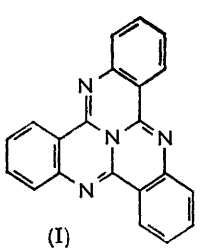
562. *Cyclic Amidines. Part XVI.*[1] *Tetra-azanaphtho*[1,2,3-*fg*]-*naphthacenes.*

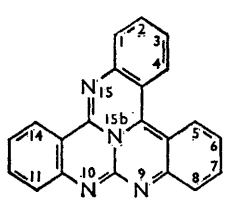
By R. T. Parfitt, M. W. Partridge, and H. J. Vipond.

Tetra-azanaphtho[1,2,3-*fg*]naphthacenes, isomeric with tricycloquinazoline, have been synthesised for examination of the significance of stereochemical fit in the carcinogen–tissue-receptor union in tricycloquinazoline carcinogenesis.

Implicit in the changes in carcinogenicity [2] induced by substitution in tricycloquinazoline (I) is the requirement for high activity of a precise stereochemical fit of the carcinogen to a tissue-receptor. The tetra-azanaphthonaphthacenes (II) and (III) have now been prepared to obtain further evidence on this point.



(I)



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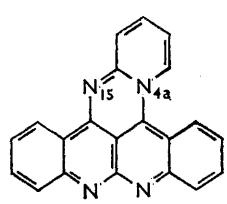


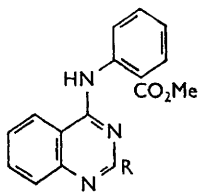
(III)

2-Anilino-4-chloroquinazoline and methyl anthranilate in acetone yielded the diamine (IV; R = NHPh). A stepwise preparation failed, since 2,4-dichloroquinazoline with

[1] Part XV, Partridge, Vipond, and Waite, *J.*, 1962, 2549.
[2] Baldwin, Cunningham, Partridge, and Vipond, *Brit. J. Cancer*, 1962, **16**, 276.

methyl anthranilate, unlike *o*-chloroaniline,[3] gave a diamine[4] (IV; R = *o*-NH·C_6H_4·CO_2Me). Contrary to its behaviour with alkylamines,[3,5] 2,4-dichloroquinazoline and anthranilic acid in aqueous alkali yielded only 2-chloro-4-hydroxy- and 2,4-dihydroxy-quinazoline.

At 210°, the diamine (IV; R = NHPh) cyclized to an anilinotriazabenzanthracene (V), also formed by treatment of the urea (VI; R = Ph) with phosphoryl chloride. The cyclohexylurea (VI; R = C_6H_{11}) could not be cyclized under similar conditions. Sodium aluminium chloride at 320° converted the triazabenzanthracene (V) into the tetra-azanaphthonaphthacene (II) in high yield, whereas a similar direct cyclization of the urea (VI; R = Ph) was very inefficient. In spite of a formal similarity of this cyclization to



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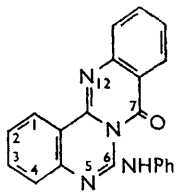

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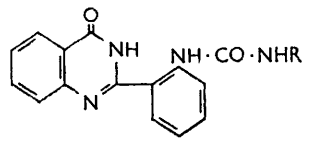


(VI)

a Bischler–Napieralski reaction, a wide variety of reagents employed in the latter reaction proved ineffective. Indeed, an attempted cyclization of the triazabenzanthracene (V) with phosphoryl chloride in nitrobenzene yielded a small quantity of tricycloquinazoline (I), the origin of which is obscure, since isomerization of compound (II) could not be effected with this reagent. The urea (VI; R = Ph) with 100% phosphoric acid also gave some tricycloquinazoline. Alkali fusion degraded both the triazabenzanthracene (V) and the urea (VI; R = Ph) to 2,4-dihydroxyquinazoline.

A useful intermediate for an alternative synthesis of the ring-system (II) would be the diamine (VII; R = NHPh) isomeric with (IV; R = NHPh). However, 4-anilino-2-hydroxyquinazoline required as an intermediate and said to be formed by partial hydrolysis of 2,4-dianilinoquinazoline[6] was shown to be 2-anilino-4-hydroxyquinazoline. Interaction of the ether (VII; R = OEt) and aniline furnished, not the diamine (VII; R = NHPh), but a triazabenzanthracene (VIII; R = NHPh) whose structure followed from its spectroscopic similarity with the known piperidino-derivative[7] (VIII; R = $C_5H_{10}N$) and dissimilarity from the triazanaphthacene[7] (IX; R = OH) (Table, p. 3066), and from its inability to yield the readily recognizable tetra-azanaphthonaphthacene (II). An anilino-derivative (IX; R = NHPh) of the triazanaphthacene was not available since with phosphoryl chloride the triazanaphthacene (IX; R = OH) underwent partial isomerization to a triazabenzanthracene.[7] However, the triazanaphthacene (IX; R = OH), aniline, and sodium aluminium chloride gave the tetra-azanaphthonaphthacene (II), presumably through the anilino-derivative (IX; R = NHPh).

