68. *Potential Trypanocides of the* N-*Heterocyclic Series. Part III. Alkoxy- and Hydroxy-phenanthridinium Salts.*

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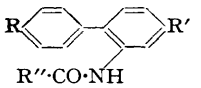
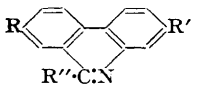
The observation that a 9-phenylphenanthridinium salt with only methoxyl as substituent possessed significant trypanocidal properties suggested the examination of a series of such compounds and of similar compounds with hydroxyl groups. They were synthesised by conventional methods, and it has emerged that salts with an alkoxyl group in the 7-position are specifically active in *T. congolense* infections, and when in addition the 9-phenyl group has an amino- or a nitro-substituent the activity of some of these substances equals that of the diamino-salts previously described.

A large number of amino-substituted phenanthridinium salts has been prepared (*J.*, 1945, 294; 1947, 67; 1948, 188) and it appeared that the presence of at least one amino-group in the diphenyl portion of the molecule was essential to trypanocidal activity (*Trypanosoma congolense*). This activity is much enhanced by the presence of a 9-phenyl group and of a second amino-group. Compounds which contain amino-groups substituted by acetyl, carbamyl,

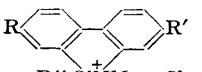
or carbalkoxy-groups are found to be much less active against *T. congolense*, although with the last-named modification some activity against the resistant trypanosome, *T. cruzi*, becomes apparent (Walls, Browning, Calver, and Leckie, *Nature*, 1946, **157**, 263; *J.*, 1946, 1031).



(I.)



(II.)



(III.)

Hitherto, the methoxy-group, which is known to exert a favourable therapeutic effect in other series, has not been introduced into the active phenanthridinium types, but its potential value was revealed when *7-methoxy-9-p-methoxyphenyl-10-methylphenanthridinium chloride* (III; R = OMe, R′ = H, R″ = *p*-OMe·C_6H_4) was found to possess significant trypanocidal activity. The effect of an association of alkoxy- and amino-groups and of hydroxy- and amino-groups was then examined, that type being selected in which the former group was located in the diphenyl portion of the molecule and the latter in the 9-phenyl group. Although compounds with amino-groups restricted to the 9-aryl group had hitherto shown practically no activity, the effect on them of the introduction of a 7-alkoxy-group is striking, many of the compounds now described being powerful trypanocides.

The alkoxy-compounds were prepared by the methods already used in this series, the essential step being the cyclisation of an appropriately substituted *o*-acylamidodiphenyl. *2-Amino-4′-methoxydiphenyl* and its higher homologues were prepared either from 4-amino-2′-acetamidodiphenyl (Petrow, *J.*, 1945, 119) or from 2-nitro-4′-hydroxydiphenyl. The latter substance had been previously prepared by Schultz, Schmidt, and Strasser (*Annalen*, 1881, **207**, 351) who gave only scanty preparative details. Our product had a much lower m. p. (114°) than that recorded by these authors (138°), but its structure was confirmed by its conversion into *2-acetamido-4′-methoxydiphenyl* (I; R = OMe, R′ = H, R″ = Me) and *2-acetamido-4′-(ethyl carbonato)diphenyl* (I; R = O·CO_2Et, R′ = H, R″ = Me), identical with the products obtained from 4-amino-2′-acetamidodiphenyl. *2-Nitro-4-methoxydiphenyl* was prepared from 3-nitro-4-aminoanisole and benzene by the Gomberg method, and reduced catalytically to *2-amino-4-methoxydiphenyl*. Condensation of these aminoalkoxydiphenyls with the appropriate acid chlorides yielded the amides (I), which were smoothly cyclised by phosphoryl chloride to the corresponding phenanthridines (II), the latter being readily converted into quaternary salts (III).

The various groups which were introduced into the 9-position are given in detail in the Experimental section (see Tables III, IV, and V); they include methyl, phenyl, phenyl substituted by nitro-, amino-, carbethoxyamino-, methoxy-, hydroxy-, or chloro-groups, and nitro- and amino-benzyl. The 9-aminophenyl compounds were prepared by cyclisation of 2-nitrobenzamidodiphenyls and subsequent reduction of the nitro-group. *2-p-Carbethoxyaminobenzamido-4′-methoxydiphenyl* (I; R = OMe, R′ = H, R″ = *p*-CO_2Et·NH·C_6H_4) was similarly cyclised to the *phenanthridine* (II; R = OMe, R′ = H, R″ = *p*-CO_2Et·NH·C_6H_4) but the corresponding quaternary *salt* could not be converted smoothly into the amino-salt, since the methoxy-group was also affected by the hydrolytic process used.

