378. *Potential Trypanocides of the* N-*Heterocyclic Series. Part VI.* Compounds derived from Phenanthridine-9-aldehydes.*

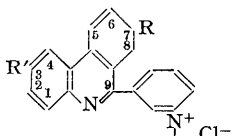
By A. G. CALDWELL.

Phenanthridine-9-aldehyde and five derivatives of it have been prepared by selenium dioxide oxidation of the 9-methylphenanthridines in dioxan. In five examples 1 : 2-di-9′-phenanthridinylethylenes have been isolated as by-products and their constitutions proved by synthesis. Phenanthridine-9-aldehyde reacts with 9-methylphenanthridine in dioxan, to give 1 : 2-di-9′-phenanthridinylethanol (IV), 1 : 2-di-9′-phenanthridinylethylene, and a little 1 : 2 : 3-tri-9′-phenanthridinylpropane (V). The alcohol (IV) is dehydrated by treatment with selenium dioxide in aqueous dioxan to form the diphenanthridinylethylene, and it is suggested that the by-products in the oxidations are produced in this way.

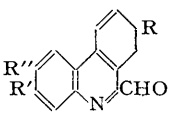
Girard derivatives (VI and VII) of some of the aldehydes and 1-methyl-2- and -4-[2′-(9″-phenanthridinyl)vinyl]pyridinium salts (VIII and IX) have no trypanocidal acitvity. 6-Amino-2-[2′-(3″-amino-9″-phenanthridinyl)-vinyl]-1-methylquinolinium bromide (X; R = R′ = NH_2, A = Br) is slightly active against *T. rhodesiense*.

THE structural features necessary to produce trypanocidal activity in phenanthridinium salts have been widely investigated, and in certain cases are now well defined (Brownlee, Goss, Goodwin, Woodbine, and Walls, *Brit. J. Pharmacol.*, 1950, **5**, 261). Although non-quaternary phenanthridine derivatives are in general inactive, it seemed of interest to investigate compounds having suitable substituents in an unquaternised phenanthridine system but with a quaternary salt grouping elsewhere in the molecule. Wien (*ibid.*, 1946, **1**, 65) has found (I; R = H, R′ = NH_2) (Petrow, *J.*, 1947, 1410) to have slight trypanocidal activity, although the 7-amino-isomer (I; R = NH_2, R′ = H) is inactive. Some compounds having the required features have now been prepared from substituted phenanthridine-9-aldehydes.

Phenanthridine-9-aldehyde (II; R = R′ = R″ = H) has previously been prepared by selenium dioxide oxidation of 9-methylphenanthridine in ethyl acetate (Ritchie, *J. Proc. Roy. Soc., New South Wales*, 1945, **78**, 164). When dioxan is the solvent, the yield of



(I)



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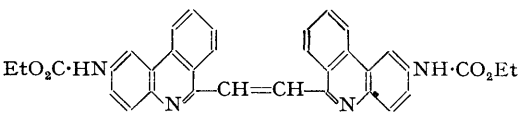


(III)

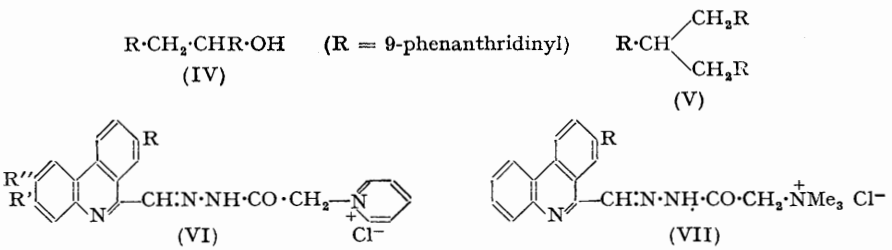
this aldehyde is somewhat inferior to that reported by Ritchie, but the method is satisfactory for substituted phenanthridine-9-aldehydes where solubilities in ethyl acetate are less favourable. The new phenanthridine-9-aldehydes prepared by this method are

* Part V, L. P. Walls, *J.*, 1950, 3511.

