1,009,301

PATENT SPECIFICATION

NO DRAWINGS

1,009,301

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Int. Cl.:—C 07 d // A 61 k

The inventors of this invention in the sense of being the devisers thereof within the meaning of Section 16 of the Patents Act 1949, are: ARTHUR PAGE PHILLIPS, 5 Hilary Way, Twickaloe, New York, and ROBERT B. BURROWS, 6 Western Drive, Ardsley, New York, both citizens and residents of the United States of America.

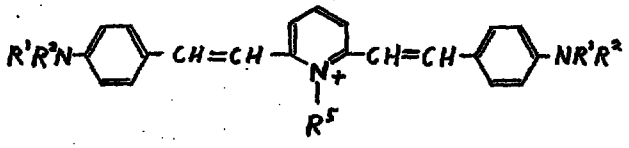
COMPLETE SPECIFICATION

Styryl-Pyridinium Compounds, the Preparation thereof, and Pharmaceutical Compositions thereof

We, THE WELLCOME FOUNDATION LIMITED, a Company incorporated in England, of 183—193 Euston Road, London, N.W.1, 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:—

The present invention relates to styryl-pyridinium compounds, to the preparation thereof and to pharmaceutical compositions thereof.

It has been found that compounds of the distilbazole cation of formula (I) are active against parasitic nematode worms, for example *Syphacia obvelata* and *Aspiculuris tetraptera* in mice, *Ancylostoma caninum*, *Toxocara canis* and *T. cati* in dogs and cats, *Uncinaria stenocephala*, *Toxascaris leonina* and *Trichuris vulpis* in dogs, *Trichuris trichiura*, *Oesophagostomum apiostomum* and *Physaloptera* spp. in monkeys and *Enterobius vermicularis* (the common threadworm or pinworm) in man.



(I)

In formula (I): NR^1R^2 is the same in each occurrence and is a dimethylamino, *N*-ethyl-*N*-methylamino, diethylamino pyrrolidino or piperidino group; and R^5 is a methyl, ethyl, n-propyl, n-butyl or benzyl group.

The iodides of the 1-methyl-2,6-bis-(*p*-dimethylaminostyryl)-pyridinium, 1-ethyl-2,6-bis-(*p*-dimethylaminostyryl)pyridinium and 1-methyl-2,6-bis-(*p*-diethylaminostyryl)-pyridinium cations have been described in the literature, but have not previously been described as having any biological activity.

The anthelmintic activity of the compounds resides in the cation, and the anion associated with the cation is relatively unimportant. However, it is preferably pharmacologically and pharmaceutically acceptable, being, for example, iodide, bromide, chloride, *p*-toluenesulphonate, methylsulphate or ethylsulphate.

The preferred compounds of the distilbazole cation of formula (I) are those wherein NR^1R^2 is a pyrrolidino or piperidino group and R^5 is a methyl, ethyl or n-propyl group. These preferred compounds have low oral toxicities in mice.

In the following Table the activities and toxicities of iodides of the distilbazole cation of formula (I) are given. The iodides were found to be sufficiently non-toxic at the doses used and were administered orally to mice in single doses measured in terms of mg. of cation to kg. body weight of the mice. The activities were measured against *Syphacia obvelata* in terms of the percentage of worms removed. The toxicities were measured as LD_{50}.

[*Price 4s. 6d.*]

TABLE

NR^1R^2	R^5	Activity		LD_{50}
		Dose	Activity	
$N(CH_3)_2$	CH_3	15	100	25
		10	97	
$N(CH_3)_2$	C_2H_5	20	100	35
		10	97	
$N(CH_3)_2$	$CH_2.C_6H_5$	20	100	
		10	93	
$N(C_2H_5)_2$	CH_3	20	99	25
		10	99	
$N[CH_2]_4$	CH_3	20	96	>1000
		10	92	
$N[CH_2]_4$	C_2H_5	20	100	1350
		10	95	
$N[CH_2]_4$	$n\text{-}C_3H_7$	20	100	>1000
		15	100	
$N[CH_2]_5$	CH_3	20	100	>1000
		10	98	
$N[CH_2]_5$	C_2H_5	20	100	800
		10	100	
$N[CH_2]_5$	$n\text{-}C_3H_7$	20	100	450
		10	98	
$N[CH_2]_5$	$n\text{-}C_4H_9$	20	99	
		10	88	

