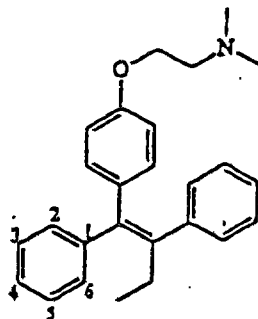


- 1 -

TAMOXIFEN AND ANALOGUES THEREOF

This invention relates to tamoxifen and analogues thereof and particularly, although not exclusively, relates to a method of preparing a desired isomer of tamoxifen or an analogue thereof.

Tamoxifen is a triphenylethylene derivative of formula



which is a drug in clinical use for the treatment of hormone dependent breast cancer. For this purpose, only the Z isomer has the required antiestrogenic activity, the E isomer being oestrogenic. The same criteria of antioestrogenicity applies to tamoxifen analogues. One of the most important analogues of tamoxifen is 4-hydroxytamoxifen (one of the main metabolites in patients), which has an affinity for binding to oestrogen receptors which is 100 times higher than for tamoxifen itself. Accordingly, processes for stereoselective synthesis and/or isolation of substantially pure Z isomer of tamoxifen, 4-hydroxytamoxifen and other analogues are desirable.

Known processes for the preparation of substantially pure Z isomer of tamoxifen and 4-hydroxytamoxifen include

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stereoselective syntheses (involving expensive catalysts) as described in J. Chem. Soc., Perkin Trans I 1987, 1101 and J. Org. Chem. 1990, 55, 6184 or chromatographic separation of an E/Z mixture of isomers as described in J. Chem. Res., 1985 (S) 116, (M) 1342, 1986 (S) 58, (M) 771.

It is an object of the present invention to provide a method of preparing tamoxifen or an analogue thereof which is rich in the desired isomer and which may be advantageous over known methods.

The invention is based on the surprising, and previously unappreciated, discovery that one geometric isomer of tamoxifen or an analogue thereof can be predominantly removed from a mixture of isomers in the presence of certain solvents.

According to a first aspect of the invention, there is provided a method of removing predominantly a first geometric isomer of tamoxifen or an analogue thereof from a mixture comprising said first geometric isomer and a second geometric isomer, the method including the step of allowing the first isomer to crystallise in a solvent.

Preferably, the method comprises contacting a mixture which comprises said first and second isomers with said solvent.

The method may include separating the crystallised product from the remainder.

Said solvent is preferably able to dissolve the isomers in said mixture and is such as to allow re-crystallisation as aforesaid. In the method, said solvent is preferably contacted with the isomers in the mixture when said solvent is at a first temperature wherein said first temperature is suitably less than the boiling point

- 3 -

of the solvent. Recrystallisation is suitably carried out at a second temperature which is less than said first temperature. It is believed that the temperature of the recrystallisation step affects the relative amounts of first and second isomers in the recrystallised product. For example, it has been observed that, if recrystallisation is carried out in a freezer at -4°C , then the ratio of the amount of the second geometric isomer to the first geometric isomer in the crystallised product is greater than the corresponding ratio observed when recrystallisation is carried out at ambient temperature (about 22°C). Thus, recrystallisation is suitably carried out at greater than -4°C , preferably greater than 0°C , more preferably greater than 10°C , especially greater than 20°C . Advantageously, recrystallisation may be carried out at at least ambient temperature.

It will be appreciated that there may be an optimum temperature of recrystallisation wherein the ratio of the amount of first geometric isomer to second geometric isomer in the crystallised product is maximised. Said second temperature may be within 30°C , suitably 25°C , preferably 20°C , more preferably 15°C , especially 10°C of the optimum temperature.

Said first temperature may be at least 50°C , suitably at least 60°C , preferably at least 70°C , more preferably at least 80°C , especially at least 90°C . Said first temperature may be less than 200°C , preferably less than 160°C , more preferably less than 140°C , especially less than 120°C .

Said first temperature may be less than the boiling point of the solvent, suitably by at least 10°C , preferably

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at least 20°C, more preferably at least 30°C, especially at least 40°C.

5 Said solvent may have a boiling point of at least 30°C, suitably at least 40°C, preferably at least 50°C, more preferably at least 60°C. Said boiling point may be less than 300°C, suitably less than 250°C, preferably less than 200°C, more preferably less than 175°C.

10 Various solvents may be selected for use in the method. Preferably, said solvent includes a first solvent part. Preferably, the first solvent part is an organic solvent with polar organic solvents being preferred.

