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(54) Title: Improvements relating to the processing of tobacco leaves

(57) Abstract: Lamina and stem components of tobacco leaf are fed simultaneously to a milling machine such that there is produced a fluent mixture of lamina and stem particles. The mixture, with little or no further particle size reduction can be fed to a cigarette making machine.

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(56) Documents cited: GB 2 187 632 A GB 1 475 811

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IMPROVEMENTS RELATING TO THE PROCESSING OF TOBACCO LEAVES

This invention relates to the processing of tobacco leaf material in the manufacture of smoking articles.

Tobacco leaves of the types used in the manufacture of cigarettes and like smoking articles comprise leaf lamina, a longitudinal main stem (rib) and veins extending from the main stem. The main stem and large veins are hereinafter jointly referred to as 'stem'. The stem has substantially different physical properties from the lamina, and it is long-established practice to separate the stem from the lamina at an early stage in the processing of tobacco leaves, the stem and lamina then being processed independently and differently.

The manner in which stem material is separated from lamina material is generally by means of a complex and large threshing plant comprising a number, eight for example, of serially arranged threshing machines with classification units disposed intermediate next adjacent threshing machines.

As is well known, the separated stem material, or a proportion of it, after suitable reduction in size, is often added back to the lamina after the lamina has been subjected to further processing. Stem material is often desirable in the tobacco blend to improve fill value.

It is general practice in the reduction of stem size for the size reduction to take place when the moisture alkyl, (1-4C)alkoxy and trifluoromethyl, and the pharmaceutically acceptable salts thereof. It has now been discovered, and herein lies the basis of the claimed invention, that particularly useful leukotriene antagonist properties are shown by novel carbamoyl derivates of formula Ia in which R^1 is 2-methyl-4,4,4-trifluorobutyl, and the other groups have specified values, as defined below.

According to the invention there is provided a 5-(2-methyl-4,4,4-trifluorobutylcarbamoyl)indole derivative of formula I both in racemic form and in the form of a substantially pure enantiomer, particularly the (<u>R</u>)-form; or a pharmaceutically acceptable salt thereof.

It will be appreciated that, owing to the asymmetrically substituted carbon atom in the 2-methyl-4,4,4-trifluorobutylcarbamoyl group, the compound of formula I may exist in, and be isolated in, optically-active and racemic forms. The compound may exhibit polymorphism. The compound may form solvates. It is to be understood that the present invention encompasses any racemic, optically-active or polymorphic form, or solvate, or mixtures thereof, which form possesses leukotriene antagonist properties, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form or by synthesis from optically-active starting materials) and how to determine the leukotriene antagonist properties by the standard tests described hereinafter. It may be preferred to use the compound of formula I in a form which is characterized as containing, for example, at least 95%, 98% or 99% enantiomeric excess (ee) of the (<u>R</u>)-form.

It is preferred that the 2-methyl-4,4,4-trifluorobutyl carbamoyl group be of the optically active (<u>R</u>)-form.

Germany (Federal Republic)

954 136

New Zealand

139 007

United Kingdom

1855/2134; 413 486; 2 026 298; 2 078 085; 2 118 817; 2 119 220 and 2 131 671

United States

55 173; 68 597; 207 140; 210 191; 250 731; 358 549; 360 797; 535 134; 2 184 567; 3 026 878; 3 128 775; 3 204 641; 3 690 328; 3 845 774; 4 195 646; 4 210 157; 4 248 253; 4 323 083; 4 392 501; 4 582 070; 4 696 312 and 4 706 691.

According to one aspect thereof the present invention provides a method of processing tobacco leaf material, wherein tobacco leaf lamina and tobacco leaf stem are fed together through a leaf reduction apparatus, the arrangement of said apparatus and the processing conditions being such that there exits said apparatus a product which is a mixture comprising flakes of said lamina and shreds of said stem.

According to another aspect thereof the present invention provides a smoking material comprising a mixture of lamina particles and stem particles, which material is the product of feeding tobacco leaf lamina and tobacco leaf stem together through a leaf reduction apparatus.

Lamina and stem fed to the leaf reduction apparatus are suitably comprised in whole leaf, as hereinbelow defined. However, the lamina, or a proportion thereof, fed to the

the range of, for example, 10 to 50 °C, but preferably at or near ambient temperature.

Alternatively, a reactive derivative of a benzoic acid of formula II, for example, an acid halide (such as the acid chloride), acid anhydride or a mixed acid anhydride (such as that formed from N,N-diphenylcarbamic acid and the benzoic acid of formula II by reaction of the sodium salt of the latter acid with N,N-diphenylcarbamoylpyridinium chloride), may be reacted with an alkali metal salt (such as the lithium, sodium or potassium salt) of 2-methylbenzenesulfonamide, conveniently at or near ambient temperature and in a suitable solvent or diluent, for example, tetrahydrofuran, dimethylformamide or methylene chloride.

A benzoic acid of formula II wherein T is a carboxy group may be obtained by decomposing a suitable benzoic ester of formula II in which T is $COOR^h$ wherein R^h is a conveniently removed acid protecting group (which compound is hereinafter referred to as "benzoic ester of formula II"), for example, phenyl, benzyl, or (1-6C)alkyl optionally bearing an acetoxy, (1-4C)alkoxy or (1-4C)alkylthio substituent. A particular value for R^h is, for example, methyl, ethyl, propyl, _t_-butyl, acetoxymethyl, methoxymethyl, 2-methoxyethyl, methylthiomethyl, phenyl, or benzyl. A preferred value for R^h is methyl.

It will be appreciated that the decomposition of a benzoic ester of formula II can be performed using any one of a variety of procedures well known in the art of organic chemistry. A preferred method for decomposing an ester of formula II comprises reacting the ester with a suitable base, for example, as described in Example 1.f. When such a method is employed, the resulting benzoic acid of formula II, wherein T is a carboxy group, is initially obtained as leaf reduction apparatus.

The feed of leaf material to the leaf reduction apparatus may be assisted by the maintenance at the product outlet of the apparatus of a reduced air pressure, as for example, by way of use of an air lift, or by the maintenance of an elevated air pressure at the product inlet of the apparatus.

Preferably, the feed of the leaf material to the leaf reduction apparatus should be a continuous feed. It is advantageous for the feed rate to be substantially constant.

According to a yet further aspect thereof the present invention provides a smoking article filler material, which filler material is a fluent mixture comprising lamina particles and stem particles, the shape factor of about 60 per cent or more of the dust free particles of which mixture is 0.5 or above.

The concept of 'shape factor' is defined hereinbelow.

According to a yet further aspect thereof the present invention provides a method of making cigarettes, wherein tobacco bale material is reduced to provide discrete whole leaf, as hereinbefore defined; the whole leaf is fed through a mill such that there exits said mill a product which is a mixture comprising flakes of lamina and shreds of stem; and said mixture is fed to a cigarette rod making machine.

We have found that, surprisingly, methods in accordance with the invention can be performed on whole leaf having a moisture content which is significantly less than the chloroformate in the presence of an organic base such as, for example triethylamine or 4-dimethylaminopyridine) or a lower alkyl ester (such as the methyl ester) may be used as the acylating agent, conveniently together with a suitable inert solvent or diluent, for example dichloromethane, tetrahydrofuran or 1,2-dimethoxyethane.

An indole carboxylic acid of formula III wherein U is a carboxy group may be obtained by decomposing a suitable indole ester of formula III in which U is $COOR^j$ wherein R^j is a conveniently removed acid protecting group (which compound is hereinafter referred to as "indole ester of formula III"), for example, phenyl, benzyl, or (1-6C)alkyl optionally bearing an acetoxy, (1-4C)alkoxy or (1-4C)alkylthio substituent. A particular value for R^j is, for example, methyl, ethyl, propyl, <u>t</u>-butyl, acetoxymethyl, methoxymethyl, 2-methoxyethyl, methylthiomethyl, phenyl, or benzyl. Preferred values for R^j include methyl and benzyl.

