725. *Polycyclic Cinnoline Derivatives. Part IV.* The Synthesis of Some Potential Carcinogens.*

By J. F. Corbett, P. F. Holt, and A. N. Hughes.

Phenanthro[9,10-*c*]cinnoline and 7,12-diphenylnaphtho[2,3-*c*]cinnoline, which are potential carcinogens, have been prepared by the reduction of 2,2′-dinitrobiaryls. The synthesis of 7,12-diphenylnaphtho[2,3-*c*]cinnoline involves the use of 2,β-dinitrostyrene as a dienophile in a Diels–Alder reaction.

Schmidt [1] and, later, others have suggested that the carcinogenic activity of polycyclic aromatic hydrocarbons containing the phenanthrene ring system is related, at least in part, to the high electron-density of the *K*-region, *i.e.*, the 9,10-bond of phenanthrene. It was suggested in Part II [2] of this series that certain polycyclic cinnoline derivatives, in which the methine groups of the *K*-region are replaced by nitrogen atoms, would be interesting as analogues of carbocyclic carcinogens, since they would have a higher electron-density at the *K*-region.

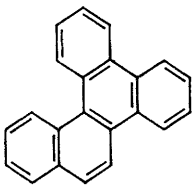
Benzo[*g*]chrysene (I) is known to be strongly carcinogenic to mice.[3] We have now prepared its heterocyclic analogue phenanthro[9,10-*c*]cinnoline (II) by the reduction of 9-nitro-10-*o*-nitrophenylphenanthrene (III). The latter was obtained by a crossed Ullmann reaction between 9-bromo-10-nitrophenanthrene and *o*-bromonitrobenzene, a large excess of the latter being used to suppress the formation of 10,10′-dinitro-9,9′-biphenanthryl.

9-Nitro-10-*o*-nitrophenylphenanthrene (III), when reduced by lithium aluminium

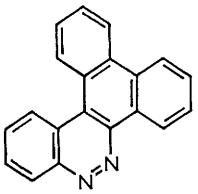
* Part III, *J.*, 1960, 3216.

[1] Schmidt, *Z. phys. Chem.*, 1938, *B*, **39**, 59; 1939, *B*, **42**, 83.
[2] Braithwaite and Holt, *J.*, 1959, 3025.
[3] Badger, Cook, Hewett, Kennaway, Kennaway, Martin, and Robinson, *Proc. Roy. Soc.*, 1940, *B*, **129**, 439, 453.

hydride, gives a low yield of phenanthro[9,10-*c*]cinnoline (II). The reduction of 2,2′-dinitrobiaryls with zinc dust and aqueous-alcoholic potassium hydroxide normally gives the corresponding cinnolines,[4] but in the present case gave a compound containing zinc.



(I)



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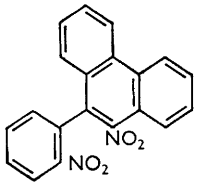

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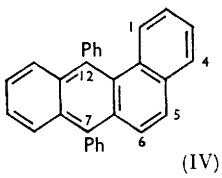
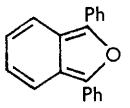


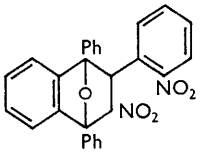
(IV)

Attempts were made to prepare phenanthro[9,10-*c*]cinnoline (II) by the cyclic dehydration of phenanthraquinone monophenylhydrazone. However, sulphuric acid does not affect the hydrazone even in many hours at 100°. Molten aluminium chloride yields a small quantity of phenanthraquinone and some polymeric material although no phenanthraquinone is formed if the reaction is performed under nitrogen.