The compounds of the distilbazole cation of formula (I) are prepared by the condensation of two equivalents of an appropriate *N,N* - disubstituted *p* - aminobenzaldehyde

$$(p\text{—}NR^1R^2.C_6H_4.CHO)$$

with one equivalent of a 1-R^5-2,6-dimethylpyridinium salt. The reaction is conveniently effected in a solvent (for example a lower alcohol) in the presence of a basic catalyst such as a secondary amine (for example piperidine).

It is preferable that the anion in the 1-R^5-2,6-dimethylpyridinium salt is the anion which is desired to be associated with the distilbazole cation of formula (I), because the compounds of the distilbazole cation are very sparingly soluble in most solvents and the double decomposition of the compounds into salts of any other anion is rather troublesome. To obtain the desired anion in the 1-R^5-2,6-dimethylpyridinium salt, the salt is prepared by quaternisation of 2,6-dimethylpyridine with a compound R^5X, wherein X is an equivalent of the desired anion, or by double decomposition of the salt prepared into that of the desired anion. For example, if R^5 is to be ethyl and X is to be iodide or ethylsulphate, ethyl iodide or diethyl sulphate respectively is used in the quaternisation of 2,6 - dimethylpyridine; or if a 1-R^5-2,6-dimethylpyridinium iodide is prepared and the chloride is desired, the double decomposition may be effected by warming the iodide with methanolic hydrogen chloride.

The chemistry of the preparation of the 1-R^5-2,6-dimethylpyridinium salt and of the compounds of the distilbazole cation of formula (I) limits fairly precisely the nature of the group R^5 in the compounds of the distilbazole cation. The normal diminution in the reactivity of alkyl halides with the increasing size of the alkyl group is accentuated by the steric hindrance of the two methyl groups in 2,6-dimethylpyridine. Therefore, R^5 is not a branched alkyl group and the alkyl group is limited to containing not more than four carbon atoms. Also, the more reactive benzyl group is usable.

The compounds of the distilbazole cation of formula (I) may be presented in

association with a pharmaceutically acceptable carrier therefor in a pharmaceutical composition for oral administration. This may be made by any known method, such as admixture. Fine powders or granules of the compounds may contain diluting, dispersing and surface active agents, and may be presented in a draft or drench in water or in a syrup; in capsules or cachets in the dry state or in a suspension, when a suspending agent may be included; in tablets when binding and lubricating agents may be included; in a suspension in water or a syrup or an oil, or in a water/oil emulsion, when flavouring, preserving, suspending, thickening and emulsifying agents may be included; or in the food of the host of the worms. The granules or the tablets may be coated.

The compounds of the distilbazole cation of formula (I) are dark-coloured crystals, whose surface colour ranges from dark red almost to black and whose solutions, if sufficiently concentrated, range from pink to red In water, however, the compounds are so insoluble that the water is not visibly coloured. The colour is due to an intense but broad absorption band; the maximum is at about 495 mμ (Cm=55,000 to 60,000), but intense absorption (Cm=40,000 or over) occurs from about 460 mμ to about 530 mμ.

The compounds of the distilbazole cation of formula (I) melt well above 200°C. They melt probably with decomposition, this being somewhat dependent on the rate of heating. Further, the dark colour of the compounds renders precise observation of the melting points extremely difficult. Therefore, the data on the melting points in the following Examples must be regarded as only approximate. They are of little value for identification and are of no value as criteria of purity.

