585. *Trypanocides of the Phenanthridine Series. Part I. The Effect of Changing the Quaternary Grouping in Dimidium Bromide.*

By T. I. Watkins.

It has been found that a change of quaternary grouping in 2 : 7-diamino-10-methyl-9-phenylphenanthridinium bromide ("Dimidium bromide") has a marked effect on the curative power of the drug in *Trypanosoma congolense* infection of mice and cattle. Eight quaternary analogues have been prepared.

2 : 7-Diamino-10-methyl-9-phenylphenanthridinium bromide ("Dimidium bromide") (I; R = Me, A = Br) (Walls, *J.*, 1945, 294) shows high activity against *Trypanosoma congolense* in laboratory tests in mice and in the field in cattle. Although analogues containing a variety of substituents in different positions have been prepared, particularly by Walls (*J.*, 1938, 389, and subsequent papers), "Dimidium bromide" is still the drug of choice, within this group of compounds, for treatment of bovine trypanosomiasis. A quaternary group in the molecule is essential for activity as the unquaternised compound is inactive. Quaternisation of the ring nitrogen atom markedly increases its basicity and it might therefore be expected that interference with the basic strength of this nitrogen, by variation of the nature of the quaternary group, would lead to changes in the activity of the molecule. In fact, substitution of the methyl by other quaternary groupings was found to cause marked changes in the curative power of the drug. The compounds prepared [I; R = Et, A = Br; R = Pr^n, A = Br; R = Bu^n, A = Cl; R = *n*-amyl, A = Cl; R = *n*-hexyl, A = Cl; R = allyl, A = Br; R = $[CH_2]_3{\cdot}NHEt_2\}I$, A = I; R = $[CH_2]_3{\cdot}NEt_2Me\}I$, A = I] were tested against *Trypanosoma congolense* in mice and three of these compounds (I; R = Et, A = Br; R = Pr^n, A = Br; R = allyl, A = Br) were outstandingly active, being many times more active (and less toxic) than dimidium bromide. The pharmacological results obtained with mice and also the results of preliminary field trials with cattle in Africa have been published elsewhere (Watkins and Woolfe, *Nature*, 1952, **169**, 506; Woolfe, *Ann. Trop. Med. Parasit.*, in the press)].

The greatly increased activity of some of the compounds is probably a result of variation of the basic strength of the ring nitrogen atom, since introduction of alkyl groupings at

other positions has little effect (unpublished work). The changes in the basic strength of the ring nitrogen atom can, however, only be small and, since, in each case, dissociation of the drugs in aqueous solution at neutral pH's is nearly complete (>99·8%), the changes effected in concentration of cations will be insignificant and certainly not great enough to account for the magnitude of the enhancement in activity. Physical measurements (by R. Hughes) on aqueous solutions of the compounds at physiological pH's, however, indicate that there are marked changes in the small concentration of drug present in the pseudo-base form. Thus a change of methyl to ethyl quaternary grouping results in a 2- or 3-fold increase in concentration of the pseudo-base form at pH 6—9. An increased concentration of neutral component (either of the pseudo-base or ion-pair) may be responsible for an increased rate of diffusion across the cell membrane into the trypanosome cytoplasm (cf. Davson and Danielli, "Permeability of Natural Membranes," Cambridge Univ. Press 1943).

Some of the compounds had a prophylactic effect in mice considerably greater than that of dimidium bromide. One such, 10-allyl-2 : 7-diamino-9-phenylphenanthridinium bromide (I; R = allyl, A = Br), was examined further with the view to increasing its prophylactic power. A change of anion to give the more insoluble iodide, perchlorate, and 2-chloro-3 : 5-dinitrobenzoate did not extend the prophylactic period appreciably. Similarly, substitution in the 2- and the 7-amino-group to form bis(sodium formaldehyde bisulphite), diglucoside, and bis(tetra-acetyl glucosyl) derivatives, had little effect in increasing the prophylactic power.

