337. *Researches in the Phenanthridine Series. Part IV. Synthesis of Plasmoquin-like Derivatives.*

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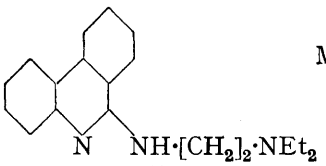
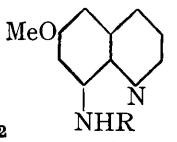
A PREVIOUS communication (J., 1934, 104) described preliminary attempts to prepare *meso*-aminophenanthridines substituted in the amino-group with basic aliphatic chains (compare I), but not the production of nuclear-substituted derivatives of this plasmoquin-like type (compare II). Such compounds have now been synthesised (compare III) and the basically substituted side chain present in plasmoquin (II) and atebrin (IV), *viz.*,



(I.)



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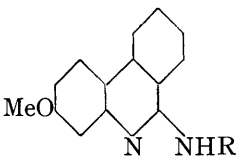
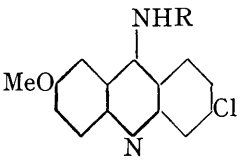


(III.)



(IV.)

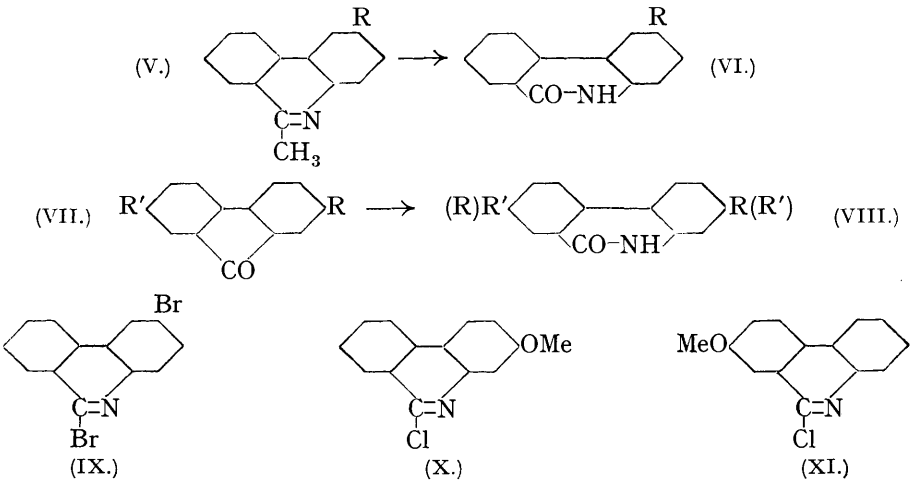
(R = CHMe·CH_2·CH_2·CH_2·NEt_2).

CHMe·CH_2·CH_2·CH_2·NEt_2, has been introduced into this series. The closer approximation to these antimalarials has not led to the appearance of similar properties in phenanthridine derivatives. The unfavourable pharmacological reports received from Professor Keilin's laboratory confirmed what has already been tentatively advanced, that phenanthridine is notably less physiologically active than its otherwise closely analogous isomeride acridine. According to the discoverers of atebrin (Mietzsch and Mauss, *Angew. Chem.*, 1934, **47**, 635) the most varied acridine derivatives of type (IV), and other ring systems containing similar basic aliphatic side chains (*e.g.*, triphenylmethane, thiazine, xanthine; see *Klin. Woch.*, 1933, **12**, 1276), are active antimalarials. Phenanthridine compounds differ also from acridine in their lack of dermatitic and sternutative action.

