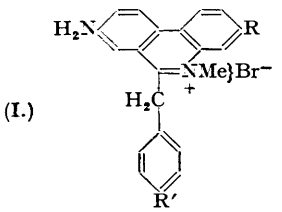
518. *Potential Trypanocides of the N-Heterocyclic Series. Part IV. 9-Benzoyl- and 9 : 10-Dihydro-phenanthridines.*

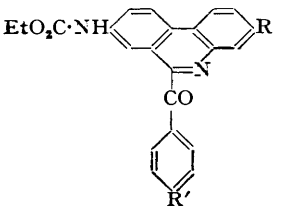
By A. G. CALDWELL, F. C. COPP, and L. P. WALLS.

7-Carbethoxyamino-9-*p*-nitrobenzoylphenanthridine (II; R = H, R′ = NO_2) was obtained by selenium dioxide oxidation of the corresponding 9-benzylphenanthridine. Reduction of its quaternary salt (III) with ferrous hydroxide gave the corresponding amino-phenanthridinium salt (V), but the iron–water method unexpectedly gave 7-carbethoxyamino-9-*p*-aminobenzoyl-10-methyl-9 : 10-dihydrophenanthridine (VIII). This anomalous reduction also occurred with 2 : 7-biscarbethoxyamino-9-benzoyl-10-methylphenanthridinium chloride. Catalytic reduction reduces other phenanthridinium salts to the 9 : 10-dihydrophenanthridines, several of which are readily converted into quaternary salts (XIII). The 9-benzoyl compounds have much feebler trypanocidal properties than the corresponding 9-phenyl compounds. The quaternary salts (XIII) are inactive.

EARLIER work in this series has established the importance, for trypanocidal activity, of the nature of the 9-substituent in phenanthridinium salts. The inactivity of the 9-*p*-aminobenzyl compound (I; R = H, R′ = NH_2) (Caldwell and Walls, *J.*, 1948, 188) might have been due to its spatial configuration, but the subsequent discovery (*J.*, 1950, 62) that the 9-benzyl analogue (I; R = NH_2, R′ = H) of Dimidium bromide is highly active renders this unlikely. The corresponding benzoyl salts (VI) and (X) have now been prepared. In the former of this pair, as in the 9-*p*-aminobenzyl compound, the possibility of additional ionic resonance between the amino-group of the 9-substituent and the hetero-N-atom is excluded.



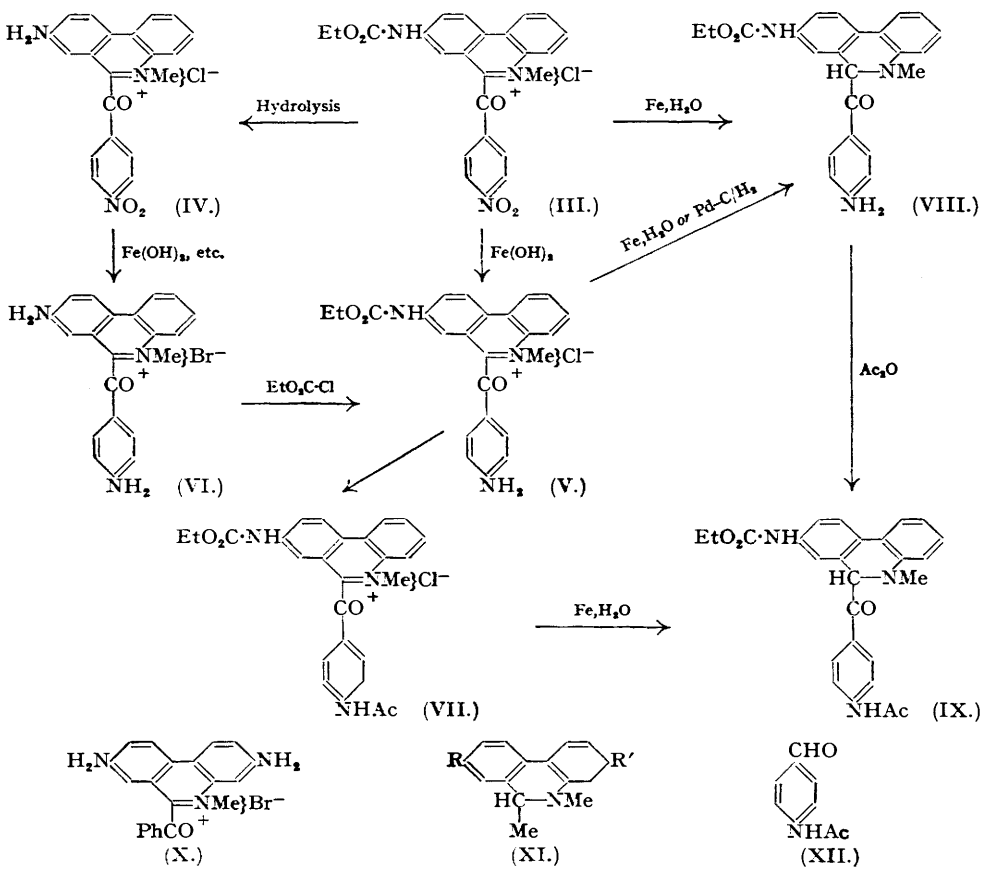
(I.)



