2. *Triazaphenanthrenes. Part IV.* Some 9-Aryl-3-methyl-1 : 2 : 10-triazaphenanthrenes.*

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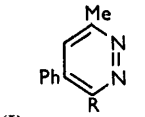
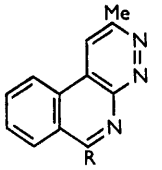
9-Aryl-3-methyl-1 : 2 : 10-triazaphenanthrenes (II) have been prepared by cyclisation of arylamidopyridazines (I; R = NH·COAr). The derived monomethiodides were biologically inactive.

Previous papers have described the synthesis of triazaphenanthrenes from quinolines and cinnolines. Work based on pyridazine derivatives (I) is now described.



(I)



(II)

The pyridazine (I; R = OH) was prepared by dehydrogenation of the pyridazinone obtained from hydrazine and α-phenyl-lævulic acid (cf. ref. 1); the latter being synthesised by a modification of Ruhemann's method [2] from 3-benzylidenepentane-2 : 4-dione [3] which also was prepared by an improved method.[4]

Methods applicable in the cinnoline [5] or quinoline [6] series did not convert the corresponding chloro-compound (I; R = Cl) into the amine (I; R = NH_2), but use of urea in a sealed tube gave reproducible yields. Treatment of the benzamido-compound (I; R = NH·COPh) with phosphorus oxychloride or phosphorus pentoxide in nitrobenzene at 180° did not give a useful product but some success was achieved with phosphorus pentoxide in boiling nitrobenzene. However, a melt of aluminium chloride and sodium chloride gave over 50% of the triazaphenanthrene (II; R = Ph). The *p*-nitrobenzamido-derivative (I; R = NH·CO·C_6H_4·NO_2) was, however, cyclised in low yields by phosphorus pentoxide in nitrobenzene, other variations being useless.

Quaternisation of 3-methyl-9-phenyl-1 : 2 : 10-triazaphenanthrene with methanolic methyl iodide yielded a mixture of two monomethiodides, but only one monomethiodide could be obtained from the 9-*p*-nitrophenyl analogue. These salts were inactive against the organisms listed in the preceding paper.

Experimental

3-Benzylidenepentane-2 : 4-dione.—A homogeneous mixture of benzaldehyde (4·0 moles, 404 c.c.), acetylacetone (4·0 moles, 424 c.c.), and piperidine (3·2 c.c.) was set aside at room temperature and shaken occasionally. After 6 days the mixture was diluted with ether (750 c.c.), and piperidine removed by washing with dilute hydrochloric acid followed by water. The ethereal layer was dried ($MgSO_4$), the solvent removed, and the residue distilled, yielding unchanged materials followed by 3-benzylidenepentanedione (470 g., 63%; b. p. 149—150°/*ca.* 4 mm.). The semicarbazone separated from alcohol in glistening plates, m. p. 223—224° (decomp.) (Found: C, 63·5; H, 6·1; N, 17·6. Calc. for $C_{13}H_{15}O_2N_3$: C, 63·7; H, 6·2; N, 17·1%). The literature [7] m. p. is 210° (decomp.).

* Part III, preceding paper.

[1] Overend and Wiggins, *J.*, 1947, 239.
[2] Ruhemann, *J.*, 1904, **85**, 1451.
[3] Knoevenagel and Faber, *Ber.*, 1898, **31**, 2773; Knoevenagel and Werner, *Annalen*, 1894, **281**, 79.
[4] Courts and Petrow, *J.*, 1952, 1; Ruhemann, *J.*, 1903, 1373; Kuhn, *J.*, 1938, 605; Baker and Lapworth, *J.*, 1925, 560.
[5] Keneford, Schofield, and Simpson, *J.*, 1948, 358.
[6] Backeberg and Marais, *J.*, 1942, 381.
[7] Ruhemann and Watson, *J.*, 1904, **85**, 460.

