PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Improvements in or relating to Heterocyclic Compounds

We, MAY & BAKER LIMITED, a British Company, of Dagenham, Essex, England, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

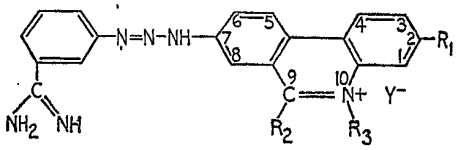
This invention is for improvements in or relating to phenanthridinium salts and to processes for their production, and has for its object the provision of new and therapeutically useful substances.

While many phenanthridine compounds, in the form of their quaternary salts, have heretofore been proposed for use as trypanocidal agents, only a few have been used to any substantial extent in the field. Not only degree of activity but also toxicity vary markedly with change in the number and nature of substituents and it is impossible at the present time to predict *a priori* the properties (if any) of any new phenanthridine compound.

As a result of research and experimentation, the present Applicants have prepared new phenanthridinium salts which have a high activity against blood parasites, such as trypanosomes, are surprisingly less toxic than known phenanthridinium salts possessing useful trypanocidal activity and, in consequence, exhibit an exceptionally high chemotherapeutic index.

The marked utility of the new compounds is manifested not only in the treatment of trypanosome infections but also in relation to babesiasis.

These new salts of the present invention are the *m* - amidinophenoyldiazoaminophenanthridinium salts represented by the formula:



I

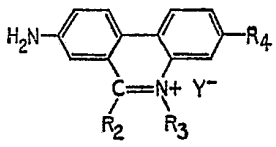
(wherein R_1 represents an amino or *m*-amidophenyldiazoamino group or a hydrogen atom, R_2 represents a phenyl or *p*-nitrophenyl group, R_3 represents a lower alkyl group and Y represents an anion, for example a chloride or bromide ion) including their acid addition salts. Insoluble acid addition salts, useful for certain applications, include those of embonic acid (2:2¹ - dihydroxy - 1:1¹ - dinaphthylmethane - 3:3¹ - dicarboxylic acid) and of suramin (symmetrical urea of *m*-aminodibenzoyl - *p* - methyl - *m* - aminobenzoyl-1-aminonaphthalene - 4:6:8 - trisulphonic acid).

According to a preferred feature of the invention R_2 represents a phenyl group and R_3 represents an ethyl group. Of outstanding importance are those salts containing the 7-(*m* - amidinophenyldiazoamino) - 2 - amino-10 - ethyl - 9 - phenylphenanthridinium or 2,7 - di - (*m* - amidinophenyldiazoamino)-10 - ethyl - 9 - phenylphenanthridinium cation.

The term "lower alkyl" as used in this specification and in the appended claims denotes that the group in question contains not more than 6 carbon atoms.

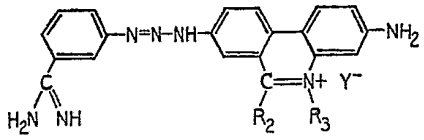
According to a feature of the invention, those salts of formula I in which R_1 represents an amino group or a hydrogen atom are prepared by coupling diazotized *m*-aminobenzamidine with an equimolecular proportion of a phenanthridinium salt of the general formula:

[*Price 3s. 6d.*]



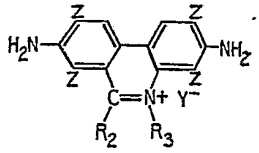
II

wherein R_4 represents a hydrogen atom or an amino group and the groups R_2, R_3 and Y are as hereinbefore defined. When R_4 is an amino group the aforesaid process inevitably leads to a mixture of isomers, the mixture containing as products red salts of the formula:



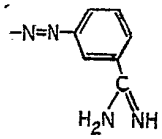
III

and isomeric purple salts of the formula:



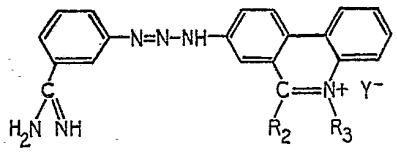
IV

wherein one of the symbols Z represents the group:—



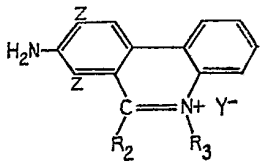
V

and the others represent hydrogen atoms. When R_4 is a hydrogen atom, an isomeric mixture of compounds is also obtained, the mixture containing as products orange salts of the formula:



VI

wherein R_2, R_3 and Y are as hereinbefore defined and the isomeric brick red salts of the formula:



VII

wherein R_2, R_3, Y and Z are as hereinbefore defined. The salts conforming to formulae III and VI (products within the scope of the invention) may be separated from those of formulae IV and VII respectively, for example, by fractional crystallisation from methanol in which the salts of formulae III and VI are less soluble than the salts of formulae IV and VII. It is not essential to effect such separation, however, as the salts of formulae IV and VII are also therapeutically active.