those with carbethoxyamino-groups in the 2-, 3-, 7-, and 2 : 7-positions, and the 3-nitro-derivative (II; R = R′ = H, R″ = NO_2). In the preparation of phenanthridine-9-aldehyde and its monosubstituted derivatives, high-melting by-products were isolated from the oxidations. These have been identified as 1 : 2-di-9′-phenanthridinylethylene derivatives [*e.g.*, (III) from the 3-carbethoxyamino-compound] by comparison with specimens synthesised by condensation of the aldehydes with their parent 9-methylphenanthridines in boiling acetic anhydride. Similar di-4′-quinolylethylenes have been reported as by-products in selenium dioxide oxidations of lepidine (Kaplan, *J. Amer. Chem. Soc.*, 1941, **63**, 2654) and 6-methoxylepidine (Walker, *J.*, 1947, 1684), but the by-product from quinaldine does not appear to be of this type (Kaplan, *loc. cit.*; Linsker and Evans, *J. Amer. Chem. Soc.*, 1946, **68**, 947; Buehler and Harris, *ibid.*, 1950, **72**, 5015; Brown and Hammick, *J.*, 1950, 628). Kaplan found that the use of old and unsublimed selenium dioxide in the oxidation of lepidine gave yields of up to 90% of by-product. In the oxidation of 9-methylphenanthridine, however, the use of freshly prepared, sublimed selenium dioxide gave a 7·5% yield of by-product, and three years old, unsublimed selenium dioxide gave 15% of by-product, with no great diminution in the yield of aldehyde.

When a slightly aqueous dioxan solution of 9-methylphenanthridine and phenanthridine-9-aldehyde was refluxed for some hours, three products were formed: 1 : 2-di-9′-phenanthridinylethanol (IV) in highest yield, 1 : 2-di-9′-phenanthridinylethylene, and a small amount of 1 : 2 : 3-tri-9′-phenanthridinylpropane (V). The alcohol (IV) was the only product of the reaction of 9-methylphenanthridine and phenanthridine-9-aldehyde in aqueous alcohol. It was slowly dehydrated in boiling dioxan, and rapidly by acetic anhydride, to diphenanthridinylethylene, and with excess of 9-methylphenanthridine in dioxan solution gave a small yield of the triphenanthridinylpropane (V). This compound was obtained in poor yield by the reaction of phenanthridine-9-aldehyde with excess of 9-methylphenanthridine in boiling dioxan, and in good yield from equivalent amounts of these reactants in the presence of sulphuric acid (cf. Tipson and Walton, *J. Amer. Chem. Soc.*, 1948, **70**, 892).

These experiments suggested that if the diphenanthridinylethylene were formed in the preparation of phenanthridine-9-aldehyde by a secondary reaction between the aldehyde and unoxidised 9-methylphenanthridine, the product should also contain some of the diphenanthridinylethanol (IV) or substances formed by its reaction with selenium dioxide. The formation of the triphenanthridinylpropane (V) by similar secondary reactions is much slower and its production in significant amount would not be expected. It was found that treatment of the diphenanthridinylethanol (IV) with selenium dioxide in boiling aqueous dioxan solution gave a high yield of 1 : 2-di-9′-phenanthridinylethylene, with the production of very little selenium. It seems probable that in the preparation of phenanthridine-9-aldehydes the main source of the ethylenic by-product is this ready dehydration by selenious acid of 1 : 2-di-9′-phenanthridinylethanols which are first formed by reaction of the phenanthridine-9-aldehyde with unchanged 9-methylphenanthridine.

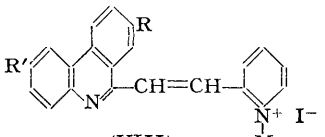


The diquaternary salt of 1 : 2-di-9′-phenanthridinylethylene was obtained in poor yield by using methyl sulphate in nitrobenzene, but no definite product was obtained on similar treatment of (III).

Phenanthridine-9-aldehyde and its 7-carbethoxyamino-derivative (II; R = NH·CO_2Et, R′ = R″ = H) condensed readily with Girard reagents P and T, to give the quaternary

salts (VI; R = H or NH·CO_2Et, R′ = R″ = H) and (VII; R = H or NH·CO_2Et). The similar 2 : 7-dicarbethoxyamino- (VI; R = R′ = NH·CO_2Et, R″ = H) and 3-nitro- (VI; R = R′ = H, R″ = NO_2) derivatives were also prepared. The use of acetic acid to catalyse these condensations (Girard and Sandulesco, *Helv. Chim. Acta*, 1936, **19**, 1095) was unnecessary, and in our experience aldehydes in general react rapidly and completely with the Girard reagents in hot alcohol (cf. Lederer and Nachmias, *Bull. Soc. chim.*, 1949, 400; Schindler and Reichstein, *Helv. Chim. Acta*, 1951, **34**, 521). An attempt to reduce (VI; R = R′ = H, R″ = NO_2) with ferrous hydroxide to the amino-compound (VI; R = R′ = H, R″ = NH_2) gave only a black tar and was not further investigated.