3-α-*Cyanobenzylpentane*-2 : 4-*dione*.—Potassium cyanide (144 g., AnalaR) in water (288 c.c.) was added during 1½ hr. at <3° to a stirred solution of 3-benzylidenepentane-2 : 4-dione (230 g.) in alcohol (2 l.). The solution was then stirred for a further hour at 0° and acidified at <10° by slow addition of dilute hydrochloric acid (1½ l.). The precipitate was washed with a small amount of cold water; after prolonged drying in a vacuum desiccator (H_2SO_4) the crude product (198 g., 75%) had m. p. 118—121°. Two crystallisations from aqueous alcohol provided needles of the cyano-compound, m. p. 127—129° (Ruhemann [2] gave m. p. 127—128°), which decomposed slowly at room temperature.

β-*Acetyl*-α-*phenylpropionic Acid*.—Crude 3-α-cyanobenzylpentane-2 : 4-dione (308 g.) and potassium hydroxide (500 g.) in water (2·5 l.) were heated under reflux for *ca.* 100 hr. The acid was isolated by acidification with dilute hydrochloric acid and extraction with ether. Evaporation of the extract and crystallisation of the residue from water (*ca.* 6 l.) (charcoal) gave pure β-acetyl-α-phenylpropionic acid as irregular plates (156 g.), m. p. 127—129° (Ruhemann [2] gave m. p. 126°). More (12 g.) pure acid was recovered from the mother liquors (total yield 168 g., 61%) (Found: C, 68·7; H, 6·5. Calc. for $C_{11}H_{12}O_3$: C, 68·7; H, 6·3%).

6-*Methyl*-4-*phenylpyridazin*-3-*one*.—A suspension of acetylphenylpropionic acid (150 g.) in alcohol (300 c.c.) was heated under reflux with hydrazine hydrate (45 c.c.; 99—100%) for 4 hr. The warm solution was stirred into water (2½ l.); the precipitate was washed with water, dried in a vacuum desiccator (H_2SO_4), and crystallised (charcoal) from benzene–light petroleum (b. p. 60—80°), giving needles of 6-*methyl*-4-*phenylpyridazin*-3-*one* (125 g., 85%), m. p. 121—123° (Found: C, 70·4; H, 6·7; N, 15·45. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4; N, 14·9%).

Hydrobromide. Bromine (24 c.c.) was added slowly to the pyridazinone (60 g.) in acetic acid (240 c.c.) without external cooling. The solid was collected next day, washed with acetic acid until colourless and then with ether, and crystallised from acetic acid, yielding the hydrobromide as brittle needles, m. p. 251—254° (decomp.) (crude yield 89%).

3-*Hydroxy*-6-*methyl*-4-*phenylpyridazine*.—(*a*) The hydrobromide (2·2 g.) was hydrolysed during crystallisation from aqueous alcohol and yielded glistening needles of the *base*, m. p. 172—174° (Found: C, 70·5; H, 5·6; N, 15·15. $C_{11}H_{10}ON_2$ requires C, 70·95; H, 5·4; N, 15·05%). (*b*) The crude hydrobromide [153 g., m. p. 250—253° (decomp.)] was treated with an excess of dilute ammonia solution and then extracted with chloroform, and the extract washed and dried ($MgSO_4$). The material (102 g., 96%), m. p. 166—168°, obtained by evaporation of the solvent, was suitable for direct conversion into the 3-chloro-compound.

3-*Chloro*-6-*methyl*-4-*phenylpyridazine*.—3-Hydroxy-6-methyl-4-phenylpyridazine (100 g.) was heated with phosphorus oxychloride (400 c.c.) on the steam-bath for 1¾ hr., after which the excess of phosphorus oxychloride was removed under reduced pressure, finally with the aid of benzene. The residue was treated with crushed ice, made alkaline with 6N-sodium hydroxide, and extracted with methylene chloride. The combined extracts were washed free from alkali, dried ($MgSO_4$), and evaporated. The solid was crystallised twice (charcoal) from light petroleum (b. p. 90—110°) giving silky needles of 3-*chloro*-6-*methyl*-4-*phenylpyridazine*, m. p. 110—112° (Found: C, 64·7; H, 4·8; N, 13·6; Cl, 17·7. $C_{11}H_9N_2Cl$ requires C, 64·5; H, 4·4; N, 13·7; Cl, 17·3%).