For the preparation of representative types such as (III) the chief problem was the synthesis of substituted phenanthridones; no useful general methods were available as for the acridones. 2 : 7-Diacetamidophenanthridone (Adkins, Steinbring, and Pickering, *J. Amer. Chem. Soc.*, 1924, **46**, 1917) and 2 : 7-diaminophenanthridone-4-carboxylic acid (Christie and Kenner, J., 1926, 470) have been obtained from diphenic acid sources. Moore and Huntress (*J. Amer. Chem. Soc.*, 1927, **49**, 1324, 2618) nitrated phenanthridone without orienting the products, and also prepared 2- and 7-nitrophenanthridones from diphenic acids, and the latter, more significantly, by the Beckmann conversion of 2-nitrofluorenoneoxime.

Two methods of general availability have now been devised: (1) Substituted 9-methylphenanthridines (V; R = H, Br, NO_2), prepared by the general synthetic method (Morgan and Walls, J., 1931, 2447), are oxidised in glacial acetic acid solution quantitatively to the corresponding phenanthridones (VI), a smooth reaction resembling the oxidation of fluorene derivatives to fluorenones. (2) The method of B.P. 333,173 has been conveniently modified by replacing a benzene solution of hydrazoic acid by a concentrated aqueous solution of commercially available sodium azide; when a concentrated-sulphuric acid solution of a fluorenone (VII; R = H, R′ = H, OH, OMe, NH_2, NO_2, and R = NO_2, R′ = Cl, NO_2) is treated with this reagent, a phenanthridone (VIII) results. The reaction, which is accompanied by a notable colour change, is analogous to a Beckmann conversion, a process hitherto employed with more conventional reagents for the conversion of fluorenone itself into a small yield of phenanthridone (Wegerhoff, *Annalen*, 1889, **252**, 39, for the first time). The purification and identification of the products were difficult owing to their insolubility and high decomposition points; moreover the unsymmetrically substituted fluorenones may give rise to 2- and 7-substituted phenanthridones. Contrary to the inferences of B.P. 333,173 that the nitro- and amino-phenanthridones obtained by the process are 2-derivatives, they are mixtures of isomerides, although Moore and Huntress

(*loc. cit.*) claim the exclusive formation of 7-nitrophenanthridone from 2-nitrofluorenone-oxime. Separation of the nitro- and amino-isomerides could not be effected, but on



conversion into hydroxy-compounds the two isomerides were isolated, and oriented by their reactions. In strong alkali their methylation was anomalous, a result due probably to the imino-group reacting.

By appropriate phosphoryl halides, 3-bromo-, 2-methoxy-, and 7-methoxy-phenanthridones were converted into 9-halogeno-derivatives (IX—XI), in which the 9-halogen is reactive and condenses with primary and secondary amines. The condensation of (IX) and (X) with β-diethylaminoethylamine (XII) and with α-diethylamino-δ-amino-*n*-pentane (XIII), and of 9-chlorophenanthridine also with (XIII), proceeded with ease, although the diamine (XIII) with the longer chain reacted much more slowly than (XII). This effect is undoubtedly a polar one, and depends on the reduction in the inductive effect of the tertiary amino-group as it becomes more remote from the reaction centre; steric hindrance by the adjacent methyl group is an unlikely cause.

The new triamines (compare III) are colourless basic oils which give very hygroscopic di-acid salts with mineral acids. Purification was effected by conversion into dipicrates, which crystallised in characteristic forms—an effective method for this type of compound, and less wasteful than the customary distillation in a high vacuum. The dihydrochlorides have a sweet taste and some local anæsthetic action; they are extremely soluble in water to colourless solutions of p_H *ca.* 5, those containing the $NH{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$ side chain being more nearly neutral than those with $NH{\cdot}[CH_2]_2{\cdot}NEt_2$. In contrast, the corresponding salts of the atebrin group are yellow and have an affinity for natural fibres. Fluorescence is only shown markedly by the methoxy-compounds, and for (III) is most striking. Their lack of chemotherapeutic value appears to be largely explicable on the grounds of their toxicity, in which they compare unfavourably with well-known antimalarials.

Experimental.

* Denotes microanalysis.