According to a further feature of the invention, those salts of formula I in which R_1 represents a hydrogen atom or a *m*-amidinophenyldiazoamino group, may be prepared by diazotizing or tetrazotizing a phenanthridinium salt of formula II wherein R_4 is a hydrogen atom or an amino group and coupling the resultant diazonium or bis-diazonium salt with *m*-aminobenzamidine.

The invention is illustrated by the following Examples, in which the temperatures stated were measured in degrees Centigrade.

EXAMPLE I

A solution of *m*-aminobenzamidine monohydrochloride dihydrate (51.9 g.) in water (225 ml.) and concentrated hydrochloric acid (56.5 ml.) was cooled to 0° and diazotised with sodium nitrite (17.6 g.) in water (100 ml.) any excess nitrous acid remaining being decomposed by the addition of sulphamic acid. The diazonium solution was added to a solution of 2:7 - diamino - 10 - ethyl-9-phenylphenanthridinium chloride (99.5 g.) in water (600 ml.) at 0°. To the stirred mixture, an ice-cold solution of sodium acetate (142.5 g.) in water (450 ml.) was added. Stirring was continued at 0° for 75 minutes and then a further quantity of sodium acetate (61.5 g.) together with sodium chloride (45 g.) dissolved in ice-cold water (450 ml.) was added. After 45 minutes the product was precipitated as a purple tar by the addition of saturated brine (600 ml.). The supernatant liquors were decanted. The purple residue was dissolved in water (1 l.) and reprecipitated with brine (500 ml.). Paper electrophoresis of the precipitated tar (No. 1 Whatman paper—"Whatman" is a Registered Trade Mark) in 3N acetic acid showed the presence of two main components, the more mobile one giving a purple spot, the less mobile one giving a yellow spot. Subsequent purification steps were followed by paper electrophoresis; the purple isomer isolated was found to correspond to the purple spot and the red isomer to the yellow spot. The presence of traces of unchanged 2:7-

diamino - 10 - ethyl - 9 - phenylphenanthridinium chloride in the unpurified reaction product was indicated, on paper electrophoresis, by the presence of a characteristic orange spot. The foregoing precipitated tar was dissolved in boiling water (300 ml.) and the solution rapidly cooled. The solid A which separated on standing in the refrigerator overnight was filtered off from the liquors B. On crystallisation of the solid A by dissolving it in boiling water and rapidly cooling the solution purple prisms, m.p. 258—260° (decomp.) were obtained.

To the liquors B, obtained as described above, saturated sodium bromide solution was added. The solid precipitate (60 g.) was washed with acetone and extracted with cold methanol (5 × 100 ml.) to leave a red residue (24.3 g., 15.5%) which was shown by paper electrophoresis to be an almost pure product. Crystallisation of this product from methanol gave 7 - (*m* - amidinophenyldiazoamino) - 2 - amino - 10 - ethyl-9-phenylphenanthridinium bromide hydrobromide as red needles, m.p. 240° (decomp.).

This bromide hydrobromide salt (1 g.) in methanol (700 ml.) was converted to the corresponding chloride hydrochloride by ion exchange through a column of Amberlite IRA 400 (" Amberlite " is a Registered Trade Mark) chloride resin. 7 - (*m* - Amidinophenyldiazoamino) - 2 - amino - 10 - ethyl-9 - phenylphenanthridinium chloride hydrochloride was obtained as red needles, m.p. 244—245° (decomp.).