Phenanthridine-9-aldehyde reacted with α-picoline methiodide in presence of piperidine to yield the pyridinium salt (VIII; R = R′ = H). Use of 3- and 7-carbethoxyamino-phenanthridine-9-aldehydes similarly gave (VIII; R = H, R′ = NH·CO_2Et, and *vice versa*, respectively), which were hydrolysed to the amino-salts (VIII; R = H, R′ = NH_2 and *vice versa*). Reaction of these three aldehydes with γ-picoline methiodide and hydrolysis of the products provided a similar series of compounds represented by (IX). Attempts to use 3-nitrophenanthridine-9-aldehyde (II; R = R′ = H, R″ = NO_2) in such reactions gave only intractable gums, and 2 : 7-dicarbethoxyaminophenanthridine-9-aldehyde (II; R = R′ = NH·CO_2Et, R″ = H), which is very sparingly soluble in alcohol, gave an ill-defined product with γ-picoline methiodide. In order to introduce the 6-



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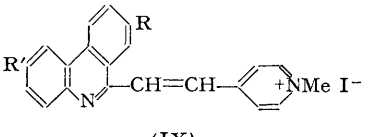
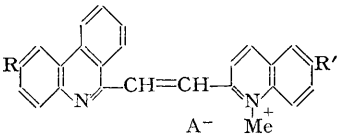


(IX)

(X)



aminoquinaldinium structure, which features in many of the trypanocidal styryl compounds (Browning, Cohen, Ellingworth, and Gulbransen, *Proc. Roy. Soc.*, 1929, *B*, **105**, 99), 3-carbethoxyaminophenanthridine-9-aldehyde (II; R = R′ = H, R″ = NH·CO_2Et) was condensed with 6-acetamidoquinaldine methochloride to yield (X; R = NH·CO_2Et, R′ = NHAc; A = Cl) which was hydrolysed to the diamino-salt (X; R = R′ = NH_2, A = Br).

Most of the compounds described above were examined by Dr. G. Brownlee and Dr. L. G. Goodwin and their colleagues for antibacterial and trypanocidal properties (*Trypanosoma congolense*, *T. rhodesiense*, and *T. cruzi*) respectively.

The Girard derivatives (VI; R = R′ = R″ = H) and (VII; R = H) had high antistreptococcal activity *in vitro* (active at a dilution of 1 : 1,000,000 in a nutrient broth), and the former was chemotherapeutic in experimental streptococcal infections in mice. The carbethoxyamino-compounds (VI; R = NH·CO_2Et, R′ = R″ = H) and (VII; R = NH·CO_2Et) were much less active. The phenanthridinylvinylpyridinium salts (VIII and IX) all possessed high antistreptococcal activity *in vitro* (inhibitory at 1 : 1,000,000 in broth), and were effective against streptococcal infections in mice, the amino- and carbethoxyamino-compounds being most active. 1 : 2-Di-9′-phenanthridinylethylene dimethochloride had high antistreptococcal activity *in vitro* and slight activity *in vivo*.

The only compound to exhibit trypanocidal activity was the quinolinium salt (X; R = R′ = NH_2, A = Br), which had slight activity against *T. rhodesiense*. It seems probable that the major factor in the production of this activity is the presence of the 6-aminoquinaldinium structure, which has also been found to product trypanocidal activity in certain 2-(2′-5″-acridinylvinyl)-1-methylquinolinium salts (Glen, Sutherland, and Wilson, *J.*, 1936, 1484; 1938, 654).

Experimental

Unless otherwise stated, the selenium dioxide used was commercial sublimed material. Compounds were dried at 100°/1 mm. before analysis.

Phenanthridine-9-aldehyde.—(*a*) A solution of 9-methylphenanthridine (Morgan and Walls, *J.*, 1931, 2450) (2 g.) and selenium dioxide (freshly prepared and sublimed) (1·2 g.) in dioxan (20 ml.) and water (0·5 ml.) was refluxed for 6½ hours. After filtration hot, the filtrate was diluted with an equal volume of alcohol and left overnight, whereupon reddish crystals (A) (150 mg.) separated. No more of this material was obtained by extracting the selenium with boiling nitrobenzene. The dioxan–alcohol filtrate was evaporated to dryness, the residue extracted with boiling N-hydrochloric acid (100 ml.), and the extract treated with charcoal and made alkaline with 5N-sodium hydroxide, to give a pale yellow solid (1·5 g.), m. p. 128—131°. The pure aldehyde (1·2 g.) crystallised from acetone–light petroleum (b. p. 60—80°) in pale yellow needles, m. p. 141—141·5° (Ritchie, *loc. cit.*, gives m. p. 139°).

The by-product A crystallised from much xylene and then nitrobenzene, giving deep yellow needles (contaminated with selenium) of 1 : 2-di-9′-phenanthridinylethylene, m. p. 304—305°, undepressed in admixture with an authentic specimen (see below).