6-*Methyl*-3-*phenoxy*-4-*phenylpyridazine*.—A stream of dry ammonia was passed into the 3-chloro-compound (2 g.) dissolved in phenol (10 g.) at 180° (oil-bath) for 40 min. The mixture was then cooled, diluted with ether, washed with dilute sodium hydroxide followed by water, and then dried ($MgSO_4$). Evaporation gave a pale yellow oil (2 g.) which crystallised; two crystallisations from light petroleum (b. p. 60—80°) (charcoal) gave glistening plates of 6-*methyl*-3-*phenoxy*-4-*phenylpyridazine* (1·85 g., 72%), m. p. 96—98° (Found: C, 77·7; H, 5·5; N, 10·85. $C_{17}H_{14}ON_2$ requires C, 77·8; H, 5·4; N, 10·7%).

3-*Amino*-6-*methyl*-4-*phenylpyridazine*.—Powdered 3-chloro-6-methyl-4-phenylpyridazine (8 g.) and urea (40 g.) were heated in a sealed tube for 40 hr. at 190°. The product was digested with boiling dilute sodium hydroxide (100 c.c.), cooled, filtered off, and washed with water. The 3-*amino*-6-*methyl*-4-*phenylpyridazine*, m. p. 191—193° formed small glistening needles (77%; from benzene) (Found: C, 71·6; H, 6·1; N, 21·5. $C_{11}H_{11}N_3$ requires C, 71·3; H, 6·0; N, 22·7%).

3-*Benzamido*-6-*methyl*-4-*phenylpyridazine*.—The amine was benzoylated with benzoyl chloride and pyridine under reflux for 6 hr. 3-*Benzamido*-6-*methyl*-4-*phenylpyridazine* (71%) formed clusters of prisms, m. p. 208—210°, from alcohol (Found: C, 75·2; H, 5·3; N, 15·0. $C_{18}H_{15}ON_3$ requires C, 74·7; H, 5·2; N, 14·5%).

3-*Methyl*-9-*phenyl*-1 : 2 : 10-*triazaphenanthrene*.—(*a*) 3-Benzamido-6-methyl-4-phenylpyridazine (8 g.) and a powdered mixture of aluminium chloride (29·6 g.) and sodium chloride (10·4 g.) were heated and stirred in an oil-bath (*ca.* 220°) for 4½ hr. Crushed ice (*ca.* 300 g.) was added to the cold mixture which was then heated, cooled, and filtered (filtrate A). The residue was digested with warm dilute sodium hydroxide, filtered off, washed, dried, and crystallised twice from methanol (charcoal), giving pale yellow needles (4·0 g., 54%), m. p. 254—256°, of 3-*methyl*-9-*phenyl*-1 : 2 : 10-*triazaphenanthrene* (Found: C, 79·8; H, 5·0: N. 14·8. $C_{18}H_{13}N_3$ requires C, 79·7; H, 4·9; N, 15·5%).

Filtrate A was made alkaline with 6N-sodium hydroxide, and the dried precipitate (1·4 g.) digested with boiling chloroform. The digest, on evaporation to dryness and crystallisation (twice) from methanol, yielded rosettes of broad blades, m. p. 191—193° alone and on admixture with authentic 3-amino-6-methyl-4-phenylpyridazine.

