118. 3,6-*Phenanthrolines Derived from* 2,2′-*Diaminobenzophenone.*

By M. W. Partridge and H. J. Vipond.

A convenient laboratory preparation of 2,2′-diaminobenzophenone is described. Benzo[*a*][3,6]phenanthroline, its dimethyl, methylphenyl, and tetra-, penta-, and hexa-cyclic derivatives have been prepared from it for biological investigation.

Hypotheses relating structure to activity in polycyclic carcinogenic compounds [1] appear to be inapplicable to tricycloquinazoline.[2] In azapolycyclic carcinogens, there are indications that activity is influenced by the number of heterocyclic nitrogen atoms and, within a given series, by their relative positions.[3] These considerations have led to an investigation of possible connexions between steric factors and activity in tricycloquinazoline. We now describe certain 3,6-phenanthrolines, which have been prepared from 2,2′-diaminobenzophenone, and which have structural features in common with tricycloquinazoline and with carbocyclic carcinogens.

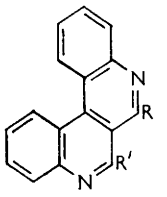
Syntheses of 2,2′-diaminobenzophenone starting with the nitration of benzophenone or of its *o*-nitro-derivative involve inconvenient separations of mixed isomers.[4] 2,2′-Dinitrodiphenylmethane would be a useful intermediate, but was produced in only 15% yield by the deamination of 4,4′-diamino-2,2′-dinitrodiphenylmethane as described by Schnitzspahn.[5] Efficient deamination was achieved when the product of diazotisation with nitrosylsulphuric acid was heated in ethanol with cuprous oxide,[6] whereas other standard methods were much less effective. Chromic acid oxidation of the crude deamination product furnished 2,2′-dinitrobenzophenone, which, on reduction, gave 2,2′-diaminobenzophenone in 44% overall yield. 2,2′-Dinitrodiphenylmethane, isolated from the deamination, and the corresponding diamine, formed by its reduction, differed from the materials hitherto reported [5,7] as these compounds.

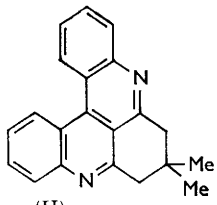
2,2′-Dinitrobenzophenone depressed the melting point of the ketone resulting from the oxidation of the 2,2′-dinitrobenzilic acid [8] previously described. Orientation of the latter ketone was effected by a Beckmann transformation of its oxime to 4,4′-dinitrobenzanilide and by its reduction to 4,4′-diaminobenzophenone. In contrast, 2,2′-dinitrobenzophenone failed to yield an oxime and to undergo a Beckmann transformation under the conditions of Anet, Bavin, and Dewar.[9]

Condensation of 2,2′-diaminobenzophenone with 1,1,3,3-tetraethoxypropane afforded the 3,6-phenanthroline (I; R = R′ = H), isosteric with the skin carcinogen, benzo[*c*]-phenanthrene,[10] but having the position corresponding to the *K*-region [1] blocked by aza-substitution. The phenanthrolines (I; R = R′ = Me, and R = Me, R′ = Ph) were prepared similarly from acetylacetone and benzoylacetone respectively. A non-planar homologue (II) was likewise obtained from dimedone. With indane-1,3-dione an analogous condensation gave the uniplanar hexacyclic compound (III), substantially isosteric with tricycloquinazoline; further a similar hexacyclic analogue (IV), in which

[1] Pullman and Pullman, "Advances in Cancer Research," Academic Press, New York, 1955, Vol. III, p. 117; Lacassagne, Buu-Hoï, Daudel, and Zajdela, *op. cit.*, 1956, Vol. IV, p. 315.
[2] Baldwin, Butler, Cooper, Partridge, and Cunningham, *Nature*, 1958, **181**, 838; Baldwin, Cunningham, and Partridge, *Brit. J. Cancer*, 1959, **13**, 94.
[3] Badger, "Advances in Cancer Research," Academic Press, New York, 1954, Vol. II, p. 73; Lacassagne, Buu-Hoï, Zajdela, Périn, and Jacquignon, *Nature*, 1961, **191**, 1005.
[4] Staedel, *Annalen*, 1883, **218**, 339; 1894, **283**, 164.
[5] Schnitzspahn, *J. prakt. Chem.*, 1902, **65**, 315.
[6] Hodgson and Turner, *J.*, 1942, 748.
[7] Bertram, *J. prakt. Chem.*, 1902, **65**, 327.
[8] Rose, *J.*, 1932, 2360.
[9] Anet, Bavin, and Dewar, *Canad. J. Chem.*, 1957, **35**, 180.
[10] Hartwell, "Survey of Compounds which have been tested for Carcinogenic Activity," U.S. Public Health Service, Washington, 1951, p. 138.