(*b*) Repetition of the above experiment with 3-years old, unsublimed selenium dioxide yielded 1·1 g. of the aldehyde, m. p. 139—141°. The yield of crude by-product (obtained partly from the dioxan solution and partly by extraction of the selenium with boiling nitrobenzene) was 300 mg., crystallising from nitrobenzene in yellow needles, m. p. 300—303°.

The semicarbazone of the aldehyde had m. p. 240° (decomp.) [Ritchie, *loc. cit.*, gives m. p. 238° (decomp.)]. The *hydrochloride* of the semicarbazone crystallised from methanol in small yellow prismatic needles, m. p. *ca.* 215° (decomp.) (Found: N, 18·3; Cl, 11·8. $C_{15}H_{13}ON_4Cl$ requires N, 18·65; Cl, 11·8%). It was readily soluble in cold water, the solution depositing the semicarbazone when warmed.

Prepared from the aldehyde and Girard reagent P in refluxing alcoholic solution, 1-[2-*oxo*-2-N′-(9-*phenanthridinylmethylene*)*hydrazinoethyl*]*pyridinium chloride* (VI; R = R′ = R″ = H) crystallised from methanol in fine pale yellow needles, m. p. 245° (decomp.) (Found: N, 15·05; Cl, 9·5. $C_{21}H_{17}ON_4Cl$ requires N, 14·85; Cl, 9·45%). Similarly, Girard reagent T gave NNN-*trimethyl*-N-[2-*oxo*-2-N″-(9-*phenanthridinylmethylene*)*hydrazinoethyl*]*ammonium chloride* (VII; R = H) as pale yellow needles (from ethanol), m. p. *ca.* 240° (decomp.) (Found: N, 15·8; Cl, 10·25. $C_{19}H_{21}ON_4Cl$ requires N, 15·7; Cl, 9·95%).

7-Carbethoxyaminophenanthridine-9-aldehyde.—7-Carbethoxyamino-9-methylphenanthridine (Walls, *J.*, 1947, 67) (5 g.) in dioxan (125 ml.) and water (5 ml.) was heated under reflux with selenium dioxide (2 g.) for 6 hours. The *aldehyde* (3·8 g.) crystallised from the hot solution after filtration of the selenium (2 g.), the last traces of which were removed by recrystallisation from a large volume of acetone to give bright yellow needles, m. p. 240° (decomp.) (Found: C, 69·65; H, 4·55; N, 9·4. $C_{17}H_{14}O_3N_2$ requires C, 69·35; H, 4·8; N, 9·5%). The selenium residues (2 g.) were extracted with boiling nitrobenzene, from which brown solid crystallised. Recrystallisation twice from pyridine gave deep yellow needles (350 mg.) (contaminated with selenium) of 1 : 2-di-(7-carbethoxyamino-9-phenanthridinyl)ethylene, m. p. 278° (decomp.), undepressed by an authentic specimen (see below).

The *semicarbazone* of the aldehyde, prepared with semicarbazide hydrochloride in pyridine solution, crystallised from aqueous dimethylformamide in fine pale yellow needes, m. p. 275—280° (decomp.) (Found: N, 20·05. $C_{18}H_{17}O_3N_5$ requires N, 19·95%). Its *hydrochloride* formed a gel, which dried to a red solid, m. p. *ca.* 215° (decomp.) (Found: N, 17·8; Cl, 8·65. $C_{18}H_{18}O_3N_5Cl$ requires N, 18·05; Cl, 9·15%). The salt was somewhat soluble in cold water, but the semicarbazone was immediately precipitated on warming of the solution.

The crude aldehyde (5 g.) and Girard reagent P (3·5 g.) were heated under reflux in methanol (250 ml.) for 30 minutes. The solution (treated with charcoal) deposited yellow needles (4·5 g.) of the *chloride* (VI; R = NH·CO_2Et, R′ = R″ = H), m. p. *ca.* 260° (decomp.) (Found: N, 14·65; Cl, 7·55. $C_{24}H_{22}O_3N_5Cl$ requires N, 15·1; Cl, 7·65%).

Prepared similarly with the Girard reagent T, the *trimethylammonium* derivative (VII; R = NH·CO_2Et) crystallised from methanol in yellow needles, m. p. 230° (effervescence) (Found: N, 15·7; Cl, 7·95. $C_{22}H_{26}O_3N_5Cl$ requires N, 15·8; Cl, 8·0%).

2-Carbethoxyaminophenanthridine-9-aldehyde.—Prepared by selenium dioxide oxidation of 2-carbethoxyamino-9-methylphenanthridine (Caldwell and Walls, *J.*, 1948, 188) (3·5 g.) as described for the 7-carbethoxyamino-compound, the pure *aldehyde* (2·25 g.) formed yellow needles, m. p. 198—199°, from alcohol or plates from dioxan (Found: C, 69·4; H, 4·65; N, 9·7.