Oxidation of 9-Methyl- and 9-ω-Chloromethyl-phenanthridine.—A solution of 9-methylphenanthridine (20 g.) in hot glacial acetic acid (120 c.c.) was treated slowly with powdered sodium dichromate (45 g.). When the vigorous reaction had subsided, the solution was refluxed for one hour and then poured into water. The precipitated phenanthridone was crystallised from nitrobenzene (yield, 14 g.).

When the same process was applied to 9-ω-chloromethylphenanthridine, a quantitative yield of phenanthridone resulted.

3-Nitrophenanthridone.—A solution of 3-nitro-9-methylphenanthridine (15 g.) in hot glacial acetic acid (150 c.c.) was treated during 30 minutes with sodium dichromate (37 g.; 1·5 equivs.).

Vigorous reaction occurred with separation of a red microcrystalline powder. The mixture was refluxed for 2 hours and left over-night. The precipitate (14·5 g.) crystallised from nitrobenzene in minute red needles (12 g.), m. p. > 350° (Found: N, 11·7. $C_{13}H_8O_3N_2$ requires N, 11·65%).

3-*Bromo*-9-*methylphenanthridine*.—When 5-bromo-2-acetamidodiphenyl (30 g.; Scarborough and Waters, J., 1927, 94) was refluxed for 2 hours with phosphorus oxychloride, vigorous reaction occurred with escape of hydrogen chloride. Excess of phosphoryl chloride was recovered by distillation under reduced pressure, and the residue was extracted repeatedly with hot dilute hydrochloric acid. On cooling, the extract deposited white talc-like crystals of a hydrochloride, from which a white crystalline *base* (25 g.) was liberated by ammonia; it formed long needles from alcohol, m. p. 129·5—130° (Found: N, 5·35; Br, 28·7. $C_{14}H_{10}NBr$ requires N, 5·15; Br, 29·4%).

3-*Bromophenanthridone*.—The foregoing bromo-compound (15 g.) in hot glacial acetic acid solution was oxidised with sodium dichromate (24 g.). After a crystalline dichromate had separated and redissolved, 3-*bromophenanthridone* crystallised in yellow needles, which were washed in turn with glacial acetic acid and water and recrystallised from nitrobenzene (yield, 11 g.); decomp. 302° after previous sintering (Found: N, 5·15; Br, 28·8. $C_{13}H_8ONBr$ requires N, 5·1; Br, 29·2%).

3 : 9-*Dibromophenanthridine* (IX).—Finely powdered 3-bromophenanthridone (10 g.) was added in small portions to phosphorus oxybromide (30 g.) at 180° (oil-bath). After being heated for 5 hours, the product was cautiously decomposed with water, and the brown solid obtained was extracted with benzene (Soxhlet); after several crystallisations from benzene, almost colourless, prismatic needles (7 g.) were obtained, m. p. 170—171° (Found: N, 4·2; Br, 47·2. $C_{13}H_7NBr_2$ requires N, 4·15; Br, 47·45%).

Phenanthridone from Fluorenone.—The almost black solution of fluorenone (16 g.) in concentrated sulphuric acid (80 c.c.), cooled in ice-water, was treated dropwise with stirring during 2 hours with a concentrated aqueous solution of sodium azide (8·5 g.). Brisk evolution of nitrogen ensued at once, the solution became light grey, and towards the end of the reaction some phenanthridone separated. The product was poured into water, and the precipitated phenanthridone, after impurities had been extracted with hot alcohol, was crystallised from nitrobenzene (yield, 12 g.).

2(or 7)-*Nitrophenanthridone*.—2-Nitrofluorenone (25 g.), dissolved in concentrated sulphuric acid (140 c.c.), was similarly treated (sodium azide, 14 g.). The brown solid precipitated on addition of water, crystallised from boiling nitrobenzene in small, dark green needles, and sublimed extremely slowly at 250°/20 mm. in small yellow needles, decomp. *ca.* 340° over a range (Found: N, 11·9. Calc. for $C_{13}H_8O_3N_2$: N, 11·7%).

