

New Ring Systems of Potential Carcinogenic Activity. Part I. Derivatives of 4 : 9 : 10-Triaza-1 : 2-5 : 6- and -1 : 2-7 : 8-dibenzanthracene.

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The unambiguous synthesis of 4 : 9 : 10-triaza-1 : 2-7 : 8- and -1 : 2-5 : 6-dibenzanthracene and 3-substituted derivatives thereof is reported. The 3-hydroxy- and 3-amino-derivatives in these series were synthesised from 1-nitroso-2- and 2-nitroso-1-naphthylamine by condensation with 2-methoxycarbonylbenzyl cyanide and 2-cyanobenzyl cyanide in the presence of sodium ethoxide. A double ring-closure occurred, the hydroxy- and amino-substituents being derived from the *o*-methoxycarbonyl and *o*-cyano-moieties respectively of the substituted benzyl cyanides.

SINCE inhibition of growth of experimental tumours may be brought about by the administration of carcinogenic polycyclic hydrocarbons (Haddow, *J. Path. Bact.*, 1938, **47**, 467) and nitrogen-containing heterocycles (Badger, Elson, Haddow, Hewett, and Robinson, *Proc. Roy. Soc.*, 1942, *B*, **130**, 255) of similar complexity and skeletal shape, the synthesis of new heterocycles of this type is of interest because their properties may confirm or provide exceptions to the apparent rule that carcinogenic and tumour-inhibiting properties are associated.

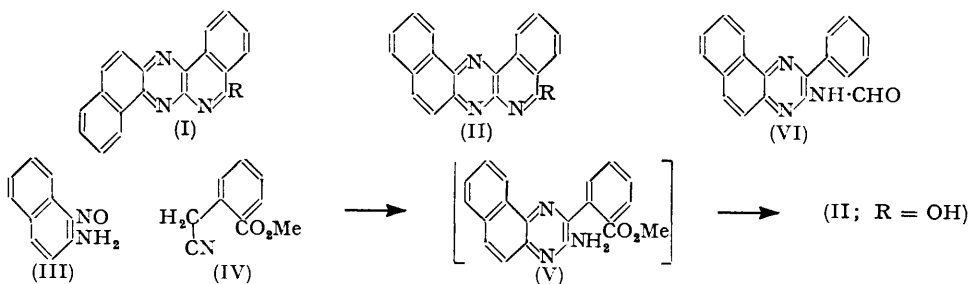
In a structurally very dissimilar case a series of acylaziridines has been found by Walpole, Roberts, Rose, Hendry, and Homer (*Brit. J. Pharmacol.*, 1954, **9**, 316) to be carcinogenic but not tumour-inhibitory. Also, new aza-analogues of the carcinogenic hydrocarbons extend the range of polycyclic structures which are being studied theoretically by Pullman

[*Ann. Chim. (France)*, 1947, **2**, 5; *Acta Int. Cancer*, 1948, **6**, 57; *Compt. rend.*, 1953, **236**, 2318, 2508; **237**, 173; *J. Chim. phys.*, 1953, **50**, 548; cf. Pullman, Pullman, and Berthier, *Compt. rend.*, 1953, **236**, 2067] in a search for fundamental causes of carcinogenicity.