The following Examples illustrate but in no way limit the scope of the present invention. All temperatures are given in degrees Centigrade.

Example 1

A mixture of 1 - ethyl - 2,6 - dimethylpyridinium iodide (2.6 g.), methanol (100 ml.), *p* - pyrrolidinobenzaldehyde (4.2 g.) and piperidine (1 ml.) was refluxed on a steam bath. In less than 1' hour solid 1 - ethyl - 2,6 - bis - (*p* - pyrrolidinostyryl)pyridinium iodide precipitated and heavy bumping started. After 2 hours the solid was collected and the filtrates refluxed for a further 20 hours. A second crop was obtained, and on standing another day a third crop was obtained. The product had a had a melting point of 282—283°.

The product was nearly insoluble in hot methanol and was purified by washing several times with ether and then digesting once or twice with ten to twenty times its weight of hot methanol. Because it was difficult to recrystallise, nearly all insoluble impurities such as dust and boiling stones were removed from the easily purified reactants before the final condensation stage and were avoided as much as possible thereafter.

On a larger scale, the bumping in the final condensation stage became a major problem. In such cases a powerful stirrer was used or the reaction-mixture was held at 60—65°, that is, below the boiling point of methanol.

Example 2

1 - Ethyl - 2,6 - dimethylpyridinium iodide (10 g.) was dissolved in methanol (200 ml.) and hydrogen chloride was run in until 20 g. had been absorbed. The solution was then warmed on a steam-bath, most of the solvent being gradually distilled out. Methanolic hydrogen chloride (100 ml.; 10%) was then added, and the procedure repeated. The flask was evacuated on a steam-bath, and the residue of 1 - ethyl - 2,6 - dimethylpyridinium chloride was suitable for synthetic purposes.

1 - Ethyl - 2,6 - dimethylpyridinium chloride and *p* - pyrrolidinobenzaldehyde were condensed in a manner similar to that described in Example 1. 1 - Ethyl - 2,6 - bis - (*p* - pyrrolidinostyryl)pyridinium chloride decomposed above 270°.

Example 3

The following compounds were prepared in a manner similar to that described in Examples 1 and 2:

a) 1 - methyl - 2,6 - bis - (*p* - pyrrolidinostyryl)pyridinium iodide, melting with decomposition at 295—297°;

b) 1 - n - propyl - 2,6 - bis - (*p* - pyrrolidinostyryl)pyridinium iodide, melting with decomposition at 265—267°; and

c) 1 - n - propyl - 2,6 - bis - (*p* - pyrrolidinostyryl)pyridinium *p* - toluenesulphonate, decomposing about 260°.

EXAMPLE 4

N-Phenylpiperidine was converted into *p* - piperidinobenzaldehyde, melting point 63—64°, by reaction with *N,N* - dimethylformamide and phosphoryl chloride, and was used to prepare the following compounds in a manner similar to that described in Example 1:

a) 1 - methyl - 2,6 - bis - (*p* - piperidinostyryl)pyridinium iodide, melting with decomposition at 222—225°;

b) 1 - ethyl - 2,6 - bis - (*p* - piperidinostyryl)pyridinium iodide, melting with decomposition at 242—244°;

c) 1 - n - propyl - 2,6 - bis - (*p* - piperidinostyryl)pyridinium iodide, melting with decomposition at 228—229°; and

d) 1 - n - butyl - 2,6 - bis - (*p* - piperidinostyryl)pyridinium iodide, melting with decomposition at 245—247°.

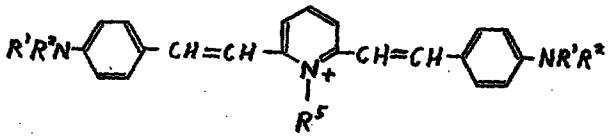
EXAMPLE 5

In a manner similar to that described in Example 1, 1 - benzyl - 2,6 - bis - (*p*-dimethylaminostyryl)pyridinium iodide, melting with decomposition at 206—207°, was prepared.