The preparation of the analogous 9-benzyl compounds (II and III; R = OMe, R′ = H, R″ = *p*-NO_2·C_6H_4·CH_2, etc.) presented no difficulty (cf. Part I, *J.*, 1948, 191). The rather low yield of 9-benzylphenanthridine reported by Ritchie (*Proc. Roy. Soc. N. S. Wales*, 1945, **78**, 150) may be attributed to the use of impure 2-phenylacetamidodiphenyl (m. p. 37°); our preparation of this compound (m. p. 85—86°) gave a 68% yield of the phenanthridine Our results therefore do not support his views on the cyclisation of the phenylacetamido-derivatives. *7-Methoxy-9-p-nitrobenzyl-10-methylphenanthridinium chloride* gave a deep-red product, presumably an anhydro-base, on treatment with water (see Part I).

The hydroxy-phenanthridines or -phenanthridinium salts (III; R or R′ = OH) were best prepared by demethylation of the appropriate methoxy-derivatives with concentrated hydrochloric acid at 160° (Woodruff and Conger, *J. Amer. Chem. Soc.*, 1938, **60**, 405). *7-Hydroxy-9-methylphenanthridine* (II; R = OH, R′ = H, R″ = Me) was thus obtained from the 7-methoxy-compound; it resulted also from the hydrolysis of *7-(ethyl carbonato)*- and *7-benzoyloxy-9-methylphenanthridine* (II; R′ = H, R″ = Me, R = O·CO_2Et and OBz, respectively), themselves the products of cyclisation of the corresponding *amides* (I; R′ = H, R″ = Me, R = O·CO_2Et and OBz, respectively) but in yields much lower than for the cyclisation of 2-acetamido-4′-methoxydiphenyl (I; R = OMe, R′ = H, R″ = Me). An

attempt to obtain a hydroxyphenanthridine by diazotisation of 7-amino-9-*p*-nitrophenylphenanthridine led only to tars (cf. Part I).

The hydroxyphenanthridines could be alkylated to yield any desired ether, and this method was essential for the preparation of *7-benzyloxy*-9-p-*nitrophenylphenanthridine*, since attempted ring-closure of 2-p-*nitrobenzamido*-4′-*benzyloxydiphenyl* led to debenzylation and the formation of an intractable resin.

Our colleagues, Dr. Brownlee and Mr. Goodwin, report that most of the quaternary salts prepared as above are powerfully antibacterial *in vitro* and one of them, *7-methoxy*-9-p-*carbethoxyaminobenzyl*-10-*methylphenanthridinium chloride* (III; R = OMe, R′ = H, R″ = p-$CO_2Et{\cdot}NH{\cdot}C_6H_4{\cdot}CH_2$), affords protection to mice against *Streptococcus pyogenes*. Certain of them (III; R = alkoxyl, R′ = H, R″ = p-$NO_2{\cdot}C_6H_4$ or p- or m-$NH_2{\cdot}C_6H_4$) possess a powerful curative action for *T. congolense* infections in mice, and consequently it can no longer be postulated that the presence of an amino-group in the diphenyl portion of the molecule is essential to high trypanocidal activity. It is of interest that the toxicity and activity of these salts are much influenced by the length of the *O*-alkyl group, the most active member being *7-propoxy*-9-p-*aminophenyl*-10-*methylphenanthridinium chloride* (III; R = OPr^n, R′ = H, R″ = p-$NH_2{\cdot}C_6H_4$). Although the 2-amino- were more active than the corresponding 7-amino-salts (Part I), the 2-methoxy- were much less active than the 7-methoxy-salts.

Experimental.

2-Acetamido-4′-hydroxydiphenyl.—4-Amino-2′-acetamidodiphenyl (42 g.) was dissolved in N-sulphuric acid (240 ml.) and diazotised with sodium nitrite (17 g.), more N-sulphuric acid (240 ml.) being added. The diazonium solution was decomposed under toluene. After 48 hours at 0°, the crude *2-acetamido-4′-hydroxydiphenyl* that crystallised from the toluene was collected and dissolved in cold sodium hydroxide solution (charcoal). The filtrate was acidified and the solid thus precipitated crystallised from methanol, forming colourless needles (35 g.), m. p. 185—186° (Found: C, 74·05; H, 5·6. $C_{14}H_{13}O_2N$ requires C, 74·0; H, 5·8%).

2-Acetamido-4′-methoxydiphenyl.—A solution of 2-acetamido-4′-hydroxydiphenyl (61 g.) in N-sodium hydroxide (274 ml.) was heated on a steam-bath, and methyl sulphate (29 ml.) added gradually with stirring. After 1 hour the mixture was cooled, the resulting solid taken up into ether, and the ethereal solution washed with N-sodium hydroxide and dried. Evaporation of the ether left *2-acetamido-4′-methoxydiphenyl*, b. p. 130°/0·01 mm. (50 g.). The colourless distillate crystallised from ethyl acetate–light petroleum (b. p. 40—60°) in plates, m. p. 134° (Found: C, 75·1; H, 6·5. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·2%).