EXAMPLE II

The coupling reaction between diazotised *m*-aminobenzamidine monohydrochloride dihydrate (103.7 g.) and 2:7 - diamino - 10-ethyl - 9 - phenylphenanthridinium chloride (199 g.) was carried out by a procedure similar to that described in Example I. Addition of saturated brine (1 l.) to the clear purple solution obtained at the end of the coupling reaction precipitated a tar from which the supernatant liquors were decanted. The tar was dissolved in water (2 l.) and reprecipitated with brine (1 l.). The tar so obtained was shown by paper electrophoresis to be free from 2:7 - diamino - 10-ethyl - 9 - phenylphenanthridinium chloride, whereas the supernatant liquors which were discarded still contained a trace of this material, in addition to a small amount of the red and purple compounds described in Example I. The tar was dissolved in water (2 l.) and saturated sodium bromide solution (500 ml.) added. The liquors were decanted and the residual tar pressed to remove as much of the aqueous phase as possible. The residue was then triturated with acetone (4 l.) until a friable solid was obtained. This solid was dried *in vacuo* over silica gel and passed through a 30 mesh sieve to give a purple powder (293 g.) containing 1.9% sodium bromide (5.5 g.). The powder was added during 20 minutes to stirred 4% (w/v) aqueous acetone (3.1) and stirring was continued for a further 45 minutes. The filtered solid was washed with 4% (w/v) aqueous acetone (1 l.) and resuspended in 4% w/v aqueous acetone (3 l.) and stirred for a further hour. The residue (275 g.) obtained after filtration and drying *in vacuo* over silica gel was free from sodium bromide. It was dissolved in 1:1 aqueous methanol (14.5 l.) and passed twice down a column (3" × 27") containing Amberlite IRA 400 chloride resin (2 kg.), which had previously been washed thoroughly with methanol (6 l.). The eluate was evaporated *in vacuo* to 800 ml. at an internal temperature of 20—30°. The remaining solvent was removed *in vacuo* over silica gel. The friable purple solid thus obtained was passed through a 30 mesh sieve and equilibrated with air for 3½ days to give a mixture [dark purple powder, m.p. (indefinite 220—230° (decomp.)] containing 7 - (*m* - amidinophenyldiazoamino) - 2 - amino - 10 - ethyl-9 - phenylphenanthridinium chloride hydrochloride.

EXAMPLE III

The coupling reaction between diazotised *m*-aminobenzamidine monohydrochloride dihydrate (51.9 g.) and 2:7 - diamino - 10-9-phenylphenanthridinium chloride (83.9 g.) and the isolation of the pure products was carried out in a manner closely similar to the procedure used in Example I. The pure purple compound was isolated as purple prisms, m.p. 278—279° (decomp.) in 26% yield. The red compound 7 - (*m* - amidinophenyldiazoamino) - 2 - amino - 10 - methyl-9- phenylphenanthridinium bromide hydrobromide was isolated as red needles, m.p. 245—246° (decomp.) in 4.5% yield.

EXAMPLE IV

A cold aqueous solution of *m* - amidinophenyldiazonium chloride (prepared from *m*-aminobenzamidine monohydrochloride dihydrate (103.8 g.), water (450 ml.) containing concentrated hydrochloric acid (113 ml.) and sodium nitrite (352 g.) in water (200 ml.)), was added, all at once, with rapid stirring, to a solution of 2:7 - diamino - 10-methyl - 9 - phenylphenanthridinium chloride hemiethanolate (167.8 g.) in water (1200 ml.) at 0°, followed by solution of sodium acetate (285 g.) in water (900 ml.). The reaction mixture was stirred at 0° for 1 hour, and then treated with an ice-cold solution of sodium acetate (124 g.), and sodium chloride (90 g.) in water (900 ml.). The dark mixture was stirred for a further 1 hour, and saturated aqueous sodium chloride (2 l.) was added. The black solid which separated was filtered off and dried over silica gel. Paper electrophoresis (by a procedure similar to that used in Example I) showed the presence

in this solid product of two components. The crude product (326 g.) was dissolved in water (7.5 l.) and potassium iodide (180 g.) added. The precipitated iodide hydriodide salt was filtered off, washed free from inorganic impurity with water, and dried under reduced pressure. The iodide hydriodide salt was converted back to the corresponding chloride hydrochloride by passing it in 2% w/v methanol solution down a suitable ion-exchange column in a manner similar to that described in Example II. The eluate from the column was evaporated to dryness under reduced pressure, giving a mixture [purple solid, m.p. 240—242° (decomp.)] containing 2 - amino - 7 - (*m* - amidinophenyldiazoamino) - 10 - methyl - 9 - phenylphenanthridinium chloride hydrochloride hemiethanolate trihydrate.

