732. *Triazaphenanthrenes. Part I. Derivatives of* 10-*Phenyl*-1 : 3 : 9-*triazaphenanthrene.*

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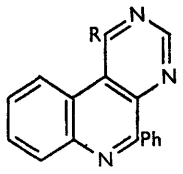
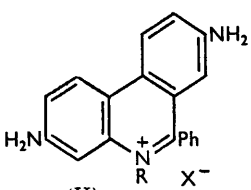
Various 4-substituted derivatives (I) of 10-phenyl-1 : 3 : 9-triazaphenanthrene have been prepared. Monomethiodides of the compounds (I; R = H or NH_2) were found to be biologically inactive; attempts to prepare an *N*-oxide yielded only hydroxy-compounds.

The preparation of salts derived from compounds of type (I) was undertaken in order to compare the biological activity with that of the related phenanthridinium compounds (II). These have been used extensively in the treatment of trypanosomiasis (II, R = Me as dimidium; R = Et as ethidium), and their effectiveness as prophylactic agents when administered as sparingly soluble complexes with suramin [1] has given added interest to this investigation.

The key intermediate for the present work, 3-amino-2-phenylquinoline-4-carboxylic acid (III; R = CO_2H, R′ = NH_2) was best prepared *via* the 3-phthalimido-derivative [incorrectly formulated as the 3-phthalamic acid (III; R = CO_2H, R′ = $NH{\cdot}CO{\cdot}C_6H_4{\cdot}CO_2H$)



(I)



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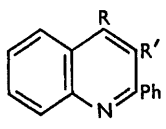

(III)

by Berlingozzi and Marzella [2]] rather than *via* the 3-benzamido-compound [3] since the yields from phenacyl bromide of the precursors (phenacylphthalimide and benzoylphenacylamine) were found to be 80% and 26%, respectively. The subsequent Pfitzinger reaction with isatin gave an 80% yield of the substituted quinoline. Experiments on the dephthaloylation of [III; R = CO_2H, R′ = $N(CO)_2C_6H_4$] did not support the claims made in the literature: Berlingozzi and Marzella's method gave a mixture of 3-amino-2-phenylquinoline-4-carboxylic acid and the product of subsequent decarboxylation in poor yield. Boiling sulphuric acid had little effect unless more concentrated than 50% (v/v) in which simultaneous hydrolysis and decarboxylation occurred; and hot phosphoric acid caused only decarboxylation. However, the amino-acid (III; R = CO_2H, R′ = NH_2) was readily obtained by treatment of the phthaloyl derivative with hydrazine in acetic acid.

4-Hydroxy-10-phenyl-1 : 3 : 9-triazaphenanthrene (I; R = OH), prepared from the amino-acid (III; R = CO_2H, R′ = NH_2) and formamide, was converted into the chloro-compound by prolonged heating in a sealed tube with phosphorus pentachloride; less drastic conditions gave undesired products. The amine (I; R = NH_2) could be prepared directly from the chloro-compound or *via* the phenoxy-derivative (I; R = OPh); it could also be made from 3-amino-4-cyano-2-phenylquinoline and formamide (cf. the synthesis of 4-aminopyrazolo[3,4-*d*]pyrimidine from 3-amino-4-cyanopyrazole and boiling formamide [4]): a derived monomethiodide was inactive against hæmolytic *Streptococcus, Staph. aureus,*

[1] Williamson and Desowitz, *Nature*, 1956, **177**, 1074.
[2] Berlingozzi and Marzella, *Atti Acad. naz. Lincei, Rend. Classe Sci. fys. mat. nat.*, 1923, **32**, ii, 403.
[3] Petrow, Stack, and Wragg, *J.*, 1943, 316.
[4] Robins, *J. Amer. Chem. Soc.*, 1956, **78**, 784.

B. coli, *Candida albicans*, *P. berghei*, *B. rodhaini*, *T. equiperdum*, *T. congolense*, and *T. cruzi*, when tested by Dr. F. Hawking and his colleagues.

The hydroxy-compound (I; R = OH), on treatment with dimethyl sulphate, gave an *N*-methyl derivative, distinct from the *O*-methyl compound obtained from the chloro-derivative (I; R = Cl) and sodium methoxide.

10-Phenyl-1 : 3 : 9-triazaphenanthrene (I; R = H) was prepared *via* the toluene-*p*-sulphonhydrazide (cf. Albert and Royer [5]) and gave a single monomethiodide which was practically inactive against all the above organisms. An attempt to prepare an *N*-oxide of the parent (I; R = H) gave a mixture of the 4-hydroxy- and the 2 : 4-dihydroxy-derivatives; the structure of the latter, although most probable in view of similar results in the quinazoline series,[6] was not confirmed; an attempted unambiguous synthesis from the amino-acid (III; R = CO_2H, R′ = NH_2) and urea gave only the acid amide (III; R = $CO{\cdot}NH_2$, R′ = H).