2(or 7)-*Chloro*-7(or 2)-*nitrophenanthridone*, obtained similarly from 2-chloro-7-nitrofluorenone (Courtot and Vignati, *Compt. rend.*, 1927, **184**, 1179), crystallised from nitrobenzene in green needles, m. p. 340° (Found: N, 10·45. $C_{13}H_7O_3N_2Cl$ requires N, 10·2%).

2 : 7-*Dinitrophenanthridone*, prepared quantitatively from 2 : 7-dinitrofluorenone (Morgan and Thomason, J., 1926, 2694), crystallised from nitrobenzene in brown plates or from pyridine in brownish-yellow needles containing combined solvent, m. p. > 340° (Found: N, 14·0. $C_{13}H_7O_5N_3$ requires N, 14·75%).

2(or 7)-*Aminophenanthridone*.—(1) *From* 2(or 7)-*nitrophenanthridone*. A suspension of the nitro-compound (2 g.) in 40 c.c. of saturated alcoholic hydrogen chloride was vigorously shaken with crushed stannous chloride (5 g.). Dissolution did not occur, but reduction proceeded with evolution of heat. When this had subsided, the product was refluxed for several hours, and then the suspended solid was dissolved in hot water and freed from tin with hydrogen sulphide. The base was precipitated by alkali in white needles of pearl-like lustre (1·2 g.), which were recrystallised from aniline; m. p. *ca.* 285° over a range (Found: N, 13·3. Calc. for $C_{13}H_{10}ON_2$: N, 13·35%).

(2) *From* 2-*aminofluorenone*. This purple base (30 g.) dissolved in concentrated sulphuric acid (200 c.c.) to a dark crimson solution, which was treated in the general manner with sodium azide (19·5 g.) solution. The light brown solution that resulted was diluted with water and cooled; a sulphate then separated. On being heated with aqueous alkali, the salt was converted into a white base (31·5 g.), which was dissolved in hot dilute hydrochloric acid (charcoal) and reprecipitated by alkali. It crystallised from aniline in almost white needles (29·5 g.) indistinguishable from the amine of (1).

2- *and* 7-*Hydroxyphenanthridones*.—Owing to the slight solubility of aminophenanthridone sulphate, the base (21 g.) was diazotised in hydrochloric acid (150 c.c. of 2*N*) at 0° with an

aqueous solution of sodium nitrite (3·5 g.). The microcrystalline diazonium salt that slowly separated was added portionwise to hot sulphuric acid (700 c.c. of 2*N*). Extraction of the brown product with aqueous alkali left dark-coloured by-products undissolved; neutralisation of the extract precipitated the hydroxy-compound as a buff-coloured mass (yield, 15—19 g.). By repeated crystallisation from pyridine, 2-hydroxyphenanthridone (8—11 g.) was separated; it was further purified by conversion into the acetyl derivative. The pyridine mother-liquor was worked up for 7-hydroxyphenanthridone.

2-*Acetoxyphenanthridone* was prepared from the foregoing (21 g.) by heating for 1 hour with acetic anhydride (14·5 c.c.; 1·5 equivs.) and glacial acetic acid (85 c.c.). Sufficient hot acetic acid was then added for complete dissolution; on cooling, clusters of plates separated, followed by long needles, which lost solvent of crystallisation on exposure (yield, 17·5 g.); white needles were formed from nitrobenzene, m. p. 273—274° (decomp.) (Found: *C, 70·8; H, 4·4; N, 5·65. $C_{15}H_{11}O_3N$ requires C, 71·15; H, 4·35; N, 5·65%).

2-*Hydroxyphenanthridone* was obtained from the foregoing by heating it with *N*-caustic soda at 100° till solution occurred. On acidification the pure hydroxy-compound was precipitated in white needles; it formed transparent plates on recrystallisation from nitrobenzene, m. p. 341—343° (Found: *C, 73·95; H, 4·3; N, 6·75. $C_{13}H_9O_2N$ requires C, 73·95; H, 4·25; N, 6·65%). When distilled in a current of hydrogen over zinc dust, this compound gave a 50% yield of phenanthridine; 2 g., oxidised with alkaline permanganate, yielded phthalic acid (1·1 g.).