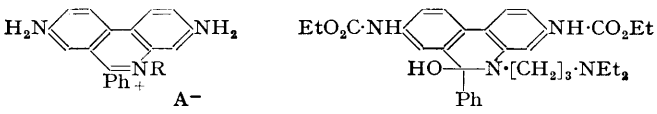
The yields of quaternary compounds obtained were low compared with that of the methyl compound, owing to the marked progressive decrease in rate of reaction of the alkylating agents as the length of the alkyl chain increased (cf. Preston and Jones, *J.*, 1912, **101**, 1931). This paralleled a decreasing stability of the reagents at the temperatures necessary for reaction.

The alkyl quaternary compounds were prepared from 2 : 7-biscarbethoxyamino-9-phenylphenanthridine and the appropriate toluene-*p*-sulphonic ester. The conditions for reaction were, as far as possible, so chosen that minimum decomposition of the toluene-*p*-sulphonic ester occurred. In every reaction, however, there was a partition of the phenanthridine between (*a*) the quaternisation reaction and (*b*) its fixation as a salt with the toluene-*p*-sulphonic acid formed by decomposition of the ester.

When attempts were made to prepare quaternary compounds with branched alkyl chains, the decomposition of the esters was much the faster reaction and in no case was the pure quaternary compound obtained. This was not surprising as the rate of quaternisation in these cases would be greatly decreased by steric hindrance.

In the preparation of the allyl quaternary compound, allyl iodide was used, as allyl toluene-*p*-sulphonate is known to decompose violently when heated (Gilman and Beaber, *J. Amer. Chem. Soc.*, 1925, **47**, 522).

The 3-bromopropyl quaternary salt prepared from 2 : 7-biscarbethoxyamino-9-phenylphenanthridine and 1 : 3-dibromopropane, when treated with diethylamine, afforded a diethylaminopropyl quaternary compound but this was isolated from the alkaline solution as the pseudo-base (II), which was then converted into the quaternary chloride hydrochloride. Further, the diethylamino-group could itself be quaternised. This reaction was



(I) (II) (III)

carried out with the pseudo-base, since attempts to liberate the diethylamino-group from the hydrochloride with alkali simultaneously converted the quaternary salt into the pseudo-base. From the reaction between the pseudo-base and methyl sulphate, 2 : 7-biscarbethoxyamino-10-3′-diethylaminopropyl-9-phenylphenanthridinium hydrogen sulphate 3′-methomethylsulphate was obtained. Hydrolysis of the pseudo-base (II) (or a corresponding salt) and its quaternary derivative proceeded normally in hot sulphuric acid solution.

The ethyl quaternary compound (I; R = Et, A = Br), which has been named "Ethidium bromide," has also been prepared from 2 : 7-dinitro-9-phenylphenanthridine by using excess of ethyl toluene-*p*-sulphonate as solvent. The effects of time and temperature on this reaction were critical as an apparent autocatalytic decomposition of the quaternary product set in after the attainment of an optimum yield and, on prolonged heating, extensive charring occurred. In the early stage of the reaction the unchanged phenanthridine exerts a "buffering" action in that it removes by salt formation the free toluene-*p*-sulphonic acid formed during decomposition of the ester. A point is reached in the reaction where no unchanged phenanthridine is present. The free toluene-*p*-sulphonic acid then initiates autocatalytic decomposition of the ester which may in turn be responsible for the observed increase in rate of decomposition of the quaternary product. For preparative purposes, therefore, it was found best to stop the reaction while there was still some unchanged dinitrophenanthridine present. This was recovered and the quaternised material was then reduced and isolation of the required material was facilitated by the ease with which the ethyl ether of its pseudo-base could be extracted into toluene. Re-extraction into acid converted the ether into a quaternary salt.

In studying the conditions for the quaternisation reaction the quaternary product was isolated as the pseudo-base (III).