It will be appreciated that the decomposition of an indole ester of formula III can be performed using any one of a variety of procedures well known in the art of organic chemistry. A preferred method for decomposing an indole ester of formula III comprises reacting the ester with a suitable base, for example, as described in Example 3.c. When such a method is employed, the resulting indole carboxylic acid of formula III, wherein U is a carboxy group, is initially obtained as the corresponding salt of the base used for the hydrolysis and may be isolated as such or converted to the free acid form by a conventional acidification procedure, for example, by reaction with a suitable strong acid such as hydrochloric or sulfuric acid.

pursued, the greater is the tobacco particle degradation likely to be. It is thus a significant advantage of the invention that it is an important feature thereof that in products of the invention the lamina particles and the stem particles are in intimate admixture.

Since the moisture content (of the stem fraction) can be relatively low, there is a reduced requirement for drying of the product of the size reduction apparatus, which can lead to considerable savings in equipment and energy costs.

A smoke modifying agent, a tobacco casing for example, can be applied to the tobacco leaf material before or after the processing thereof by a method in accordance with the invention.

Products of the invention can be subjected to a tobacco expansion process. Examples of expansion processes which could be employed are disclosed in United Kingdom Patent Specifications Nos. 1 484 536 and 2 176 385.

It has been found that the moisture content of whole leaf is generally the main factor which determines whether, on the one hand, stem particles are produced, or on the other hand, substantially intact stem is produced, and that, surprisingly, a sharp transition from the one product to the other product occurs at a fairly precise moisture content.

The moisture content at which this transition occurs will hereinafter be referred to as the 'transition moisture content'.

The starting materials of formulae II and III conveniently may be prepared beginning with indole-5-carboxylic acid (formula IV wherein U is carboxy). Thus, the acid of formula IV wherein U is carboxy may be esterified by a conventional method to form a corresponding ester of formula IV wherein U has the value $COOR^j$ and R^j is defined as above. An ester of formula IV wherein U is $COOR^j$ may be substituted at the 3-position of the indole using an α-bromo toluic ester of formula V wherein T is $COOR^h$ and R^h has the values defined above, using a similar method to that described in Example 1.b. to provide a corresponding diester of formula VI wherein T is $COOR^h$ and U is $COOR^j$. An α-bromo toluic ester of formula V may be prepared by a conventional method, for example as described in European Patent Application publication number 220,066 or in U.S. patent 4,859,692. A diester of formula VI may be converted into a corresponding diester of formula VII by alkylation at the 1-position of the indole using a similiar procedure to that described in Example 1.c. and a conventional alkylating agent, for example methyl iodide.

By selective conversion of the ester group of formula $COOR^j$ into a carboxy group, a diester of formula VII wherein T is $COOR^h$ and U is $COOR^j$ may be converted into a corresponding indole carboxylic acid of formula VII wherein T is $COOR^h$ and U is carboxy. For example, a diester of formula VII wherein T is $COOR^h$ in which R^h is methyl and U is $COOR^j$ in which R^j is benzyl may be converted into a corresponding indole carboxylic acid of formula VII wherein U is carboxy and T is $COOR^h$ in which R^h is methyl by hydrogenolysis of the benzyl group using a similar method to that described in Example 1.d. The resulting indole carboxylic acid of formula VII may be converted into a corresponding starting material benzoic ester of blend, it can be the case that even if the single grade is of a moisture content less than the transition moisture content, a product of the invention can be produced so long as the mean moisture content of the blend is above the transition moisture content.

Since a leaf reduction apparatus used in carrying out a method in accordance with the invention is substantially more compact than a conventional threshing plant, with its plurality of threshing machines and classifiers and extensive associated air trunking, there will be, in use of our invention, a capital cost saving relative to the use of a conventional threshing plant. There will also be a saving in energy consumption. Furthermore, capital and energy cost savings will accrue from simplification of the primary leaf-process section in the tobacco factory. It is thus the case that by use of the present invention significant savings can be made in the overall tobacco leaf process, i.e. that process which commences with tobacco leaf as received from the farm and which ends with the making of cigarettes or other smoking articles.

It is to be observed that not only does the invention provide methods of simultaneously size reducing lamina and stem, to provide a mixture of discrete lamina particles and discrete stem particles, without a requirement for a serially arranged plurality of leaf processing machines, but furthermore, the invention provides methods which are readily carried out without a requirement to recirculate

Thus, it antagonises at least one of the actions of one or more of the arachidonic acid metabolites known as leukotrienes, for example, C_4, D_4, and/or E_4, which are known to be powerful spasmogens (particularly in the lung), to increase vascular permeability and to be implicated in the pathogenesis of asthma and inflammation, as well as of endotoxic shock and traumatic shock. The compound of formula I is thus useful in treatment of diseases in which leukotrienes are implicated and in which antagonism of their action is desired. Such diseases include, for example, allergic pulmonary disorders such as asthma, hay fever and allergic rhinitis and certain inflammatory diseases such as bronchitis, ectopic and atopic eczema, and psoriasis, as well as vasospastic cardiovascular disease, and endotoxic and traumatic shock conditions.

The compound of formula I is a potent leukotriene antagonist and is useful whenever such activity is desired. For example, the compound of formula I is of value as a pharmacological standard for the development and standardization of new disease models and assays for use in developing new therapeutic agents for treating the diseases in which the leukotrienes are implicated.

When used in the treatment of one or more of the above mentioned diseases, the compound of formula I is generally administered as an appropriate pharmaceutical composition which comprises the compound of formula I as defined hereinbefore together with a pharmaceutically acceptable diluent or carrier, the composition being adapted for the particular route of administration chosen. Such compositions are provided as a further feature of the invention. They may be obtained employing conventional procedures and excipients and binders and may be in a variety of dosage forms. For example, they may be in the form of the discs, the size of the gap between the discs and the configuration of the milling projections at the operative faces of the discs.

Another mill which it may be possible to use for purposes of the present invention is a so-called cross-beater mill, which mill comprises a barrel-form housing in which is rotatively mounted a rotor, the shaft of which is coaxial of the housing. The inner curved surface of the housing is provided with rib-form projections extending parallel to the axis of the housing, whilst the rotor carries three equi-angularly spaced blades which extend parallel to the rotor shaft and are disposed in close proximity to the rib-form projections of the housing.

It has been found that so-called "mills" of the kind which employ an impact action, such as hammer mills, will not generally be suitable for carrying out the desired milling action.

We have examined a mill called a Robinson pin mill (model designation - Sentry M3 Impact Disrupter). This mill comprises a rotative disc and a disc-like stator, both of which elements are provided with circular arrays of pins extending perpendicularly of the opposing faces of the elements. The pins of one element interdigitate with those of the other element. The limited experience gained with the Robinson pin mill indicated that such a mill might be useful in carrying out methods in accordance with the invention.

ed in vitro using the standard guinea-pig tracheal strip preparation described by Krell (J. Pharmacol. Exp. Ther., 1979, 211, 436) and as also described in European Patent Application publication number 220,066 and in U.S. patent 4,859,692.

The selectivity of action of compounds as leukotriene antagonists as opposed to non-specific smooth muscle depressants may be shown by carrying out the above in vitro procedure using the non-specific spasmogen barium chloride at a concentration of 1.5×10^{-3}M, again in the presence of indomethacin at 5×10^{-6}M.

Alternatively, the antagonistic properties of the compound of formula I can be demonstrated in vitro by a receptor-ligand binding assay described by Aharony (Fed. Proc., 1987, 46, 691). According to this procedure, membrane fractions, containing the LTD_4/E_4 receptors, are prepared from guinea-pig lung parenchyma and incubated for 30 minutes at 22 °C with 1nM ^3H-LTD_4 in the absence or presence of tested antagonist. Specific binding, determined under conditions that prevent enzymatic metabolism of ^3H-LTD_4, is the net result of total ^3H-LTD_4 binding minus nonspecific binding determined in the presence of 1-2000 fold excess unlabelled LTD_4. Each assay is done in duplicate and results (Ki values) are typically a mean of several such determinations in individual receptor batches.