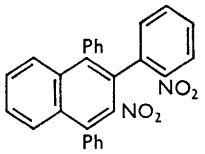
Benz[*a*]anthracene derivatives are also known to be strongly carcinogenic. The activity of the parent compound is increased by methyl or ethyl groups in the 7- or 12-position [5] although 7,12-diphenylbenz[*a*]anthracene (IV) is inactive.[6] The preparation of the 2,2′-dinitrobiaryls required for the synthesis of the cinnoline analogues of benz[*a*]anthracenes is difficult owing to the inaccessibility of suitable 2-halogeno-3-nitronaphthalenes for the crossed Ullmann reaction with *o*-bromonitrobenzene. However, we have found that 2,β-dinitrostyrene and 1,3-diphenylisobenzofuran (V) undergo Diels–Alder addition in refluxing benzene, giving an adduct (VI) which is dehydrated to 2-nitro-3-*o*-nitrophenyl-1,4-diphenylnaphthalene (VII) by acetic acid containing hydrogen bromide under reflux. We found no previous record of the use of 2,β-dinitrostyrene as a dienophile, although β-nitrostyrene gives adducts with a number of dienes.[7]



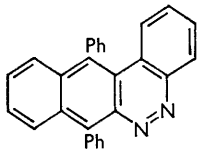
(V)



(VI)



(VII)



(VIII)

Reduction of the biaryl (VII) with lithium aluminium hydride gives a small yield of 7,12-diphenylnaphtho[2,3-*c*]cinnoline (VIII) which is the heterocyclic analogue of 7,12-diphenylbenz[*a*]anthracene. This compound gives an intensely violet picrate whereas other polycyclic cinnoline derivatives give yellow picrates.[1]

Experimental

9-*Bromo*-10-*nitrophenanthrene*.—This compound, prepared by Callow and Gulland's method [8] in 9% yield, had m. p. 198—203°. Callow and Gulland record 34% and m. p. 175—190°.

9-*Nitro*-10-o-*nitrophenylphenanthrene* (III).—Copper-bronze powder (15 g.) was added

[4] Braithwaite, Holt, and Hughes, *J.*, 1958, 4073.

[5] Shear, *Amer. J. Cancer*, 1938, **33**, 499; Dunlap and Warren, *Cancer Res.*, 1946, **6**, 454; *Chem. Abs.*, 1947, **41**, 386; Shabad and Kleĭnenberg, *Byull. Eksptl. Biol. Med.*, 1944, **17**, 57; *Chem. Abs.*, 1945, **39**, 5316.

[6] Cook, *Proc. Roy. Soc.*, 1932, *B*, **111**, 485.

[7] Allen, Bell, and Gates, *J. Org. Chem.*, 1943, **8**, 373.

[8] Callow and Gulland, *J.*, 1929, 2424.

portionwise in 25 min. with stirring to a mixture of 9-bromo-10-nitrophenanthrene (6 g.) and *o*-bromonitrobenzene (12 g.) at 220°. After a further 35 min. at 240° the mixture was cooled and extracted repeatedly with hot benzene. Boiling the extract with charcoal followed by filtration and concentration gave 9-*nitro*-10-o-*nitrophenylphenanthrene* which recrystallised from alcohol as pale yellow granules (2·13 g.), m. p. 167° (Found: C, 69·9; H, 3·6; N, 8·3. $C_{20}H_{12}N_2O_4$ requires C, 69·8; H, 3·5; N, 8·2%).

Phenanthro[9,10-c]*cinnoline*.—The dinitro-compound (III) (250 mg.) in benzene (200 ml.) and ether (100 ml.) was treated with lithium aluminium hydride (0·5 g.) in ether (100 ml.) and heated under reflux for 30 min. Excess of hydride was decomposed with water, and the mixture filtered. The filtrate was concentrated to give a crude product which was dissolved in acetone, filtered through alumina, and allowed to crystallise. *Phenanthro*[9,10-c]*cinnoline* was obtained as orange-yellow needles (30 mg.), m. p. 223° (Found: C, 85·9; H, 4·4; N, 9·8. $C_{20}H_{12}N_2$ requires C, 85·7; H, 4·3; N, 10·0%).