The following 2-acetamido-4′-alkoxydiphenyls were similarly prepared: *4′-Ethoxy*-, b. p. 135°/0·01 mm., crystallised from aqueous *iso*propanol, m. p. 91° (Found: C, 75·1; H, 6·75. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7%). 4′-iso*Propoxy*-, crystallised from light petroleum (b. p. 60—80°) in prisms, m. p. 108—109·5° (Found: C, 75·9; H, 7·1. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 6·95%). 4′-n-*Butoxy*-, b. p. 155°/1 × 10^{-5} mm., crystallised from ether–light petroleum (b. p. 40—60°), m. p. 98° (Found: C, 76·6; H, 7·4; N, 4·8. $C_{18}H_{21}O_2N$ requires C, 76·3; H, 7·5; N, 4·9%). *4′-Benzyloxy*-, b. p. 190—200°/1 × 10^{-5} mm., crystallised from ethyl acetate, m. p. 138° (Found: C, 79·6; H, 5·8. $C_{21}H_{19}O_2N$ requires C, 79·5; H, 6·0%). 4′-(*Ethyl carbonato*)-, prepared from an alkaline solution of 2-acetamido-4′-hydroxydiphenyl and ethyl chloroformate, and crystallised from ethanol in colourless needles, m. p. 127—128° (Found: C, 68·2; H, 5·8. $C_{17}H_{17}O_4N$ requires C, 68·2; H, 5·7%). *4′-Benzoyloxy*-, prepared by the Schotten–Baumann method, crystallised from methanol, m. p. 187—188° (Found: N, 4·4. $C_{21}H_{17}O_3N$ requires N, 4·2%).

2-Nitro-4′-hydroxydiphenyl.—A solution of 2-nitro-4′-aminodiphenyl (35·2 g.) in boiling N-sulphuric acid (640 ml.) was rapidly cooled to produce a fine paste, which was diazotised with sodium nitrite (9·5 g.). The diazonium solution was decomposed under toluene, which extracted the phenol as it was formed. After cooling, the toluene layer was extracted with aqueous sodium hydroxide, the phenol regenerated, and then crystallised from trichloroethylene as brownish crystals (22 g.), m. p. 110—112°, pure enough for the next stage. Its further purification was effected by percolating a benzene solution through a short column of alumina and extracting the filtrate with aqueous sodium hydroxide. The regenerated product now crystallised from trichloroethylene in lemon-coloured prisms, m. p. 114° (Found: C, 66·8; H, 4·3; N, 6·9. Calc. for $C_{12}H_9O_3N$: C, 67·0; H, 4·2; N, 6·5%).

From this product were prepared the *acetate*, m. p. 122° (Found: C, 65·6; H, 4·3. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3%), *methyl ether*, m. p. 60—60·5° (Found: C, 68·0; H, 5·1; N, 6·1. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8; N, 6·1%), *ethyl ether*, m. p. 51° (Found: C, 69·2; H, 5·3. $C_{14}H_{13}O_3N$ requires C, 69·2; H, 5·4%), and *ethyl carbonate*, m. p. 121° (Found: C, 62·5; H, 4·4. $C_{15}H_{13}O_5N$ requires C, 62·4; H, 4·5%).

2-Amino-4′-methoxydiphenyl.—This was obtained in almost quantitative yield by catalytic reduction (5% palladium–charcoal) of 2-nitro-4′-methoxydiphenyl at 70° with hydrogen (50 atm.). The *amine* was an oil, b. p. 118—120°/0·1 mm., which, subsequently solidified, had m. p. 36° (Found: C, 78·4; H, 6·8. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6%); its *hydrochloride* crystallised from 2N-hydrochloric acid in colourless needles, m. p. 227—228° (Found: C, 66·6; H, 6·4. $C_{13}H_{14}ONCl$ requires C, 66·4; H, 6·0%). Acetylation of the base with acetic anhydride gave 2-acetamido-4′-methoxydiphenyl identical with the product prepared from 4-amino-2′-acetamidodiphenyl as already described. By similar processes were prepared *2-amino-4′-ethoxydiphenyl*, b. p. 130—135°/0·1 mm., m. p. 56° (Found: C, 79·1; H, 7·1; OEt, 20·9. $C_{14}H_{15}ON$ requires C, 78·8; H, 7·1; OEt, 21·1%), and *2-amino-4′-(ethyl*

carbonato)diphenyl, which crystallised from *cyclo*hexane in colourless prisms, m. p. 65—66° (Found: C, 70·3; H, 5·9. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·8%). Acetylation of the latter gave 2-acetamido-4′-(ethyl carbonato)diphenyl, identical with that previously described.

TABLE I.

o-*Acylamidodiphenyls* (I).