These workers claim that an active K region, *e.g.*, the double bond at the 3 : 4- and the 5 : 6-position in 1 : 2-7 : 8-dibenzanthracene, is necessary for carcinogenic activity. 1 : 2-5 : 6- and 1 : 2-7 : 8-Dibenzanthracene are also of interest because they are respectively strong (Shimkin and Wyman, *J. Nat. Cancer Inst.*, 1947, **8**, 49) and weak (Barry, Cook, Haslewood, Hewett, Hieger, and Kennaway, *Proc. Roy. Soc.*, 1935, *B*, **117**, 318) carcinogens, and the former is a tumour inhibitor (Haddow, *loc. cit.*). Activity is retained when carbon in the 9- or 10-position is replaced by one or two nitrogen atoms as in 1 : 2-5 : 6- and 1 : 2-7 : 8-dibenzacridine (Badger, Cook, Hewett, Kennaway, Kennaway, Martin, and Robinson, *Proc. Roy. Soc.*, 1940, *B*, **129**, 439; Haddow, *loc. cit.*) and 1 : 2-5 : 6-dibenzophenazine (Rudali, Chalvet, and Winternitz, *Compt. rend.*, 1955, **240**, 1738). Introducing a third ring-nitrogen atom we have now synthesised new triazadibenzanthracene derivatives in which the carbon-carbon link in the 3 : 4-position has been replaced by an azamethine link. Boyland (*Cancer Res.*, 1952, **12**, 77) has suggested, after a study of many examples, that, in polycyclic carcinogenic hydrocarbons whose structure can be based on that of anthracene two centres of reactivity are necessary for biological activity, *i.e.*, either two K regions or one K region and the *meso*-position of this anthracene moiety. Since in our structures there is one K region and no anthracene nucleus, their investigation for carcinogenicity will show whether Boyland's hypothesis can be strengthened by application to triazadibenzanthracenes.

In a preliminary communication (*Chem. and Ind.*, 1954, 404) we have shown that by condensing 2 : 4-diamino-1-nitrosobenzene with 2-methoxycarbonylbenzyl cyanide a double ring-closure occurred, leading to the formation of 6-amino-3-hydroxy-4 : 9 : 10-triaza-1 : 2-benzanthracene. Analogously it was shown that derivatives of 4 : 9 : 10-triaza-1 : 2-5 : 6- (I) and 1 : 2-7 : 8-dibenzanthracene (II) could be obtained from 2-nitroso-1 and 1-nitroso-2-naphthylamine respectively. The synthesis determines the structure of the product without ambiguity.

When 1-nitroso-2-naphthylamine (III) was treated with 2-methoxycarbonylbenzyl cyanide (IV) in boiling ethanol containing 1 mol. of sodium ethoxide, 3-hydroxy-4 : 9 : 10-triaza-1 : 2-7 : 8-dibenzanthracene (II; R = OH) was precipitated as the sodium salt in good yield. Evidence for the intermediate formation of the amino-ester (V) is contained elsewhere (*J.*, 1955, 2214).

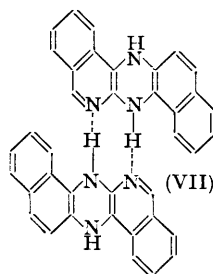


Similarly 2-nitroso-1-naphthylamine and the ester (IV) yielded 3-hydroxy-4 : 9 : 10-triaza-1 : 2-5 : 6-dibenzanthracene (I; R = OH). An attempt to obtain the two parent compounds (I and II; R = H) by replacement of the hydroxy-group in our products by chlorine and subsequent dechlorination, failed in the case of the 1 : 2-7 : 8-dibenzo-series at the replacement stage (treatment with phosphoryl chloride, phosphoryl chloride plus phosphorus pentachloride, or purified thionyl chloride). Replacement by chlorine of the 3-hydroxy-group in the 1 : 2-5 : 6-dibenzo-series was readily achieved with phosphoryl chloride, but attempted dehalogenation of the 3-chloro-derivative (I; R = Cl) with hydrogen in the presence of palladium-charcoal in acetic acid only yielded the phenol (I; R = OH).

As an alternative approach, the 3-hydroxy-derivatives (I and II; R = OH) were converted into thiols by phosphorus pentasulphide in dry pyridine (Klingsberg and Papa, *J. Amer. Chem. Soc.*, 1951, **73**, 4988), high yields being obtained. 3-Mercapto-4 : 9 : 10-triaza-1 : 2-5 : 6-dibenzanthracene (I; R = SH) was converted into the 3-methylthio-derivative (I; R = SMe) and this with aniline yielded the 3-anilino-compound (I; R = NHPH). Both the thiols (I and II; R = SH) on prolonged heating with aniline yielded the 3-anilino-derivatives (I and II; R = NHPH).