Experimental

2 : 7-*Biscarbethoxyamino*-9-*phenylphenanthridine*.—This compound is described by Walls (*J.*, 1947, 67). It was found that a purer product was more readily obtained by reduction of 2 : 7-dinitro-9-phenylphenanthridine and subsequent carbethoxylation. Powdered 2 : 7-dinitro-9-phenylphenanthridine (14·3 g.) (Walls, *J.*, 1945, 294) and iron powder (17 g.) were stirred together in water (300 c.c.), alcohol (50 c.c.), and 5N-hydrochloric acid (2 c.c.), and the mixture was heated under reflux for 5 hours. The whole was then cooled, made alkaline with ammonia solution, and filtered, and the residue washed with water. 2 : 7-Diamino-9-phenylphenanthridine was extracted from the dried solid residue with chloroform and, on concentration of the extract, separated in yellow prisms, m. p. 197—198° (10·75 g., 91%) (Walls, *loc. cit.*, records m. p. 198°). A stirred solution of the diamine (10·4 g.) in dry pyridine (75 c.c.) was treated with ethyl chloroformate (7·5 c.c.) at 25—30°. The dark red solution was slowly stirred at room temperature for 5 hours, then poured into water, and the yellow solid collected. It crystallised from aqueous methanol as white needles, m. p. 138° (not sharp) (Found: C, 70·3; H, 5·2; N, 10·0. Calc. for $C_{25}H_{23}O_4N_3$: C, 69·9; H, 5·4; N, 9·8%). This compound, which is not described by Walls, was also obtained by his procedure. Heating with water for 2 hours converted it into Walls's high-melting compound, m. p. 218—220° (decomp.) (12·5 g., 80%).

Toluene-p-*sulphonic Esters*.—The following esters were prepared by the general method of Marvel and Sekera (*Org. Synth.*, 1940, **20**, 50): ethyl, *n*-propyl, *iso*propyl, *n*-butyl, *iso*butyl, *n*-amyl, *iso*amyl, and *n*-hexyl. Each was repeatedly fractionated to remove traces of toluene-*p*-sulphonyl chloride. Decomposition of the esters was catalysed by small amounts of the sulphonyl chloride during the quaternisation reactions, with consequent loss in yield of quaternary product.

General Method of Preparation of the Quaternary Compounds.—2 : 7-Biscarbethoxyamino-9-phenylphenanthridine and the sulphonic ester (2 mols.) were heated with slow stirring either alone or in nitrobenzene under various conditions of time and temperature. On cooling, the crude quaternary salt separated or was precipitated by dilution with ether. It was hydrolysed by heating it with 75—80% (w/w) sulphuric acid at 125—130° according to Walls's general method (*J.*, 1947, 67). The cooled mixture was added to water or, in the case of the higher alkyl compounds, to aqueous alcohol, and the pH was raised to 7—7·5 by dilute ammonia solution. The mixture was then heated and the pH again adjusted to 7—7·5 if necessary. Ammonium bromide (or ammonium chloride when the final product was required as a chloride) was added, and the precipitated tar was extracted with hot water. Ammonium bromide (or chloride) was again added to the filtered extract to precipitate the crude quaternary halide. Crystallisation from an alcoholic solvent yielded the pure quaternary salt.

In the reaction of 2 : 7-biscarbethoxyamino-9-phenylphenanthridine with *iso*propyl, *iso*butyl, and *iso*amyl toluene-*p*-sulphonates under the above conditions, no crystalline quaternary compound was isolated. There was much evolution of gas (olefin) throughout each experiment, even at relatively low temperatures, and the major product was 2 : 7-biscarbethoxyamino-9-

phenylphenanthridine toluene-*p*-sulphonate. If the hydrolysis with sulphuric acid was omitted, an 85—90% yield of recovered 2 : 7-biscarbethoxyamino-9-phenylphenanthridine was obtained by basification.

2 : 7-*Diamino*-10-*ethyl*-9-*phenylphenanthridinium Bromide*.—Quaternisation was effected in nitrobenzene solution during 2·5 hours at 155—160°. The *bromide* crystallised from methanol as dark red elongated plates, m. p. 248—249° (decomp.) (55% from 2 : 7-biscarbethoxyamino-9-phenylphenanthridine). Even after 10 hours' drying at 100° it retained 1·2% of water (Found : C, 62·8; H, 5·1; N, 10·3; Br, 19·85. $C_{21}H_{20}N_3Br$ containing 1·2% of water requires C, 63·2; H, 5·2; N, 10·5; Br, 20·05%. Found, for compound dried for 2 hours at 150°/1 mm. : N, 10·7; Br, 20·1; H_2O, 0·1. $C_{21}H_{20}N_3Br$ requires N, 10·65; Br, 20·3%). The *ethonaphthalene*-β-*sulphonate monohydrate* crystallised from methanol–propan-2-ol as dark red plates, m. p. 255° (decomp.) (Found : N, 7·7; H_2O, 3·7. $C_{31}H_{29}O_4N_3S$ requires N, 7·8; H_2O, 3·3%). (For the alternative method of preparation of this compound from 2 : 7-dinitro-9-phenylphenanthridine, see below.)