the six-membered rings were retained, resulted from the condensation of 4-hydroxycoumarin with 2,2'-diaminobenzophenone.


(I)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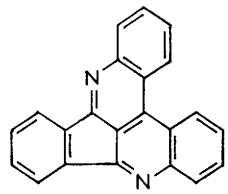
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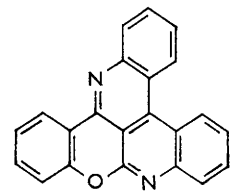
(IV)

Aza-substitution in a polycyclic hydrocarbon usually results in a bathochromic shift in the ultraviolet absorption maxima of group II and III bands. In contrast, the longest-wavelength maximum of the 3,6-phenanthroline (I; R = R' = H) occurs at a shorter wavelength than that of benzo[*c*]phenanthrene [11] and a number of its aza-derivatives.[12]

Preliminary observations of biological tests by Dr. R. W. Baldwin indicate that the 3,6-phenanthrolines (I; R = R' = H), (III), and (IV) cause tumours.

Experimental

4,4'-Diamino-2,2'-dinitrodiphenylmethane Di(hydrogen Sulphate).—The method of Schnitzspahn [5] was adapted. Potassium nitrate (50 g.) was added in portions during 45 min. to a vigorously stirred solution of 4,4'-diaminodiphenylmethane (50 g.) in sulphuric acid (*d* 1·84; 550 ml.), the temperature being maintained between 0° and 5° during the addition and for 1 hr. afterwards. The mixture was poured on crushed ice (2 kg.), partially neutralised with aqueous ammonia (*d* 0·88; 800 ml.), and cooled to 15°; the resulting precipitate was crystallised from 2N-sulphuric acid (500 ml.) to give the salt (70—75 g.) as yellow needles, m. p. 226—228° (decomp.); Butler and Adams [13] record m. p. 228—229° (decomp.).

2,2'-Dinitrobenzophenone.—The foregoing sulphate (115 g.) was added in portions, with vigorous stirring, to a solution of sodium nitrite (46 g.) in concentrated sulphuric acid (450 ml.) maintained at <18°. Glacial acetic acid (620 ml.) was then added slowly at <20° and, after 2 hr., the solution was run into a vigorously stirred suspension of cuprous oxide (180 g.) in ethanol (1250 ml.) during 50 min.; the temperature quickly rose to 70° and was kept at 70—73° for a further 30 min. The hot mixture was filtered, the residue was washed with hot ethanol (200 ml.), and the combined filtrate and washing was added to water (10 l.). The dark brown product (51 g.) which separated overnight was heated under reflux with glacial acetic acid (250 ml.) and, to it, part of a solution of chromic anhydride (100 g.) in water (100 ml.) and acetic acid (200 ml.) was added dropwise until the vigorous reaction subsided. After the addition of the remaining oxidising solution, the mixture was refluxed for 2 hr. and poured into water (2 l.). A solution of the white solid (36 g.) which separated was prepared in boiling acetic acid (150 ml.) and cooled to 75°; 2,2'-dinitrobenzophenone (13 g.; m. p. 189—191°) separated. The mother-liquor, when refluxed for 2 hr. with chromic anhydride (70 g.) in water (70 ml.) and acetic acid (140 ml.) and poured into water (2 l.), gave a second crop (m. p. 189—191°; 18·2 g., after recrystallisation from acetic acid). Further recrystallisation from acetic acid gave m. p. 190—191° (Staedel [4] records m. p. 188—189°) (Found: C, 57·2; H, 3·0. Calc. for $C_{13}H_8N_2O_5$: C, 57·4; H, 3·0%).