A direct synthesis of the tetra-azanaphthonaphthacene (II) in moderate yield was readily achieved by interaction of 2,2′-diaminobenzophenone and 2,4-dichloroquinazoline.

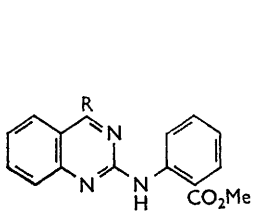
Although 4-chloro-2-*o*-nitrophenylquinazoline reacted readily with bases, its lack of reactivity with *o*-chloronitrobenzene and copper prevented completion of a synthesis of compound (II) through 2,4-di-*o*-nitrophenylquinazoline.

The tetra-azanaphthonaphthacene (II) forms dark green, dichroic crystals from chloroform or on vacuum-sublimation. Chromatography on alumina causes partial decomposition. Differences in the annellation of tricycloquinazoline (I) and the tetra-azanaphthonaphthacene (II) are reflected in the appearance of two additional bands at

[3] Curd, Hoggarth, Landquist, and Rose, *J.*, 1948, 1766.
[4] Lange and Sheibley, *J. Amer. Chem. Soc.*, 1931, **53**, 3867.
[5] Curd, Landquist, and Rose, *J.*, 1947, 775.
[6] Dymek, Brzozowska, and Brzozowski, *Ann. Univ. M. Curie-Sklodowska*, 1954, **9**, 35.
[7] Butler and Partridge, *J.*, 1959, 1512.

505 and 720 mμ in the spectrum of the latter. It is a stronger base than tricycloquinazoline, forming dark red salts with mineral acids and an *N*-oxide. Unlike tricycloquinazoline, it is decomposed by concentrated acids and alkalis and is readily oxidised. On hydrogenation, 2 mol. of hydrogen were absorbed, but the product was rapidly reoxidized in air to give some tetra-azanaphthonaphthacene (II) and an unidentified, neutral material.

The product [8] from treatment of the diazanaphthacene [8] (X; R = R′ = OH) and 2-aminopyridine with phosphorus pentachloride interacted briskly to yield the tetra-azanaphthonaphthacene (III) in low yield. Interaction of the chloro-hydroxy-compound [8] (X; R = Cl, R′ = OH) with 2-aminopyridine was accomplished only in the presence of copper powder, but the product was the fully cyclized compound (III). Loss of the cycl[3,3,3]azine structure in this compound causes a considerable simplification in its absorption spectrum.



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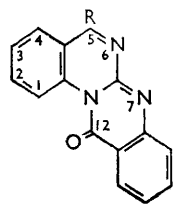
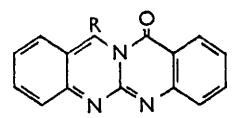


(VIII)



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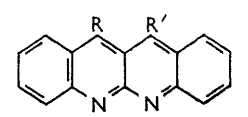

(X)

Biological tests, carried out by Dr. R. W. Baldwin, showed that the tetra-azanaphthonaphthacene (II) is a weak epidermal carcinogen, whereas tricycloquinazoline is intermediate in activity between 1,2:5,6-dibenzanthracene and 3,4-benzopyrene.[2] This contrast provides further evidence of the importance of stereochemical fit in tricycloquinazoline carcinogenesis. The isomer (III) is too insoluble in appropriate solvents for biological test.

Experimental

2-*Anilino*-4-o-*methoxycarbonylanilinoquinazoline* (IV; R = NHPh) separated as its *hydrochloride* (4·9 g.) when freshly made 2-anilino-4-chloroquinazoline [9] (4 g.) and methyl anthranilate (2·4 g.) were shaken in dry acetone (50 ml.) for 30 min.; crystallization from ethanol gave yellow needles, m. p. 360—364° (Found: N, 13·5. $C_{22}H_{19}ClN_4O_2$ requires N, 13·8%). The *base*, formed therefrom in ethanolic ammonia, crystallized from aqueous acetic acid as needles, m. p. 210—212° (Found: C, 71·2; H, 4·9; N, 14·8. $C_{22}H_{18}N_4O_2$ requires C, 71·3; H, 4·9; N, 15·1%).