1 - Methyl - 2,6 - bis - (*p* - diethylaminostyryl)pyridine iodide melting with decomposition at 235—236°C, may be prepared in a manner similar to that described in Example 1.

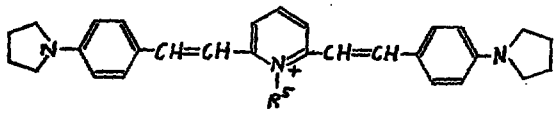
WHAT WE CLAIM IS:—

1. A method for the preparation of compounds of the distilbazole cation of the formula:



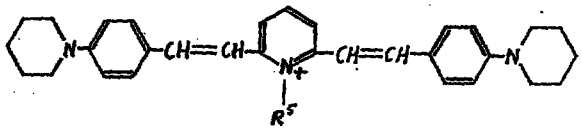
wherein NR^1R^2 is the same in each occurrence is a dimethylamino - *N* - ethyl - *N* - methylamino, diethylamino, pyrrolidino or piperidino group, and R^5 is a methyl, ethyl, n-propyl, n-butyl or benzyl group, other than the iodides of the 1-methyl-2,6-bis - (*p* - dimethylaminostyryl) - pyridinium, 1 - methyl - 2,6 - bis - (*p* - diethylaminostyryl)pyridinium and 1 - ethyl - 2,6 - bis - (*p* - dimethylaminostyryl)pyridinium cations; characterised in that two equivalents of an appropriate *N,N* - di - substituted *p* - aminobenzaldehyde of formula $R—R^1R^2N—C_6H_5.CHO$ are condensed with one equivalent of a 1-R^5-2,6-dimethylpyridinium salt.

2. A method for the preparation of a compound with a cation of the formula



wherein R^5 is a methyl, ethyl or n-propyl group characterised in that two equivalents of *p* - pyrrolidinobenzaldehyde are condensed with one equivalent of a 1-R^5-2,6-dimethylpyridinium salt in a solvent in the presence of a basic catalyst.

3. A method for the preparation of a compound with a cation of the formula



wherein R^5 is a methyl, ethyl or n-propyl group characterised in that 2 equivalents of *p* - piperidinobenzaldehyde are condensed with one equivalent of a 1-R^5-2,6-dimethylpyridinium salt.

4. A method for the preparation of a 1 - ethyl - bis - 2,6 - (*p* - pyrrolidinostyryl)pyridinium salt which comprises the reaction of two equivalents of *p* - pyrrolidinobenzaldehyde with one equivalent of a 1 - ethyl - 2,6 - dimethylpyridinium salt in a solvent in the presence of a basic catalyst.

5. A method for the preparation of 1 - ethyl - bis - 2,6 - (*p* - pyrrolidinostyryl)-pyridinium iodide which comprises the reaction of two equivalents of *p* - pyrrolidino-

EXAMPLE 4

N-Phenylpiperidine was converted into *p* - piperidinobenzaldehyde, melting point 63—64°, by reaction with *N,N* - dimethylformamide and phosphoryl chloride, and was used to prepare the following compounds in a manner similar to that described in Example 1:

a) 1 - methyl - 2,6 - bis - (*p* - piperidinostyryl)pyridinium iodide, melting with decomposition at 222—225°;

b) 1 - ethyl - 2,6 - bis - (*p* - piperidinostyryl)pyridinium iodide, melting with decomposition at 242—244°;

c) 1 - n - propyl - 2,6 - bis - (*p* - piperidinostyryl)pyridinium iodide, melting with decomposition at 228—229°; and

d) 1 - n - butyl - 2,6 - bis - (*p* - piperidinostyryl)pyridinium iodide, melting with decomposition at 245—247°.