Experimental

ω-Bromoacetophenone.—This was prepared in 60% yield by the method of Petrow *et al.*,[3] in batches: acetophenone (200 g.) and bromine (86 c.c., *not* 180 g. as in the reference quoted). Although the yield is much lower, this method is more convenient than that described in *Org. Synth., Coll. Vol. II*, p. 480.

2-Phenyl-3-phthalimidoquinoline-4-carboxylic Acid.—A solution of phenacylphthalimide (54 g.) in hot ethanol (200 c.c.), mixed with aqueous potassium hydroxide (40 g. in 40 c.c.), was added slowly with stirring to a solution of isatin (30 g.) in absolute ethanol (200 c.c.) containing potassium hydroxide (12 g. in 15 c.c. of water). Another aqueous solution of potassium hydroxide (25 g. in 50 c.c.) was added gradually and the solution was set aside for 3 days. The mixture was then almost neutralised with concentrated hydrochloric acid (approx. 28 c.c.), alcohol was distilled off under reduced pressure, water added, and the mixture acidified. The solid was collected, washed with water, and after digestion with hot 1% hydrochloric acid (1 l.) provided the acid (65 g.), m. p. 265—266° (decomp.), as an orange powder. Recrystallisation from dioxan yielded colourless crystals, m. p. 278° (decomp.).

3-Amino-2-phenylquinoline-4-carboxylic Acid.—100% Hydrazine hydrate (40 c.c.) and 2-phenyl-3-phthalimidoquinoline-4-carboxylic acid (80 g.) were heated under reflux in acetic acid (300 c.c.) for ½ hr. After 1 : 4-dihydroxyphthalazine (25 g.), m. p. *ca.* 340°, had been collected from the cold mixture, the filtrate was concentrated under reduced pressure to *ca.* 100 c.c. and set aside at 0°. The amino-acid (32 g.), m. p. 223—224°, separated and crystallised best from dioxan. The *acetyl derivative*, m. p. 271° (decomp.), was prepared under reflux by means of acetic anhydride containing a few drops of concentrated sulphuric acid (Found: C, 70·45; H, 4·7; N, 9·5. $C_{18}H_{14}O_3N_2$ requires C, 70·6; H, 4·6; N, 9·1%); Berlingozzi and Marzella [2] report m. p. 257—258° but give no analysis.

2-Phenyl-3-phthalimidoquinoline-4-carboxyamide.—The acid (105 g.) was heated under reflux with thionyl chloride (300 c.c.) for 15 min., excess of the reagent was removed under reduced pressure, and the granular solid was dissolved in benzene (1250 c.c.). A stream of dry ammonia was passed into this cold solution for 30 min., the solvent was removed, and the residue was washed with water and then alcohol, to yield the *amide* (75 g.), m. p. 325—330°; this separated from acetic acid in colourless needles, m. p. 343° (Found: C, 73·1; H, 3·9; N, 10·4. $C_{24}H_{15}O_3N_3$ requires C, 73·3; H, 3·8; N, 10·7%).

3-Amino-2-phenylquinoline-4-carboxyamide.—The foregoing amide (112 g., crude) was heated under reflux with 100% hydrazine hydrate (200 c.c.) and pyridine (400 c.c.) for 2 hr. The hot solution was poured into water (2 l.), and the white precipitate (66 g.), m. p. 265°, collected. Recrystallisation from methanol gave pale yellow needles, m. p. 265°, of the *amino-amide* (Found: C, 72·8; H, 5·0; N, 15·0. $C_{16}H_{13}ON_3$ requires C, 73·0; H, 5·0; N, 16·0%). Use of acetic acid as solvent for this reaction gave a much reduced yield (≯40%).

3-Amino-4-cyano-2-phenylquinoline.—An intimate mixture of the preceding compound (50 g.) and phosphoric oxide (125 g.) was heated at 175° for 1 hr. and then added to ice and water

[5] Albert and Rover, *J.*, 1949. 1148.

(500 g. each) with stirring. The mixture was made alkaline with ammonia (*d* 0·880), to yield the *nitrile* (48 g.), m. p. 188—190°, which separated from benzene in pale yellow needles (31 g.), m. p. 194° (Found: C, 78·7; H, 5·0; N, 16·3. $C_{16}H_{11}N_3$ requires C, 78·35; H, 4·5; N, 17·1%).

4-Hydroxy-10-phenyl-1 : 3 : 9-triazaphenanthrene.—3-Amino-2-phenylquinoline-4-carboxylic acid (15 g.) was heated under reflux for 1 hr. with formamide (25 c.c.), and the product (8 g.) was collected from the cold mixture. The *hydroxy-derivative*, m. p. 307—308°, formed colourless needles from dioxan (Found: C, 74·3; H, 3·8; N, 15·1. $C_{17}H_{11}ON_3$ requires C, 74·7; H, 4·1; N, 15·4%).