The % inhibition by a tested antagonist, relative to control binding (vehicle alone), is expressed as a fraction of log[antagonist] concentration (in molar units) and the half-maximal inhibition (IC_{50}) determined by computerized non-linear least-square analysis. The binding constant (Ki) is then calculated from IC_{50} by the Cheng-Prusoff equation:

invention is characterised by 50% to 65% of the particles being retained on a sieve the apertures of which are of 1.4 mm x 1.4 mm square shape.

Preferably, products of the invention are substantially absent intact stem.

Products can be provided by the invention which can be fed to a smoking article making machine without being first subjected to further particle size reduction, or which require at most a minor degree only of further particle size reduction. That is not to say, of course, that a minor, heavy fraction and/or a minor dust fraction may not be removed from the product before incorporation of the product in smoking articles.

When incorporated in cigarettes by having been fed to a cigarette making machine, products of the invention have an appearance similar to that of conventional cigarette filler thus incorporated in cigarettes.

Conventional cut tobacco smoking material which is used in the making of cigarettes is a long stranded, non-fluent, tangled material. For this reason the feed unit of cigarette making machines comprises carding means operative to disentangle the filler material. In that products of the invention are fluent, non-tangled mixtures of lamina and stem particles, when the products are incorporated in cigarettes the carding means, or at least elements thereof, can be dispensed with.

If a leaf material size reduction process in accordance way of comparison, an oral ED_{50} of 19.2 µmol/kg was measured for the compound of formula Ia wherein R^1 is cyclopentylmethyl, Ra is hydrogen, Rd is methyl, Rc is methoxy, and M is a residue of formula $-CO.NH.SO_2 R^6$ in which R^6 is 2-methylphenyl (Example 10 of European Patent Application publication number 220,066).

The invention will now be illustrated by the following non-limiting examples in which, generally, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 °C; air or moisture sensitive reactions were performed under an inert (argon or nitrogen) atmosphere;

(ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals; 4.5-30 mm Hg) with a bath temperature of up to 60 °C;

(iii) flash chromatography was carried out on Merck Kieselgel (Art 9385) and column chromatography on Merck Kieselgel 60 (Art 7734); [these materials were obtained from E. Merck, Darmstadt, W. Germany]; thin layer chromatography (TLC) was carried out on Analtech 0.25 mm silica gel GHLF plates (Art 21521), obtainable from Analtech, Newark, DE, USA; gas-liquid chromatography (GLC) was carried out on a 0.2 mm x 25 m fused silica glass capillary column with 5% phenyl methyl silicone as the stationary phase, with a flow rate of 0.7 mL/min and an oven temperature program of 50 °C for 5 min, then 10 °C/min increase to 275 °C; the injector temperature was 225 °C and detector 275 °C; retention times (t_R) are given in min;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

blended include tobacco materials, reconstituted tobacco materials and tobacco substitute materials.

Products of the invention being of different tobacco grades can be blended.

In the blending of a United States type cigarette filler material there could be blended 1. the product provided by subjecting whole Virginia tobacco leaf to a method in accordance with the invention and 2. the lamina fraction of the product provided by subjecting whole Burley tobacco, at a moisture content below the transition moisture content, to a milling operation such that the product consist of a mixture of lamina particles and substantially intact stem lengths.

In order that the invention may be clearly understood and readily carried into effect reference will now be made, by way of example, to the accompanying drawings, of which:-

Figure 1 is a block diagram relating to a conventional processing of flue-cured whole tobacco leaf;

Figure 2 is a block diagram relating to a processing of flue-cured whole tobacco leaf in accordance with the invention;

Figure 3 is a histogram relating particle shape factor values (horizontal axis) to frequency of occurrence, measured in units of a million, (vertical axis) for a conventional cut lamina cigarette filler material;

Figure 4 is a histogram giving the same information to the same format as Figure 3, but for a cigarette filler abbreviations have also been used: v (volume), w (weight), mp (melting point), bp (boiling point);

(xi) solvent ratios are given in volume: volume (v/v) terms; and

(xii) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode or electron impact (EI) mode; generally only the peak attributable to the parent ion is reported.

9 - Conditioning
10 - Blending
11 - Rolling
12 - Cutting
13 - Water Treated Stem Process (WTS)
14 - Drying
15 - Lamina
16 - Drying
17 - Packing
18 - Lamina
19 - Conditioning
20 - Blending
21 - Cutting
22 - Drying
23 - Blending and Adding
24 - Cut Tobacco Store
25 - Cigarette Making

Steps 1-4, 5-7 and 15-17 take place in a tobacco growing region, whereas steps 8-14, 18-22 and 23-25 take place in a cigarette factory, which factory is commonly far remote from the tobacco growing region.

The process carried out at steps 8-14 and 18-22 constitute the primary leaf-process section of the factory, which section is sometimes referred to as the primary process department (PMD). The steps 8-14 are commonly referred to as constituting a 'stem line', and the steps 18-22 as constituting a 'lamina line'.

mixture was allowed to warm to room temperature. The reaction was stirred for 24 hours and then evaporated. The residue was taken up in diethyl ether (1 L) and filtered. The filtrate was evaporated to give a yellow syrup which was purified by flash chromatography, eluting sequentially with 2:1, 1:1 and 1:2 hexane:methylene chloride, to afford a yellow-white solid. This material was triturated with 1:1 hexane: methylene chloride (300 mL) and filtered to give benzyl indole-5-carboxylate as a white solid (74.2 g, 70%); mp 127-129 °C; partial NMR (300 MHz, $CDCl_3$): 5.39 (s, 2H, CH_2), 6.61 (m, 1H, indole-H(2)), 8.56 (br, 1H, NH).

b. Methyl 4-(5-benzyloxycarbonylindol-3-ylmethyl)-3-methoxybenzoate.

A solution of benzyl indole-5-carboxylate (86.8 g), methyl 4-bromomethyl-3-methoxybenzoate (89.5 g) and potassium iodide (57.4 g) in N,N-dimethylformamide (900 mL) was heated to 80 °C for 10 hours. The reaction mixture was evaporated and partitioned between diethyl ether and water. The organic layer was separated and washed with water. The aqueous washes were combined and extracted with diethyl ether. The combined organic extract was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography, eluting sequentially with 0:1:1, 2:48:50, 4:46:50, 5:45:50, and 10:40:50 ethyl acetate:hexane:methylene chloride, to afford methyl 4-iodomethyl-3-methoxybenzoate (27.8 g), recovered benzyl indole-5-carboxylate (29.6 g), and the crude product as a tan solid (50.6 g). Treatment of the recovered benzyl indole-5-carboxylate (29.6 g) in N,N-dimethylformamide (250 mL) with methyl 4-iodomethyl-3-methoxybenzoate (29.8 g) at 80 °C for

The conditioning steps are carried out in such manner as to avoid, or substantially avoid, the removal of water extractible components.

The input material at step 26 is whole green tobacco leaf.

As may be observed from a comparison of the conventional processing method depicted in Figure 1 and the inventive processing method depicted in Figure 2, the latter method is much simpler.

Details will now be given of experiments relating to the invention.

EXPERIMENT 1

The tobacco leaf material used in this experiment was a single grade of Canadian flue-cured whole green leaf, which was purchased in farm bales of a moisture content of about 18%. The bales were sliced using a guillotine slicer to provide large leaf portions, in accordance with the definition of 'whole leaf' hereinabove, the majority of which portions were about 10 cm to about 20 cm wide.

The whole leaf material thus obtained was conditioned to a moisture content of about 26% and was then gravity fed in continuous manner, at a rate of 150 kg/hr, to a Quester disc mill (model SM11). The rotatable disc of the mill was driven at 1,000 r.p.m. The rotatable disc and the stationary 'disc' or plate, which were the standard such items for model SM 11, comprised, at the operative, opposed faces thereof, a pattern of radially extending, linear, rib-residue was triturated with warm diethyl ether and filtered to give methyl 4-(5-benzyloxycarbonyl-1-methylindol-3-ylmethyl)-3-methoxybenzoate as an ivory solid (42.4 g, 89%); partial NMR (300 MHz, $CDCl_3$): 3.75 (s, 3H, NCH_3), 3.87 (s, 3H, CO_2CH_3), 3.90 (s, 3H, OCH_3), 4.12 (s, 2H, CH_2), 5.36 (s, 2H, OCH_2), 6.82 (s, 1H, indole-H(2)), 8.38 (d, 1H, indole-H(4)).

d. Methyl 4-(5-carboxy-1-methylindol-3-ylmethyl)-3-methoxybenzoate.