Since the substitution of an amino-group in the 5-position of 1 : 2-benzanthracene appears to confer tumour-inhibitory and possibly carcinogenic activity (Badger *et al.*, *loc. cit.*) an amino-group was introduced into the two heterocycles by treating 1-nitroso-2- and 2-nitroso-1-naphthylamine with 2-cyanobenzyl cyanide under conditions similar to those used for the preparation of the phenols (I and II; R = OH). The 3-amino-derivatives of 4 : 9 : 10-triaza-1 : 2-7 : 8- and -1 : 2-5 : 6-dibenzanthracene (II and I; R = NH₂) were obtained in good yield.

In the preparation of the two parent compounds (I and II; R = H) the 3-mercapto-derivatives were desulphurised with freshly prepared Raney nickel (Brown, *J. Soc. Chem.*



Ind., 1950, **69**, 355) in 80% aqueous dioxan, to yield orange dihydro-derivatives of the two parent compounds. The solutions of both compounds in butanol showed intense green fluorescences in ultraviolet light. With palladium-charcoal at *ca.* 280° in a high vacuum, they gave the parent compounds (I and II; R = H) as light yellow crystals, which in solution showed intense blue fluorescence in ultraviolet light. We designate the reduced derivatives as dihydro- in preference to the conceivably alternative tetrahydro-compounds mainly on the strength of the analytical figures. This structure enables us to suggest an explanation, which could not apply to the tetrahydro-form, for the orange colour of the dihydro-derivative

which in each case, compared with the pale yellow of the parent compound, was surprising. The dihydro-derivative of the 1 : 2-5 : 6-dibenzo-compound (I; R = H) was unaffected by bromine or iodine in hot acetic acid but was easily oxidised by nitrous acid in hot acetic acid to the parent compound (I; R = H) in good yield. These properties suggest that the two hydrogen atoms have been taken up by the pyridoquinoxaline moiety and we suggest speculatively that the orange colour could be attributed to a dimeric structure whose stability depended upon double hydrogen bonding, *e.g.* (VII). Clemo and McIlwain (*J.*, 1935, 738) observed that the complex formed from phenazine (yellow) and two mols. of diphenylamine (colourless) was orange.

Attempted hydrogenation of the compound (I; R = H) in acetic acid with palladium-charcoal failed.

As an alternative synthesis of 4 : 9 : 10-triaza-1 : 2-7 : 8-dibenzanthracene, benzyl cyanide was condensed in ethanol with 1-nitroso-2-naphthylamine in the presence of sodium ethoxide, to yield 2-amino-3-phenyl-5 : 6-benzoquinoxaline but attempts to prepare the *N*-formyl derivative (VI), which it was hoped could by ring-closure yield (II; R = H), failed : formic acid with and without addition of a trace of sulphuric acid, sodium formate, or anhydrous zinc chloride, and also ethyl orthoformate, were used.

EXPERIMENTAL

M. p.s were determined in an electrically heated block. The analyses are by Mr. P. R. W. Baker, Beckenham. "Fluorescence" refers to illumination in ultraviolet light.

2-Amino-3-phenyl-5 : 6-benzoquinoxaline.—To a solution of sodium (0.01 g.) in 2-ethoxy-ethanol (25 ml.) was added 1-nitroso-2-naphthylamine (1.72 g.) followed by benzyl cyanide (1.3 g.), and the mixture was boiled under reflux for 5 min. The dark brown solution was concentrated at the pump and the residue was triturated with ether. Several crystallisations from ethanol (charcoal) yielded *2-amino-3-phenyl-5 : 6-benzoquinoxaline* as yellow needles, m. p. 193° (Found : C, 79.8; H, 4.9; N, 15.7. C₁₈H₁₃N₃ requires C, 79.7; H, 4.8; N, 15.5%).

3-Amino-2-phenyl-5:6-benzoquinoline.—2-Nitroso-1-naphthylamine (1.72 g.) and benzyl cyanide (1.3 g.) were added to a solution of sodium (0.25 g.) in ethanol (25 ml.), and the mixture was boiled for 1.5 hr. After cooling, the material was collected (1.8 g.). Several crystallisations from ethanol (charcoal) yielded the 5:6-benzoquinoline as yellow needles, m. p. 180° (Found: C, 80.0; H, 4.8; N, 15.5%). The ethanol solution showed an intense blue fluorescence.