(*b*) To a solution of the 3-benzamide (0·4 g.) in dry nitrobenzene (12 c.c.) at 140° phosphorus pentoxide (1·5 g.) was added and the mixture heated under reflux in an oil-bath for 3½ hr. Water was carefully added and nitrobenzene then removed by steam-distillation. The residual aqueous portion was filtered hot and the filtrate made alkaline with dilute sodium hydroxide. The solid (150 mg.; m. p. 226—246°) was dissolved in acid and reprecipitated with alkali. Extraction of the dry product with chloroform yielded material which crystallised from methylene chloride as straw-coloured needles, m. p. 254—256° alone and when mixed with a sample prepared as above.

Quaternisation of 3-*Methyl*-9-*phenyl*-1 : 2 : 10-*triazaphenanthrene*.—(*a*) The base (2 g.) was heated under reflux with methyl iodide (5 c.c.) in nitromethane (30 c.c.) for 45 min., and the orange needles (0·6 g.) which separated on cooling crystallised twice from nitromethane, giving pure α-*monomethiodide*, m. p. 243—246° (decomp.) (Found: C, 54·75; H, 4·6; N, 9·75; I, 30·6. $C_{19}H_{16}N_3I$ requires C, 55·2; H, 3·9; N, 10·2; I, 30·7%).

The initial filtrate was treated with an excess of dry ether, and the precipitate (2·6 g.) crystallised twice from alcohol, giving dark red blades of pure β-*monomethiodide*, m. p. 212—213° (decomp.) (Found: C, 54·9; H, 4·6; N, 10·0; I, 30·3%).

(*b*) The base (0·3 g.) was heated with dimethyl sulphate (0·6 c.c.) in nitrobenzene (30 c.c.) at 150—160° (oil-bath) for 4 hr. The mixture was cooled, diluted with ether, and extracted with water. The aqueous extract was saturated with potassium iodide and the precipitate crystallised from alcohol, providing tawny needles (0·04 g.), m. p. 158—160° (decomp.); recrystallisation gave a mixture of blades and fine needles. Concentration of the mother-liquor furnished dark red blades (0·19 g.), m. p. 212—213° (decomp.) not depressed on admixture with the β-monomethiodide obtained as above.

3-m-*Nitrobenzamido*-6-*methyl*-4-*phenylpyridazine*.—3-Amino-6-methyl-4-phenylpyridazine (2 g.), *m*-nitrobenzoyl chloride (from 2·4 g. of the corresponding acid), and pyridine (20 c.c.) were heated on the steam-bath for 4 hr. 6-*Methyl*-3-m-*nitrobenzamido*-4-*phenylpyridazine* formed feathery needles (from acetone) (3·0 g., 83%), m. p. 216—218° (Found: C, 64·6; H, 4·55; N, 15·25. $C_{18}H_{14}O_3N_4$ requires C, 64·7; H, 4·2; N, 16·8%).

6-*Methyl*-3-p-*nitrobenzamido*-4-*phenylpyridazine*.—Similarly prepared the p-*nitrobenzamide* formed pale yellow crystals (72%), m. p. 227—229° (from methanol) (Found: C, 64·5; H, 4·0; N, 15·2%).

3-*Methyl*-9-p-*nitrophenyl*-1 : 2 : 10-*triazaphenanthrene*.—6-*Methyl*-3-p-*nitrobenzamido*-4-*phenylpyridazine* (6 g.) in dry nitrobenzene (180 c.c.) and phosphorus pentoxide (*ca.* 12 g.) were stirred at *ca.* 180° for 7 hr., more phosphorus pentoxide (6 g.) being added after 3½ hr. 3-*Methyl*-9-p-*nitrophenyl*-1 : 2 : 10-*triazaphenanthrene* formed pale yellow blades (0·86 g., 15%), m. p. 338—339° (decomp.), from nitromethane (Found: C, 67·5; H, 3·9; N, 17·4. $C_{18}H_{12}O_2N_4$ requires C, 68·35; H, 3·8; N, 17·7%).