A solution of methyl 4-(5-benzyloxycarbonyl-1-methylindol-3-ylmethyl)-3-methoxybenzoate (41.0 g) and formic acid (40 mL) in N,N-dimethylformamide (600 mL) was treated with 10% (w/w) palladium on carbon (10 g) and shaken under hydrogen (3.45 bar) for 24 hours. The catalyst was removed by filtration through diatomaceous earth and the filtrate evaporated to give an amber solid. The solid was triturated with warm diethyl ether and filtered to afford methyl 4-(5-carboxy-1-methylindol-3-ylmethyl)-3-methoxybenzoate as a light gray solid (28.9 g, 88%); mp 249-251 °C; partial NMR (250 MHz, DMSO-d_6): 3.78 (s, 3H, NCH_3), 3.64 (s, 3H, CO_2CH_3), 3.93 (s, 3H, OCH_3), 4.09 (s, 2H, CH_2), 7.12 (s, 1H, indole-H(2)), 8.16 (s, 1H, indole-H(4)), 12.44 (br, 1H, CO_2H).

e. Methyl 3-methoxy-4-[1-methyl-5-(2-methyl-4,4,4-trifluorobutylcarbamoyl)indol-3-ylmethyl]-benzoate.

A solution of methyl 4-(5-carboxy-1-methylindol-3-ylmethyl)-3-methoxybenzoate (2.0 g), 4-dimethylaminopyridine (0.71 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.3 g), triethylamine (1.0 mL) and 4,4,4-trifluoro-2-methylbutylamine material fed to the mill was of a moisture content which was less than the transition moisture content prevailing for the conditions appertaining to the experiment.

EXPERIMENT 4

Experiment 1 was repeated with the whole leaf material conditioned to a moisture content of 20% and with a feed rate of 180 kg/hr. Runs were made at nominal disc gap settings of 0.30 mm and 1.2 mm. When the nominal gap was 0.30 mm, the product was in accordance with the invention and consisted of an intimate, fluent mixture of lamina particles and stem particles. The product obtained when the nominal disc gap was 1.2 mm was, however, not in accordance with the invention and comprised a mixture of lamina particles and intact stem lengths.

A comparison of the results of this experiment and of Experiment 3 indicates that disc gap can be a determinant of the value of the transition moisture content.

EXPERIMENT 5

The tobacco leaf materials used in this experiment were three redried Zimbabwean flue-cured grades, designated A, B and C. These grades were bale sliced with the slicer set to produce 15 cm to 20 cm wide leaf portions. The whole leaf materials thus obtained were conditioned to a target moisture content of 24% and were then milled, one grade at a time, in the Quester SM11 mill at a nominal disc gap of 0.3 mm.

The products obtained with the grades B and C were

The 4,4,4-trifluoro-2-methylbutylamine used in step e., above, was prepared as follows:

g. Ethyl 4,4,4-trifluoro-2-methylbutyrate.

A solution of diisopropylamine (19.5 mL) in tetrahydrofuran (200 mL) at 0 °C was treated with n-butyllithium (71 mL, 1.5M in hexanes). The resulting solution was stirred for 30 minutes at 0 °C, then was cooled to -70 °C. A solution of ethyl 4,4,4-trifluorobutyrate (14 mL) in tetrahydrofuran (150 mL) was slowly added to the lithium diisopropylamide solution and the resulting mixture was stirred at -70 °C for 30 minutes. A solution of iodomethane (11.5 mL) in tetrahydrofuran was added in one portion, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was quenched with water and evaporated. The residue was dissolved in methylene chloride, washed (10% (w/v) hydrochloric acid, water, and brine), dried ($MgSO_4$), filtered, and evaporated. The resulting pale yellow liquid was purified by distillation to yield ethyl 4,4,4-trifluoro-2-methylbutyrate as a colorless liquid (7.8 g, 46%); bp 125-128 °C; partial NMR: (300 MHz, $CDCl_3$): 1.30 (m, 6H, $C\underline{H}_3$), $CH_2C\underline{H}_3$), 2.15 (m, 1H, H-C(3)), 2.64 (m, 1H, H-C(3)), 2.72 (m, 1H, H-C(2)), 4.16 (q, 2H, OCH_2).

h. 4,4,4-Trifluoro-2-methylbutyric acid.

A solution of ethyl 4,4,4-trifluoro-2-methylbutyrate (7.7 g) in methanol (21 mL), tetrahydrofuran (21 mL) and water (8.4 mL) was treated with lithium hydroxide monohydrate (3.5 g). The mixture was stirred for 48 hours and the organic solvents evaporated. The resulting aqueous solution was diluted with water and acidified with 6N hydrochloric materials, at a target mean moisture content of 24%, was milled in the Quester SM11 mill with a nominal disc gap of 0.3 mm and with steam supplied at 1 bar pressure. There was thus produced a product in accordance with the invention, being an intimate, fluent mixture of lamina particles and stem particles.

EXPERIMENT 9

Whole leaf material the product of bale slicing was mixed with stem at a 60:40 ratio. This mixture of materials, at a target mean moisture content of 24%, was milled in the Quester SM11 mill with a nominal disc gap of 0.3 mm and with steam supplied at 1 bar pressure. There was thus produced a product in accordance with the invention, being an intimate, fluent mixture of lamina particles and stem particles.

In Experiments 7, 8 and 9 each of the three materials used, i.e. strips, stem and whole leaf, was a blend of the three Zimbabwean grades mentioned in Experiment 5.

EXPERIMENT 10

Three grades of United States flue cured, redried tobacco leaf material were bale sliced, the slicer being set to produce 15 cm to 20 cm wide leaf portions. The three grades of whole leaf material thus obtained were mixed before being conditioned to a target moisture content of 28%. The mixed material was fed through a Bauer model 400 disc mill with a disc gap of 3.9 mm and with a drive speed of 700 r.p.m. for each of the two discs. The discs, being a reflux. The reaction was heated at reflux temperature for 2 hours, cooled to 0 °C, and quenched by sequential addition of water (1.2 mL), 10% (w/v) aqueous sodium hydroxide solution (1.2 mL), and water (3.6 mL). The resulting suspension was filtered. The filtrate was dried ($MgSO_4$) and filtered. Anhydrous hydrogen chloride was bubbled through the filtrate for 5 minutes and the solvent evaporated to afford 4,4,4-trifluoro-2-methylbutylamine hydrochloride as a white solid (3.3 g, 88%); mp 224-225 °C; partial NMR (300 MHz, DMSO-d_6): 1.04 (d, 3H, CH_3), 2.81-2.60 (br, 2H, NCH_2), 8.29 (br, 2H, NH_2).

An alternative preparation of the amine hydrochloride used in step e., above, is as follows:

k. 2-Methyl-4,4,4-trifluorobutyric acid.

To sodium hexamethyldisilazane (0.945 M in tetrahydrofuran) (667 mL, 0.63 mol) in tetrahydrofuran (0.9 L) at -78 °C, under nitrogen, was added a solution of ethyl 4,4,4-trifluorobutyrate (90.6 mL) in tetrahydrofuran (100 mL). After stirring for 1.5 hour, to the vigorously stirred mixture was added methyl iodide (112 mL) as fast as possible. The reaction was warmed with a 0 °C bath for 2 hours. Methanol (1 L) and 1 N lithium hydroxide (1.2 L) were added and stirring continued for 48 hours. The mixture was acidified with 2N hydrochloric acid and extracted with ethyl acetate. The combined organic phase was washed (brine), dried ($MgSO_4$), and evaporated at 30 °C. After combination with product from separate conversions of ethyl 4,4,4-trifluorobutyrate (97.79 g), distillation afforded 2-methyl-4,4,4-trifluorobutyric acid (173.24 g, 96%)

sieve were of a fine dust form and were disregarded.