15 Said first solvent part may be an unsubstituted hydrocarbon or may include one or more functional groups. Such groups may be selected from -OH, -NO₂, -CN, -O- and optionally substituted, especially unsubstituted, alkyl groups.

20 The first solvent part may include two or, more preferably, one or fewer functional groups. Especially preferred is the case wherein the first solvent part includes only one functional group.

25 Said first solvent part is preferably a protic solvent.

30 A preferred functional group of said first solvent part is an -OH group.

Said first solvent part may be aliphatic, alicyclic, aromatic or heteroaromatic. Said first solvent part is preferably aliphatic.

35

- 5 -

Said first solvent part may include one or more, suitably at least two, preferably at least three, more preferably at least four, especially at least five carbon atoms. Said first solvent part may include twelve or
5 fewer, suitably ten or fewer, preferably nine or fewer, more preferably eight or fewer, especially seven or fewer, carbon atoms.

Said first solvent part may have a boiling point of
10 at least 50°C, suitably at least 75°C, preferably at least 100°C, more preferably at least 125°C, especially at least 150°C. Said boiling point may be less than 300°C, suitably less than 250°C, preferably less than 225°C, more preferably less than 200°C, especially less than 175°C.

15

Said first solvent part is preferably an alcohol having one -OH group. Said first solvent part is more preferably hexanol.

20 Said solvent may include a mixture comprising said first solvent part and a second solvent part. Said second solvent part may include any feature of said first solvent part described herein. Preferably, however, said solvent consists essentially of said first solvent part as
25 described.

The method preferably includes a first step comprising allowing the first isomer to crystallise in a solvent as aforesaid and a second step which comprises
30 allowing the product of the first step to crystallise in a solvent.

The solvent used in the second step (hereinafter "said second solvent") may have any feature of the solvent
35 used in the first step (hereinafter "said first solvent").

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Preferably, said first solvent and said second solvent are different. Preferably, said second solvent has a lower boiling point than said first solvent, suitably by at least 30°C, preferably at least 50°C, more preferably at least 70°C, especially at least 85°C.

The boiling point of the second solvent may be less than 95°C, is suitably less than 80°C, is preferably less than 70°C and is, more preferably, less than about 65°C.

Said second solvent is preferably an alcohol, preferably a C₁₋₄ alcohol, especially a C₁₋₂ alcohol, with methanol being most preferred.

Preferably, the mixture used in the first step of the method is substantially pure. Thus, prior to said first step, there may be a purifying step. This may simply comprise washing a mixture to be used in said first step with a solvent. The solvent used in the washing (hereinafter "said third solvent") may have any feature of said second solvent as described. Preferably, the temperature of the third solvent in said washing step is less than the temperature of said first solvent when it is used and/or the temperature of said second solvent when it is used. Said third solvent preferably is the same as said second solvent and is, therefore, preferably methanol.

Preferably, said first geometric isomer is crystallised at some stage of said method from a solvent which includes or, preferably consists essentially of methanol.

By "consists essentially", we mean that a solvent comprises at least 80 wt%, preferably at least 90 wt%,

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more preferably at least 95 wt%, especially at least 99 wt% of the referenced solvent, for example methanol.

Said first step and/or said second step may be carried out under less than ambient light conditions. Preferably, said step(s) is/are carried out substantially in the dark. Preferably, the method uses a receptacle which is substantially opaque. Excluding or reducing the light intensity in said first and/or second steps is found to increase the amount of the preferred isomer isolated.

In the context of this specification, the term "analogue" includes: a derivative of tamoxifen wherein one or more atoms or groups of tamoxifen have been replaced by other atoms or groups; or wherein a ring or rings is/are formed between juxtaposed atoms or groups of tamoxifen; and a precursor of tamoxifen or a derivative thereof which precursor exists in at least two geometric isomeric forms and which can be converted to tamoxifen or a said derivative thereof, suitably by a substitution reaction.

Various analogues of tamoxifen which fall within the scope of the present invention are described in Endocrine Reviews, 11(4), 1990, 578-603.

Analogues of tamoxifen may include optionally-substituted triphenylalkyl or alkylene compounds. Preferred optionally-substituted triphenyl compounds are of general formula



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wherein A, B and P each independently represents an optionally-substituted phenyl group and Q represents a hydrogen atom or an optionally-substituted alkyl, alkenyl, alkynyl or phenyl group; and

- 5 wherein a pair of adjacent substituents A, B, P and Q are optionally arranged together to form part of a ring structure.

10 It will be appreciated that the compound of general formula I may exist in different geometric isomeric forms and the formula is not intended, unless otherwise stated herein, to be limited to any such form.