(II.)

7-Carbethoxyamino-9-*p*-nitrobenzoylphenanthridine (II; R = H, R′ = NO_2) was obtained in 70% yield by selenium dioxide oxidation of the corresponding benzyl compound (*J.*, 1948, 191), and converted into the quaternary salt (III) by the nitrobenzene–methyl sulphate method. Hydrolysis then yielded the nitroamino-salt (IV), but reduction of (III) and (IV) to the corresponding amino-salts presented some difficulty (see chart). The desired products, (V) and (VI) respectively, were eventually obtained in good yield by the ferrous hydroxide method (*J.*, 1950, 41). The *p*-amino-group of these amino-salts reacts differently from that of the analogous 9-*p*-aminophenyl compounds; an aqueous solution of (V) was unaffected by ethyl chloroformate (Walls, *J.*, 1946, 1031) and, in spite of the presence of a free amino-group, addition of hydrochloric acid precipitated it unchanged. Likewise only one amino-group of (VI) reacted in aqueous solution with ethyl chloroformate with formation of (V) which, however, did give an acetyl derivative (VII) with acetic anhydride. The biscarbethoxyamino-salt (VII; NH·CO_2Et for NHAc) was obtained by oxidation of 7-carbethoxyamino-9-*p*-carbethoxy-aminobenzylphenanthridine (see Experimental section) with selenium dioxide to (II; R = H, R′ = NH·CO_2Et), and reaction of the product with methyl sulphate.

The iron–water method of reduction, which has been successfully used for the reduction of nitro-groups in a wide range of quaternary salt in this series, behaved anomalously with 7-carbethoxyamino-9-*p*-nitrobenzoyl-10-methylphenanthridinium chloride (III), the product being a crystalline base which did not melt sharply even after recrystallisation. On acetylation it gave a characteristic orange-red acetyl derivative, which also did not melt sharply. It seemed likely that both the nitro-group and the 9 : 10-double bond of (III) had been reduced to yield (VIII), and this explanation was supported by the following evidence. The amino-salt (V), as obtained by the ferrous hydroxide method, was converted by iron–water into an insoluble base, yielding the same acetyl derivative (IX), which was also obtained by iron–water reduction of the salt (VII). In the presence of palladium–charcoal catalyst and sodium acetate (see below) the amino-salt (V) absorbed one molecule of hydrogen, giving the same product, again identified as the acetyl derivative (IX). A 9 : 10-dihydrophenanthridine of this structure would

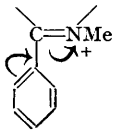


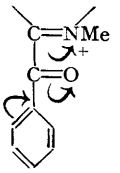
be expected to exhibit light absorption corresponding to the sum of the absorptions of its two chromophores (on the assumption that the effect of their interaction is small; cf. Braude, *J.*, 1949, 1902). In fact, the ultra-violet light absorption of the acetyl derivative (IX) is closely similar to that calculated for an equimolecular mixture of 7-acetamido-9 : 10-dimethyl-9 : 10-dihydrophenanthridine (XI; R = NHAc, R′ = H) (see below) and *p*-acetamidobenzaldehyde (XII) (Fig. 1).

For the preparation of the related series, 2 : 7-biscarbethoxyamino-9-benzoylphenanthridine (II; R = NH·CO_2Et, R′ = H) was obtained by selenium dioxide oxidation of the corresponding benzyl compound (*J.*, 1950, 62). The quaternary salt derived from it was hydrolysed to the diamino-salt (X) and readily reduced by iron–water to 2 : 7-biscarbethoxyamino-9-benzoyl-10-methyl-9 : 10-dihydrophenanthridine. The structure of this compound was confirmed by comparison of its ultra-violet light absorption with that of an equimolecular mixture of 2 : 7-bis-

carbethoxyamino-9 : 10-dimethyl-9 : 10-dihydrophenanthridine (XI; R = R′ = NH·CO_2Et) (see below) and benzaldehyde (Fig. 2).

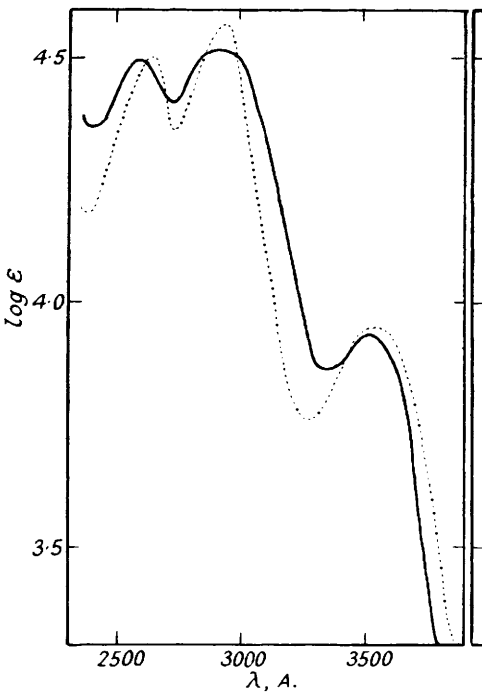
It is clear that the 9-benzoylphenanthridinium salts are more susceptible to certain reducing agents than are the 9-phenyl salts, and this difference may be interpreted as follows. In the 9-phenylphenanthridinium salts the polarity of the  system tends to be reduced by