0.5 g sub-samples of the four recovered fractions were distributed on respective flat surfaces such that each lamina particle was spacially separated from the other particles. Each of the sub-samples was then subjected to geometric analysis by use of a Magiscan Image Analyser model 2 supplied by Joyce - Loebl. The analyser was set to obtain data as to particle area (two dimensional), length (greatest linear dimension) and perimeter length.

From the data thus obtained there were produced a histogram relating particle shape factor to frequency of occurrence (Figure 3) and a scatter diagram relating particle length to shape factor (Figure 5).

EXPERIMENT 12

A 100 g sample of a product according to the invention, obtained by milling U.S. flue cured whole leaf material at 22% moisture content in the Quester mill at a 0.3 mm disc gap, was subjected to the sieving procedure detailed in Experiment 11. Four 0.5 g sub-samples, from the upper four sieves, i.e. dust free, were geometrically analysed as per Experiment 11.

From the data thus obtained there were produced the shape factor/frequency histogram and the length/shape factor scatter diagram which constitute Figures 4 and 6 respectively.

A comparison between the histograms of Figures 3 and 4 shows the product of the invention (Figure 4) to be of a

91%) as a colorless solid; mp 90.5-91.5 °C; GLC: t_R = 12.04 min, MS(CI): 156 (M+H).
Analysis for $C_5H_8F_3NO$:
Calculated: C, 38.72; H, 5.20; N, 9.03
Found: C, 38.59; H, 5.11; N, 8.56

n. 2-Methyl-4,4,4-trifluorobutylamine hydrochloride.

To a suspension of lithium aluminum hydride (15.5 g) in diethyl ether (290 ml) was added a solution of 2-methyl-4,4,4-trifluorobutyramide (31.74 g) in diethyl ether (0.5 L) at a rate to obtain a gentle reflux. After heating at reflux for 12 hours and cooling to 0 °C, the reaction was quenched with saturated sodium sulfate solution and allowed to warm to ambient temperature. The mixture was dried (Na_2SO_4) and filtered through diatomaceous earth with diethyl ether wash. The filtrate was treated with gaseous hydrochloric acid (14.9 g, 0.409 mol) and then the solvent was evaporated. The residue was dissolved in methylene chloride and combined with product from a similar reaction of 2-methyl-4,4,4-trifluorobutyramide (25 g). Recrystallization from methylene chloride and diethyl ether, followed by trituration with ethyl acetate, afforded 2-methyl-4,4,4-trifluorobutylamine hydrochloride (51.35 g, 79%) as a light pink solid; mp 224.5-225.5 °C; MS(CI): 142 (M+H-HCl).
Analysis for $C_5H_{11}ClF_3N$:
Calculated: C, 33.81; H, 6.24; N, 7.89
Found: C, 33.93; H, 6.13; N, 8.17

A comparison of Figures 7 and 8 again strongly evidences the very different characteristics of conventional lamina material and a material a product of the invention.

EXPERIMENT 15

Virginia lamina strips, Burley lamina strips and Oriental lamina strips, all of which were pre-cased, i.e. pretreated with a smoke modifying agent, were fed to a blending bin together with stem to provide a mixture in which the respective proportions of the four materials were 44%, 23%, 16% and 17% respectively. The mixture of the four materials, at a target moisture content of 24%, was fed to the Bauer 400 mill, which was operated with a disc gap of 2.7 mm and a disc drive speed of 700 r.p.m. The product was dried to a target moisture content of 14.5% and was then fed to a Molins Mk. 9.5 cigarette making machine, thus to make cigarettes the filler of which was composed 100% of the product.

CLAIMS

1. A method of processing tobacco leaf material, wherein tobacco leaf lamina and tobacco leaf stem, at least a major proportion of which is above the transition moisture content, as hereinbefore defined, is fed to a mill comprising first and second leaf reduction elements, a material flow path between and across opposed faces of said elements, and drive means operative to cause relative transverse movements between said elements, there exiting said mill a product comprising flakes of said lamina and shreds of said stem.

2. A method according to Claim 1, wherein said product requires substantially no further size reduction before being incorporated in smoking articles.

3. A method according to Claim 1 or 2, wherein lamina and stem fed to said apparatus are comprised in whole leaf, as hereinbefore defined.

4. A method according to Claim 1, 2 or 3, wherein lamina fed to said apparatus is lamina prior separated from attached stem.

5. A method according to any one of Claims 1 to 4, wherein stem fed to said apparatus is stem prior separated from attached lamina.

6. A method according to any one of the preceding claims, wherein said product is fluent.

~~7. A method according to any one of the preceding claims, wherein the moisture content of at least a major proportion of the tobacco leaf material fed to said apparatus is above the transition moisture content, as hereinbefore defined.~~

7\. ~~8.~~ A method according to any one of the preceding claims, wherein the tobacco leaf material fed to said apparatus is gravity fed thereto.

~~9. A method according to any one of the preceding claims, wherein said apparatus comprises first and second leaf reduction elements, a material flow path between and across opposed faces of said elements, and drive means operative to cause relative transverse movement between said elements.~~

8\. ~~10.~~ A method according to Claim ~~9~~ 1, wherein at least one of said elements ~~is~~ discoid.

9\. ~~11.~~ A method according to Claim ~~9~~ 1, wherein said faces are substantially conoidal.

10\. ~~12.~~ A method according to ~~Claim 9, 10 or 11~~ any one of the preceding claims, wherein said elements, at the said opposed faces thereof, comprise projections.

11\. ~~13.~~ A method according to Claim ~~12~~ 10, wherein said projections are of generally linear configuration and said projections are disposed with the linear axes thereof extending perpendicularly of the direction of said relative movement between said elements.

12\. ~~14.~~ A method according to any one of ~~Claims 9 to 13~~ the preceding claims, wherein said drive means is operative to drive one only of said elements.

13\. ~~15.~~ A method according to any one of ~~Claims 9 to 13~~ the preceding claims, wherein said drive means is operative to drive both of said elements.

14. ~~16~~. A method according to any one of the preceding claims ~~Claims 9 to 15~~, wherein said relative movement is rotative relative movement.

15. ~~17~~. A method according to any one of the preceding claims, wherein said lamina and said stem pass once only through said apparatus.

16. ~~18~~. A method according to any one of the preceding claims, wherein during the passage of the leaf material through said apparatus, low pressure steam is brought into contact with said leaf material.

17. ~~19~~. A method according to any one of the preceding claims, wherein the flow of the leaf material to and through said apparatus is assisted by the maintenance at the product outlet of said apparatus of a reduced air pressure.

18. ~~20~~. A method according to any one of the preceding claims, wherein prior to the leaf material being fed to said apparatus, said leaf material or a part thereof is treated with a smoke modifying agent.

19. ~~21~~. A method according to any one of the preceding claims, wherein said product is subjected to a tobacco expansion process.

20. ~~22~~. A method according to any one of the preceding claims, wherein said product is incorporated in smoking articles.

21. ~~23~~. A method according to Claim 20 ~~22~~, said smoking articles being cigarettes.

22\. ~~24~~. A method according to Claim ~~22~~ 20, said smoking articles being cigars.

23\. ~~25~~. A method according to Claim ~~22~~ 20, ~~23~~ 21 or ~~24~~ 22, wherein said product is fed to a smoking article making machine.

24\. ~~26~~. A method according to Claim ~~25~~ 23, wherein, prior to being fed to said making machine, said product is subjected to no further particle size reduction, or to a minor degree only of further particle size reduction.

25\. ~~27~~. A method according to any one of Claims ~~22~~ 20 to ~~26~~ 24, wherein before said product is incorporated in smoking articles, said product is blended with another smoking material.

26\. ~~28~~. A smoking article comprising a smoking material which is the product of a method of processing tobacco leaf material according to any one of Claims 1 to ~~21~~ 19.

27\. ~~29~~. A smoking article according to Claim ~~28~~ 26 and being a cigarette.

28\. ~~30~~. A smoking article according to Claim ~~28~~ 26 and being a cigar.