Optional substituents as described herein include any
15 substituents generally used to affect the activity of drugs for oral administration or which represent leaving groups and/or protecting groups which aid the preparation of such drugs. In relation to alkyl, alkenyl, alkynyl and phenyl groups, preferred optional substituents include
20 halogen atoms, haloalkyl and hydroxy groups and optionally-substituted alkylcarboxy, alkoxy, phenoxy, alkylamino and alkylcarbonyl groups.

Preferred alkyl, alkenyl and alkynyl groups may have
25 up to 12, preferably up to 6, more preferably up to 4 carbon atoms.

Preferably, Q represents an optionally-substituted, preferably unsubstituted, alkyl group. Preferably, said
30 alkyl group is a C₁ to C₄, more preferably a C₁ to C₂, alkyl group. Q preferably represents an ethyl group.

Preferably, groups A, B and P independently represent an unsubstituted or monosubstituted phenyl group. Where
35 a group A, B or P is substituted, it is preferably

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substituted in the 3- or, more preferably, the 4-position.

Preferably, group B is unsubstituted.

5

Group P is preferably unsubstituted or substituted by a halogen atom or hydroxy, optionally-substituted alkoxy or phenoxy, groups. Where group P is substituted, it is preferably substituted in the 4-position. More preferably,
10 group P is unsubstituted or substituted by an optionally-substituted phenoxy group. In an especially preferred embodiment, P is unsubstituted. Thus, preferably, P represents an unsubstituted phenyl group.

15 Preferably, group A is monosubstituted by a halogen atom or hydroxy, optionally-substituted alkoxy or phenoxy, groups. Preferably, group A is monosubstituted by an optionally-substituted alkoxy group. A preferred optionally-substituted alkoxy group is of general formula

20



wherein n represents an integer preferably in the range 1 to 8, more preferably 1 to 4, especially 1 to 2; and
25 X represents a leaving group, for example a halogen, especially a chlorine, atom, or a group of general formula

30



wherein R¹ and R² independently represent a hydrogen atom or an optionally-substituted, preferably unsubstituted,
35 alkyl group.

- 10 -

Preferably, n represents 2. In a preferred embodiment, group A is monosubstituted by an alkoxy group of general formula II, wherein n represents 2.

5 Preferably, said mixture used in the method comprises a first analogue of tamoxifen (preferably a precursor of tamoxifen or tamoxifen derivative as described above) and the method includes the further step of derivatising the first geometric isomer removed in order to prepare
10 tamoxifen or a derivative, especially an antiestrogenic derivative, thereof. Preferably, the first analogue of tamoxifen, more preferably said first geometric isomer of said first analogue, has less antiestrogenic activity compared to tamoxifen or a said derivative which is
15 prepared in said further derivatising step.

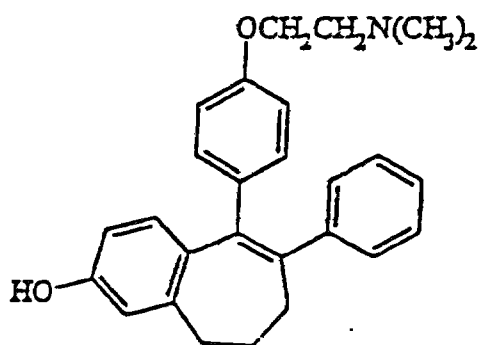
Preferably, said precursor is a compound of general formula I described above wherein B, P and Q are as described above. Preferably, A represents a phenyl group
20 substituted, preferably at least at the 4-position, by a first moiety which includes an active atom or group which is arranged to react with a second moiety which includes a group of general formula III as described above in order to produce an optionally substituted alkoxy group of
25 general formula II as described above. Preferably, said first moiety includes a leaving group which is suitably X as described above. Preferably, said first moiety comprises a group of general formula II as described above. Said first moiety is preferably reacted with an
30 amine of general formula R^1R^2NH wherein R^1 and R^2 are as described above.