2,2'-Diaminobenzophenone.—Iron powder (22 g.) and water (30 ml.) were added, during 1½ hr. with occasional swirling, to a suspension of 2,2'-dinitrobenzophenone (10 g.) in glacial acetic acid (120 ml.) and water (30 ml.) at 90—95°. After a further 30 min., water (300 ml.) was added, and the mixture was filtered. A bulked ether extract (4 × 200 ml.) of the filtrate and residue was washed free from acid with aqueous sodium carbonate, dried, and evaporated. The residue crystallised from 80% aqueous methanol to give the diamine (7·2 g., 92%), m. p. 134—135°; Staedel [4] records m. p. 134—135°. Its diacetyl derivative had m. p. 159—160°

[11] Mayneord and Roe, *Proc. Roy. Soc.*, 1937, *A*, **158**, 634.
[12] Badger and Walker, *J.*, 1956, 122; Mills and Schofield, *ibid.*, p. 4213; Corbett, Holt, and Hughes, *J.*, 1961, 1363.
[13] Butler and Adams, *J. Amer. Chem. Soc.*, 1925, **47**, 2610.

(lit.,[14] 154°) after crystallisation from 50% aqueous methanol (Found: C, 69·1; H, 5·3; N, 9·7. Calc. for $C_{17}H_{16}N_2O_3$: C, 68·9; H, 5·4; N, 9·45%).

2,2'-*Dinitrodiphenylmethane*.—The crude deamination product from 4,4'-diamino-2,2'-dinitrodiphenylmethane di(hydrogen sulphate) (75 g.) in benzene (200 ml.) was poured through a column of alumina (200 g.), and the first yellow band was developed with benzene (250 ml.). The solid (24 g.) recovered from the eluate was distilled twice, to give the *dinitro-compound* (17·1 g., 43%), b. p. 166—168°/0·05 mm., m. p. 80—82°, which crystallised from 80% aqueous methanol as pale yellow needles, m. p. 84—85° (Found: C, 60·0; H, 4·1; N, 10·6. $C_{13}H_{10}N_2O_4$ requires C, 60·5; H, 3·9; N, 10·85%). Schnitzspahn [5] gives m. p. 159°, for material said to be 2,2'-dinitrodiphenylmethane. Oxidation of our dinitro-compound with chromic anhydride in acetic acid afforded 2,2'-dinitrobenzophenone which after recrystallisation had m. p. and mixed m. p. 190—191° (yield 63%).

2,2'-*Diaminodiphenylmethane*.—The foregoing dinitro-compound (1 g.) on reduction with tin and hydrochloric acid afforded the *diamine* (0·54 g.) which crystallised from aqueous methanol as pale yellow needles, m. p. 132—134° (Found: C, 78·8; H, 7·0; N, 13·8. $C_{13}H_{14}N_2$ requires C, 78·8; H, 7·1; N, 14·1%). A substance, m. p. 160°, has been said [7] to be this diamine. The *diacetyl derivative* crystallised from aqueous methanol as needles, m. p. 201—202° (Found: C, 72·3; H, 6·4; N, 9·7. $C_{17}H_{18}N_2O_2$ requires C, 72·3; H, 6·4; N, 9·9%).

4,4'-*Dinitrobenzophenone*.—Benzilic acid (200 g.) when nitrated as described by Rose [8] yielded 4,4'-*dinitrobenzilic acid* (28·4 g.) which crystallised from ethyl acetate–light petroleum as prisms, m. p. 177—178° (decomp.) [Rose gives m. p. 171—172° (decomp.) for the supposed 2,2'-dinitro-isomer] (Found: C, 53·2; H, 3·5; N, 8·6. $C_{14}H_{10}N_2O_7$ requires C, 52·8; H, 3·2; N, 8·8%). On oxidation with chromic anhydride in acetic acid, this gave 4,4'-dinitrobenzophenone (94%), m. p. 190—191°, depressed to 165—168° by 2,2'-dinitrobenzophenone (Staedel [15] records m. p. 189°) (Found: C, 57·8; H, 3·4. Calc. for $C_{13}H_8N_2O_5$: C, 57·4; H, 3·0%). The oxime in agreement with Chapman and Fidler [16] had m. p. 195° (decomp.) (Found: C, 54·6; H, 3·5. Calc. for $C_{13}H_9N_3O_5$: C, 54·4; H, 3·2%). Beckmann rearrangement of this oxime (0·5 g.) with phosphorus pentachloride (0·75 g.) in ether (20 ml.), followed by treatment with water and crystallisation from acetone gave 4,4'-dinitrobenzanilide (0·35 g.), m. p. 268—269°, undepressed by an authentic specimen.[17]