EXAMPLE V

A cold aqueous solution of *m*-amidinophenyldiazonium chloride (prepared from *m*-aminobenzamidine monohydrochloride dihydrate [15g.]) was added, all at once, to a stirred solution of 2:7—diamino - 10 - methyl - *p*-nitrophenylphenanthridinium chloride monohydrate (Walls and Whittaker, J. Chem. Soc., 1950, p. 46) in water (3 l.) at 10°. Sodium acetate (41.25 g.) in water (130 ml.) was quickly added, and the reaction mixture was stirred at 10° for 4 hours. The precipitate was filtered off and the sticky solid purified by precipitation from solution in water (1500 ml.) with sodium chloride (130 g.). The dark red solid thus obtained was dried over silica gel. Paper electrophoresis (by a procedure similar to that used in Example I) showed that the red solid was predominantly unchanged material together with a little of the expected red compound 7 - (*m* - amidinophenyldiazoamino) - 2 - amino - 10 - methyl-9 - *p* - nitrophenylphenanthridinium chloride hydrochloride tetrahydrate.

EXAMPLE VI

2:7 - Diamino - 10 - ethyl - 9 - phenylphenanthridinium chloride (9.6 g.) suspended in 2N hydrochloric acid (65 ml.) was tetrazotised with sodium nitrite (3.45 g.) in water (20 ml.) at 0—5°. Excess nitrous acid was removed by the addition of sulphamic acid, and the dark red solution was treated at 0°, with a solution of *m*-aminobenzamidine monohydrochloride dihydrate (10.375 g.) in water (30 ml.), containing 2N hydrochloric acid (20 ml.). A cooled solution of sodium acetate (21.3 g.) in water (67 ml.) was quickly added, and the reaction mixture was stirred at 0° for 1 hour. The brown precipitate was filtered off, washed with water (150 ml.) containing sodium chloride (20 g.) and dried over silica gel. 2:7 - Di - (*m* - amidinophenyldiazoamino) - 10 - ethyl - 9 - phenylphenanthridinium chloride dihydrochloride trihydrate was obtained as a brown solid, m.p. 245° (decomp.).

EXAMPLE VII

To a stirred solution of the product of Example II (8.8 g.) in water (120 ml.) at 20° a filtered solution of Suramin B.P. (7.5 g.) in water (50 ml.) was added. A clear solution was obtained instantaneously, from which a purple solid separated rapidly. Water (50 ml.) was added and the suspension obtained was stirred for 10 minutes. The gelatinous precipitate was filtered off, washed by resuspension in water (5 × 200 ml.) and dried *in vacuo* over silica gel. The dry solid was passed through a 30 mesh sieve and equilibrated with air for four days. The mixture obtained [a free running purple powder m.p. 290—295° (decomp.)] contained the suramin salt of the 7 - (*m* - amidinophenyldiazoamino) - 2 - amino - 10 - ethyl - 9 - phenylphenanthridinium anion as the 14 hydrate.

EXAMPLE VIII

A solution of the product of Example II (5.86 g.) in water (100 ml.) was added, all at once, to a stirred, freshly prepared solution of "embonic acid" (2:2¹ - dihydroxy-1:1¹ - dinaphthyl - methane - 3:3¹ - dicarboxylic acid) (4 g.) in water (50 ml.) and 2N ammonia (20 ml.) at 40°. Water (30 ml.) was added, and the suspension stirred for 20 minutes. The gelatinous precipitate was filtered off, washed by suspension in water (2 × 1 l.), and dried over silica gel.

The mixture obtained [a purple solid, m.p. 245—246° (decomp.)] contained the "embonate" (2:2¹ - dihydroxy - 1:1¹ - dinaphthylmethane - 3:3¹ - dicarboxylate) salt of the 7 - (*m* - amidinophenyldiazoamino)-2 - amino - 10 - ethyl - 9 - phenyl phenanthridinium anion as the trihydrate.

EXAMPLE IX

A fine suspension of 7 - acetamido - 2-amino - 10 - ethyl - 9 - phenylphenanthridinium chloride (16.5 g.) (prepared as described in British Patent Specification No. 746,027) in water (135 ml.) containing 2N sulphuric acid (63.5 ml.) was diazotised at 0—5° C. by the addition of sodium nitrite (3.3. g.) in water (10 ml.). After stirring at 0—5° C. for 2 hours, the trace of insoluble material was filtered off, and the solution was added to boiling ethanol (1.51 ml.) over 5 minutes. The pale red reaction mixture was refluxed for an hour, filtered, and the solution evaporated to dryness under reduced pressure. Trituration of the residue with acetone, filtration, followed by crystallisation of the yellow solid from 0.1N hydrochloric acid gave 7 - acetamido - 10 - ethyl - 9-phenylphenanthridinium chloride trihydrate as fine yellow needles, decomposing at 241% 242° C.