2 : 7-*Diamino*-9-*phenyl*-10-n-*propylphenanthridinium Bromide*.—Quaternisation was effected in nitrobenzene during 6 hours at 155—160°. The *bromide* was obtained in 25% yield as red plates (from methanol–propan-2-ol), m. p. 261—263° (decomp.) (Found : C, 64·6; H, 5·7; N, 10·35; Br, 19·0. $C_{22}H_{22}N_3Br$ requires C, 64·7; H, 5·4; N, 10·3; Br, 19·6%). The intermediate 2 : 7-*biscarbethoxyamino*-9-*phenyl*-10-n-*propylphenanthridinium toluene*-p-*sulphonate* crystallised from propan-2-ol or a large volume of water as orange needles, m. p. 220—222° (decomp.; slow heating) (Found : N, 6·7. $C_{35}H_{37}O_7N_3S$ requires N, 6·5%).

2 : 7-*Diamino*-10-n-*butyl*-9-*phenylphenanthridinium Chloride*.—Quaternisation was effected in nitrobenzene solution during 4 hours at 150°. The decomposition of ester became rapid after this time. The *chloride* was obtained in 22% yield as purple plates (from propan-2-ol), m. p. 238—240° (decomp.) (Found, in compound dried for 4 hours at 100° : N, 10·5; Cl, 9·6; H_2O, 1·7. $C_{23}H_{24}N_3Cl,0·5H_2O$ requires N, 10·8; Cl, 9·2; H_2O, 2·3. Found, in compound dried for 2 hours at 150°/1 mm. : N, 11·0; Cl, 9·2; H_2O, 0. $C_{23}H_{24}N_3Cl$ requires N, 11·1; Cl, 9·4%).

2 : 7-*Diamino*-10-n-*amyl*-9-*phenylphenanthridinium Chloride*.—Quaternisation was effected without a solvent during 4 hours at 150°. The *chloride* was obtained in 24% yield as purple plates (from propan-2-ol), m. p. 235—238° (decomp.; slow heating) (Found : N, 10·9; Cl, 8·7. $C_{24}H_{26}N_3Cl$ requires N, 10·7; Cl, 9·1%). Before hydrolysis partial purification of the intermediate 10-*n*-amyl-2 : 7-biscarbethoxyamino-9-phenylphenanthridinium toluene-*p*-sulphonate was effected by extraction of the crude product with warm methanol and precipitation with ether.

2 : 7-*Diamino*-10-n-*hexyl*-9-*phenylphenanthridinium Chloride*.—Quaternisation (without solvent; 6 hours; 150°) gave the *chloride* in 22% yield as purple plates (from propan-2-ol), m. p. 240—241° (decomp.; slow heating) (Found : N, 10·5; Cl, 8·4. $C_{25}H_{28}N_3Cl$ requires N, 10·3; Cl, 8·7%). Partial purification of the intermediate 2 : 7-biscarbethoxyamino-10-*n*-hexyl-9-phenylphenanthridinium toluene-*p*-sulphonate was effected as for the *n*-amyl compound.