$C_{17}H_{14}O_3N_2$ requires C, 69·35; H, 4·8; N, 9·5%). 1 : 2-Di-(2-carbethoxyamino-9-phenanthridinyl)ethylene (120 mg.) was obtained by extraction of the selenium residues with boiling nitrobenzene, from which it crystallised in orange needles (contaminated with selenium), m. p. 310° (put in bath at 295°), undepressed by an authentic specimen (see below).

3-*Carbethoxyaminophenanthridine-9-aldehyde*, obtained similarly [27·8 g. of pure aldehyde from 40 g. of the 9-methyl compound (Walls, *J.*, 1946, 1031)], crystallised from benzene in yellow needles, m. p. 188—189° (Found : C, 69·4; H, 4·9; N, 9·7%). The corresponding diphenanthridinylethylene (3·5 g.) formed yellow needles (contaminated with selenium), m. p. above 340°, from nitrobenzene.

Similarly, 3-*nitrophenanthridine-9-aldehyde* (3·3 g.), deep yellow needles, m. p. 241—242°, from benzene, was prepared from the 9-methyl compound (Morgan and Walls, *J.*, 1932, 2228) (5 g.) (Found : C, 66·55; H, 3·05; N, 11·3. $C_{14}H_8O_3N_2$ requires C, 66·65; H, 3·2; N, 11·1%). The by-product 1 : 2-di-(3-nitro-9-phenanthridinyl)ethylene crystallised from nitrobenzene or pyridine in deep yellow fibrous needles, unmolten at 360°.

The *pyridinium chloride* (VI; R = R′ = H, R″ = NO_2) formed yellow matted needles, m. p. 260° (decomp.), from aqueous acetone (Found : Cl, 8·1. $C_{21}H_{16}O_3N_5Cl$ requires Cl, 8·4%).

2 : 7-*Dicarbethoxyaminophenanthridine-9-aldehyde.*—2 : 7-Dicarbethoxyamino-9-methylphenanthridine (Walls, *J.*, 1947, 71) (2 g.) and selenium dioxide (610 mg.) in dioxan (80 ml.) and water (2 ml.) were heated under reflux for 7 hours. The filtered solution deposited greenish solid (1·6 g.) on cooling. The substance could not be freed from selenium by crystallisation, and accordingly it (1 g.) was boiled with 2N-hydrochloric acid (1 l.) and treated with charcoal. The cooled filtrate deposited fluffy orange needles, which when boiled with sodium hydrogen carbonate solution became bright yellow. Recrystallisation from dioxan gave bright yellow plates or needles (450 mg.) of the pure *aldehyde*, m. p. 270—275° (decomp.) (Found : C, 62·95; H, 5·15; N, 11·45. $C_{20}H_{19}O_5N_3$ requires C, 63·0; H, 5·0; N, 11·05%).

The crude aldehyde (1 g.) and Girard reagent P (500 mg.) in alcohol (100 ml.) were heated under reflux for 4 hours. The suspended solid (1·25 g.) was extracted with boiling water (*ca.* 50 ml.), and the extract treated with charcoal and diluted to *ca.* 400 ml. with dioxan. On scratching and cooling of the solution deep yellow crystals (800 mg.) were obtained. Recrystallised from methanol, 1-[2-N′-(2 : 7-*dicarbethoxyaminophenanthridinylmethylene)hydrazino-2-oxoethyl]pyridinium chloride* (VI; R = R′ = $NH{\cdot}CO_2Et$, R″ = H) formed bright yellow flat needles, shrinking and darkening from *ca.* 220°, but unmolten at 350° (Found : N, 15·6; Cl, 6·5. $C_{27}H_{27}O_5N_6Cl$ requires N, 15·25; Cl, 6·45%).

1 : 2-*Di-9′-phenanthridinylethylene.*—9-Methylphenanthridine (500 mg.) and phenanthridine-9-aldehyde (500 mg.) were heated under reflux in acetic anhydride (4 ml.) for 10 minutes, during which time 1 : 2-*di-9′-phenanthridinylethylene* (800 mg.) separated rapidly from the solution. It crystallised from nitrobenzene in deep yellow needles, m. p. 305—306° (Found : C, 87·9; H, 4·6; N, 7·4. $C_{28}H_{18}N_2$ requires C, 87·9; H, 4·75; N, 7·35%).