29\. ~~31~~. A smoking material comprising a mixture of lamina particles and stem particles, which material is the product of feeding tobacco leaf lamina and tobacco leaf stem together through a leaf reduction apparatus.

30\. ~~32~~. A smoking material according to Claim ~~31~~ 29, the angle of repose thereof being not more than about 45 degrees to the horizontal.

31\. ~~33~~. A smoking material according to Claim ~~32~~ 30, the angle of repose thereof being not more than about 35 degrees to the horizontal.

32. ~~34~~. A smoking material according to Claim 29 ~~31~~, 30 ~~32~~ or 31 ~~33~~, the shape factor of about 60 per cent or more of the dust free particles of which is 0.5 or above.

33. ~~35~~. A smoking material according to Claim 32 ~~34~~, the shape factor of about 70 per cent or more of the dust free particles of which is 0.5 or above.

34. ~~36~~. A smoking material according to any one of Claims 29 ~~31~~ to 33 ~~35~~, the Borgwaldt filling value of which is less than that of comparable conventional cut lamina cigarette filler material.

35. ~~37~~. A smoking article comprising a smoking material according to any one of Claims 29 ~~31~~ to 34 ~~36~~.

36. ~~38~~. A smoking article according to Claim 35 ~~37~~ and being a cigarette.

37. ~~39~~. A smoking article according to Claim 36 ~~37~~ and being a cigar.

38. ~~40~~. A method of processing tobacco leaf material to provide smoking article filler material, wherein tobacco as whole leaf, as hereinbefore defined, passes through a passage defined by co-extensive portions of first and second, relatively moving, milling elements of a leaf reduction apparatus from an inlet of said passage to an outlet of said passage remote said inlet, so as to provide at said outlet filler material comprising a mixture of flakes of lamina ~~particles~~ and shreds of stem ~~particles~~.

39. ~~41~~. A method according to Claim ~~40~~ 38, wherein said outlet is situated at the margin of the co-extensive portions.

40. ~~42~~. Smoking article filler material the product of a method according to Claim ~~40~~ 38 or ~~41~~ 39.

41. ~~43~~. A method of making smoking articles, wherein filler material the product of the method according to Claim ~~40~~ 38 or ~~41~~ 39 is fed to a smoking article making machine.

42. ~~44~~. A smoking article, which smoking article is the product of the method according to Claim ~~43~~ 41.

43. ~~45~~. Smoking article filler material, which filler material is a fluent mixture comprising lamina particles and stem particles, the shape factor of about 60 per cent or more of the dust free particles of which mixture is 0.5 or above.

44. ~~46~~. A method of making smoking articles, wherein filler material according to Claim ~~45~~ 43 is fed to a smoking article making machine.

45. ~~47~~. A smoking article, which smoking article is the product of the method according to Claim ~~46~~ 44.

46. ~~48~~. A method of making cigarettes, wherein tobacco bale material is reduced to provide discrete whole leaf, as hereinbefore defined; the whole leaf is fed through a mill such that there exits said mill a product which is a mixture comprising flakes of lamina and shreds of stem; and said mixture is fed to a cigarette rod making machine.

~~49. A method of processing tobacco leaf material~~

~~substantially as described in any one of Experiments 1 and 2, and 4 to 10 detailed above, so as to obtain directly a mixture comprising flakes of lamina and shreds of stem.~~

DATED THIS 20th DAY OF February 1991

FISHER CORMACK & BOTHA
Patent Agents for the Applicants

AP/P/91/36

Fig.1.

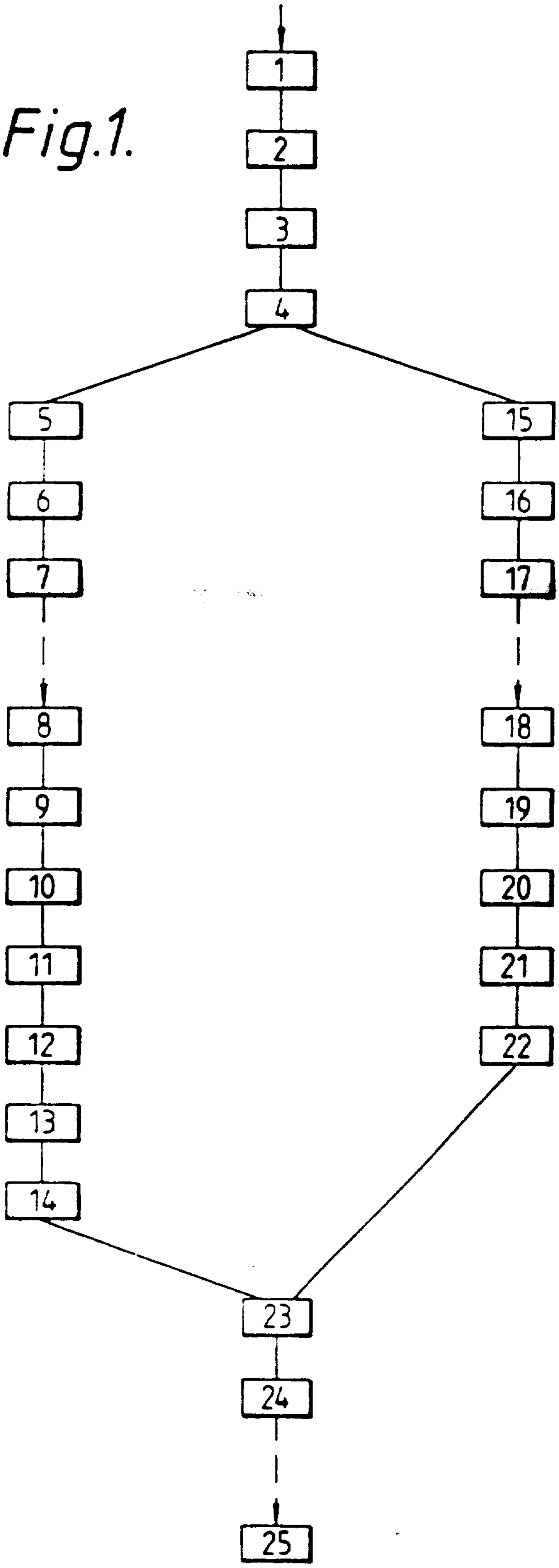
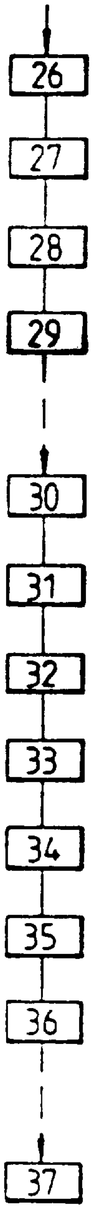


Fig.2.