7-Acetamido - 10 - ethyl - 9 - phenylphenanthridinium chloride trihydrate (7.3 g.) was hydrolysed by refluxing with 2N hydrochloric acid (73 ml.) for 1.5 hours. The red solution was cooled to 5° C., diluted with N

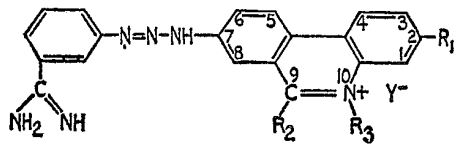
hydrochloric acid (55 ml.), and diazotized at 0—5° C. by the addition of sodium nitrite (1.9 g.). Excess nitrous acid was destroyed by the addition of sulphamic acid, and the diazonium solution was treated at 5—15° C. with *m*-aminobenzamidine monohydrochloride (4.6 g.) in water (14 ml.) and 2N hydrochloric acid (9 ml.). Anhydrous sodium acetate (23 g.) in water (69 ml.) was added, and the solution was stirred for 2 hours at 5—15° C. Sodium chloride (20 g.) was added, and the precipitate obtained was filtered off, ground with saturated brine, refiltered, and crystallised from aqueous ethanol. 7 - (*m* - Amidinophenyldiazoamino)10-ethyl-9 - phenylphenanthridinium chloride hydrochloride hydrate hemiethanolate separated as orange needles, decomposing at 260° C.

EXAMPLE X

2:7-Diamino-10-methyl - 9 - phenylphenanthridinium chloride (8.1 g.) in 2N hydrochloric acid (65 ml.) and water (20 ml.) was tetrazotized at 5° C. by the slow addition of sodium nitrite (3.45 g.). After removal of excess nitrous acid by the addition of sulphamic acid, the filtered solution was treated with *m* - aminobenzamidine monohydrochloride (8.6 g.) in water (30 ml.) and 2N hydrochloric acid (20 ml.), at 5—10° C. The reaction mixture was treated with anhydrous sodium acetate (21.3 g.) in water (67 ml.), and mechanically stirred for 1 hour at 5—10° C. The brown solid was filtered off, washed well with dilute aqueous sodium chloride, and dried over sulphuric acid. 2:7-Di - (*m* - amidinophenyldiazoamino) - 10-methyl - 9 - phenylphenanthridinium chloride dihydrochloride dihydrate was obtained as brown granules, decomposing at 243° C.

WHAT WE CLAIM IS:—

1. The *m*-amidinophenyldiazoaminophenanthridinium salts represented by the formula:



(wherein R_1 represents an amino or *m*-amidinophenyldiazoamino group or a hydrogen atom, R_2 represents a phenyl or *p*-nitrophenyl group, R_3 represents a lower alkyl group and Y represents an anion) including their acid addition salts.

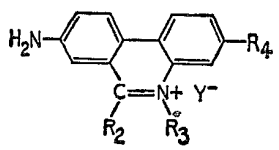
2. Phenanthridinium salts as claimed in claim 1 wherein R_2 represents a phenyl group and R_3 represents an ethyl group.

3. A salt according to claim 1 containing the 7 - (*m*- amidinophenyldiazoamino) - 2-amino - 10 - ethyl-9-phenylphenanthridinium cation.

4. A salt according to claim 1 containing the 2,7 - di - (*m* - amidinophenyldiazoamino)-10 - ethyl - 9 - phenylphenanthridinium cation.

5. An acid addition salt of a compound as claimed in either of claims 3 and 4.

6. Process for the preparation of a mixture of isomeric compounds including a phenanthridinium salt as defined in any of claims 1 to 3 wherein R_1 represents an amino group or a hydrogen atom which comprises diazotizing *m*-aminobenzamidine and coupling the resulting diazonium salt with an equimolecular proportion of a phenanthridinium salt of the general formula:



wherein R_4 represents a hydrogen atom or an amino group and the groups R_2, R_3 and Y are as defined in claim 1.