3-Hydroxy-4:9:10-triaza-1:2:5:6-dibenzanthracene (I; R = OH).—2-Nitroso-1-naphthylamine (1.72 g.) and 2-methoxycarbonylbenzyl cyanide (1.9 g.) were added to a solution of sodium (0.25 g.) in dry ethanol (50 ml.), and the mixture was boiled under reflux for 10 min. After cooling, the deposited material was collected and dried (1.8 g.). Several crystallisations from glacial acetic acid yielded the 3-hydroxy-derivative as pale yellow needles, m. p. 308—309° (Found, on a sample dried *in vacuo* at 150°: C, 76.7; H, 3.9; N, 13.95. $C_{19}H_{11}ON_3$ requires C, 76.75; H, 3.7; N, 14.1%). The acetic acid solution showed an intense yellow fluorescence.

3-Hydroxy-4:9:10-triaza-1:2:7:8-dibenzanthracene (II; R = OH).—To a solution of sodium (0.8 g.) in ethanol (100 ml.) were added 1-nitroso-2-naphthylamine (5.16 g.) and 2-methoxycarbonylbenzyl cyanide (5.7 g.), and the mixture was boiled under reflux for 5 min. After cooling, the material was collected and dried (5.5 g.). Several crystallisations from acetic acid yielded the 3-hydroxy-derivative as yellow needles, m. p. 362—363° (Found, after drying *in vacuo* at 150°: C, 76.7; H, 3.8; N, 14.05%). The acetic acid solution showed an intense blue fluorescence.

3-Chloro-4:9:10-triaza-1:2:5:6-dibenzanthracene (I; R = Cl).—The 3-hydroxy-derivative (1.0 g.), phosphoryl chloride (20 ml.), and phosphorus pentachloride (1.0 g.) were heated under reflux condenser for 30 min., during which the colour of the solution darkened, a tar was deposited, and evolution of hydrogen chloride ceased. The excess of phosphoryl chloride was removed and the residue was treated with crushed ice, a yellow material being obtained. After being washed, this was dried (P_2O_5) (yield, 1.3 g.), and several crystallisations from benzene yielded the 3-chloro-derivative as flat yellow needles, m. p. 288° (Found, after drying *in vacuo* at 150°: C, 72.9; H, 3.4; N, 13.2. $C_{19}H_{10}N_3Cl$ requires C, 72.3; H, 3.2; N, 13.3%).

3-Amino-4:9:10-triaza-1:2:5:6-dibenzanthracene (I; R = NH_2).—To a solution of sodium (0.25 g.) in ethanol (25 ml.) were added 2-cyanobenzyl cyanide (1.56 g.) and 2-nitroso-1-naphthylamine (1.72 g.), and the mixture was boiled under reflux for 10 min. A black crystalline precipitate was formed (2.25 g.) which after several crystallisations from acetic acid yielded the 3-amino-derivative as yellow plates, m. p. 338° (Found, on a sample dried *in vacuo* at 190°: C, 76.6; H, 4.2; N, 18.9. $C_{19}H_{12}N_4$ requires C, 77.0; H, 4.1; N, 18.9%). The acetic acid solution showed an intense yellow-green fluorescence.

3-Amino-4:9:10-triaza-1:2:7:8-dibenzanthracene (II; R = NH_2).—This amine (1.35 g.) was prepared as in the above experiment, from 1-nitroso-2-naphthylamine (1.72 g.), as yellow needles (from acetic acid), m. p. >360° (Found, on a sample dried *in vacuo* at 180°: C, 76.5; H, 4.2; N, 19.0%). The acetic acid solution showed an intense bright green fluorescence.