Diphenyls.	Solvent for recrystn.	M. p.	Formula.	Analysis. Found, %. C.	H.	N.	Required, %. C.	H.	N.
2-*Benzamido*-4′-*methoxy*-	Methanol	108°	$C_{20}H_{17}O_2N$	79·1	5·5	4·8	79·2	5·6	4·6
2-*Anisamido*-4′-*methoxy*-	Acetone	146	$C_{21}H_{19}O_3N$	76·0	5·7	—	75·6	5·9	—
2-p-*Chlorobenzamido*-4′-*methoxy*-	Ethanol	142—143	$C_{20}H_{16}O_2NCl$	(Cl, 10·0)		4·1	(Cl, 10·5)		4·1
2-p-*Nitrobenzamido*-4′-*methoxy*-	Ethanol	164—165	$C_{20}H_{16}O_4N_2$	69·0	4·55	8·3	69·0	4·6	8·1
2-m-*Nitrobenzamido*-4′-*methoxy*-	Ethanol	136·5—137	,,	69·1	4·8	8·4	,,	,,	,,
2-p-*Carbethoxyaminobenzamido*-4′-*methoxy*-	Methanol	178	$C_{23}H_{22}O_4N_2$	70·8	5·8	7·4	70·75	5·7	7·2
2-(3 : 5-*Dinitrobenzamido*)-4′-*methoxy*-	Acetic acid	179—180·5	$C_{20}H_{15}O_6N_3$	61·5	3·9	10·4	61·1	3·8	10·6
2-p-*Nitrobenzamido*-4′-*ethoxy*-	Ethanol	147	$C_{21}H_{18}O_4N_2$	—	—	7·9	—	—	7·7
2-p-*Nitrobenzamido*-4′-iso*propoxy*-	Ethanol	139	$C_{22}H_{20}O_4N_2$	69·9	5·2	7·5	70·2	5·4	7·4
2-p-*Nitrobenzamido*-4′-n-*butoxy*-	Ethanol	118	$C_{23}H_{22}O_4N_2$	—	—	7·2	—	—	7·2
2-p-*Nitrobenzamido*-4′-*benzyloxy*-	Ethyl acetate	146—147	$C_{26}H_{20}O_4N_2$	73·6	4·7	6·3	73·6	4·7	6·6
2-p-*Nitrobenzamido*-4′-*methoxy*-	Benzene	170	$C_{20}H_{16}O_4N_2$	—	—	8·0	—	—	8·1
2-*Phenylacetamido*-	*cyclo*Hexane	85—86	$C_{20}H_{17}ON$	83·2	6·1	5·1	83·6	5·95	4·9
2-p-*Methoxyphenylacetamido*-	*cyclo*Hexane	105	$C_{21}H_{29}O_2N$	79·7	6·2	4·7	79·5	6·0	4·4
2-p-*Nitrophenylacetamido*-4′-*methoxy*-	Benzene	149—150	$C_{21}H_{18}O_4N_2$	—	—	8·0	—	—	7·7

Alternatively, 2-acetamido-4′-methoxydiphenyl (50 g.) (prepared as previously described, from 4-amino-2′-acetamidodiphenyl) was dissolved in a mixture of concentrated sulphuric acid (24 ml.) and ethanol (450 ml.), and the mixture refluxed for 1½ hours. After neutralisation with ammonia the solution was evaporated under reduced pressure, the residue treated with excess of ammonia, and the precipitated oil extracted with ether. The ethereal solution was washed with water, dried, and evaporated; distillation of the residue gave 2-amino-4′-methoxydiphenyl (31 g.). By analogous processes were prepared: 2-*amino*-4′-iso*propoxydiphenyl*, b. p. 128—134°/0·05 mm. (Found: N, 6·3. $C_{15}H_{17}ON$ requires N, 6·2%), 2-*amino*-4′-n-*butoxydiphenyl*, b. p. 140°/0·003 mm. (Found: C, 79·6; H, 7·7; N, 6·1. $C_{16}H_{19}ON$ requires C, 79·65; H, 7·9; N, 5·8%), and 2-*amino*-4′-*benzyloxydiphenyl* which, crystallised directly from ethanol, had m. p. 122° (Found: N, 5·15. $C_{19}H_{17}ON$ requires N, 5·1%).

2-*Nitro*-4-*methoxydiphenyl*.—3-Nitro-4-aminoanisole (150 g.) (Fanter and Tarbell, *Org. Synth.*, **25**, 78) was dissolved in hot 10N-hydrochloric acid (280 ml.) with just enough water (75 ml.) to give a clear solution, which was cooled to 0° and diazotised with sodium nitrite (67·5 g.). It was then stirred vigorously with benzene (2 l.) at 5—10° and sodium acetate (300 g.) in concentrated aqueous solution added. After 48 hours the benzene layer was separated and washed with alkali, whereupon a thick tar separated; the benzene layer was decanted, washed with fresh alkali, and finally with water. The residue left after evaporation of the benzene was exhaustively extracted with boiling ether, the combined extracts were evaporated, and the residue was distilled in a vacuum. 2-*Nitro*-4-*methoxydiphenyl*, b. p. 120—135°/0·05 mm., subsequently solidified, and crystallised from carbon tetrachloride–light petroleum (b. p. 40—60°) as pale yellow needles, m. p. 75—77° (Found: C, 68·4; H, 4·5; N, 6·35. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8; N, 6·1%).