electron transfer from the phenyl group, whereas in the 9-benzoyl salts this effect is reduced by the presence of the carbonyl group, which operates in the opposite sense, so that the above system is in a more highly polarised state and consequently more susceptible to attack by nascent hydrogen (see inset). This difference in behaviour to reducing agents may well affect the relationship of these salts towards enzyme systems concerned with oxidation and reduction, and it is of interest that (VI) is almost completely inactive and (X) only slightly active in trypanosome infections.

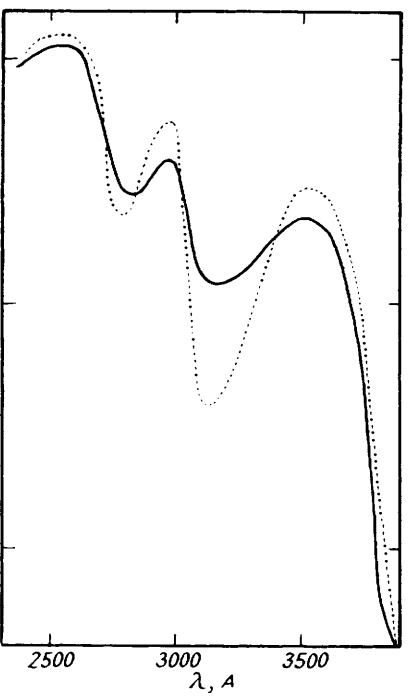
FIG. 1.



——— 7-*Carbethoxyamino*-9-p-*acetamido*-*benzoyl*-10-*methyl*-9 : 10-*dihydrophenanthridine.*

----- *Mixture of* 7-*acetamido*-9 : 10-*dimethyl*-9 : 10-*dihydrophenanthridine and* p-*acetamidobenzaldehyde.*

FIG. 2.



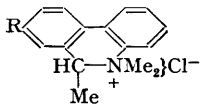
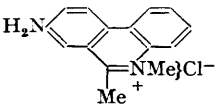
——— 2 : 7-*Biscarbethoxyamino*-9-*benzoyl*-10-*methyl*-9 : 10-*dihydrophenanthridine.*

----- *Mixture of* 2 : 7-*biscarbethoxyamino*-9 : 10-*dimethyl*-9 : 10-*dihydrophenanthridine and benzaldehyde.*

Although, in general, phenanthridinium salts are unaffected by iron–water, they are readily converted into dihydro-compounds by catalytic hydrogenation in aqueous or alcoholic solution at room temperature and pressure in the presence of palladium–charcoal and a weak alkali such as sodium acetate. Reduction is more rapid with Adams's catalyst, but in the absence of other susceptible groups ceases when one molecule of hydrogen has been absorbed, even under pressure. The reduction of phenanthridine methiodide to 10-methyl-9 : 10-dihydrophenanthridine by tin and hydrochloric acid has also been reported (Ankersmit, Diss., Berne, 1891).

A series of 9 : 10-dihydrophenanthridines was prepared by this catalytic reduction method in the hope that on parenteral injection in oil into infected animals they would be oxidised by the host to the trypanocidal phenanthridinium salts from which they were derived, but would show

modified properties. They crystallise rather poorly and it was not possible to obtain pure substances from aminophenanthridinium salts, the class to which the powerful (*Trypanosoma congolense*) trypanocides belong, but 2 : 7-biscarbethoxyamino-9 : 10-dimethylphenanthridinium methyl sulphate and 3-carbethoxyamino-9-*p*-carbethoxyaminophenyl-10-methylphenanthridinium chloride, which are active against the resistant *T. cruzi* (Browning, Calver, Leckie, and

(XIII.)   (XIV.)

Walls, *Nature*, **1946**, **157**, 263), readily gave crystalline dihydro-compounds. From the appropriate quaternary salts were also obtained 9 : 10-dihydro-compounds (see Table I) with methyl, phenyl, and benzyl groups in the 9-position, and similar compounds with acetamido- (XI; R = NHAc, R′ = H), carbethoxyamino- (XI; R = NH·CO_2Et, R′ = H; and R = R′ = NH·CO_2Et), hydroxy- (XI; R = OH, R′ = H), ethylcarbonato- (XI; R = O·CO_2Et, R′ = H), and methoxy-groups in the phenanthridine nucleus. Compounds of this series usually show an intense blue fluorescence in neutral or alkaline solution (Pictet and Ankersmit, *Annalen*, 1891, **266**, 138). Most of these dihydro-compounds were readily converted into non-fluorescent quaternary salts (compare XIII), which do not show promising pharmacological or therapeutic properties. 7-Acetamido-9 : 10 : 10-trimethyl-9 : 10-dihydrophenanthridinium chloride (XIII; R = NHAc) was hydrolysed to the corresponding amino-chloride hydrochloride (as XIII; R = NH_2), but this salt in contrast to the analogous (XIV) is devoid of trypanocidal properties.