10-*Allyl*-2 : 7-*diamino*-9-*phenylphenanthridinium Bromide*.—2 : 7-Biscarbethoxyamino-9-phenylphenanthridine and allyl iodide (2·5 mols.) were heated together with slow stirring in nitrobenzene at 95—100° for 4 hours. 10-*Allyl*-2 : 7-*biscarbethoxyamino*-9-*phenylphenanthridinium iodide*, which separated as orange needles during the heating, was collected after cooling of the mixture (66%). A specimen crystallised from ethanol–ether as orange needles, m. p. 220° (decomp.; slow heating) (Found : N, 7·0; I, 21·5. $C_{28}H_{28}O_4N_3I$ requires N, 7·0; I, 21·3%). To avoid complications arising from the liberation of iodine and hydrogen iodide by action of sulphuric acid during the hydrolysis, the crude iodide was converted in 92% yield into the corresponding methanesulphonate by silver methanesulphonate in aqueous methanol which had been acidified with methanesulphonic acid. It separated as yellow needles, m. p. *ca.* 220° (decomp.; slow heating). The methanesulphonate was then hydrolysed with 75—80% (w/w) sulphuric acid, and the product finally isolated as a quaternary *bromide* (49%), dark red (from water) or permanganate-coloured plates (from ethanol), m. p. 230—231° (decomp.) (Found : C, 64·85; H, 5·1; N, 10·35; Br, 19·2. $C_{22}H_{20}N_3Br$ requires C, 65·2; H, 5·0; N, 10·3; Br, 19·7%). 10-*Allyl*-2 : 7-*diamino*-9-*phenylphenanthridinium iodide*, prepared from the bromide, crystallised from water as small red needles, m. p. 234—235° (decomp.) (Found : N, 9·5; I, 27·6. $C_{22}H_{20}N_3I$ requires N, 9·3; I, 28·0%). 10-*Allyl*-2 : 7-*diamino*-9-*phenylphenanthridinium perchlorate*, prepared from the bromide, crystallised from hot water containing a little potassium perchlorate as small red needles, m. p. 250—252° (decomp.) (Found : N, 10·0. $C_{22}H_{20}O_4N_3Cl$ requires N, 9·8%). 10-*Allyl*-2 : 7-*diamino*-9-*phenylphenanthridinium* 2-*chloro*-3 : 5-*dinitrobenzoate*, prepared from the bromide, crystallised from ethanol as a microcrystalline red solid, m. p. 243—245° (decomp.) (Found : N, 12·5. $C_{29}H_{22}O_6N_5Cl$ requires N, 12·3%).

10-*Allyl*-2 : 7-*diamino*-9-*phenylphenanthridinium Iodide Bis*(*formaldehyde Bisulphite*) *Dihydrate*.—10-Allyl-2 : 7-diamino-9-phenylphenanthridinium bromide, sodium formaldehyde bisulphite (2·2 mols.), and sufficient water to form a solution at 100° were heated at this temperature for 2 hours. The solution was decanted from a small amount of tar, potassium iodide (*ca.* 4 mols.) added, and ethanol then added to the hot solution until crystallisation commenced. The purple *salt* obtained on cooling crystallised from aqueous ethanol as small purple plates, m. p. >310° (72%) (Found : N, 5·6; H_2O, 4·5. $C_{24}H_{22}O_6N_3S_2INa_2,2H_2O$ requires N, 5·8; H_2O, 5·0%).

10-*Allyl*-2 : 7-*bisglucosylamino*-9-*phenylphenanthridinium Bromide*.—10-Allyl-2 : 7-diamino-9-phenylphenanthridinium bromide (4 g.), glucose monohydrate (4·1 g., 2·1 mols.), acetic acid (1·2 c.c., 2 mols.), methanol (80 c.c.), and ammonium chloride (trace) were boiled for 3 minutes and the solution then kept at 40° for 5 hours. Ether was added to precipitate a red solid which was separated and extracted with cold water (30 c.c.). The filtered aqueous extract was evaporated to dryness in a vacuum and the residue crystallised from ethanol–ether as a microcrystalline red solid (70%), m. p. *ca.* 200° (with charring) (Found : N, 5·7. $C_{34}H_{40}O_{10}N_3Br$ requires N, 5·8%).

10-*Allyl*-9-*phenyl*-2 : 7-*bis*(*tetra-acetyl glucosylamino*)*phenanthridinium Bromide*.—The above glucoside in pyridine solution was slowly treated at 25° with acetic anhydride (11 mols.), and the solution then set aside overnight. Addition of ether precipitated a pink solid, and water was then added to the mixture until the solid dissolved. The aqueous layer was separated and extracted several times with ether until it deposited an orange-coloured solid, which was collected, washed with ice-water, and dried in a vacuum. It crystallised from ethanol–ether as a microcrystalline pink solid (78%), m. p. 185° (with charring) (Found : N, 4·3; Br, 8·3. $C_{50}H_{56}O_{18}N_3Br$ requires N, 3·9; Br, 7·5%).