6-*Anilino*-7H-5,6*a*,12-*triazabenz*[a]*anthracen*-7-*one* (V) crystallized as yellow needles (88%), m. p. 190—192°, from a butanol extract of the melt obtained when the diamine (IV; R = NHPh) was heated at 210° for 1 hr.; it had $\lambda_{max.}$ (in EtOH) 240, 246, 251, 270, 376 mμ (log ε 4·51, 4·50, 4·49, 4·43, 4·20, respectively) (Found: C, 74·7; H, 4·4; N, 16·7. $C_{21}H_{14}N_4O$ requires C, 74·5; H, 4·2; N, 16·6%).

The urea (VI; R = Ph) (0·5 g.) in phosphoryl chloride (15 ml.) was kept for 12 hr., or refluxed for 1 hr., and poured on crushed ice (200 g.). The precipitate furnished the pure triazabenzanthracene (74%), m. p. and mixed m. p. 190—192°, when crystallized from butanol.

This compound was unreactive to acetic anhydride and toluene-*p*-sulphonyl chloride.

4-*Hydroxy*-2-o-N′-*phenylureidophenylquinazoline* (VI; R = Ph).—A suspension of 2-*o*-aminophenyl-4-hydroxyquinazoline (5 g.) in dry benzene (300 ml.) and phenyl isocyanate (3 g.) was refluxed for 1 hr. The precipitated *urea* (6·1 g.) crystallized from aqueous formic acid as needles, m. p. 304—306° (Found: N, 16·1. $C_{21}H_{16}N_4O_2$ requires N, 15·7%). Sodium hydroxide fusion at 220—230° for 15 min. gave 2,4-dihydroxyquinazoline (71%), m. p. and mixed m. p. 349—355°.

[8] Dziewonski and Dymek, *Roczniki Chem.*, 1946, **20**, 38.
[9] Grout and Partridge, *J.*, 1960, 3540.

2-o-N′-*Cyclohexylureidophenyl*-4-*hydroxyquinazoline* (VI; R = C_6H_{11}) crystallized when a suspension of 2-*o*-aminophenyl-4-hydroxyquinazoline (5 g.) in dry benzene (400 ml.) and cyclohexyl isocyanate (10 g.) were refluxed for 6 hr. (yield 98%). It formed needles, m. p. 242—244°, from formic acid (Found: N, 15·3. $C_{21}H_{22}N_4O_2$ requires N, 15·5%).

9,10,15,15*b*-*Tetra-azanaphtho*[1,2,3-fg]*naphthacene* (II).—(i) The triazabenzanthracene (V) (1 g.) was added to a melt of sodium chloride (0·4 g.) and aluminium chloride (2 g.) at about 100° and the mixture was heated at 320° for 1 hr. Repeated extraction of the powdered product with water (10 × 30 ml.) at 65° furnished a solution from which the *nitrate* (0·9 g., 76%) was precipitated by saturated aqueous sodium nitrate (50 ml.). The pure nitrate was obtained as dark red prisms, m. p. 216—218°, by repeated precipitation from aqueous solution with nitric acid, and had $\lambda_{max.}$ (in water) 248, 280, 302, 368, 373, 388, 394, 543 mμ (log ε 4·29, 4·15, 4·19, 3·58, 3·60, 3·58, 3·58, 2·36, respectively) (Found: C, 65·3; H, 3·6; N, 17·8; HNO_3, 16·0. $C_{21}H_{12}N_4,HNO_3$ requires C, 65·8; H, 3·4; N, 18·3; HNO_3, 16·4%). This cyclization started at 180°, but the yield was optimum under the foregoing conditions.