Experimental.

7-*Carbethoxyamino*-9-p-*nitrobenzoylphenanthridine*.—A solution of 7-carbethoxyamino-9-*p*-nitrobenzylphenanthridine (5 g.) and selenium dioxide (1·5 g.) in dioxan (120 ml.) and water (5 ml.) was heated under reflux for 6½ hours, during which period the solution became deep red and selenium separated. The filtered solution on cooling deposited a bulky orange precipitate (2·5 g.), m. p. 242—243°. The mother-liquor was evaporated to dryness and the residue extracted with boiling benzene. The extract (charcoal) on evaporation to small bulk furnished a further 1·2 g. of product, m. p. 240—242°. On crystallisation from acetone, the pure *ketone* was obtained as a voluminous mass of fine orange needles, m. p. 243—244° (Found : C, 66·3; H, 4·2; N, 10·05; OEt, 10·85. $C_{23}H_{17}O_5N_3$ requires C, 66·5; H, 4·15; N, 10·1; OEt, 10·85%). The *oxime*, prepared by refluxing the ketone with hydroxylamine hydrochloride in pyridine solution, crystallised from methanol in small almost colourless needles, m. p. 235° (decomp.) (Found : C, 64·3; H, 4·75; N, 13·25. $C_{23}H_{18}O_5N_4$ requires C, 64·15; H, 4·2; N, 13·0%).

Hydrolysis of the urethane (1 g.) by heating for 20 minutes at 150° with concentrated sulphuric acid (2·8 ml.) and water (2·5 ml.), followed by dilution with water and neutralisation, yielded 7-*amino*-9-p-*nitrobenzoylphenanthridine*, which crystallised from aqueous pyridine in fine dull-red matted needles, m. p. 280° (decomp.) (Found : C, 70·45; H, 4·0; N, 12·4. $C_{20}H_{13}O_3N_3$ requires C, 69·95; H, 3·8; N, 12·25%).

7-*Carbethoxyamino*-9-p-*nitrobenzoyl*-10-*methylphenanthridinium Chloride* (III).—A solution of the foregoing ketone (5 g.) in nitrobenzene (40 ml.) was treated with methyl sulphate (2·5 ml.) at 160°. After 3 minutes at this temperature more methyl sulphate (2·5 ml.) was added, and the temperature held at 160° for a further 5 minutes. The deep yellow solid that crystallised on cooling was collected and extracted with hot water. Addition of sodium chloride to the extract precipitated the *chloride* (3·8 g.), which crystallised from water or alcohol in small yellow needles, m. p. 237—238° (Found : C, 61·75; H, 4·7; N, 9·3; Cl, 7·8. $C_{24}H_{20}O_5N_3Cl$ requires C, 61·85; H, 4·35; N, 9·0; Cl, 7·6%).

7-*Carbethoxyamino*-9-p-*aminobenzoyl*-10-*methylphenanthridinium Chloride* (V).—The foregoing carbethoxyamino-nitro-salt (3 g.) in water (200 ml.) was reduced by a suspension of ferrous hydroxide, prepared by mixing solutions of crystalline ferrous sulphate (12·9 g.) in water (150 ml.) and barium hydroxide (14·1 g.) in water (150 ml.). After a few minutes' warming on the steam-bath the dark-brown precipitate was removed by filtration, and on cooling, the filtrate deposited 7-*carbethoxyamino*-9-p-*aminobenzoyl*-10-*methylphenanthridinium chloride* (2·3 g.) as long fibrous, deep yellow needles, m. p. 198° (decomp.) (Found : N, 9·55; Cl, 7·75. $C_{24}H_{22}O_3N_3Cl$ requires N, 9·65; Cl, 8·15%). The *acetyl* derivative (VII), prepared by warming this amino-salt with glacial acetic acid and acetic anhydride, crystallised from water in light yellow micro-needles, m. p. *ca.* 288° (decomp.) (Found : N, 8·65; Cl, 7·25. $C_{26}H_{24}O_4N_3Cl$ requires N, 8·8; Cl, 7·45%).

7-*Amino*-9-p-*nitrobenzoyl*-10-*methylphenanthridinium Chloride* (IV).—A solution of 7-carbethoxyamino-9-*p*-nitrobenzoyl-10-methylphenanthridinium chloride (1 g.) in concentrated sulphuric acid (2·8 ml.) and water (2·5 ml.) was heated at 150° for 20 minutes, and then diluted with water. The maroon-coloured precipitate was collected and dissolved in water. After neutralisation with 2N-ammonium hydroxide, barium chloride was added to the hot solution; on cooling, the filtered solution deposited the *amino-nitro-chloride* in deep-red needles, m. p. 175° (decomp.) (Found : N, 10·8; Cl, 9·0. $C_{21}H_{16}O_3N_3Cl$ requires N, 10·65; Cl, 9·0%).