3-Mercapto-4:9:10-triaza-1:2:5:6-dibenzanthracene (I; R = SH).—3-Hydroxy-4:9:10-triaza-1:2:5:6-dibenzanthracene (1.5 g.), phosphorus pentasulphide (1.2 g.), and dry pyridine (20 ml.) were heated under reflux for 4 hr. The hot solution was filtered into boiling water (250 ml.), an orange precipitate being formed. Collection after cooling, and drying (yield, 1.5 g.), and recrystallisation from pyridine (charcoal) and then 2-ethoxyethanol gave the 3-thiol as deep yellow needles, m. p. 352° (Found, after drying *in vacuo* at 180°: C, 72.85; H, 3.7; N, 13.3; S, 10.2. $C_{18}H_{11}N_3S$ requires C, 72.8; H, 3.5; N, 13.4; S, 10.2%).

3-Methylthio-4:9:10-triaza-1:2:5:6-dibenzanthracene (I; R = SMe).—The 3-thiol (I; R = SH) (1.0 g.) was dissolved in 2-ethoxyethanol (50 ml.) containing sodium (80 mg.), and the deep red solution was boiled under reflux for 5 min. When methyl iodide (1 ml.) was added the solution became bright yellow. After cooling, the yellow crystalline precipitate was collected and dried (0.87 g.). Several crystallisations from ethanol yielded the 3-methylthio-derivative as bright yellow needles, m. p. 280° (Found, after drying *in vacuo* at 110°: C, 72.9; H, 4.2; N, 13.0; S, 9.5. $C_{20}H_{13}N_3S$ requires C, 73.4; H, 4.0; N, 12.8; S, 9.8%).

3-Anilino-4:9:10-triaza-1:2:5:6-dibenzanthracene (I; R = NHPH).—(a) The above 3-methylthio-derivative (0.4 g.) and aniline (2.5 ml.) were boiled under an air-condenser for 2.5 hr. during which evolution of methanethiol ceased. A yellow crystalline precipitate was deposited on cooling which was collected and crystallised several times from xylene (charcoal), to yield the 3-anilino-derivative as bright yellow prisms, m. p. 282—283° (Found, on a sample dried *in vacuo* at 110°: C, 80.4; H, 4.2; N, 15.2. $C_{25}H_{16}N_4$ requires C, 80.6; H, 4.3; N, 15.05%).

(b) The 3-thiol (I; R = SH) (0.5 g.) and aniline (5 ml.) were boiled under an air-condenser for 8 hr. Working up as in the previous experiment yielded the 3-anilino-derivative, m. p. and mixed m. p. 282—283°.

The solution in xylene showed an intense blue-green fluorescence.

Dihydro-4 : 9 : 10-triaza-1 : 2-5 : 6-dibenzanthracene.—The 3-thiol (I; R = SH) (2.0 g.), freshly prepared Raney nickel (*ca.* 10 g., moist), and dioxan (150 ml.; 80%) were boiled vigorously under reflux for 6 hr. The hot solution was filtered and the Raney nickel was washed with acetone. The solution was concentrated, to give an orange material (1.5 g.). Several crystallisations from butanol yielded *dihydro-4 : 9 : 10-triaza-1 : 2-5 : 6-dibenzanthracene* as orange needles, m. p. 275° (Found, on a sample dried *in vacuo* at 110°: C, 80.6; H, 4.7; N, 14.7. C₁₉H₁₃N₃ requires C, 80.5; H, 4.6; N, 14.8%). The butanol solution showed a bright green fluorescence.

4 : 9 : 10-Triaza-1 : 2-5 : 6-dibenzanthracene (I; R = H).—(a) Palladium-charcoal (0.3 g.) and the above dihydro-derivative (0.3 g.) were mixed and sublimed at 280°/0.05 mm. A bright yellow powder was obtained. Two sublimations, followed by crystallisation from ethanol, yielded 4 : 9 : 10-triaza-1 : 2-5 : 6-dibenzanthracene as long yellow needles, m. p. 282—283° (Found, after drying *in vacuo* at 110°: C, 80.9; H, 3.8; N, 15.05. C₁₉H₁₁N₃ requires C, 81.1; H, 3.9; N, 14.9%).