2-*Methoxyphenanthridone*.—When a solution of the hydroxy-compound in concentrated caustic soda solution was shaken with methyl sulphate, an intractable gum was precipitated; acidification of the filtrate also yielded a gum. With a minimum of dilute alkali solution reaction proceeded smoothly: a hot solution of 2-hydroxyphenanthridone (5 g.) in *N*-caustic soda (40 c.c.) was shaken with methyl sulphate (4·5 g.; 1·5 equivs.), added portionwise. After 30 minutes on the steam-bath the white precipitate of methoxy-compound was crystallised from pyridine or chlorobenzene, forming plates, m. p. 251° after previous sintering (Found: *C, 74·55; H, 4·9; N, 6·3; *M*, 216. $C_{14}H_{11}O_2N$ requires C, 74·65; H, 4·9; N, 6·2%; *M*, 225).

9-*Chloro*-2-*methoxyphenanthridine* (X).—In this preparation a high temperature is to be avoided. 2-Methoxyphenanthridone (10 g.) and phosphorus oxychloride (30 g.) were heated at 175° for 6 hours. The crude non-basic product (9·5 g.) after several crystallisations from benzene (charcoal) occurred in white needles (7·5 g.), m. p. 137·5° (Found: N, 5·85; Cl, 14·55. $C_{14}H_{10}ONCl$ requires N, 5·75; Cl, 14·6%).

7-*Hydroxyphenanthridone*.—The pyridine mother-liquor from the crystallisation of 2-hydroxyphenanthridone was evaporated to dryness, and the dark-coloured residue (25 g. taken) was dissolved in hot 2*N*-caustic soda (about 60 c.c.; charcoal); a crudely crystalline sodium salt slowly separated. The hydroxy-compound liberated from it by acid was freed from most of the 2-isomeride by crystallisation from glacial acetic acid–anhydride (1 : 5), which retained the latter, and from which solvated 7-hydroxyphenanthridone crystallised on cooling in colourless elongated pointed prisms (7 g.); fractional crystallisation from nitrobenzene yielded 7-*hydroxyphenanthridone* (5 g.) in flat plates, m. p. 320—322° (decomp.) (Found: *C, 73·6; H, 4·4; *N, 6·9. $C_{13}H_9O_2N$ requires C, 73·95; H, 4·25; N, 6·65%). 7-Hydroxyphenanthridone is sparingly soluble in hot water or alcohol, from which it separates in white needles. By repetition of the above process a further quantity (4 g.) was obtained. Distilled over zinc dust in a current of hydrogen, it gave a small quantity of phenanthridine; oxidation with permanganate in the same way as for its isomeride yielded no phthalic acid.

7-*Acetoxyphenanthridone* is less readily prepared than its isomeride. The hydroxy-compound (0·5 g.) in hot pyridine (4 c.c.) was treated with acetic anhydride (1 c.c.) and gently refluxed for 30 minutes. On cooling, the acetyl derivative separated in white needles, conveniently recrystallised from nitrobenzene, m. p. 261—264° (decomp.) (Found: *C, 70·6; H, 4·45; *N, 5·45. $C_{15}H_{11}O_3N$ requires C, 71·15; H, 4·35; N, 5·65%).

7-*Methoxyphenanthridone*, prepared in high yield in the same way as for its isomeride, formed white plates from pyridine, m. p. 271—272° (Found: *C, 74·65; H, 5·0; N, 6·4. $C_{14}H_{11}O_2N$ requires C, 74·65; H, 4·9; N, 6·2%).