7-*Amino*-9-p-*aminobenzoyl*-10-*methylphenanthridinium Bromide* (VI).—7-Carbethoxyamino-9-*p*-aminobenzoyl-10-methylphenanthridinium chloride was similarly hydrolysed by sulphuric acid. After dilution with water, the clear red solution was neutralised with 2N-ammonium hydroxide and the *diamino*-

TABLE I.

10-*Methyl*-9 : 10-*dihydrophenanthridines*.

No.	Compound.	Solvent for crystn.	Form and m. p.	Formula.	Analyses. Found, %. C.	H.	N.	Required, %. C.	H.	N.
1	9-*Phenyl*-	Petroleum (b. p. 60—80°)	Prisms, 102—103°	$C_{20}H_{17}N$	88·95	6·45	5·05	88·55	6·25	5·15
2	9-*Benzyl*-, *hydrochloride*	EtOH	,, 175—177	$C_{21}H_{20}NCl$	78·0	6·3	— (Cl, 11·3)	78·3	6·3	— (Cl, 11·0)
3	9-p-*Methoxybenzyl*-, *hydrochloride*	,,	,, 168	$C_{22}H_{22}ONCl$	75·6	6·4	4·1	75·1	6·3	4·0
4	7-*Methoxy*-9-p-*methoxyphenyl*-	MeOH	,, 94	$C_{22}H_{21}O_2N$	80·0	6·5	4·4	79·7	6·4	4·2
5	7-*Ethylcarbonato*-9-*methyl*-	,,	,, 90	$C_{18}H_{19}O_3N$	73·3	6·5	—	72·7	6·4	—
6	7-*Hydroxy*-9-*methyl*-	,,	,, 182	$C_{15}H_{15}ON$	80·3	6·9	—	80·0	6·7	—
7	7-*Acetoxy*-9-*methyl*-	,,	,, 110—111	$C_{17}H_{17}O_2N$	76·5	6·1	—	76·4	6·4	—
8	7-*Acetamido*-9-*methyl*-	,,	,, 172—173	$C_{17}H_{18}ON_2$	76·6	6·3	10·3	76·65	6·85	10·5
9	7-*Amino*-9-*methyl*-	—	Glass, $100/10^{-3}$ mm. (bath temp.)	$C_{15}H_{16}N_2$	—	—	12·6	—	—	12·5
10	7-*Carbethoxyamino*-9-*methyl*-, *hydrochloride*	2N-HCl	Plates, 199 (decomp.)	$C_{18}H_{21}O_2N_2Cl$	(Cl, 10·75)		8·75	(Cl, 10·7)		8·45
11	2 : 7-*Diacetamido*-9-*phenyl*-	EtOH	Buff prisms, 184—186	$C_{24}H_{23}O_2N_3$	—	—	11·0	—	—	10·9
12	2 : 7-*Biscarbethoxyamino*-9-*methyl*-	C_6H_6–petroleum, (b. p. 60—80°)	Prisms, 169—171 (efferv.)	$C_{21}H_{25}O_4N_3$	66·2	6·7	11·0	65·75	6·6	10·95
13	3-*Carbethoxyamino*-9-p-*carbethoxyaminophenyl*-	$COMe_2$	165—170 (decomp.)	$C_{26}H_{27}O_4N_3$	70·1	5·9	10·0	70·1	6·1	9·45

The dihydro-compounds, except where otherwise stated, were obtained from the corresponding phenanthridinium salts, some of which are described in this paper and the others as follows: (2)—(4), (6), *J.*, 1950, 311. (9), (10), (12), Walls, *J.*, 1947, 71. (11), *J.*, 1945, 299. (13), *J.*, 1946, 1033.

TABLE II.

10 : 10-*Dimethyl*-9 : 10-*dihydrophenanthridinium salts*.