2-*Amino*-4-*methoxydiphenyl*.—A solution of 2-nitro-4-methoxydiphenyl in ethanol (250 ml.) was reduced over palladium–charcoal (4 g. of 5%) at 40—60° with hydrogen (50 atm.). The *amine* was an oil, b. p. 128—130°/0·08 mm. (Found: C, 78·4; H, 6·8; N, 7·2. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6; N, 7·0%).

p-*Carbethoxyaminobenzoic Acid*.—This acid has been described by Boehm and Mehta (*Ber.*, 1938, **71**, 1797) but their method has little preparative value. This acid is readily obtained by the action of ethyl chloroformate on an alcoholic solution of *p*-aminobenzoic acid in the presence of an equivalent of diethylaniline, or, alternatively, by the action of excess of this ester on an aqueous solution of the hydrochloride of *p*-aminobenzoic acid. The product crystallised from methanol in colourless needles,

TABLE II.

Phenanthridines (II).

Phenanthridines.	Solvent for recrystn.	M. p.	Yield, %.	Formula.	Analysis. Found, %. C.	H.	N.	Required, %. C.	H.	N.
7-*Methoxy*-9-*methyl*-	Distilled, b. p. 141—148°/0·003 mm.	57°	60	$C_{15}H_{13}ON$	80·4	5·8	6·4	80·7	5·9	6·3
7-(*Ethyl carbonato*)-9-*methyl*-	*cyclo*Hexane	98—99	Variable	$C_{17}H_{15}O_3N$	72·6	5·5	—	72·6	5·4	—
7-(*Ethyl carbonato*)-9-*methyl*-, HCl	Ethanol	205—206	—	$C_{17}H_{16}O_3NCl$	64·4	5·4	—	64·2	5·1	—
7-*Benzoyloxy*-9-*methyl*-	Benzene	208—209	20	$C_{21}H_{15}O_2N$	80·7	4·75	4·5	80·5	4·8	4·5
7-*Methoxy*-9-*phenyl*-	Distilled, b. p. 190—192°/0·01 mm.	Gum	67	$C_{20}H_{15}ON$	—	—	4·7	—	—	4·9
7-*Methoxy*-9-*phenyl*-, *picrate*	Acetic acid	270—271	—	$C_{26}H_{18}O_8N_4$	—	—	10·75	—	—	10·9
7-*Methoxy*-9-p-*methoxyphenyl*-	Light petroleum (b. p. 80—100°)	94	80	$C_{21}H_{17}O_2N$	79·9	5·6	—	80·0	5·4	—
7-*Methoxy*-9-p-*chlorophenyl*-	Benzene and light petroleum (b. p. 80—100°)	157—158	73	$C_{20}H_{14}ONCl$	75·1	4·1	4·3	75·1	4·4	4·4
7-*Methoxy*-9-p-*nitrophenyl*-	Benzene	233—234	72	$C_{20}H_{14}O_3N_2$	72·6	4·3	8·4	72·7	4·3	8·5
7-*Methoxy*-9-m-*nitrophenyl*-	Benzene	183—184	81	,,	73·0	4·4	8·4	,,	,,	,,
7-*Methoxy*-9-p-*carbethoxyamino*-*phenyl*-	Benzene	132—136	70	$C_{23}H_{20}O_3N_2,0{\cdot}5H_2O$	72·2	5·35	—	72·4	5·5	—
7-*Methoxy*-9-(3 : 5-*dinitrophenyl*)-	Pyridine	252—253	57	$C_{20}H_{13}O_5N_3$	—	—	11·1	—	—	11·2
7-*Ethoxy*-9-p-*nitrophenyl*-	Chloroform	233	60	$C_{21}H_{16}O_3N_2$	—	—	8·1	—	—	8·1
* 7-n-*Propoxy*-9-p-*nitrophenyl*-	Ethanol	169	60	$C_{22}H_{18}O_3N_2$	74·0	5·3	7·65	73·7	5·1	7·8
* 7-n-*Propoxy*-9-m-*nitrophenyl*-	Ethanol	146	60	,,	—	—	7·8	—	—	,,
7-iso*Propoxy*-9-p-*nitrophenyl*-	Ethanol	159—160	60	,,	74·1	5·2	7·9	73·7	5·1	,,
7-n-*Butoxy*-9-p-*nitrophenyl*-	Benzene	173	67	$C_{23}H_{20}O_3N_2$	—	—	7·6	—	—	7·5
* 7-*Benzyloxy*-9-p-*nitrophenyl*-	*n*-Propanol	180	70	$C_{26}H_{18}O_3N_2$	76·5	4·1	7·0	76·85	4·4	6·9
2-*Methoxy*-9-p-*nitrophenyl*-	Benzene	199	90	$C_{20}H_{14}O_3N_2$	—	—	8·3	—	—	8·5
9-Benzyl-	Ethanol	111—112	68	—	—	—	—	—	—	—
9-p-*Methoxybenzyl*-	Ethanol	125—127	70	$C_{21}H_{17}ON$	84·2	5·75	—	84·3	5·7	—
7-*Methoxy*-9-p-*nitrobenzyl*-	Toluene	142	93	$C_{21}H_{16}O_3N_2$	—	—	8·1	—	—	8·1
† 7-*Hydroxy*-9-*methyl*-	Nitrobenzene	298—300	95	$C_{14}H_{11}ON$	79·8	5·2	—	80·3	5·3	—
† 7-*Hydroxy*-9-*methyl*-, HCl	Water	285—287	—	$C_{14}H_{12}ONCl$	68·9	5·2	—	68·4	4·9	—
7-*Hydroxy*-9-p-*nitrophenyl*-	Acetic acid	275	80	$C_{19}H_{12}O_3N_2$	—	—	8·7	—	—	8·9
7-*Hydroxy*-9-m-*nitrophenyl*-	*iso*Propanol	250	75	,,	—	—	8·6	—	—	,,