10-3′-*Bromopropyl*-2 : 7-*biscarbethoxyamino*-9-*phenylphenanthridinium Bromide*.—2 : 7-Biscarbethoxyamino-9-phenylphenanthridine (22 g.) was heated with stirring with 1 : 3-dibromopropane (60 c.c.) in an oil-bath at 170—175° for 60 minutes. Yellow plates were deposited after 20 minutes. The mixture was cooled, and dry ether (40 c.c.) was added, and the mixture filtered. The yellow solid was washed with dry ether and dried at 100° [yield 30 g.; m. p. 195—200° (decomp.)]. Recrystallisation of the *bromide* from a large volume of ethanol yielded yellow plates, m. p. 235—236° (decomp.) (27·5 g., 84%) (Found : C, 52·7; H, 5·0; N, 6·5; Br, 23·8. $C_{28}H_{29}O_4N_3Br_2$ requires C, 53·3; H, 4·6; N, 6·7; Br, 25·4%).

2 : 7-*Biscarbethoxyamino*-10-3′-*diethylaminopropyl*-9-*phenylphenanthridinium Chloride Hydrochloride*.—The above bromopropyl quaternary compound (20 g.) was stirred under reflux with diethylamine (150 c.c.). The original compound dissolved and a white crystalline solid was deposited. The heating was continued for 1 hour and the mixture was filtered. The solid (8·1 g.) was diethylamine hydrobromide, plates (from ethanol–ether), m. p. 212° unchanged on admixture with the authentic material. The diethylamine filtrate was evaporated nearly to dryness under reduced pressure and the residue treated with water. The insoluble material (halogen-free) was purified by dissolution in acid and reprecipitation with alkali as the pseudo-base (II). It was washed with water and dried in a vacuum over phosphoric oxide and then dissolved in warm ethanolic hydrogen chloride, and warm ether was added to crystallisation point. The *salt* was obtained as yellow needles, which were recrystallised from ethanol–ether [12·5 g., 64%; m. p. 192—194° (decomp.)] (Found : C, 63·0; H, 6·8; N, 8·9; Cl, 10·9. $C_{32}H_{40}O_4N_4Cl_2$ requires C, 62·4; H, 6·5; N, 9·1; Cl, 11·5%).

2 : 7-*Diamino*-10-3′-*diethylaminopropyl*-9-*phenylphenanthridinium Iodide Hydriodide*.—The foregoing salt (8 g.) was added to sulphuric acid (16 c.c.) and, when the liberation of hydrogen chloride ceased, water (8 c.c.) was added. The solution was slowly stirred at 130°, for 30 minutes, and then cooled. It was poured into ice and water, and the pH of the resulting solution raised to 7·3 by addition of ammonia solution. On addition of potassium iodide a red solid was deposited. Crystallisation from water containing a little potassium iodide gave the dihydrate of the *salt* as red needles [5·5 g., 60%; m. p. 180—201° (decomp.)] (Found : C, 45·5; H, 5·2; N, 8·2; I, 36·2; H_2O, 5·6. $C_{26}H_{32}N_4I_2.2H_2O$ requires C, 45·2; H, 5·2; N, 8·1; I, 36·7; H_2O, 5·2%).

2 : 7-*Biscarbethoxyamino*-10-3′-*diethylaminopropyl*-9-*phenylphenanthridinium Hydrogen Sulphate* 3′-*Methomethylsulphate*.—2 : 7-Biscarbethoxyamino-10-3′-diethylaminopropyl-9 : 10-dihydro-9-hydroxy-9-phenylphenanthridine [pseudo-base (II)] (6 g.) was dissolved in ethyl acetate (100 c.c.) and ethanol (60 c.c.), and methyl sulphate (2·8 c.c., 2·5 mols.) was added. The solution was refluxed for 30 minutes and cooled but no deposit formed. It was accordingly diluted with benzene–ether, to give a yellow solid *salt* which crystallised from ethanol–ethyl acetate as

yellow acicular prisms (6·3 g.), m. p. indefinite, *ca.* 250° (decomp.) (Found : C, 53·7; H, 6·1; N, 7·4. $C_{34}H_{46}O_{12}N_4S_2$ requires C, 53·3; H, 6·0; N, 7·3%).