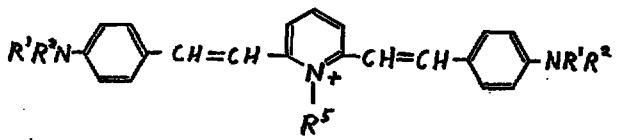
EXAMPLE 5

In a manner similar to that described in Example 1, 1 - benzyl - 2,6 - bis - (*p*-dimethylaminostyryl)pyridinium iodide, melting with decomposition at 206—207°, was prepared.

1 - Methyl - 2,6 - bis - (*p* - diethylaminostyryl)pyridine iodide melting with decomposition at 235—236°C, may be prepared in a manner similar to that described in Example 1.

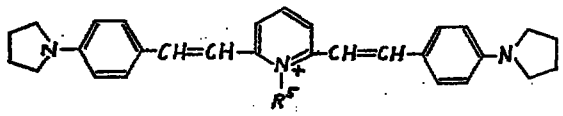
WHAT WE CLAIM IS:—

1. A method for the preparation of compounds of the distilbazole cation of the formula:



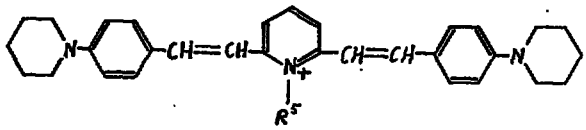
wherein NR^1R^2 is the same in each occurrence is a dimethylamino - *N* - ethyl - *N* - methylamino, diethylamino, pyrrolidino or piperidino group, and R^5 is a methyl, ethyl, n-propyl, n-butyl or benzyl group, other than the iodides of the 1-methyl-2,6-bis - (*p* - dimethylaminostyryl) - pyridinium, 1 - methyl - 2,6 - bis - (*p* - diethylaminostyryl)pyridinium and 1 - ethyl - 2,6 - bis - (*p* - dimethylaminostyryl)pyridinium cations; characterised in that two equivalents of an appropriate *N,N* - di - substituted *p* - aminobenzaldehyde of formula $R—R^1R^2N—C_6H_5.CHO$ are condensed with one equivalent of a 1-R^5-2,6-dimethylpyridinium salt.

2. A method for the preparation of a compound with a cation of the formula



wherein R^5 is a methyl, ethyl or n-propyl group characterised in that two equivalents of *p* - pyrrolidinobenzaldehyde are condensed with one equivalent of a 1-R^5-2,6-dimethylpyridinium salt in a solvent in the presence of a basic catalyst.

3. A method for the preparation of a compound with a cation of the formula



wherein R^5 is a methyl, ethyl or n-propyl group characterised in that 2 equivalents of *p* - piperidinobenzaldehyde are condensed with one equivalent of a 1-R^5-2,6-dimethylpyridinium salt.

4. A method for the preparation of a 1 - ethyl - bis - 2,6 - (*p* - pyrrolidinostyryl)pyridinium salt which comprises the reaction of two equivalents of *p* - pyrrolidinobenzaldehyde with one equivalent of a 1 - ethyl - 2,6 - dimethylpyridinium salt in a solvent in the presence of a basic catalyst.

5. A method for the preparation of 1 - ethyl - bis - 2,6 - (*p* - pyrrolidinostyryl)-pyridinium iodide which comprises the reaction of two equivalents of *p* - pyrrolidino-

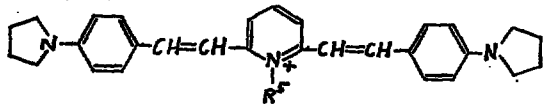
* C L M S *

benzaldehyde with one equivalent of 1 - ethyl - 2,6 - dimethylpyridinium iodide in a solvent in the presence of piperidine.

6. A method for the preparation of styrylpyridinium compounds as defined in claim 1 substantially as hereinbefore described.

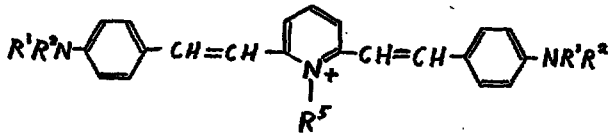
7. A method for the preparation of styrylpyridinium compounds as defined in claim 1 substantially as hereinbefore described in any of the examples.