* Prepared by alkylation of the appropriate 7-hydroxyphenanthridine.

† Prepared by alkaline hydrolysis of 7-(ethyl carbonato)-9-methylphenanthridine as well as by demethylation of 7-methoxy-9-methylphenanthridine.

m. p. 203° (Found : N, 6·9. Calc. for $C_{10}H_{11}O_4N$: N, 6·7%). It was converted into p-*carbethoxyaminobenzoyl chloride* by hot thionyl chloride ; white needles, m. p. 110°, separated from benzene, (Found : N, 6·6; Cl, 15·6. $C_{10}H_{10}O_3NCl$ requires N, 6·15; Cl, 15·6%).

o-*Acylamidodiphenyls*.—The amides (Table I) were (with one exception) prepared by the following method. To a solution of the appropriate 2-amino-4′-alkoxydiphenyl (0·1 mole) in chloroform (200 ml.), anhydrous sodium carbonate (16 g.) was added, followed by the appropriate acid chloride (10% excess). The mixture was stirred for 30 minutes and then heated under reflux for a further 30 minutes. The hot solution was filtered, and the insoluble residue washed with warm chloroform. The combined filtrate and washings were evaporated to give the crude amide. *p*-Carbethoxyaminobenzoyl chloride and 2-amino-4′-methoxydiphenyl were condensed in boiling chlorobenzene.

TABLE III.

Alkoxy-10-*methylphenanthridinium salts* (III ; R or R′ = alkoxyl).

(Chlorides, except where otherwise stated. All salts in this and succeeding tables were dried at 100° before analysis.)