The following were prepared similarly in high yields, and crystallised from nitrobenzene :

1 : 2-*Di-(7-carbethoxyamino-9-phenanthridinyl)ethylene*, deep yellow needles, m. p. 280° (decomp.) (Found : C, 73·4; H, 4·95; N, 10·05. $C_{34}H_{28}O_4N_4$ requires C, 73·35; H, 5·05; N, 10·05%).

1 : 2-*Di-(2-carbethoxyamino-9-phenanthridinyl)ethylene*, orange needles, m. p. 310° (decomp.) (in bath at 295°) or above 360° (slow heating) (Found : C, 73·15; H, 5·05; N, 10·0%).

1 : 2-*Di-(3-carbethoxyamino-9-phenanthridinyl)ethylene*, yellow needes, unmolten at 340° (Found : C, 73·45; H, 4·8; N, 10·0%).

1 : 2-*Di-(3-nitro-9-phenanthridinyl)ethylene*, deep orange needles, unmolten at 360° (Found : C, 70·5; H, 3·4; N, 11·35. $C_{28}H_{16}O_4N_4$ requires C, 71·15; H, 3·4; N, 11·85%).

Reaction of 9-Methylphenanthridine with Phenanthridine-9-aldehyde in Dioxan.—A solution of 9-methylphenanthridine (1 g.) and phenanthridine-9-aldehyde (1 g.) in dioxan (20 ml.) and water (0·5 ml.) was refluxed for 7 hours, during which yellow solid separated. After cooling, the deep yellow solid (A) was collected (400 mg.), m. p. *ca.* 270° (decomp.). The dioxan mother-liquor was diluted with alcohol and set aside overnight, giving a yellow solid (B) (450 mg.), m. p. *ca.* 200°. The filtrate was evaporated to dryness and the residue boiled with alcohol to give an insoluble yellow solid (C) (450 mg.), m. p. *ca.* 180—185°.

Solid A was recrystallised twice from nitrobenzene and once from pyridine, to give yellow needles (300 mg.) of 1 : 2-di-9′-phenanthridinylethylene, m. p. and mixed m. p. 302—304.°

Solid B was extracted with boiling benzene, leaving an insoluble residue (50 mg.), m. p. 262—266°, undepressed by 1 : 2 : 3-tri-9′-phenanthridinylpropane (V) (see below). The filtrate

on evaporation and cooling deposited 1 : 2-di-9′-phenanthridinylethanol (IV) (200 mg.), m. p. 190—192°, undepressed by an authentic specimen (see below).

Solid C, recrystallised from benzene and then chloroform–light petroleum (b. p. 60—80°), gave more 1 : 2-di-9′-phenanthridinylethanol (250 mg.), m. p. 191—192°.

1 : 2-*Di*-9′-*phenanthridinylethanol* (IV).—A solution of 9-methylphenanthridine (1·5 g.) and phenanthridine-9-aldehyde (1·5 g.) in 80% alcohol (30 ml.) was boiled for 3½ hours. The pale yellow solid which had separated (1·95 g.) had m. p. 191—192°, unchanged by recrystallisation, but two crystallisations from benzene and one from chloroform–light petroleum (b. p. 60—80°) were necessary to remove the yellow colour and give fine colourless needles of 1 : 2-*di*-9′-*phenanthridinylethanol* (Found: C, 83·85; H, 4·85; N, 7·15. $C_{28}H_{20}ON_2$ requires C, 83·95; H, 5·05; N, 7·0%).

When this substance (200 mg.) in dioxan (10 ml.) was boiled for 6 hours, 1 : 2-di-9′-phenanthridinylethylene (30 mg.) was obtained.

A little of the substance was treated with boiling acetic anhydride. The clear solution rapidly deposited 1 : 2-di-9′-phenanthridinylethylene.

Dehydration of 1 : 2-*Di*-9′-*phenanthridinylethanol with Selenious Acid.*—A solution of 1 : 2-di-9′-phenanthridinylethanol (900 mg.) in dioxan (27 ml.) and water (1 ml.) was refluxed with selenium dioxide (freshly prepared and sublimed) (250 mg.) for 4 hours. The solution was originally green and contained suspended solid, which gradually dissolved to a red solution and more dark solid was precipitated. The mixture was filtered hot. The residue was recrystallised from dioxan (charcoal), to give deep yellow needles (600 mg.), m. p. 302—304°, undepressed by authentic 1 : 2-di-9′-phenanthridinylethylene. The original dioxan filtrate, on cooling, deposited more (100 mg.) of the same compound.