Reduction of 4,4'-dinitrobenzophenone with iron powder and acetic acid gave 4,4'-diaminobenzophenone, m. p. 244—245°; Biltz [18] gives m. p. 244°. Its diacetyl derivative had m. p. 240—242°; Fierz and Koechlin [19] record m. p. 237° for this compound.

Benzo[a][3,6]*phenanthroline* (I; R = R' = H).—2,2'-Diaminobenzophenone (2·3 g.) and 1,1,3,3-tetraethoxypropane (2·5 g.) in glacial acetic acid (15 ml.) were refluxed for 1 hr.; water (150 ml.) and aqueous ammonia (*d* 0·88; 18 ml.) were added. The precipitated *phenanthroline* (2·4 g.) crystallised from light petroleum as very pale yellow needles, m. p. 171—172°, $\lambda_{max.}$ (in EtOH) 268, 315 inf., 332 inf., 349, 366 mμ (log ε 4·65, 3·84, 3·58, 3·51, 3·53, respectively) (Found: C, 82·8; H, 4·1; N, 12·1. $C_{16}H_{10}N_2$ requires C, 83·45; H, 4·3; N, 12·2%). Its *hydrochloride* formed yellow prisms, m. p. 284—286°, from dilute hydrochloric acid (Found: Cl, 23·0. $C_{16}H_{10}N_2$,2HCl requires Cl, 23·4%); the *picrate* (needles from acetic acid) had m. p. 271—273° (decomp.) (Found: C, 57·5; H, 3·3. $C_{22}H_{13}N_5O_7$ requires C, 57·5; H, 2·85%). Its *methiodide* separated from an excess of methyl iodide and crystallised from methanol as orange prisms, m. p. 264—266° (Found: C, 54·4; H, 3·1; N, 7·2. $C_{17}H_{13}IN_2$ requires C, 54·9; H, 3·5; N, 7·5%).

6,7-*Dimethylbenzo*[a][3,6]*phenanthroline* (I; R = R' = Me), prepared similarly from 2,2'-diaminobenzophenone (2·3 g.) and acetylacetone (2 ml.) in acetic acid (20 ml.), crystallised (2·2 g., 79%) as almost colourless needles, m. p. 162—163°, from acetone, $\lambda_{max.}$ (in EtOH) 266, 295 inf., 337 inf., 355, 373 mμ (log ε 4·61, 4·26, 3·55, 3·51, 3·51, respectively) (Found: C, 84·0; H, 5·5; N, 10·8. $C_{18}H_{14}N_2$ requires C, 83·7; H, 5·5; N, 10·85%). The *picrate* crystallised from acetic acid as flat needles, m. p. 240—242° (decomp.) (Found: C, 59·4; H, 3·6; N, 14·2. $C_{24}H_{17}N_5O_7$ requires C, 59·1; H, 3·5; N, 14·4%).

[14] Heyl, *J. prakt. Chem.*, 1899, **59**, 434.
[15] Staedel, *Ber.*, 1894, **27**, 2109.
[16] Chapman and Fidler, *J.*, 1936, 448.
[17] Barnett and Nixon, *Chem. News*, 1924, **129**, 190.
[18] Biltz, *Annalen*, 1897, **296**, 219.
[19] Fierz and Koechlin, *Helv. Chim. Acta*, 1918, **1**, 218.