4-Chloro-10-phenyl-1 : 3 : 9-triazaphenanthrene.—The pure 4-hydroxy-compound (7 g., recrystallised) and phosphorus pentachloride (11·5 g.) were heated at 150—160° for 22 hr. in a sealed tube. The cold product was removed with hot dry benzene (200 c.c.) and was shaken with ice (150 g.) and 6N-sodium hydroxide (100 c.c.) for 15 min.; the benzene layer was washed, dried (Na_2CO_3), and evaporated under reduced pressure. The *chloro-compound* (7·2 g.), m. p. 157°, crystallised from ethyl acetate or light petroleum (b. p. 80—100°) as needles, m. p. 167—168° (Found: C, 69·6; H, 3·5; N, 13·4; Cl, 10·85. $C_{17}H_{10}N_3Cl$ requires C, 69·9; H, 3·45; N, 14·4; Cl, 12·1%). The use of boiling phosphorus oxychloride, alone or with phosphorus pentachloride, did not give the desired product.

4-Amino-10-phenyl-1 : 3 : 9-triazaphenanthrene.—(*a*) A stream of dry ammonia was passed into a mixture of the chloro-compound (5 g.) and phenol (20 g.) for 1½ hr. at 180°. The mixture was heated on a steam-bath with 3N-sodium hydroxide (120 c.c.) for ½ hr., then filtered, and the precipitate washed with more sodium hydroxide solution and then copiously with water. The *amine* (4·6 g.) formed colourless blades, m. p. 233—234°, from benzene (Found: C, 75·3; H, 4·8; N, 19·8. $C_{17}H_{12}N_4$ requires C, 75·0; H, 4·4; N, 20·6%).

(*b*) 3-Amino-4-cyano-2-phenylquinoline (10 g.) and formamide (70 c.c.) were heated under reflux for 1 hr., then cooled, and the solid (9·5 g.) was collected and washed with water and then ethanol. Recrystallisation from ethyl acetate gave pale yellow platelets (3·15 g.), m. p. 233—234° identical with the authentic amine.

(*c*) The amine was also prepared in lower yield by heating the chloro-compound with urea in a sealed tube for 44 hr. at 190°.

(*d*) The 4-phenoxy-compound (50 mg.) was heated at 180° ± 10° with ammonium acetate (1 g.) for 30 min., dilute sodium hydroxide solution was added to the cold mixture, and the product was collected; recrystallisation from ethyl acetate gave the amine, m. p. and mixed m. p. 233°.

The *acetyl derivative*, m. p. 251—252°, prepared by boiling the amine with acetic anhydride for a few minutes, formed colourless needles from acetic acid (Found: C, 72·0; H, 4·4; N, 16·9. $C_{19}H_{14}ON_4$ requires C, 72·6; H, 4·5; N, 17·8%).

4-Amino-10-phenyl-1 : 3 : 9-triazaphenanthrene Methiodide.—The amine (2·5 g.) was heated under reflux with methyl iodide (25 c.c.) in methanol (25 c.c.) for 21 hr. The mixture was evaporated to dryness under reduced pressure and the *salt* (3·5 g.) crystallised from methanol or nitromethane as pale yellow needles, m. p. 239° (decomp.) (Found: C, 54·1; H, 3·6; N, 13·4; I, 28·2. $C_{18}H_{15}N_4I$ requires C, 52·2; H, 3·6; N, 13·5; I, 30·6%). Concentration of the mother-liquors yielded small clusters of dark red needles of another salt, m. p. 216° (decomp.), of which there was insufficient for analysis.

4-Phenoxy-10-phenyl-1 : 3 : 9-triazaphenanthrene.—The chloro-compound (1 g.) was heated in phenol (5 g.) containing potassium hydroxide (0·25 g.) on a steam-bath for 1½ hr., cooled, and shaken with 1·5N-sodium hydroxide (60 c.c.) for 30 min., and the product (1 g.) was collected. The *phenoxy-derivative*, m. p. 193—194°, formed colourless plates from benzene (Found: C, 78·9; H, 4·1; N, 10·2. $C_{23}H_{15}ON_3$ requires C, 79·1; H, 4·3; N, 12·0%).

10-Phenyl-1 : 3 : 9-triazaphenanthrene.—The chloro-compound (9·3 g.) was heated under reflux with toluene-*p*-sulphonhydrazide (11·6 g.) in dry chloroform (220 c.c.) for 2½ hr. The bright yellow intermediate (15·8 g.) was collected and added portionwise to N-sodium hydroxide (200 c.c.) on a steam-bath and left there for ½ hr. The crude *base* (7·5 g.) crystallised from methanol (charcoal) as colourless needles (4·2 g.), m. p. 173—175°, raised to 174—175·5° by recrystallisation from light petroleum (b. p. 80—100°) (Found: C, 78·8; H, 4·5; N, 16·6. $C_{17}H_{11}N_3$ requires C, 79·4; H, 4·3; N, 16·3%).