Where a pair of adjacent substituents A, B, P and Q are arranged together to form part of a ring structure,
35 the ring structure may be formed between pairs of

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substituents A, B, P and Q which are *cis* to one another.
Examples of compounds of general formula I which have ring
structures as described include:

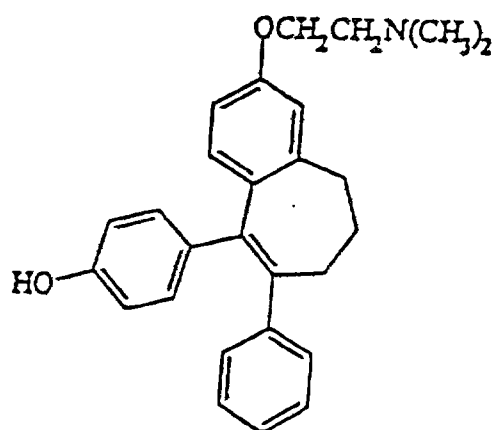
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IV

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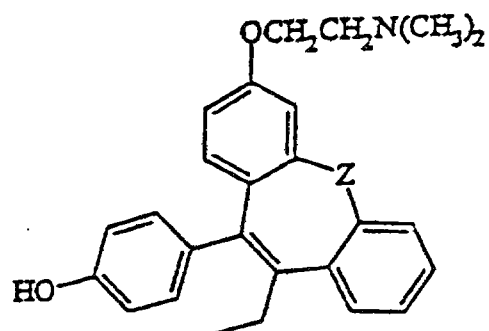
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V

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VI

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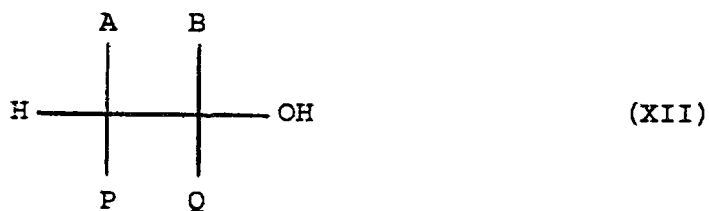
- 12 -

wherein Z represents an oxygen or sulphur atom or a group
-CH₂CH₂-.

Preferably, adjacent substituents A, B, P and Q do
5 not form part of a ring structure.

When the method involves contacting a mixture which
comprises first and second isomers, the mixture used may
be prepared by known routes to tamoxifen and its
10 derivatives for example as described in J.Chem. Research,
1985(S) 116, (M) 1342 and 1986 (S) 58, (M) 0771.

A precursor of tamoxifen or tamoxifen derivative for
use in the method may be prepared from a compound of
15 general formula

