1 : 2-*benzanthracene* formed pale yellow crystals, m. p. 217·5—219·5° (Found: C, 89·8; H, 4·3. $C_{18}H_{11}N$ requires C, 89·6; H, 4·6%). The *picrate* formed dark brown needles, from benzene, m. p. 191—192° (Found: C, 61·4; H, 3·0. $C_{24}H_{14}O_7N_4$ requires C, 61·3; H, 3·0%).

10-*Amino*-1 : 2-*benzanthracene.*—A mixture of 1 : 2-benzanthracene-10-carboxylic acid (1 g.) in chloroform (50 c.c.) and concentrated sulphuric acid (15 c.c.) was treated, at 40—50°, with sodium azide (2 g.) in small portions, with hand stirring, during 1 hour. The mixture was poured into water, filtered, and the solid washed with water, followed by hot dilute sodium carbonate, and then hot water. The product, 10-amino-1 : 2-benzanthracene, was recrystallised from benzene–light petroleum (b. p. 60—80°), and formed yellow plates (0·35 g.), m. p. 174·5—175·5°, in agreement with the literature (Found: C, 89·1; H, 5·5. Calc. for $C_{18}H_{13}N$: C, 88·9; H, 5·35%). The *acetyl* derivative formed fine colourless needles, from acetic acid, m. p. 276·5—277·5° (Found: C, 84·0; H, 5·1. $C_{20}H_{15}ON$ requires C, 84·2; H, 5·3%).

2′-*Acetamido*-1 : 2-*benzanthraquinone.*—2′-Amino-1 : 2-benzanthraquinone (Part I) was acetylated by brief boiling with acetic anhydride and sodium acetate. The *acetamido*-compound formed small orange-yellow prisms, m. p. 286—288°, from chlorobenzene (Found: C, 76·3; H, 4·3. $C_{20}H_{13}O_3N$ requires C, 76·1; N, 4·2%).

2′-*Acetamido*-1 : 2-*benzanthracene.*—The *acetyl* derivative of 2′-amino-1 : 2-benzanthracene (Part I) formed colourless needles, m. p. 235—236°, from methanol (Found: C, 84·3; H, 5·25. $C_{20}H_{15}ON$ requires C, 84·2; H, 5·3%).

4 : 10-*Oxalyl*-1 : 2-*benzanthracene.*—The following procedure was found to be superior to that used by Dansi (*loc. cit.*). A mixture of 1 : 2-benzanthracene (20 g.) and oxalyl chloride (12·5 g.) in dry tetrachloroethane (250 c.c.) was cooled in ice and treated with aluminium chloride (56 g.) in small portions, with stirring. After 2 hours the mixture was warmed on the steam-bath for 8 hours. The residue obtained on removal of the tetrachloroethane in steam was extracted with boiling sodium carbonate, and the insoluble material then extracted with boiling acetic acid. Acidification of the sodium carbonate solution gave 1 : 2-benzanthracene-10-carboxylic acid (0·2 g.), identified, after recrystallisation, by comparison with an authentic specimen. The yield of 4 : 10-oxalyl-1 : 2-benzanthracene, obtained from the acetic acid solution, was 8·0 g., and a black insoluble material (9 g.), which was not further examined, was also obtained. Similar results were obtained when the above reaction was repeated using carbon disulphide as solvent; but more acid and less ketone were isolated.

1 : 2-*Benzanthraquinone*-4-*carboxylic Acid.*—Finely powdered oxalylbenzanthracene (8 g.), in boiling glacial acetic acid (300 c.c.), was treated with a solution of sodium dichromate (40 g.) in 80% acetic acid (100 c.c.) during 1 hour. After refluxing for a further hour, the solution was filtered (to remove a little unchanged ketone), evaporated to small bulk under reduced pressure, and poured into water. The product was extracted with boiling sodium carbonate solution, from which, on acidification, 1 : 2-benzanthraquinone-4-carboxylic acid (4 g.) was obtained. After recrystallisation from acetic acid it had m. p. 294—296°, not depressed by admixture with an authentic specimen. The residue (3·5 g.), insoluble in boiling sodium carbonate, purified by sublimation in a high vacuum and recrystallised from acetic acid, was identified as 1 : 2-benzanthraquinone by comparison with an authentic specimen. The acid was further identified by reduction, with zinc dust and boiling dilute ammonium hydroxide, to 1 : 2-benzanthracene-4-carboxylic acid, which formed yellow needles, m. p. 276—278°, not depressed by admixture with an authentic specimen, m. p. 281—282°. No non-acidic material was obtained when this acid was submitted to the Schmidt reaction as described for the 10-isomer.

Conversion of 1 : 2-*Benz*-10-*anthranylglyoxylic Acid into* 1 : 2-*Benzanthracene*-10-*carboxylic Acid.*—In an attempt to convert the glyoxylic acid into oxalylbenzanthracene by conversion into the acid chloride, and treatment with stannic chloride in benzene, the chief product isolated was 1 : 2-benzanthracene-10-carboxylic acid. The following procedure was also found to effect the degradation. 1 : 2-Benz-10-anthranylglyoxylic acid (0·4 g.) was boiled for ¼ hour with excess of thionyl chloride, and the excess then

removed in a vacuum, on the steam-bath. The solid product was boiled for ½ hour with dilute sodium hydroxide, and the solution filtered and acidified. The acid, recrystallised from acetic acid, formed small needles, m. p. 218—220°, not depressed by admixture with 1 : 2-benzanthracene-10-carboxylic acid.

2-(2′-*Methoxybenzoyl*)-1-*naphthoic Acid.*—In another paper, Badger (*J.*, **1947**, 940) described the interaction of *o*-anisylmagnesium bromide and 1 : 2-naphthalic anhydride, and the isolation, after purification through the acetoxy-lactone, of an acid which was designated 2-*o*-methoxybenzoyl-1-naphthoic acid. The prior use of this reaction by Newman and Wise (*J. Amer. Chem. Soc.*, 1941, **63**, 2109) was inadvertently overlooked. These workers purified the crude acid by fractional crystallisation, and isolated two isomeric acids, and determined their structure. Through the courtesy of Professor Newman, who kindly supplied specimens of his acids, it has been possible to confirm, by mixed m. p. determinations, that the acid described by Badger does, in fact, have the structure assigned to it.

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