Compound.		Solvent for crystn.	Form and m. p.	Formula.	Analyses. Found, %. C.	H.	N.	Cl or I.	Required, %. C.	H.	N.	Cl or I.
9-*Phenyl*-	*iodide*	H_2O	Needles, 162—164° (decomp.)	$C_{21}H_{20}NI$	—	—	3·3	30·9	—	—	3·4	30·75
9-*Benzyl*-	*iodide*	EtOH	Prisms, 174—175	$C_{22}H_{22}NI$	61·8	5·4	3·5	—	61·8	5·2	3·3	—
	chloride	Pr^iOH–$COMe_2$	,, 173	$C_{22}H_{22}NCl$	78·9	6·6	4·4	10·5	78·65	6·6	4·2	10·6
9-p-*Methoxybenzyl*-	*iodide*	EtOH	Prisms, 166	$C_{23}H_{24}ONI$	60·2	5·5	—	—	60·4	5·3	—	—
	chloride	,,	,, 159	$C_{23}H_{24}ONCl$	—	—	4·1	10·3	—	—	3·8	9·7
7-*Methoxy*-9-p-*methoxyphenyl*-	*iodide*	MeOH	Plates, 169	$C_{23}H_{24}O_2NI$	58·4	5·7	3·2	—	58·3	5·1	3·0	—
7-*Ethylcarbonato*-9-*methyl*-	*iodide*	EtOH–Et_2O	Prisms, 154	$C_{19}H_{22}O_3NI$	51·9	5·15	—	—	51·95	5·05	—	—
7-*Hydroxy*-9-*methyl*-	*iodide*	H_2O	Needles, 143—144	$C_{16}H_{18}ONI$	—	—	—	34·65	—	—	—	34·6
7-*Acetoxy*-9-*methyl*-	*iodide*	EtOH–Et_2O	Prisms, 155	$C_{18}H_{20}O_2NI$	52·8	5·3	—	31·25	52·8	4·9	—	31·0
7-*Carbethoxyamino*-9-*methyl*-	*iodide*	H_2O	Prisms, 176—177 (decomp.)	$C_{19}H_{22}O_2N_2I$	—	—	6·4	28·95	—	—	6·4	29·05
7-*Acetamido*-9-*methyl*-	*iodide*	,,	Plates, 189 (decomp.)	$C_{18}H_{21}ON_2I$	—	—	6·65	30·75	—	—	6·85	31·15
	chloride	EtOH–Et_2O	190—191 (decomp.)	$C_{18}H_{21}ON_2Cl$	—	—	8·75	11·05	—	—	8·85	11·2
7-*Amino*-9-*methyl*-,	*chloride hydrochloride*	,,	Hygroscopic)	$C_{16}H_{20}N_2Cl_2$	—	—	9·35	22·8	—	—	9·0	22·85

bromide obtained by metathesis with potassium bromide; it crystallised from water in deep-red needles, m. p. 217° (decomp.) (Found: N, 10·4; Br, 19·75. $C_{21}H_{18}ON_3Br$ requires N, 10·3; Br, 19·6%). The same product was obtained by ferrous hydroxide reduction of 7-amino-9-*p*-nitrobenzoyl-10-methylphenanthridinium chloride. When a warm aqueous solution of the salt was shaken with excess of ethyl chloroformate, 7-carbethoxyamino-9-*p*-aminobenzoyl-10-methylphenanthridinium chloride crystallised, m. p. 198° (decomp.).

7-*Carbethoxyamino*-9-p-*carbethoxyaminobenzylphenanthridine*.—A solution of 7-carbethoxyamino-9-*p*-nitrobenzylphenanthridine (13·3 g.) in alcohol (500 ml.) was treated with stannous chloride (23 g.) and concentrated hydrochloric acid (26·6 ml.) and refluxed for 2 hours. The filtered solution was made strongly alkaline with 5N-sodium hydroxide to precipitate 7-*carbethoxyamino*-9-p-*aminobenzylphenanthridine* (11 g.), which crystallised from a large volume of benzene in cream-coloured felted needles, m. p. 207—208° (efferv.) (Found: C, 74·7; H, 5·95; N, 11·3. $C_{23}H_{21}O_2N_3$ requires C, 74·35; H, 5·7; N, 11·3%). The crude amine (11 g.) in hot alcohol (350 ml.) was treated with ethyl chloroformate (2·8 ml.) and diethylaniline (5·6 ml.), and refluxed for 30 minutes. The solution was poured into water and the voluminous precipitate was collected and crystallised from aqueous alcohol (charcoal) and then from acetone–light petroleum (b. p. 40—60°), giving the *bisurethane* as small plates, m. p. 212° (efferv.) (8 g.) (Found: C, 70·15; H, 5·55; N, 9·5. $C_{26}H_{25}O_4N_3$ requires C, 70·4; H, 5·7; N, 9·45%).

7-*Carbethoxyamino*-9-p-*carbethoxyaminobenzoylphenanthridine*.—The foregoing compound (3 g.) in dioxan (65 ml.) and water (3 ml.) was boiled under reflux with selenium dioxide (750 mg.) for 7 hours. The filtered solution was evaporated to dryness, and the residue extracted with boiling acetone. The extract on cooling deposited the *phenanthridine* (2·2 g.), m. p. 242—245° (efferv.), which on recrystallisation from acetone formed small cream-coloured needles, m. p. 247° (efferv.) (Found: C, 68·5; H, 5·7; N, 9·65. $C_{26}H_{23}O_5N_3$ requires C, 68·25; H, 5·05; N, 9·2%). The quaternary salt was obtained by the methyl sulphate–nitrobenzene method. Metathesis in aqueous solution with sodium chloride converted it into 7-*carbethoxyamino*-9-p-*carbethoxyaminobenzoyl*-10-*methylphenanthridinium chloride*, which crystallised from methanol in fine, yellow needles, m. p. 226° (decomp.) (Found: N, 8·45; Cl, 6·95. $C_{27}H_{26}O_5N_3Cl$ requires N, 8·25; Cl, 7·0%). When this salt was hydrolysed with sulphuric acid 7-amino-9-*p*-aminobenzoyl-10-methylphenanthridinium bromide was obtained, identical with that already described.