7. Process according to claim 6 which comprises the further step of isolating from the mixture of isomers the phenanthridinium salt as defined in any of claims 1—4.

8. Process for the preparation of phenanthridinium salts as claimed in claim 1 or 2 wherein R_1 represents a hydrogen atom which comprises diazotizing a salt of the formula specified in claim 6 wherein R_4 is a hydrogen atom and coupling the resulting diazonium salt with *m*-aminobenzamidine.

9. Process for the preparation of phenanthridinium salts as claimed in claim 1 or 2 wherein R_1 represents a *m*-amidinophenyldiazoamino group, which comprises tetrazotizing a salt of the formula specified in claim 6 wherein R_4 is an amino group and coupling the resulting bis-diazonium salt with *m*-aminobenzamidine.

10. Process as claimed in claim 6, 7, 8 or 9 when carried out substantially as described in any one of the foregoing Examples.

11. A mixture of isomeric compounds including a compound as defined in any of claims 1—4 when prepared by the process of claim 6.

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PROVISIONAL SPECIFICATION

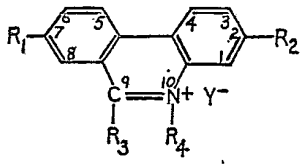
Improvements in or relating to Heterocyclic Compounds

We, MAY & BAKER LIMITED, a British Company, of Dagenham, Essex, England, do hereby declare this invention to be described in the following statement:—

This invention is for improvements in or relating to phenanthridinium salts and to processes for their production, and has for its object the provision of new and therapeutically useful substances. This application is a division of Application No. 21814/56 (Serial No. 855,231).

While phenanthridine compounds, in the form of their quaternary salts, have heretofore been proposed for use as trypanocidal agents, only a few have been used to any substantial extent in the field. Not only degree of activity but also toxicity vary markedly with change in the number and nature of substituents and it is impossible at the present time to predict *a priori* the therapeutic properties (if any) of any new phenanthridine compound.

In the specification of co-pending Application No. 9217/56 (Serial No. 834,231) the present Applicants have disclosed new phenanthridinium salts which have a high activity against blood parasites, such as trypanosomes, are surprisingly less toxic than known phenanthridinium salts possessing useful trypanocidal activity and, in consequence, exhibit an exceptionally high chemotherapeutic index. These new salts are the *p*-amidinophenyldiazoaminophenanthridinium salts represented by the general formula:



wherein one of R_1 and R_2 represents a *p*-amidinophenyldiazoamino group and the other represents an amino or *p*-amidinophenyldiazoamino group or a hydrogen atom, R_3 represents an alkyl, aryl or substituted aryl group, including a *p*-(*p*-amidinophenyldiazoamino)phenyl group, R_4 represents an alkyl (preferably lower alkyl group) and Y represents an anion, for example a chloride or bromide ion.

As the result of further development work further, chemically related compounds possessing similar chemotherapeutic properties, have now been prepared. These new compounds are also substituted phenyldiazoaminophenanthridinium salts and conform to the foregoing formula if one of R_1 and R_2 represents a *meta*-amidinophenyldiazoamino group and the other is a substituted phenyldiazoamino group, an amino group or a hydrogen atom, R_3 represents an alkyl, aryl or substituted aryl group and R_4 and Y are as hereinbefore defined.

The compounds of the present invention may be prepared by diazotizing the appropriate substituted aniline and coupling the resultant diazonium salt with an aminophenanthridinium salt as disclosed in the aforesaid prior specification. Alternatively, they may be obtained by diazotizing or tetrazotizing the appropriate phenanthridinium salt and coupling the resultant salt with the appropriate substituted aniline.

The invention is illustrated by the following Example which discloses the preparation of an individual compound believed to be of outstanding importance.

EXAMPLE

7(or 2) - (*m*- Amidinophenyldiazoamino)-2(or 7) - amino - 10 - ethyl - 9 - phenylphenanthridinium bromide hydrobromide methanolate, purple prisms, m.p. 257—258° C. (decomp.), was prepared in a manner similar to that described in Example I of copending Application No. 21814/56 (Serial No. 855,231) by coupling diazotized *m*-aminobenzamidine with 2:7 - diamino - 10-ethyl - 9 - phenylphenanthridinium chloride and treating an aqueous solution of the crude product with sodium bromide before crystallisation from methanol.

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