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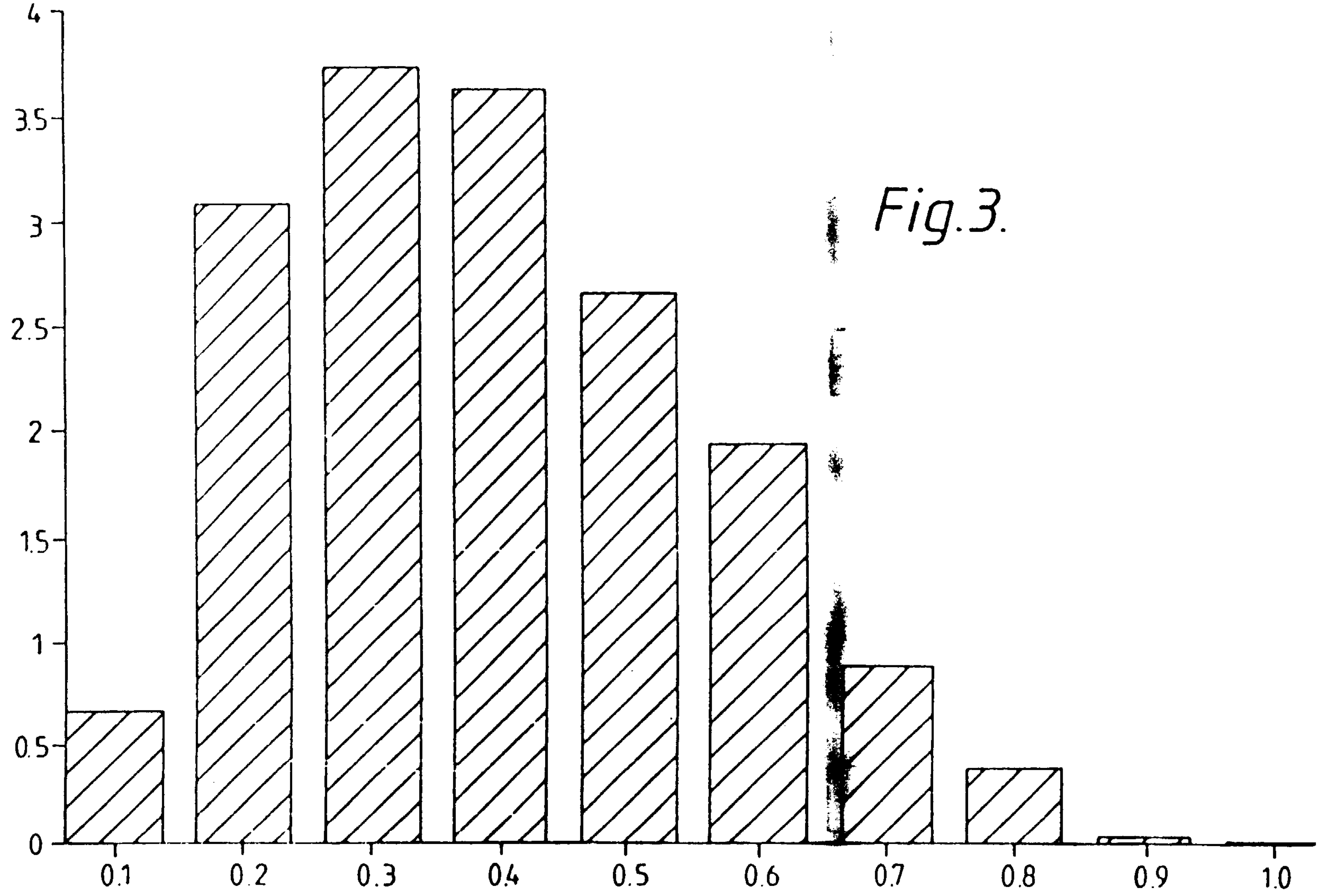

Fig.3.

Fig.4.

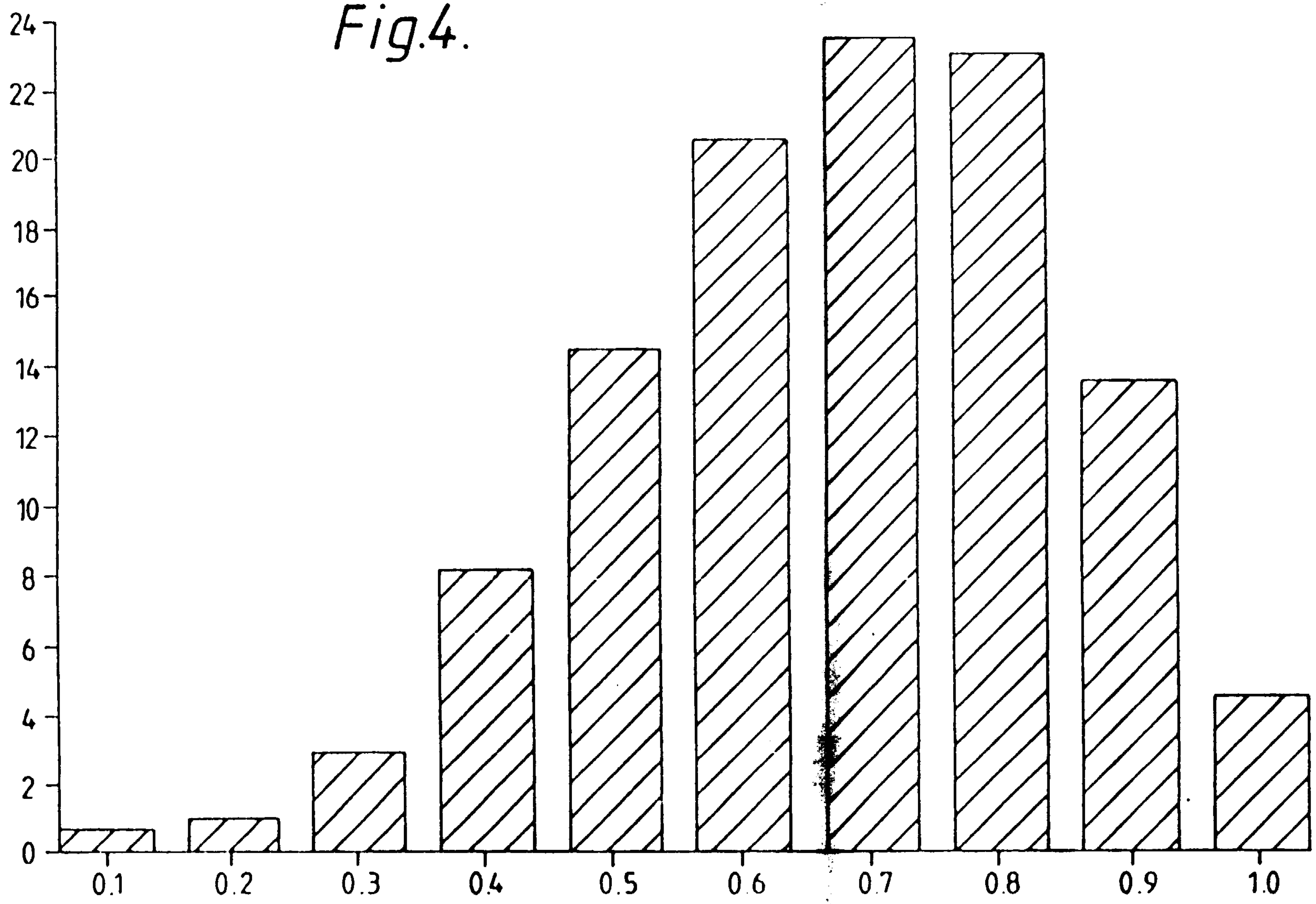

Fig.5.