Quaternisation of 3-*Methyl*-9-p-*nitrophenyl*-1 : 2 : 10-*triazaphenanthrene*.—The base (1 g.), methyl iodide (20 c.c.), and nitromethane (200 c.c.) were heated under reflux for 1 hr. The solution was then concentrated to *ca.* 50 c.c., cooled, and diluted with ether. The precipitate after three crystallisations from methanol gave dark red blades of a *monomethiodide*, m. p. 218—220° (decomp.) (Found: C, 48·8; H, 3·5; N, 11·9; I, 27·6. $C_{19}H_{15}O_2N_4I,\frac{1}{2}H_2O$ requires C, 48·8; H, 3·5; N, 12·1; I, 27·2%).

Nitration of 3-*Chloro*-6-*methyl*-4-*phenylpyridazine*.—Powdered 3-chloro-6-methyl-4-phenylpyridazine (48 g.) was added portionwise to stirred fuming nitric acid (160 c.c.), below 10°, and the resultant solution kept at room temperature; after 3 days the mixture was poured on ice

and water (*ca.* 1 l.) and basified with dilute ammonia solution. The product gave by three recrystallisations from methanol (charcoal) needles of a *mononitro-derivative* of 3-chloro-6-methyl-4-phenylpyridazine (32·7 g., 56%), m. p. 221—223° (Found: C, 53·3; H, 3·5; N, 16·3; Cl, 14·2. $C_{11}H_8O_2N_3Cl$ requires C, 52·8; H, 3·2; N, 16·8; Cl, 14·2%).

3-*Amino*-6-*methyl*-4-x-*nitrophenylpyridazine*.—Powdered 3-chloro-compound (8 g.) and urea (40 g.) were heated in a sealed tube at 190° for *ca.* 30 hr. The product was digested with hot dilute sodium hydroxide and then filtered cold, the solid taken up in dilute acetic acid, the solution filtered (charcoal), and solid reprecipitated with alkali. Extraction with boiling chloroform, evaporation of the filtered extract, and crystallisation of the residue from acetone (charcoal) gave yellow rectangular prisms of 3-*amino*-6-*methyl*-4-x-*nitrophenylpyridazine* (3·5 g., 48%), m. p. 221—223° (Found: C, 57·2; H, 4·5; N, 24·5. $C_{11}H_{10}O_2N_4$ requires C, 57·4; H, 4·4; N, 24·3%).

3-*Benzamido*-6-*methyl*-4-x-*nitrophenylpyridazine*.—Prepared in the usual way from the foregoing amine 3-*benzamido*-6-*methyl*-4-x-*nitrophenylpyridazine* (4·0 g., 69%) formed blades (from ethanol), m. p. 198—200° (Found: C, 64·1; H, 4·2; N, 16·65. $C_{18}H_{14}O_3N_4$ requires C, 64·7; H, 4·2; N, 16·8%).

4-x-*Aminophenyl*-3-*benzamido*-6-*methylpyridazine*.—Powdered 3-benzamido-6-methyl-4-*x*-nitrophenylpyridazine (4 g.) was added to stannous chloride reagent [8] (120 c.c.). After 3½ hr. at room temperature with occasional shaking the mixture was filtered and the white granular precipitate treated with ice and an excess of dilute ammonia. The resultant mixture was extracted five times with chloroform and the washed and dried ($MgSO_4$) extract was evaporated to yield 4-x-*aminophenyl*-3-*benzamido*-6-*methylpyridazine* (2·8 g., 77%), yellow prisms (2·5 g., 69%), m. p. 205—207° (from alcohol) (Found: C, 70·7; H, 5·2; N, 18·0. $C_{18}H_{16}ON_4$ requires C, 71·0; H, 5·3; N, 18·4%).

We are indebted to the Medical Research Council for a grant and to Dr. F. Hawking of the National Institute for Medical Research, who arranged the biological tests for this and the preceding paper.

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[8] Albert and Linnell, *J.*, 1936, 1617.