2 : 7-*Diamino*-10-3′-*diethylaminopropyl*-9-*phenylphenanthridinium Iodide Methiodide*.—A solution of the foregoing compound in sulphuric acid (10 c.c.) and water (5 c.c.) was heated at 130° for 30 minutes and the product isolated as a *di-iodide* by the usual procedure. It crystallised from water containing potassium iodide, in red needles, m. p. 210—230° (decomp.), depressed on admixture with 2 : 7-diamino-10-3′-diethylaminopropyl-9-phenylphenanthridinium iodide hydriodide (3·6 g., 92%) (Found : C, 48·1; H, 5·0; N, 8·3; I, 37·2. $C_{27}H_{34}N_4I_2$ requires C, 48·5; H, 5·1; N, 8·4; I, 38·0%).

Reaction between 2 : 7-*Dinitro*-9-*phenylphenanthridine and Ethyl Toluene*-p-*sulphonate*.—2 : 7-Dinitro-9-phenylphenanthridine was heated with ethyl toluene-*p*-sulphonate, the quantity of ester, time of heating and temperature being varied. The mixture when cold was treated with dry ether, which was then decanted from the precipitated gum. The ethereal extract was shaken with a known volume of dilute alkali, and the alkaline layer back-titrated with standard acid to determine the amount of free toluene-*p*-sulphonic acid present. The value so obtained did not represent the exact amount formed as some acidity would probably be lost through pyrolysis of the acid. The residue from the ether-treatment was extracted with boiling water, and the extract, after cooling, was made alkaline (pH >8) to precipitate the red pseudo-base (III), which was collected and weighed. The residue from the aqueous extract from experiments with reaction times of 4 hours or less consisted of practically pure 2 : 7-dinitro-9-phenylphenanthridine (m. p., mixed m. p. with authentic material, and analysis), but, in those experiments where the decomposition had set in with a more prolonged heating, the residues were charred and the phenanthridine was then extracted with hot 2-ethoxyethanol.

The results obtained when the phenanthridine was heated with 5 mols. of ester at 185° have been tabulated. The figures in parentheses indicate the estimated amount of decomposition of the ester (mols.) when the phenanthridine was omitted in the above experiments.

Time of heating (hours)	Mols. of ester decomposed (approx.) (≡ free acid titre)	Phenanthridine : Recovered (%)	Converted into pseudo-base (%)
2	0 (0·15)	65	30
3	*ca.* 0 (0·45)	51	43
4	0·12 (1·0)	31	61
5	0·3	16	68
6	0·48 (1·7)	5	71
7	—	*ca.* 0	53
8	2·5	0	33
9	—	0	*ca.* 10

2 : 7-*Diamino*-10-*ethyl*-9-*phenylphenanthridinium Bromide* (*Alternative Method of Preparation*).—2 : 7-Dinitro-9-phenylphenanthridine (20 g.) and ethyl toluene-*p*-sulphonate (60 g., *ca.* 5 mols.) were heated together under slow stirring for 4½ hours at 185°. The viscous solution was cooled and diluted with toluene or ether. The viscous residue was extracted with aqueous alcohol acidified with sulphuric acid. The residue from this extraction consisted of 2 : 7-dinitro-9-phenylphenanthridine (7·4 g., 37% recovery; m. p. 271—272°, unchanged on admixture with authentic material) (Found : N, 12·3. Calc. for $C_{19}H_{11}O_4N_3$: N, 12·2%). The hot aqueous-alcoholic extract was added to a hot stirred suspension of reduced iron (13 g.) in water (400 c.c.), and the mixture stirred under reflux for 4 hours. It was cooled, sodium hydroxide solution (40% w/w) added, and the pseudo-base ethyl ether extracted with toluene. The nearly black toluene layer was shaken with dilute hydrochloric acid solution, the pH of the acid layer was then raised to 7, and the required product salted out by addition of ammonium bromide. It crystallised from aqueous alcohol containing ammonium bromide as dark red plates (9·5 g.), m. p. 246—248°, raised to 248—250° by recrystallisation from methanol (Found, in material dried for 2 hours at 150°/1 mm. : N, 10·75; Br, 20·05. $C_{21}H_{20}N_3Br$ requires N, 10·65; Br, 20·3%).

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RESEARCH LABORATORIES,
BOOTS PURE DRUG CO. LTD., NOTTINGHAM.

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