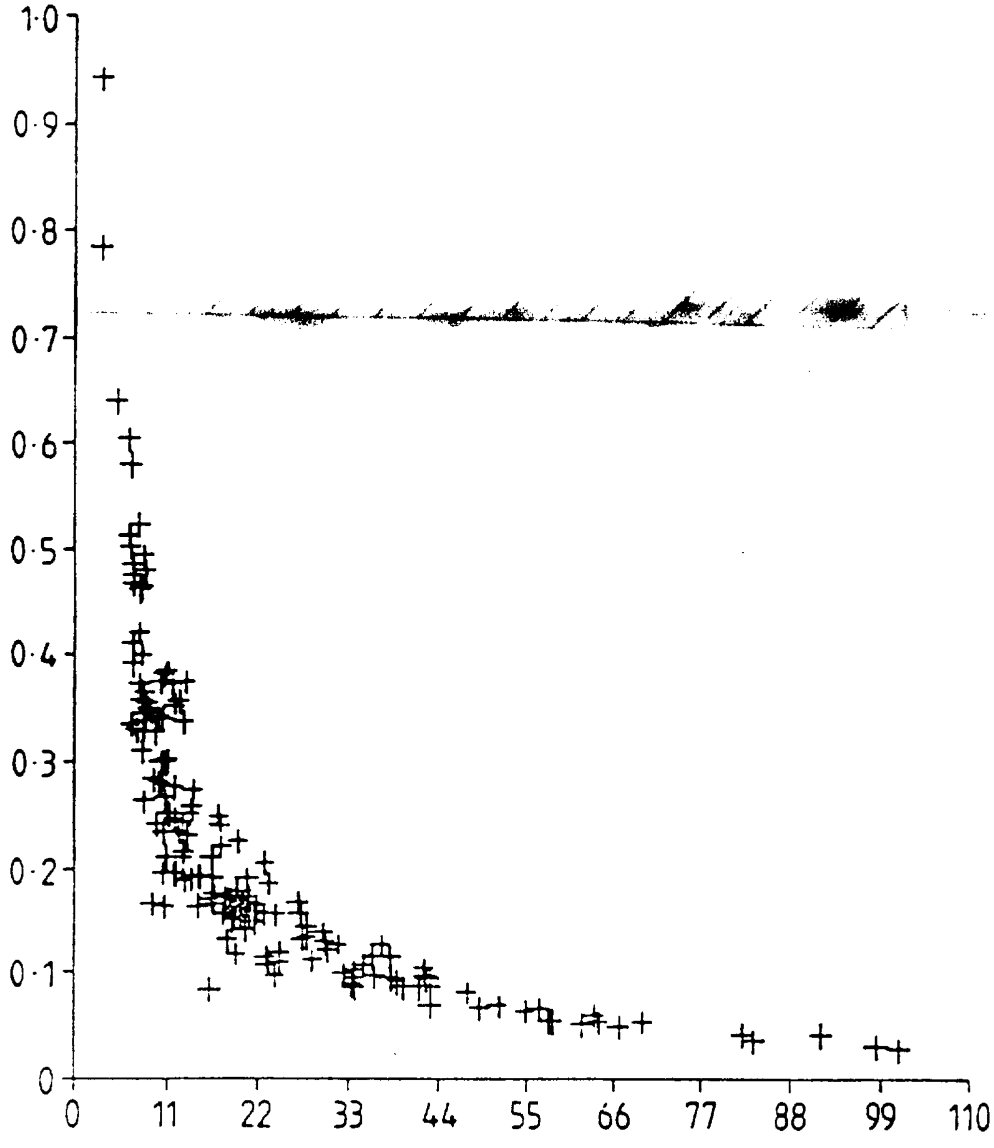

Fig. 6.

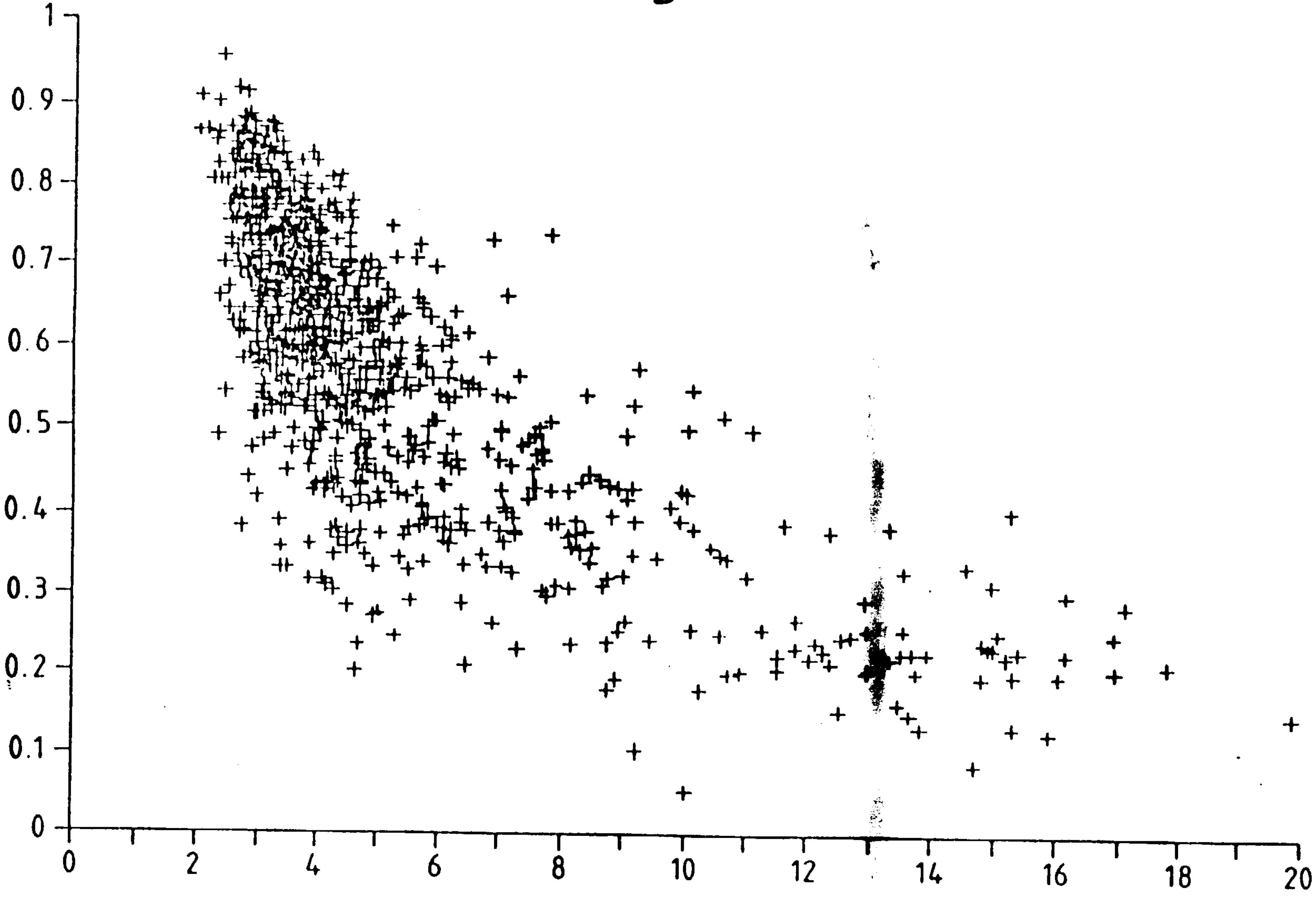

Fig.7.

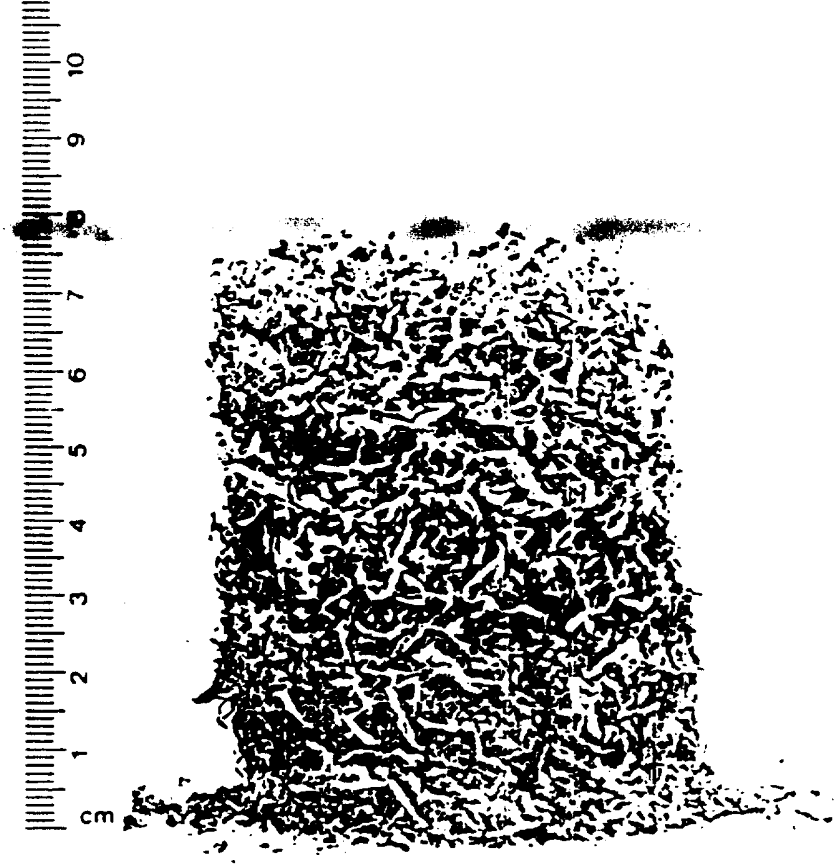

Fig.8.