Reduction of 9-*Nitro*-10-o-*nitrophenylphenanthrene with Zinc Dust and Alkali*.—The dinitro-compound (III) (530 mg.) in 90% ethanol (250 ml.) was treated with aqueous potassium hydroxide (5 g. in 15 ml.) and zinc dust (15 g.). The mixture was heated under reflux for 2 hr., filtered, evaporated, and poured into water. Recrystallisation of the precipitate from acetone gave yellow plates of a *complex* containing zinc (53 mg.; m. p. 222°). An acid solution of the complex gave a white colour, characteristic of zinc, with molybdenum ferrocyanide paper [Found: C, 71·9; H, 4·2; N, 8·5; residue, 15·0. Calc. for $C_{40}H_{24}N_4,Zn(OH)_2$: C, 72·8; H, 4·0; N, 8·5; ZnO, 12·4%].

2,β-*Dinitrostyrene*.—2-Nitro-1-*o*-nitrophenylethyl nitrate was prepared by the method of Fieser and Daudt.[9] The nitrate (14·8 g.) was heated under reflux in 1 : 1 acetone–alcohol (200 ml.) for 3 hr. On evaporation and cooling, 2,β-dinitrostyrene separated as pale yellow prisms, m. p. 106—107° (lit., m. p. 106·5—107·5°).

1,4-*Epoxy*-1,2,3,4-*tetrahydro*-2-*nitro*-3-o-*nitrophenylnaphthalene*.—1,3-Diphenylisobenzofuran (0·7 g.) and 2,β-dinitrostyrene (0·5 g.) were heated under reflux in benzene (30 ml.) under nitrogen for 24 hr. Evaporation of the solution followed by the addition of light petroleum gave the *adduct* as almost colourless crystals (0·9 g.), m. p. 159° (Found: C, 72·4; H, 4·2; N, 6·1. $C_{28}H_{20}N_2O_5$ requires C, 72·5; H, 4·3; N, 6·0%).

2-*Nitro*-3-o-*nitrophenyl*-1,4-*diphenylnaphthalene*.—The adduct (2 g.) was suspended in acetic acid (10 ml.) containing 35% hydrogen bromide and left overnight, then heated to the b. p. and cooled, to give 2-*nitro*-3-o-*nitrophenyl*-1,4-*diphenylnaphthalene* (0·8 g.). Recrystallisation from alcohol gave pale yellow needles, m. p. 226° (Found: C, 75·5; H, 4·2; N, 6·4. $C_{28}H_{18}N_2O_4$ requires C, 75·4; H, 4·0; N, 6·3%).

7,12-*Diphenylnaphtho*[2,3-c]*cinnoline*.—2-Nitro-3-*o*-nitrophenyl-1,4-diphenylnaphthalene (0·12 g.) in benzene (20 ml.) and ether (30 ml.) was treated with lithium aluminium hydride (0·2 g.) in ether (20 ml.). Next morning the mixture was warmed for 15 min., then cooled, and the excess of hydride decomposed with water. After filtering, the mixture was evaporated to low bulk and percolated through alumina. Further evaporation gave 7,12-*diphenylnaphtho*-[2,3-c]*cinnoline* (VIII) as yellow rhombs (0·67 g.), m. p. 226°, $\lambda_{max.}$ (log ε): 222 (4·6); 259 (4·6); 293 (4·6); 336 (3·8); 351 (3·9); 368 (4·0); 402 (3·6); 420 (3·5) (Found: C, 88·0; H, 4·6; N, 7·2. $C_{28}H_{18}N_2$ requires C, 88·0; H, 4·7; N, 7·3%), giving a deep purple-brown colour with concentrated sulphuric acid. The *monopicrate*, prepared in alcohol, was obtained as violet needles, m. p. 114° (decomp.) (Found: C, 67·2; H, 3·7; N, 12·1. $C_{34}H_{21}N_5O_7$ requires C, 66·9; H, 3·4; N, 11·5%).

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[9] Fieser and Daudt, *J. Amer. Chem. Soc.*, 1946, **68**, 2248.