7-*Carbethoxyamino*-9-p-*acetamidobenzoyl*-10-*methyl*-9 : 10-*dihydrophenanthridine* (IX).—(*a*) A solution of 7-carbethoxyamino-9-*p*-nitrobenzoyl-10-methylphenanthridinium chloride (1 g.) in water (50 ml.) was refluxed gently with iron powder (1 g.) for 1 hour. The insoluble material was extracted with hot methanol, and the evaporated solution allowed to crystallise. The solid (700 mg.) so obtained was recrystallised twice from methanol, giving deep-yellow platelets, m. p. 174—175° (efferv.), shrinking from 170° (Found: C, 71·55; H, 5·3; N, 10·7. $C_{24}H_{23}O_3N_3$ requires C, 71·8; H, 5·8; N, 10·45%).

Acetylation of this compound with acetic anhydride gave a good yield of the *acetyl-dihydro*-compound, which crystallised from methanol in orange-red plates, m. p. 205—210° (efferv.) [Found: C, 70·15; H, 5·6; N, 9·8; Ac, 9·45. $C_{26}H_{25}O_4N_3$ requires C, 70·4; H, 5·7; N, 9·5; Ac (1 per mol), 9·7%]. Light absorption in alcohol: maxima, 2580, 2920, 3520 A.; log ε, 4·50, 4·52, 3·94, respectively. (*b*) 7-Carbethoxyamino-9-*p*-aminobenzoyl-10-methylphenanthridinium chloride (500 mg.) was similarly reduced with iron and water, and the crude dihydro-compound (300 mg.) that resulted was acetylated to give the same acetyl derivative (250 mg.). (*c*) 7-Carbethoxyamino-9-*p*-acetamidobenzoyl-10-methylphenanthridinium chloride (350 mg.) on treatment with iron and water gave the identical acetyl-dihydro-compound (250 mg.). (*d*) 7-Carbethoxyamino-9-*p*-aminobenzoyl-10-methylphenanthridinium chloride (500 mg.), suspended in alcohol (25 ml.), was hydrogenated with palladium–charcoal catalyst (250 mg.; 5%) in presence of sodium acetate (100 mg.) until 1 mol. of hydrogen had been absorbed (*ca.* 3 hours). The crude dihydro-compound (250 mg.), isolated by evaporation of the filtered solution to small bulk and precipitation with water, was acetylated to give the acetyl compound (200 mg.) described above.

2 : 7-*Biscarbethoxyamino*-9-*benzoylphenanthridine*.—2 : 7-Biscarbethoxyamino-9-benzylphenanthridine (3 g.) in dioxan (60 ml.) and water (1·5 ml.) was refluxed with selenium dioxide (800 mg.) for 7 hours. The solid remaining after evaporation of the filtered solution was crystallised from acetone to give small bright yellow plates of the *benzoyl* compound (2·05 g.), m. p. 241° (efferv.), raised to 244° (efferv.) on recrystallisation from acetone (Found: C, 68·3; H, 4·9; N, 9·05. $C_{26}H_{23}O_5N_3$ requires C, 68·25; H, 5·05; N, 9·2%). Treatment of this base in nitrobenzene solution with excess of methyl sulphate at 150—160° for 5 minutes, followed by conversion of the resulting methosulphate into chloride, gave 2 : 7-*biscarbethoxyamino*-9-*benzoyl*-10-*methylphenanthridinium chloride*, which formed fine orange needles, m. p. 195° (decomp.), from methanol–ethyl acetate (Found: N, 8·05; Cl, 6·65. $C_{27}H_{26}O_5N_3Cl$ requires N, 8·25; Cl, 7·0%). Hydrolysis of this salt (6 g.) with sulphuric acid afforded 2 : 7-*diamino*-9-*benzoyl*-10-*methylphenanthridinium bromide* (X) (4·1 g.), which crystallised from methanol in large deep-purple flat needles, decomposing slowly above 250° (Found: C, 61·55; H, 4·35; N, 10·2; Br, 19·9. $C_{21}H_{18}ON_3Br$ requires C, 61·75; H, 4·45; N, 10·3; Br, 19·6%).

2 : 7-*Biscarbethoxyamino*-9-*benzoyl*-10-*methyl*-9 : 10-*dihydrophenanthridine*.—2 : 7-Biscarbethoxyamino-9-benzoyl-10-methylphenanthridinium chloride (500 mg.) in water (50 ml.) was refluxed gently with iron powder (500 mg.) for 1 hour. The solution was filtered hot, and the residue extracted with boiling alcohol. Water was added to induce crystallisation and the crude product (350 mg.) was crystallised twice from methanol to give the *dihydrophenanthridine* as yellow needles, m. p. 193—195° (efferv.) (Found: C, 68·5; H, 5·85; N, 8·8. $C_{27}H_{27}O_5N_3$ requires C, 68·45; H, 5·75; N, 8·85%). Light absorption in alcohol: Maxima, 2570, 2980, 3520 A.; log ε, 4·53, 4·30, 4·18, respectively.