Phenanthridinium salts.	Solvent for crystn.	M. p.	Formula.	Analysis. Found, %. N.	Cl.	Required, %. N.	Cl.
7-*Methoxy*-9-*methyl*- (*bromide*)	Water	238°	$C_{16}H_{16}ONBr$	(Br, 24·7)		(Br, 25·1)	
7-*Methoxy*-9-*phenyl*-	PrⁱOH and Et_2O	216—217	$C_{21}H_{18}ONCl$	4·35	10·6	4·2	10·55
7-*Methoxy*-9-p-*methoxyphenyl*-	,,	215—216	$C_{22}H_{20}O_2NCl$	4·0	—	3·8	—
7-*Methoxy*-9-p-*chlorophenyl*-	Water	229—230	$C_{21}H_{17}ONCl_2$	,,	19·1	,,	19·2
7-*Methoxy*-9-p-*nitrophenyl*-	Dil. HCl	230—232	$C_{21}H_{17}O_3N_2Cl$	—	9·6	—	9·3
7-*Methoxy*-9-p-*aminophenyl*-	*iso*Propanol	253—254	$C_{21}H_{19}ON_2Cl$	—	10·3	—	10·1
7-*Methoxy*-9-p-*acetamidophenyl*-	Ethanol	258—259	$C_{23}H_{21}O_2N_2Cl$	7·3	—	7·1	—
7-*Methoxy*-9-p-*carbethoxyaminophenyl*-	Ethanol	248—249	$C_{24}H_{23}O_3N_2Cl$	6·7	8·3	6·6	8·4
7-*Methoxy*-9-m-*nitrophenyl*-	Dil. HCl	229	$C_{21}H_{17}O_3N_2Cl$	7·3	—	7·4	—
7-*Methoxy*-9-m-*aminophenyl*-	Water	236—238	$C_{21}H_{19}ON_2Cl$	—	10·2	—	10·1
7-*Methoxy*-9-m-*carbethoxyaminophenyl*-	EtOH and Et_2O	232—233	$C_{24}H_{23}O_3N_2Cl$	6·9	8·35	6·6	8·4
7-*Methoxy*-9-(3 : 5-*dinitrophenyl*)-	Water	260	$C_{21}H_{16}O_5N_3Cl$	10·0	8·6	9·9	8·3
7-*Methoxy*-9-(3 : 5-*diaminophenyl*)-	Ethanol	232—233	$C_{21}H_{20}ON_3Cl$	11·8	9·9	11·5	9·7
7-*Ethoxy*-9-p-*nitrophenyl*-	Dil. HCl	233	$C_{22}H_{19}O_3N_2Cl$	6·95	9·0	7·1	9·0
7-*Ethoxy*-9-p-*aminophenyl*-	Ethanol	225—226	$C_{22}H_{21}ON_2Cl$	7·6	9·6	7·7	9·7
7-n-*Propoxy*-9-p-*nitrophenyl*-	Dil. HCl	222	$C_{23}H_{21}O_3N_2Cl$	6·5	8·6	6·85	8·7
7-n-*Propoxy*-9-p-*aminophenyl*-	*iso*Propanol	215	$C_{23}H_{23}ON_2Cl$	—	9·5	—	9·4
7-n-*Propoxy*-9-m-*nitrophenyl*-	*iso*Propanol	212	$C_{23}H_{21}O_3N_2Cl$	—	8·4	—	8·7
7-n-*Propoxy*-9-m-*aminophenyl*-	Water	206	$C_{23}H_{23}ON_2Cl$	7·6	9·0	7·4	9·4
7-n-*Propoxy*-9-m-*carbethoxyaminophenyl*-	*iso*Propanol	207	$C_{26}H_{27}O_3N_2Cl$	6·5	8·2	6·2	7·9
7-iso*Propoxy*-9-p-*nitrophenyl*-	Dil. HCl	239—240	$C_{23}H_{21}O_3N_2Cl$	6·8	8·9	6·85	8·7
7-iso*Propoxy*-9-p-*aminophenyl*- (*dihydrate*)	Water	174—175	$C_{23}H_{23}ON_2Cl$	7·4	9·6	7·4	9·4
7-n-*Butoxy*-9-p-*nitrophenyl*-	Water	234	$C_{24}H_{23}O_3N_2Cl$	6·7	8·8	6·6	8·4
7-n-*Butoxy*-9-p-*aminophenyl*-	*iso*Propanol	190	$C_{24}H_{25}ON_2Cl$	7·3	9·1	7·1	9·0
7-*Benzyloxy*-9-p-*nitrophenyl*-	Water	226	$C_{27}H_{21}O_3N_2Cl$	6·2	7·9	6·2	7·9
7-*Benzyloxy*-9-p-*aminophenyl*-	Dil. EtOH	184	$C_{27}H_{23}ON_2Cl$	6·2	8·3	6·6	8·3
2-*Methoxy*-9-p-*nitrophenyl*-	Methanol	234	$C_{21}H_{17}O_3N_2Cl$	7·2	9·1	7·4	9·3
2-*Methoxy*-9-p-*aminophenyl*-	Water	235	$C_{21}H_{19}ON_2Cl$	8·1	—	8·0	—

Phenanthridines and Phenanthridinium Salts.—These compounds (Tables II—V) were prepared by the following general methods. The *o*-acylamidodiphenyl was suspended in phosphoryl chloride (1 ml. to 1 g. of amide), and the mixture refluxed for 5 hours, and then decomposed with ice and water. The resulting solid was ground with a mixture of chloroform and concentrated hydrochloric acid, and the insoluble residue collected and washed with a little fresh chloroform and hydrochloric acid. Unchanged starting material was recovered from the chloroform solution. The chloroform-insoluble material, on being treated with aqueous ammonia, gave the almost pure phenanthridine. After recrystallisation from the appropriate solvent, the phenanthridine was treated with excess of methyl sulphate in nitrobenzene at 150° for 15 minutes. After cooling, the nitrobenzene was removed in steam, and the residual product extracted with hot water. The methochlorides were precipitated from the extract with concentrated hydrochloric acid. The aminophenanthridinium salts were prepared by reduction of the corresponding nitrophenanthridinium salts with a small excess of iron powder or a sludge of ferrous hydroxide. Demethylation of methoxyphenanthridines or methoxyphenanthridinium salts was effected by heating the starting material with excess of concentrated hydrochloric acid in a sealed tube at 160—170° for 3 hours. With cooling, the hydrochloride or chloride was collected, and the former basified to give the corresponding hydroxyphenanthridine.