The *base*, liberated to chloroform by triethylamine, was recovered as a green resin which eventually furnished dark green needles, m. p. 296—298°, from chloroform. Sublimation at 265—270°/0·1 mm. gave prisms, m. p. 296—298°, $\lambda_{max.}$ (in EtOH) 240, 277, 300, 380, (in $CHCl_3$) 480, 484, 492, 505, 620, 720 mμ (log ε 4·29, 4·45, 4·37, 3·96, 3·35, 3·35, 3·33, 3·37, 2·89, 3·10, respectively) (Found: C, 78·8; H, 3·8; N, 17·8. $C_{21}H_{12}N_4$ requires C, 78·7; H, 3·8; N, 17·5%). The *hydrochloride*, dark red needles, m. p. 328—330°, was obtained pure on being digested for 2 days with N-hydrochloric acid in acetic acid (Found: Cl, 10·0. $C_{21}H_{12}N_4,HCl$ requires Cl, 10·0%). The green *picrate*, m. p. 259—260°, crystallized from acetic acid (Found: C, 58·8; H, 3·0. $C_{27}H_{15}N_7O_7$ requires C, 59·0; H, 2·7%). A solution of the base and phosphoric acid in ether deposited a deliquescent *phosphate*, m. p. 154—156°, as dark red needles during 10 days (Found: H_3PO_4, 47·2. $C_{21}H_{12}N_4,3H_3PO_4$ requires H_3PO_4, 47·8%). The base (0·4 g.) in acetic acid (25 ml.) and 30% aqueous hydrogen peroxide (5 ml.) on being boiled for 15 min. and basified with ammonia gave its N-*oxide* (0·17 g.) (pale yellow prisms from aqueous dimethylformamide), m. p. 276—277° (Found: N, 16·5. $C_{21}H_{12}N_4O$ requires N, 16·8%).

(ii) Heating the urea (VI; R = Ph) (0·5 g.) and sodium aluminium chloride (0·6 g.) at 320° for 1 hr. gave the naphthonaphthacene which was isolated as its nitrate (25 mg., 5%), m. p. and mixed m. p. 216—218°.

(iii) The triazanaphthacene [7] (IX; R = OH) (1·3 g.), aniline (0·52 g.), and sodium aluminium chloride (2 g.) were heated together at 320° for 1 hr. and worked up for isolation of the naphthonaphthacene (0·12 g., 7·5%), m. p. and mixed m. p. 294—296°.

(iv) 2,2′-Diaminobenzophenone (1·06 g.) and 2,4-dichloroquinazoline (1 g.) were boiled together in acetic acid (20 ml.) for 30 min. and worked up for isolation of the above-mentioned hydrochloride (0·75 g., 47%), m. p. and mixed m. p. 328—330°.

Recoveries of this compound after being refluxed with the named reagents for stated times were: 4N-hydrochloric acid (8 hr.) 100%; 11N-hydrochloric acid (12 hr.) 42%; 5N-sodium hydroxide (5 hr.) 96%; 10N-sodium hydroxide (5 hr.) 24%; 2N-nitric acid (24 hr.) 14%; 1·5N-chromic acid (4 hr.) 41%; 2N-alkaline potassium permanganate (24 hr.) 20%.

Tricycloquinazoline (I).—(i) The triazabenzanthracene (V) (1 g.) was refluxed in nitrobenzene (6 ml.) with phosphoryl chloride (0·45 g.) for 15 hr. After basification with ammonia and steam-distillation of the solvent, the resulting tar furnished, by chromatography on alumina, tricycloquinazoline (75 mg.), m. p. and mixed m. p. 317—319° and having the eight characteristic light-absorption maxima between 250 and 460 mμ.

(ii) Purification of the precipitate, obtained when the urea (VI; R = Ph) (0·5 g.) was heated in 100% phosphoric acid (20 ml.) at 223° for 6 hr. and poured into water, gave tricycloquinazoline (15 mg.).

2-*Anilino*-4-*hydroxyquinazoline*.—This base was produced when 2,4-dianilinoquinazoline hydrochloride [4] (20 g.) was refluxed in ethylene glycol (250 ml.) containing potassium hydroxide (50 g.) for 4 hr., cooled, diluted, and acidified. The alcohol-soluble fraction of the precipitate, after recovery (9·5 g.), had m. p. 254—256°, raised by recrystallization from acetic acid to 260—262°, undepressed by an authentic specimen.[9] Hydrolysis with ethanolic potassium hydroxide as described by Dymek, Brzozowska, and Brzozowski [6] gave 61% of the same material, m. p. 252—254°, which after recrystallization had m. p. and mixed m. p. 260—262°. This compound afforded an acetyl derivative,[9] m. p. and mixed m. p. 201—203°, and was readily converted into the diamine (IV; R = NHPh).

Ultraviolet absorption (λ in mμ) spectra in chloroform.

Compound											
VIII; R = NHPh	$\lambda_{max.}$	[268]		287		311	318		[363]		
	log ε	4·38		4·28		4·26	4·26		4·07		
VIII; R = $C_5H_{10}N$	$\lambda_{max.}$	270		[285]		[303]	313		364		
	log ε	4·29		4·23		4·22	4·25		4·11		
IX; R = OH	$\lambda_{max.}$		283		293			326		370	
	log ε		4·32		4·38			3·89		3·66	

Data in square brackets refer to points of inflexion.