9-*Chloro*-7-*methoxyphenanthridine* (XI) was obtained in good yield when the foregoing was heated with four times its weight of phosphorus oxychloride at 180° for 6 hours; it formed long radiating needles from benzene (charcoal) or from ligroin, m. p. 107° (Found: *N, 5·55; *Cl, 14·85. $C_{14}H_{10}ONCl$ requires N, 5·75; Cl, 14·6%).

2-*Hydroxy- and* 2-*Methoxy-fluorenones and Hydrazoic Acid*.—Both these compounds reacted

according to the general process, but the isolation of pure products did not follow readily. In the case of the first-named, considerable decomposition occurred, but application of the methods already described of fractional crystallisation led to the isolation of small amounts of 2- and 7-hydroxyphenanthridones.

α-Diethylamino-δ-aminopentane (XIII).—This was prepared according to German Patent 486,079 from β-diethylaminoethyl chloride and acetoacetic ester with one variation: α-diethylaminopentan-δ-one, a stage in the synthesis, may be liberated directly from the aqueous liquor in which it is formed by salting out with potassium carbonate; steam-distillation is unnecessary (Found for the diamine: 0·244 g. neutralised 31·1 c.c. of 0·937*N*-hydrochloric acid. Calc. for diamine, 32·9 c.c.).

The diamine was characterised by its *dipicrate*, which, after repeated crystallisations from alcohol, yielded fine transparent yellow prisms, m. p. 134—135° (Found: N, 18·25. $C_{19}H_{22}N_2,2C_6H_3O_7N_3$ requires N, 18·2%).

δ-Diethylamino-α-methylbutylamino-9-phenanthridine Sulphate.—9-Chlorophenanthridine (4 g.) and α-diethylamino-δ-aminopentane (4 g.) were heated for 2 hours at 130° (oil-bath). The product was extracted with dilute hydrochloric acid, leaving unreacted 9-chlorophenanthridine (0·5 g.). Addition of alkali liberated the oily triamine, which was washed with very dilute caustic soda solution (water caused emulsification), dissolved in hot alcohol, and treated with a hot alcoholic solution of picric acid (2 equivs.). The *dipicrate* separated as a gum, which set slowly to a crystalline powder, conveniently purified by extraction with acetone (Soxhlet); an almost quantitative yield of small yellow plates, m. p. 196—197° after earlier progressive sintering, was obtained (Found: N, 16·35, 16·25. $C_{22}H_{29}N_3,2C_6H_3O_7N_3$ requires N, 15·9%). A monopicrate could not be prepared.

The dipicrate was decomposed slowly by heating with an excess of *N*-caustic soda, and the oily triamine liberated was extracted with methylene dichloride and dried over anhydrous potassium carbonate. Difficulty was experienced in isolating a crystalline salt of the base, but the *sulphate* was eventually obtained; it formed a gum with alcohol, but crystallised from a small quantity of water in long radiating needles which lost water of crystallisation on exposure; at 90—100° water was lost rapidly, leaving a very hygroscopic "glass" [Found for dried salt: N, 9·1 (Kjeldahl); SO_4, 21·9. $C_{22}H_{29}N_3,H_2SO_4$ requires N, 9·7; SO_4, 22·15%]. The 2% colourless aqueous solution has p_H *ca.* 4·5.

3-Bromo-9-β-diethylaminoethylaminophenanthridine Dihydrochloride.—3:9-Dibromophenanthridine (3 g.) and β-diethylaminoethylamine (3 g.) reacted vigorously at 120° with ebullition of the latter. After 2 hours the product was lixiviated with hot dilute hydrochloric acid; the oily base liberated on neutralisation of the extract was washed free from diamine by very dilute aqueous alkali, and then converted into its *dihydrochloride* by solution in hot dilute acid (2 equivs.): on cooling, white plates with pearly lustre (4·2 g.) separated. This hydrated salt was very soluble in water; the colourless 2% solution had p_H *ca.* 4 (Found for anhydrous salt: N, 9·45; Cl, 15·7; Br, 18·25. $C_{19}H_{22}N_3Br,2HCl$ requires N, 9·45; Cl, 15·95; Br, 18·0%. Found for hydrated salt: loss at 100°/red. press., 10·55. $3H_2O$ requires loss, 10·85%).