9-*Phenyl*-10-*methylphenanthridinium Chloride*.—An aqueous suspension of silver chloride and 9-phenyl-10-methylphenanthridinium iodide was refluxed for 20 minutes to give a solution of the *chloride*; this salt crystallised from a small volume of water in colourless prisms, m. p. 211° (decomp.) (Found: N, 4·5; Cl, 11·8. $C_{20}H_{16}NCl$ requires N, 4·6; Cl, 11·6%).

7-Ethylcarbonato-9 : 10-dimethylphenanthridinium bromide was obtained from 7-ethylcarbonato-9-methylphenanthridine (Copp and Walls, *J.*, 1950, 311) in the usual manner. Its *hemihydrate* crystallised from methanol in buff-coloured prisms which decomposed at 194—195° (bath preheated to 170°) (Found : C, 56·6; H, 5·3. $C_{18}H_{18}O_3NBr,0{\cdot}5H_2O$ requires C, 56·2; H, 5·0%).

7-Acetamido-9 : 10-dimethylphenanthridinium methyl sulphate was obtained from 7-acetamido-9-methylphenanthridine (*J.*, 1947, 71) by the methyl sulphate–nitrobenzene method, and crystallised from water : small yellow needles, m. p. 275° (decomp.) (Found : N, 7·4; S, 8·35. $C_{18}H_{20}O_5N_2S$ requires N, 7·5; S, 8·5%).

Dihydrophenanthridines.—The most convenient method of preparation was as follows : 9-phenyl-10-methylphenanthridinium chloride (5 g.) was suspended in ethanol (50 ml.), together with sodium acetate (1·1 g.) and Adams's catalyst (200 mg.), and the mixture was shaken under hydrogen at 1—10 atm. pressure. Absorption of hydrogen took place fairly quickly and was complete in about 3 hours when 1 mol. of hydrogen had been absorbed; as reduction progressed a very striking bright-blue fluorescence appeared. On addition of water to the filtered solution the product separated in almost colourless prisms (3·1 g.). The same product resulted on using palladium–charcoal as the catalyst, but the reduction was much slower.

7-Acetoxy-9 : 10-dimethyl-9 : 10-dihydrophenanthridine.—7-Hydroxy-9 : 10-dimethyl-9 : 10-dihydrophenanthridine (1 g.) (Table I) was dissolved in acetic anhydride (4 ml.), and the solution heated under reflux for 15 minutes. After cooling, excess of acetic anhydride was decomposed with water and the insoluble gummy layer crystallised from methanol.

7-Amino-9 : 10-dimethyl-9 : 10-dihydrophenanthridine was obtained by hydrolysis of the acetyl derivative (Table I) with 20% alcoholic hydrochloric acid. On dilution of the reaction mixture with water and neutralisation with ammonia, the amine was precipitated as a gum which could not be induced to crystallise even after distillation in a high vacuum. With acetic anhydride it was reconverted into the acetyl derivative.

Quaternary Salts from Dihydrophenanthridines.—The compounds of Table II were prepared by the following method. 9-Phenyl-10-methyl-9 : 10-dihydrophenanthridine (4·6 g.) was suspended in a mixture of methanol (46 ml.) and methyl iodide (9·2 ml.), and the mixture refluxed for 12 hours. After cooling, the crystalline methiodide (5·6 g.) was collected and recrystallised from hot water.

7-Hydroxy-9 : 10 : 10-trimethyl-9 : 10-dihydrophenanthridinium Iodide.—A solution of 7-acetoxy-9 : 10 : 10-trimethyl-9 : 10-dihydrophenanthridinium iodide (1 g.) in dilute hydrochloric acid (10 ml.) was heated on the steam-bath for 45 minutes. The cooled solution (charcoal) was evaporated in a vacuum; the residue was redissolved in a little water and excess potassium iodide added, and the gum that was precipitated crystallised from water.

7-Amino-9 : 10 : 10-trimethyl-9 : 10-dihydrophenanthridinium Chloride Hydrochloride.—7-Acetamido-9 : 10 : 10-trimethyl-9 : 10-dihydrophenanthridinium chloride (1 g.) was refluxed with 2N-hydrochloric acid (5 ml.) for 2 hours. The solution was then evaporated to dryness under reduced pressure, and the residual gum dissolved in dry alcohol. After addition of ether colourless prisms of the hygroscopic hydrochloride separated.

The authors thank Mr. L. G. Goodwin and his colleagues of the Wellcome Laboratories of Tropical Medicine for examination of the trypanocidal properties of many of these compounds, Messrs. A. R. Brown, W. E. King, and R. G. W. Spickett for valuable assistance, Mr. A. Bennett for microanalyses, and Dr. T. S. G. Jones for the light-absorption measurements.

CHEMICAL DIVISION, WELLCOME RESEARCH LABORATORIES,
BECKENHAM, KENT.

[*Received, May 4th*, 1950.]