Alkylation of Hydroxyphenanthridines.—The appropriate hydroxyphenanthridine was dissolved in an equivalent amount of sodium hydroxide solution and the solution stirred in an oil-bath at 120°

together with an excess (50%) of the appropriate alkyl iodide (or benzyl chloride). The reaction was slow and usually took about 12 hours for completion. The precipitated solid was collected, washed with water, and extracted with hot aqueous sodium hydroxide to remove unchanged starting material. The residue was then crystallised from the appropriate solvent.

TABLE IV.

Hydroxy-10-*methylphenanthridinium chlorides* (III; R or R′ = OH).

				Analysis.			
				Found, %.		Required, %.	
Phenanthridinium salts.	Solvent for crystn.	M. p. (decomp.).	Formula.	N.	Cl.	N.	Cl.
7-*Hydroxy*-9-*methyl*-	Methanol	262—263°	$C_{15}H_{14}ONCl$	5·4	13·6	5·4	13·6
7-*Hydroxy*-9-*phenyl*-	Water	263—264	$C_{20}H_{16}ONCl$	4·3	11·4	4·35	11·0
7-*Hydroxy*-9-p-*hydroxyphenyl*-	Aq. alcohol	264—265	$C_{20}H_{16}O_2NCl$	4·5	—	4·15	—
7-*Hydroxy*-9-p-*chlorophenyl*-	Dil. HCl	244—245	$C_{20}H_{15}ONCl_2$	4·0	20·0	3·9	19·9
7-*Hydroxy*-9-p-*nitrophenyl*-	Methanol	252	$C_{20}H_{15}O_3N_2Cl$	7·6	9·4	7·6	9·7
7-*Hydroxy*-9-p-*aminophenyl*-	Water	269—271	$C_{20}H_{17}ON_2Cl$	8·45	10·8	8·3	10·5
7-*Hydroxy*-9-p-*carbethoxyaminophenyl*-	Methanol	281—282	$C_{23}H_{21}O_3N_2Cl$	7·1	—	6·7	—
7-*Hydroxy*-9-m-*aminophenyl*-	Water	275—277	$C_{20}H_{17}ON_2Cl$	8·6	10·4	8·3	10·5
7-*Hydroxy*-9-m-*carbethoxyaminophenyl*-	Ethanol	198—200	$C_{23}H_{21}O_3N_2Cl$	(OEt, 11·5)	8·9	(OEt, 11·0)	8·7
2-*Hydroxy*-9-p-*nitrophneyl*-	Water	330	$C_{20}H_{15}O_3N_2Cl$	7·4	9·6	7·6	9·7
2-*Hydroxy*-9-p-*aminophenyl*-	Water	297—298	$C_{20}H_{17}ON_2Cl$	8·4	10·35	8·3	10·5

TABLE V.

9-*Benzyl*-10-*methylphenanthridinium chlorides* (III; R″ = benzyl).

				Analysis.			
				Found, %.		Required, %.	
Phenanthridinium salts.	Solvent for crystn.	M. p. (decomp.).	Formula.	N.	Cl.	N.	Cl.
9-*Benzyl*-	*iso*Propanol	205—207°	$C_{21}H_{18}NCl$	4·6	—	4·4	—
9-p-*Methoxybenzyl*-	*iso*Propanol	192	$C_{22}H_{20}ONCl$	—	9·8	—	10·1
7-*Methoxy*-9-p-*nitrobenzyl*-	Methanol	151	$C_{22}H_{19}O_3N_2Cl$	7·0	—	7·1	—
7-*Methoxy*-9-p-*aminobenzyl*-	Water	241	$C_{22}H_{21}ON_2Cl$	7·4	9·5	7·7	9·7
7-*Methoxy*-9-p-*carbethoxyaminobenzyl*-	Ethanol	220	$C_{25}H_{25}O_3N_2Cl$	6·5	8·0	6·4	8·1
7-*Methoxy*-9-p-*propionamidobenzyl*-	Water	218	$C_{25}H_{25}O_2N_2Cl$	6·6	8·0	6·6	8·4
7-*Hydroxy*-9-p-*aminobenzyl*-	Water	252	$C_{21}H_{19}ON_2Cl$	7·8	10·0	8·0	10·1
7-*Hydroxy*-9-p-*carbethoxyaminobenzyl*-	Dil. HCl	265	$C_{24}H_{23}O_3N_2Cl$	6·8	—	6·6	—

The phenanthridines are colourless or very pale yellow solids. The phenanthridinium salts are light yellow, except those with a 9-*p*-aminophenyl substituent which are bright red, and the 9-*m*-aminophenyl analogues which are very deep orange.

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