5-*Anilino*-12H-6,7,12*a*-*triazabenz*[a]*anthracen*-12-*one* (VIII; R = NHPh).—The quinazoline [7] (VII; R = OEt) (0·5 g.) and aniline (5 ml.) were heated together at 180° for 6 hr., cooled, and mixed with acetone (5 ml.). The resulting *triazabenzanthracene* (0·29 g.) crystallized from 2-ethoxyethanol as yellow prisms, m. p. 298—300° (Found: C, 74·6; H, 4·3; N, 16·9. $C_{21}H_{14}N_4O$ requires C, 74·5; H, 4·2; N, 16·6%). The mother-liquor slowly deposited the hydroxyquinazoline (VII; R = OH) (0·07 g.), m. p. and mixed m. p. 210—212°, with resolidification and second [7] m. p. 290—296°.

6,12-*Dihydro*-5,12-*dioxo*-5H-6,7,12*a*-*triazabenz*[a]*anthracene*.—11,12-Dihydro-11,12-dioxo-5H-5,6,11a-triazanaphthacene [7] (2 g.) was heated at 120—140° for 6 hr. in phosphoryl chloride (50 ml.). The precipitate formed when the cold solution was poured on crushed ice was extracted with chloroform. The triazabenzanthracene hydrochloride [7] (0·44 g.) crystallized from the concentrated chloroform solution; it had m. p. and mixed m. p. 254—256° and the same ultraviolet absorption spectrum as the authentic compound. Unchanged triazanaphthacene (1·4 g.) was recovered from the chloroform-insoluble fraction.

4-*Methylamino*-2-o-*nitrophenylquinazoline*, m. p. 169—171° (from aqueous ethanol) (0·46 g.), was precipitated by basification of an ethanolic solution of the water-insoluble fraction of the melt formed when 4-chloro-2-*o*-nitrophenylquinazoline [1] (0·5 g.) and methylamine acetate (5 g.) were heated together at 180° for 1 hr. (Found: C, 63·9; H, 4·45; N, 19·7. $C_{15}H_{12}N_4O_2$ requires C, 64·3; H, 4·3; N, 20·0%). Its *picrate* had m. p. 279—281° (Found: N, 19·3. $C_{21}H_{15}N_7O_9$ requires N, 19·3%).

4-*Anilino*-2-o-*nitrophenylquinazoline*.—The *hydrochloride* (3·1 g.), m. p. 192—195° (decomp.) (from methanol), of this base separated when 4-chloro-2-*o*-nitrophenylquinazoline (2·9 g.), aniline (0·83 g.), and hydrochloric acid (0·5 ml.) were boiled together in acetone (150 ml.) for 30 min. (Found: N, 14·5. $C_{20}H_{14}N_4O_2$,HCl requires N, 14·8%). The *base* crystallized from butanol as yellow plates, m. p. 177—178° (decomp.) (Found: C, 69·7; H, 4·0. $C_{20}H_{14}N_4O_2$ requires C, 70·2; H, 4·1%).

4a,9,10,15-*Tetra*-*azanaphtho*[1,2,3-fg]*naphthacene* (III).—(i) 5,6-Diazanaphthacene-11,12-diol [8] (2 g.), phosphorus pentachloride (8 g.), and phosphoryl chloride (12 ml.) were heated together at 120—140° for 3 hr. and kept for 12 hr. The red crystals (1·14 g.) which separated were rapidly collected, washed with dry benzene, and mixed with 2-aminopyridine (5 g.). After the vigorous exothermic reaction has subsided, the mixture was kept molten for 30 min., cooled, and repeatedly extracted with water. The residue furnished the *product* (III) (0·17 g., 16%) as yellow prisms (from acetic acid), m. p. 370—372°, with sublimation, $\lambda_{max.}$ (in EtOH) 227, 260, 279, 363, 418 mμ (log ε 4·31, 4·55, 4·62, 3·80, 3·79, respectively) (Found, for sublimed sample: C, 78·9; H, 3·8; N, 17·6. $C_{21}H_{12}N_4$ requires C, 78·7; H, 3·8; N, 17·5%). Its *sulphate* (yellow needles from 2N-aqueous-ethanolic sulphuric acid) had m. p. 326—330° (decomp.) (Found: N, 13·8. $C_{21}H_{12}N_4,H_2SO_4$ requires N, 13·4%).

(ii) 11-Chloro-5,6-diazanaphthacen-12-ol [8] (0·55 g.), copper powder (0·5 g.), and 2-aminopyridine (5 g.) when boiled together for 4 hr. yielded the product (III) (0·11 g., 17%).

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