1 : 2 : 3-*Tri*-9′-*phenanthridinylpropane* (V).—9-Methylphenanthridine (2 g.), phenanthridine-9-aldehyde (1 g.), and concentrated sulphuric acid (0·15 ml.) were heated at 145° (bath-temp.) for 1½ hours. The cooled mixture was crushed and warmed on the steam-bath with 2N-sodium hydroxide. The yellow solid was collected and boiled with alcohol, and the mixture filtered whilst hot. Recrystallisation of the residue from pyridine (charcoal) gave a pale yellow solid (2·1 g.), m. p. 260—263°. Further crystallisation from pyridine gave small colourless plates, m. p. 264—266° of the *product* with one molecule of pyridine of crystallisation [Found: C, 86·2; H, 5·1; N, 8·6; loss at 150°/1 mm., 12·05 (none at 100°). $C_{42}H_{29}N_3,C_5H_5N$ requires C, 86·2; H, 5·25; N, 8·55; C_5H_5N, 12·1%]. The pyridine was removed by solution in a mixture of alcohol and 2N-hydrochloric acid, reprecipitation with alkali, and crystallisation twice from dioxan, to give the solvent-free *triamine* as small plates, m. p. 264—266° (Found: C, 87·55; H, 5·05; N, 7·5. $C_{42}H_{29}N_3$ requires C, 87·6; H, 5·1; N, 7·3%).

The same compound (80 mg.) was obtained by 6 hours' refluxing of 1 : 2-di-9′-phenanthridinylethanol (200 mg.) and 9-methylphenanthridine (500 mg.) in dioxan (10 ml.). It was also produced (400 mg.) when a dioxan (20 ml.) solution of phenanthridine-9-aldehyde (500 mg.) and 9-methylphenanthridine (2·5 g.) was boiled for 6 hours.

1 : 2-*Di*-9′-*phenanthridinylethylene Dimethochloride.*—1 : 2-Di-9′-phenanthridinylethylene (8·0 g.) in nitrobenzene (80 ml.) was treated with methyl sulphate (12 ml.) at 180° for 5 minutes. The solid which crystallised on cooling was dissolved in water, and hydrochloric acid was added to precipitate yellow solid (5·6 g.), m. p. *ca.* 220° (decomp.). Recrystallisation from ethanol gave the diquaternary *salt* (3·0 g.) as small yellow needles, m. p. 255° (decomp.) (Found: N, 5·7; Cl, 14·85. $C_{30}H_{24}N_2Cl_2$ requires N, 5·8; Cl, 14·7%).

1-*Methyl*-2-[2′-(9″-*phenanthridinyl*)*vinyl*]*pyridinium Iodide* (VIII; R = R′ = H).—A solution of α-picoline methiodide (2·4 g.) and phenanthridine-9-aldehyde (3·0 g.) in methanol (40 ml.) with piperidine (0·5 ml.) was refluxed for 2½ hours. The almost pure *product* (2·25 g.), which had separated, crystallised from water or alcohol as fine yellow needles, m. p. 224—226° (effervescence) (Found: N, 6·4; I, 30·0. $C_{21}H_{17}N_2I$ requires N, 6·6; I, 29·95%).

From γ-picoline methiodide (5 g.), phenanthridine-9-aldehyde (4·6 g.), and piperidine (0·8 ml.) in methanol (50 ml.), heated under reflux for 4 hours, was obtained 1-*methyl*-4-[2′-(9″-*phenanthridinyl*)*vinyl*]*pyridinium iodide* (IX; R = R′ = H) (6·75 g.), forming deep yellow needles, m. p. 295° (decomp.), from methanol (Found: N, 6·35; I, 29·95%).

2-[2′-(7″-*Carbethoxyamino*-9″-*phenanthridinyl*)*vinyl*]-1-*methylpyridinium Iodide* (VIII; R = NH·CO_2Et, R′ = H).—A mixture of α-picoline methiodide (600 mg.), 7-carbethoxyamino-phenanthridine-9-aldehyde (750 mg.), piperidine (0·1 ml.), and alcohol (10 ml.) was refluxed for 3 hours, during which time the aldehyde dissolved and was replaced by the *product* (1·05 g.) which crystallised from methanol in orange needles, m. p. 248° (decomp.) (Found: N, 8·3; I, 24·9. $C_{24}H_{22}O_2N_3I$ requires N, 8·2; I, 24·85%).

Hydrolysis of this salt with concentrated sulphuric acid (2·8 ml.) and water (2·5 ml.) at 150° for 30 minutes, and treatment of the diluted and neutralised (aqueous ammonia) solution with potassium iodide, gave 2-[2′-(7″-*amino*-9″-*phenanthridinyl*)*vinyl*]-1-*methylpyridinium iodide* (VIII; R = NH_2, R′ = H), forming deep red needles, m. p. 234—235°, from methanol (Found: N, 9·7. $C_{21}H_{18}N_3I$ requires N, 9·55%).