The *dipicrate* crystallised from acetone in thick yellow prisms, decomp. *ca.* 156° (Found: N, 15·0. $C_{19}H_{22}N_3Br,2C_6H_3O_7N_3$ requires N, 15·2%).

3-Bromo-9-δ-diethylamino-α-methylbutylaminophenanthridine Dihydrochloride.—The product obtained by heating equal quantities of 3:9-dibromophenanthridine and α-diethylamino-δ-aminopentane at 140° for 3 hours dissolved almost completely in dilute hydrochloric acid. The oily triamine liberated on neutralisation was converted into the *dipicrate*, which crystallised in almost quantitative yield from acetone in transparent yellow plates, decomp. 217—218° (Found: N, 14·55. $C_{22}H_{28}N_3Br,2C_6H_3O_7N_3$ requires N, 14·45%).

The salts of the triamine were very hygroscopic and had little tendency to crystallise; a *dihydrochloride*, after salting out from aqueous solution as an ill-defined white solid, crystallised from alcohol in microscopic needles extremely soluble in water; a 2% solution had p_H *ca.* 5, and showed a faint violet fluorescence (Found for salt dried at 90° in a vacuum: N, 8·5; Cl, 14·45; Br, 16·45. $C_{22}H_{28}N_3Br,2HCl$ requires N, 8·6; Cl, 14·55; Br, 16·45%).

2-Methoxy-9-β-diethylaminoethylaminophenanthridine Dihydrochloride.—9-Chloro-2-methoxyphenanthridine and β-aminotriethylamine condensed readily at 120° during 2 hours. The oily triamine was purified through its *dipicrate*, which crystallised from acetone or acetone–alcohol in thick yellow prisms, m. p. 207° (decomp.) after previous softening (Found: N, 15·95. $C_{20}H_{25}ON_3,2C_6H_3O_7N_3$ requires N, 16·1%). The triamine regenerated from its dipicrate was converted into a microcrystalline *dihydrochloride* after solution in hot alcoholic hydrochloric acid. This hygroscopic salt was extremely soluble in water; its solution (2%) showed notable

violet fluorescence, and had p_H 4·5 (Found for anhydrous salt: N, 10·9; Cl, 17·85. $C_{20}H_{25}ON_3,2HCl$ requires N, 10·6; Cl, 17·95%).

2-*Methoxy*-9-δ-*diethylamino*-α-*methylbutylaminophenanthridine Dihydrochloride* (III).—9-Chloro-2-methoxyphenanthridine (3 g.) and α-diethylamino-δ-aminopentane (3 g.), heated at 140° for 4 hours, yielded an oily triamine and 0·4 g. of unreacted chloro-compound. The *dipicrate* crystallised quantitatively from acetone in clusters of transparent acicular prisms, decomp. 192—193° (Found: N, 15·2. $C_{23}H_{31}ON_3,2C_6H_3O_7N_3$ requires N, 15·3%).

Isolation of the deliquescent dihydrochloride of the base liberated from this dipicrate presented unusual difficulty. An ethereal extract of the triamine was left for 24 hours over a potassium carbonate–charcoal mixture; the colourless supernatant solution was then treated with dry hydrogen chloride, a white salt separating which became sticky on exposure. It was dissolved in hot absolute alcohol and cooled in a desiccator; the liquid filled with colourless transparent plates of a *dihydrochloride*, which was dried in a vacuum over soda lime. This salt was extremely soluble in water; its 2% solution had p_H 5·5. Solutions of the salt in water or alcohol, or of the base itself in alcohol showed brilliant purple fluorescence (Found for the anhydrous salt: N, 10·1; Cl, 16·0. $C_{23}H_{31}ON_3,2HCl$ requires N, 9·6; Cl, 16·2%).

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