The base (2·6 g.) was heated at 100° for 10 min. with dimethyl sulphate (15 c.c.). The mixture was dissolved in warm water (50 c.c.) and shaken with benzene (3 × 15 c.c.), and the aqueous layer was treated with a saturated solution of potassium iodide (15 c.c.); the cream

solid (3·6 g.), m. p. 207° (decomp.), was collected and washed successively with water, acetone, and ether. Recrystallisation from water gave yellow needles of a *monomethiodide*, m. p. 209° (decomp.) (Found: C, 52·8; H, 4·2; N, 9·85; I, 29·5. $C_{18}H_{16}ON_3I$ requires C, 51·9; H, 3·9; N, 10·1; I, 30·5%).

4-*Methyl*-10-*phenyl*-1 : 3 : 9-*triazaphenanthrene*.—4-Acetyl-3-amino-2-phenylquinoline (1 g.) was heated under reflux with formamide (10 c.c.) and acetic acid (7 c.c.) for 1 hr. and the crystalline product (0·35 g.) was collected. The *base* formed pale yellow needles, m. p. 157°, from ethyl acetate or light petroleum (b. p. 80—100°) (Found: C, 80·5; H, 4·9; N, 15·3. $C_{18}H_{13}N_3$ requires C, 79·7; H, 4·8; N, 15·5%).

Reaction of Hydrogen Peroxide with 10-*Phenyl*-1 : 3 : 9-*triazaphenanthrene*.—The base (2·5 g.) was heated on a steam-bath for ¾ hr. with hydrogen peroxide (10 c.c., " 100-vol.") in acetic acid (20 c.c.), the mixture was cooled, and the product (2·3 g.), m. p. 295—299°, collected. Successive recrystallisation from acetic acid and dimethylformamide gave pale yellow needles of 4-hydroxy-10-phenyl-1 : 3 : 9-triazaphenanthrene, m. p. and mixed m. p. 305—306°.

The acetic acid mother-liquors and residues from recrystallisations (25 c.c. in all) were heated with hydrogen peroxide (200 c.c., " 100-vol.") at 75—80° for 2 hr., then cooled, and the pale yellow needles (0·8 g.), m. p. 324° (decomp.), were collected. This *substance* was identical with the compound, m. p. 330° (decomp.), prepared from the hydroxy-compound under the above conditions, which separated from dimethylformamide in colourless crystals (Found: C, 70·3; H, 3·85; N, 14·9. $C_{17}H_{11}O_2N_3$ requires C, 70·6; H, 3·8; N, 14·5%).

Reaction between 3-*Amino*-2-*phenylquinoline*-4-*carboxylic Acid and Urea*.—The amino-acid (1 g.) was heated at 160° ± 10° with urea (4 g.) for ½ hr., then warmed with water (20 c.c.) and acidified with concentrated hydrochloric acid (1 c.c.). A trace of solid, m. p. 360°, was collected and the filtrate was basified with aqueous ammonia to provide material (0·55 g.), m. p. 260—262° alone and when mixed with 3-amino-2-phenylquinoline-4-carboxyamide.

Methylation of 4-*Hydroxy*-10-*phenyl*-1 : 3 : 9-*triazaphenanthrene*.—A solution of the hydroxy-compound (1 g.) in 3N-sodium hydroxide (10 c.c.) was shaken at 60—70° with dimethyl sulphate (1 c.c.) for 15 min. and the product (0·7 g.) was collected and washed with dilute sodium hydroxide and then water. Recrystallisation from ethanol gave colourless needles, m. p. 174—175°, of 1(or 3)-*methyl*-4-*oxo*-10-*phenyl*-1 : 3 : 9-*triazaphenanthrene* (Found: C, 75·8; H, 4·6; N, 14·8. $C_{18}H_{13}ON_3$ requires C, 75·2; H, 4·6; N, 14·6%).

4-*Methoxy*-10-*phenyl*-1 : 3 : 9-*triazaphenanthrene*.—The 4-chloro-derivative (0·6 g.) and sodium methoxide [from sodium (0·25 g.) and methanol (15 c.c.)] were heated under reflux for 20 min.; the solution was evaporated to half-volume, cooled, and filtered. The solid was recrystallised from methanol and then from light petroleum (b. p. 80—100°) to yield colourless needles, m. p. 163°, of the *methoxy-compound* (Found: C, 75·4; H, 4·5; N, 14·7. $C_{18}H_{13}ON_3$ requires C, 75·2; H, 4·6; N, 14·6%).

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