In the same fashion was prepared 4-[2′-(7″-*carbethoxyamino*-9″-*phenanthridinyl*)*vinyl*]-1-*methylpyridinium iodide* (IX; R = NH·CO_2Et, R′ = H) (900 mg.), orange needles, m. p. 265° (decomp.), from water (Found: N, 8·15; I, 24·85. $C_{24}H_{22}O_2N_3I$ requires N, 8·2; I, 24·85%), hydrolysed to 4-[2′-(7″-*amino*-9″-*phenanthridinyl*)*vinyl*]-1-*methylpyridinium iodide* (IX; R = NH_2, R′ = H), small red needles, m. p. 257—258°, from water (Found: N, 9·6: I, 29·2. $C_{21}H_{18}N_3I$ requires N, 9·55; I, 28·9%).

2-[2′-(3″-*Carbethoxyamino*-9″-*phenanthridinyl*)*vinyl*]-1-*methylpyridinium Iodide* (VIII; R = H, R′ = NH·CO_2Et).—Obtained in 1·7 g. yield by 4 hours' refluxing of α-picoline methiodide (1·2 g.) and 3-carbethoxyaminophenanthridine-9-aldehyde (1·5 g.) with piperidine (0·1 ml.) in alcohol (20 ml.), the *iodide* crystallised from methanol in orange needles, m. p. 242° (decomp.) (Found: N, 8·15; I, 25·2. $C_{24}H_{22}O_2N_3I$ requires N, 8·2; I, 24·85%). When this carbethoxyamino-compound was hydrolysed with sulphuric acid, 2-[2′-(3″-*amino*-9″-*phenanthridinyl*)*vinyl*]-1-*methylpyridinium iodide* (VIII; R = H, R′ = NH_2) was obtained as dark red needles, m. p. 215° (decomp.), from methanol (Found: N, 9·2. $C_{21}H_{18}N_3I$ requires N, 9·55%).

4-[2′-(3″-*Carbethoxyamino*-9″-*phenanthridinyl*)*vinyl*]-1-*methylpyridinium iodide* (IX; R = H, R′ = NH·CO_2Et) (7·7 g.) was prepared from γ-picoline methiodide (4 g.), 3-carbethoxyaminophenanthridine-9-aldehyde (5 g.), and piperidine (0·3 ml.) in alcohol (50 ml.) under reflux for 3 hours. It crystallised from methanol in orange needes, m. p. 255° (decomp.) (Found: N, 7·9; I, 25·15. $C_{24}H_{22}O_2N_3I$ requires N, 8·2; I, 24·85%). Hydrolysis with sulphuric acid, etc., gave 4-[2′-(3″-*amino*-9″-*phenanthridinyl*)*vinyl*]-1-*methylpyridinium bromide* (IX; R = H, R′ = NH_2; bromide), forming deep red needles, m. p. 270—271°, from methanol (Found: Br, 20·15. $C_{21}H_{18}N_3Br$ requires Br, 20·4%).

6-*Acetamido*-2-[2′-(3″-*carbethoxyamino*-9″-*phenanthridinyl*)*vinyl*]-1-*methylquinolinium Chloride* (X; R = NH·CO_2Et, R′ = NHAc, A = Cl).—A solution of 6-acetamidoquinaldine methochloride (Browning, Cohen, Ellingworth, and Gulbransen, *Proc. Roy. Soc.*, 1926, *B*, **100**, 302) (4·5 g.), 3-carbethoxyaminophenanthridine-9-aldehyde (5 g.), and piperidine (0·1 ml.) in alcohol (50 ml.) was refluxed for 3 hours. The *product* (7·5 g.) which had separated was washed with acetone and recrystallised from methanol, forming bright red needles, m. p. 260° (decomp.) (Found: N, 10·95; Cl, 6·75. $C_{30}H_{27}O_3N_4Cl$ requires N, 10·65; Cl, 6·75%).

6-*Amino*-2-[2′-(3″-*amino*-9″-*phenanthridinyl*)*vinyl*]-1-*methylquinolinium bromide* (X; R = R′ = NH_2, A = Br) was obtained by hydrolysis of the carbethoxyamino-salt with sulphuric acid, etc. It crystallised from a large volume of methanol as small deep red plates with a green reflex, decomposing gradually above 280° without melting (Found: N, 12·1; Br, 17·6. $C_{25}H_{21}N_4Br$ requires N, 12·25; Br, 17·5%).

Thanks are due to Dr. L. P. Walls for his interest in this work, to Mr. A. Bennett for the microanalyses, and to Mr. W. E. King for valuable technical assistance.

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[*Received, January 25th,* 1952.]