6-*Methyl*-7-*phenylbenzo*[a][3,6]*phenanthroline* (I; R = Me, R′ = Ph) separated as a gum (2·9 g.) when 2,2′-diaminobenzophenone (2 g.) and benzoylacetone (1·7 g.) were boiled together in acetic acid (25 ml.) for 75 min. and poured into hot 2N-sodium hydroxide (250 ml.). The solid *phenanthroline*, formed overnight, gave pale yellow prisms (1·53 g., 55%), m. p. 153—154° (after several recrystallisations from acetone), $\lambda_{max.}$ (in EtOH) 272, 360, 378 mμ (log ε 4·60, 3·39, 3·32, respectively) (Found: C, 86·7; H, 5·0; N, 8·9. $C_{23}H_{16}N_2$ requires C, 86·2; H, 5·0; N, 8·7%). Its *picrate*, m. p. 226° (decomp.), separated as elongated prisms from acetic acid (Found: C, 62·8; H, 3·25; N, 12·5. $C_{29}H_{19}N_5O_7$ requires C, 63·4; H, 3·5; N, 12·8%).

7,8-*Dihydro*-7,7-*dimethyl*-6H-*dibenzo*[a,de][3,6]*phenanthroline* (II).—2,2′-Diaminobenzophenone (2 g.), dimedone (2 g.), acetic acid (25 ml.), and concentrated hydrochloric acid (0·1 ml.) were refluxed together for 1½ hr. and poured into 2N-sodium hydroxide (300 ml.). The precipitated *phenanthroline* crystallised from aqueous acetone as pale yellow flat prisms, m. p. 170—171° (2·29 g., 81%), $\lambda_{max.}$ (in EtOH) 228 inf., 269, 290 inf., 337, 353, 371 mμ (log ε 4·17, 4·65, 4·30, 3·57, 3·69, 3·76, respectively) (Found: C, 84·4; H, 5·9; N, 9·9. $C_{21}H_{18}N_2$ requires C, 84·5; H, 6·1; N, 9·4%). The *picrate* (prisms from acetic acid) had m. p. 233° (decomp.) (Found: C, 61·2; H, 4·2; N, 13·7. $C_{27}H_{21}N_5O_7$ requires C, 61·5; H, 4·0; N, 13·3%).

Benz[a]*indeno*[1,2,3-de][3,6]*phenanthroline* (III) was obtained when 2,2′-diaminobenzophenone (0·78 g.) and indane-1,3-dione (0·75 g.) were refluxed together in acetic acid (25 ml.) for 20 min., and the solid which crystallised was boiled with an excess of aqueous ammonia and then recrystallised from xylene. It occurred as pale yellow prisms, m. p. 270—271° (0·77 g.), $\lambda_{max.}$ (in EtOH) 234, 285, 305, 365 inf., 388 inf., mμ (log ε 4·63, 4·66, 4·66, 3·70, 3·12, respectively) (Found: C, 86·8; H, 4·0. $C_{22}H_{12}N_2$ requires C, 86·8; H, 4·0%). The *picrate* formed needles, m. p. 286—287° (decomp.), from acetic acid (Found: C, 63·4; H, 3·1; N, 12·6. $C_{28}H_{15}N_5O_7$ requires C, 63·1; H, 2·8; N, 13·1%).

Benzo[a]*chromeno*[2,3,4-de][3,6]*phenanthroline* (IV) was obtained (2·05 g., 63%) by crystallising from 2-ethoxyethanol the cooled melt produced when 2,2′-diaminobenzophenone (2·3 g.), 4-hydroxycoumarin (1·7 g.), and glacial acetic acid (0·1 ml.) were heated together at 180—190° for 1½ hr.; it formed yellow needles, m. p. 238—239°, $\lambda_{max.}$ (in hexane) 230, 273, 285, 303, 334, 349, 366, 385, 407 mμ (log ε 4·76, 4·59, 4·50, 4·41, 4·10, 4·05, 3·83, 4·22, 4·44, respectively), and [in 0·3N-ethanolic (90%) hydrochloric acid] 230, 254, 264, 280, 302, 331, 350 inf., 366, 386, 408, 430, 450 mμ (log ε 4·67, 4·44, 4·47, 4·55, 4·42, 4·29, 4·00, 3·71, 3·89, 4·03, 3·73, 3·80, respectively) (Found: C, 82·9; H, 3·6; N, 8·75. $C_{22}H_{12}N_2O$ requires C, 82·5; H, 3·8; N, 8·75%). This compound did not form a picrate and its hydrochloride, m. p. 238—239°, lost hydrogen chloride when dried.

THE UNIVERSITY, NOTTINGHAM. [*Received, October 2nd*, 1961.]