(b) The dihydro-derivative (0.5 g.), dissolved in glacial acetic acid (100 ml.), at 90° was treated with sodium nitrite (3 g.) in water (6 ml.) with stirring, and the mixture boiled gently until all solid had dissolved. The product, precipitated by adding water, crystallised from ethanol in yellow needles (0.4 g.), m. p. 280°. After recrystallisation identity was indicated by mixed m. p. (Found, after drying *in vacuo* at 110°: C, 81.3; H, 3.9; N, 14.8%).

The solution in ethanol gave a bright blue fluorescence.

Hydrogenation in the presence of palladium-charcoal in acetic acid could not be achieved.

Reduction of the material in acetic acid with zinc dust in excess gave a deep red solution which became yellow when heated. Working up yielded the dihydro-derivative and starting material, identified by mixed m. p. Perhaps a free radical is initially formed and later disproportionates.

3-Mercapto-4 : 9 : 10-triaza-1 : 2-7 : 8-dibenzanthracene (II; R = SH).—The 3-hydroxy-derivative (II; R = OH) (1.5 g.), phosphorus pentasulphide (1.2 g.), and dry pyridine (30 ml.) were boiled under reflux for 4 hr. The mixture, which almost solidified, was kept overnight and then poured into boiling water (250 ml.), and the orange precipitate was collected and dried (1.55 g.). Several crystallisations from pyridine yielded the 3-thiol as orange needles, m. p. 317—318° (Found, on a sample dried *in vacuo* at 150°: C, 73.0; H, 3.5; N, 12.8; S, 9.8. C₁₈H₁₁N₃S requires C, 72.8; H, 3.5; N, 13.4; S, 10.2%).

3-Anilino-4 : 9 : 10-triaza-1 : 2-7 : 8-dibenzanthracene (II; R = NPh).—Aniline (5.0 ml.) and the 3-thiol (II; R = SH) (0.5 g.) were boiled under an air-condenser for 12 hr. during which time evolution of hydrogen sulphide ceased. After cooling, ether was added. The brown precipitate was crystallised several times from benzene (charcoal), to give the 3-anilino-derivative, m. p. 263° (Found, after drying *in vacuo* at 110°: C, 80.9; H, 4.4; N, 14.5. C₂₅H₁₆N₄ requires C, 80.6; H, 4.3; N, 15.05%).

Dihydro-4 : 9 : 10-triaza-1 : 2-7 : 8-dibenzanthracene.—A mixture of the 3-thiol (II; R = SH) (6.0 g.), freshly prepared Raney nickel (*ca.* 30 g., moist), and dioxan (60 ml.; 80%) was boiled vigorously under reflux for 6 hr. during which an intense green fluorescence developed and a bright yellow precipitate was deposited. The solution was filtered hot; crystals were then deposited (1.5 g.; m. p. 260°). The Raney nickel was continuously extracted with acetone, yielding a further 2.5 g. of material of m. p. 265°. The bulked materials were crystallised twice from butanol, to yield the *dihydro-derivative*, m. p. 275° as orange-yellow needles (Found, after drying *in vacuo* at 110°: C, 80.3; H, 4.3; N, 15.1. C₁₉H₁₃N₃ requires C, 80.5; H, 4.6; N, 14.8%). The butanol solution showed an intense bright green fluorescence.

4 : 9 : 10-Triaza-1 : 2-7 : 8-dibenzanthracene (II; R = H).—Palladium-charcoal (0.5 g.) and the above dihydro-compound (0.5 g.) were mixed and heated at 260°/0.05 mm. The bright yellow sublimate obtained was resublimed and then crystallised from butanol, to yield 4 : 9 : 10-triaza-1 : 2-7 : 8-dibenzanthracene as pale yellow rods, m. p. 293° (Found, after drying *in vacuo* at 150°: C, 81.0; H, 3.8; N, 15.0. C₁₉H₁₁N₃ requires C, 81.1; H, 3.9; N, 14.9%). The butanol solution showed an intense bright blue fluorescence.

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