8. A method for the preparation of a compound with a cation of the formula



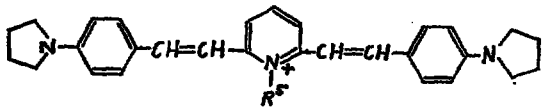
wherein R^5 is a methyl, ethyl, or n-propyl group which comprises the reaction between 2 equivalents of *p*-pyrrolidinobenzaldehyde with one equivalent of a 1 - (methyl, ethyl or n-propyl) - 2,6 - dimethylpyridinium salt.

9. An oral pharmaceutical composition comprising a therapeutically acceptable salt having a cation of the formula



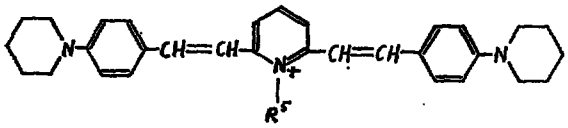
wherein NR^1R^2 is the same in each occurrence and is a dimethylamino, diethylamino or *N* - ethyl - *N* - methylamino group and R^5 is a methyl, ethyl, n-propyl, n-butyl or benzyl group together with a pharmaceutically acceptable carrier therefor, but not including a simple solution or suspension of the said salt in a liquid or mixture of liquids of the type commonly employed in chemical work as solvents, unless another pharmaceutical excipient is also included.

10. An oral pharmaceutical composition comprising a therapeutically acceptable salt having a cation of the formula



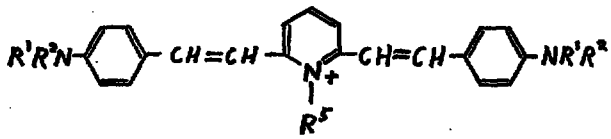
wherein R^5 is a methyl, ethyl, n-propyl, n-butyl or benzyl group together with a pharmaceutically acceptable carrier therefor.

11. An oral pharmaceutical composition comprising a therapeutically acceptable salt having a cation of the formula



wherein R^5 is a methyl, ethyl, n-propyl, n-butyl or benzyl group together with a pharmaceutically acceptable carrier therefor.

12. A compound with a cation of the formula



wherein NR^1R^2 is the same in each occurrence and is a dimethylamino, *N* - ethyl - *N*-methylamino, diethylamino, pyrrolidino or piperidino group, and R^5 is a methyl, ethyl, n-propyl, n-butyl or benzyl group; other than the iodides of the 1-methyl-2,6-bis-(*p*-dimethylaminostyryl)pyridinium 1 - methyl - 2,6 - bis - (*p* - diethylaminostyryl) pyridinium and 1 - ethyl - 2,6 - bis - (*p* - dimethylaminostyryl) - pyridinium cations.

* C L M S *

13. A compound of the 1 - methyl - 2,6 - bis - (*p* - pyrrolidinostyryl) - pyridinium cation.

14. A compound of the 1 - ethyl - 2,6 - bis - (*p* - pyrrolidinostyryl)pyridinium cation.

15. A compound of the 1 - n - propyl - 2,6 - bis - (*p* - pyrrolidinostyryl) - pyridinium cation.

16. A compound of the 1 - methyl - 2,6 - bis - (*p* - piperidinostryl)pyridinium cation.

17. A compound of the 1 - ethyl - 2,6 - bis - (*p* - piperidinostyryl)pyridinium cation.

18. A compound of the 1 - n - propyl - 2,6 - bis - (*p* - piperidinostyryl)pyridinium cation.

19. 1 - Ethyl - 2,6 - bis - (*p* - pyrrolidinostyryl)pyridinium iodide.

20. Styryl - pyridinium compounds when prepared by the method claimed any of the claims 1 to 8.

R. F. HASLAM,
Agent for the Applicants
Chartered Patent Agent.

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