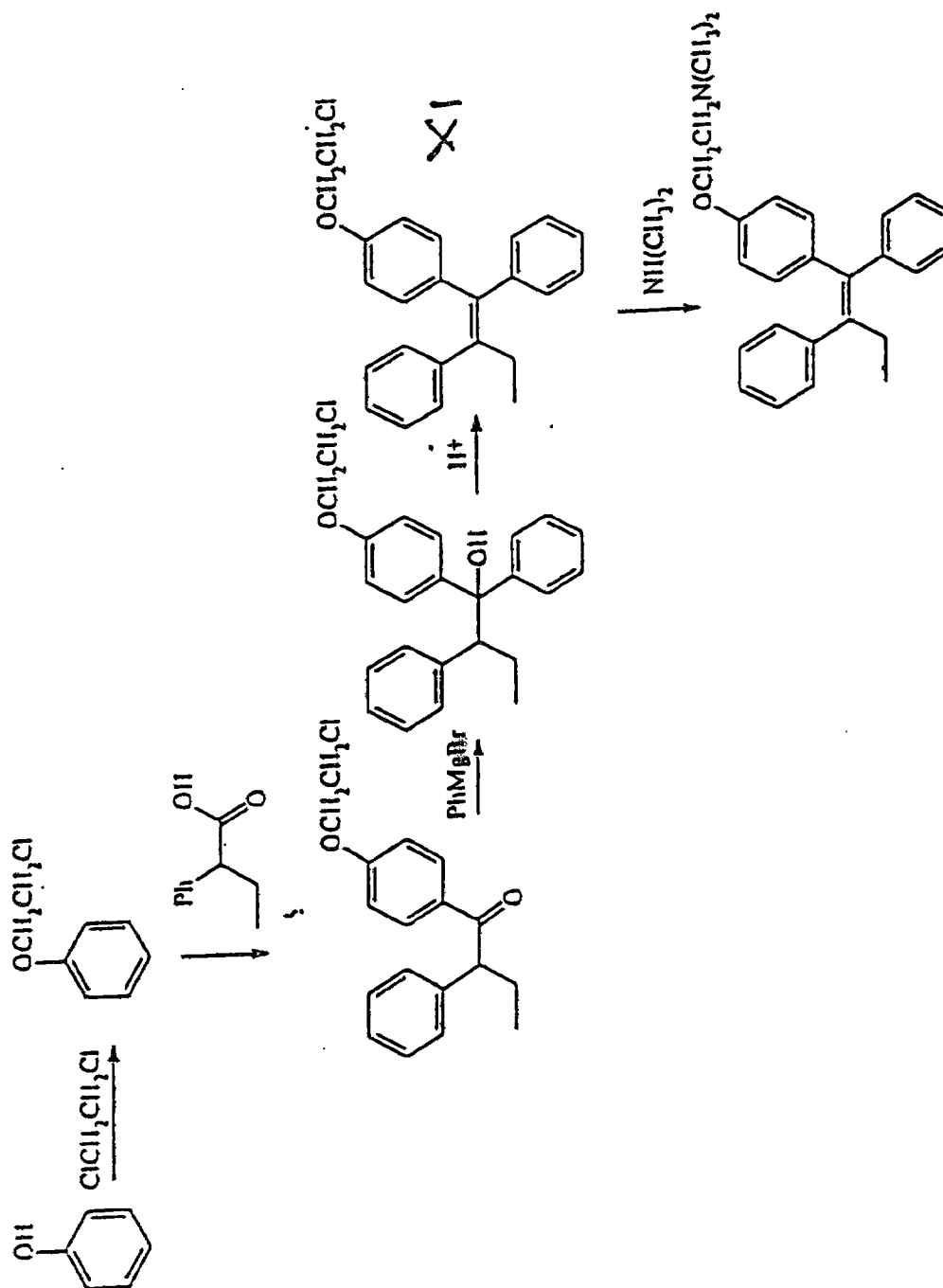


wherein A, B, P and Q are as described in any statement
herein. Preferably, A, B, P and Q in said compounds of
25 formula I and XII represent the same atoms or groups.

Advantageously, the compound of formula XII may be
dehydrated to prepare the compound of formula I.
Dehydration may involve refluxing the compound of formula
30 XII in a solvent in the presence of a strong acid, for
example concentrated hydrochloric acid.

A typical reaction scheme for preparing tamoxifen is
as shown below in Scheme I.

35

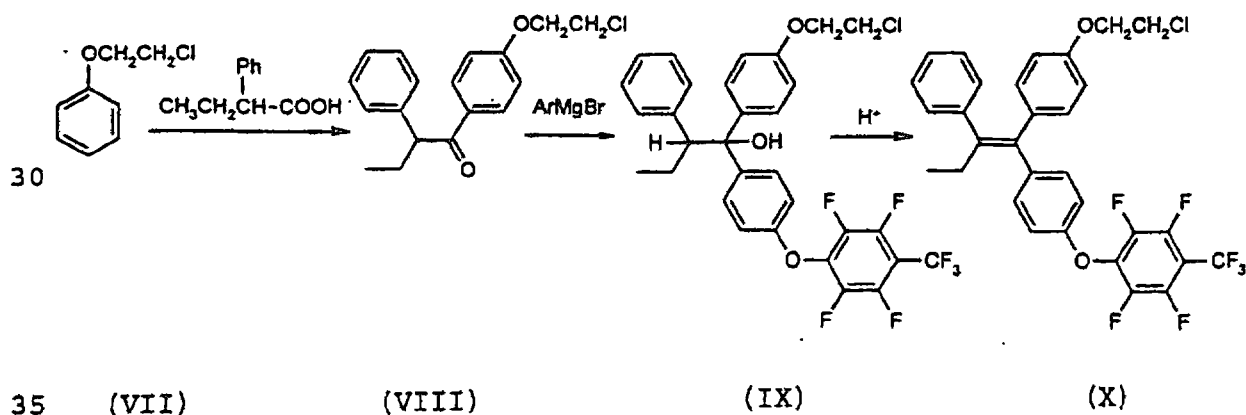
Scheme 1

- 14 -

Referring to Scheme I, preferably, the alkene derivative of formula XI is contacted with said solvent prior to the reaction with dimethylamine. In one embodiment, it is found that, after washing a mixture of geometric isomers of said compound XI with methanol, followed by a first recrystallisation step using hexanol and a second recrystallisation step using methanol, the compound XI prepared contains 100% (according to HPLC analysis) of the desired Z isomer (which has the stereochemical configuration of compound XI shown in Scheme I). Compound XI can then be converted by a simple reaction to tamoxifen with the stereochemistry being maintained. Thus, in general terms, the method described above may be used to prepare tamoxifen or an analogue which includes greater than 99 wt%, suitably greater than 99.5 wt%, preferably greater than 99.7 wt%, more preferably greater than 99.8 wt%, especially greater than 99.9 wt%, of said first geometric isomer.

A typical process for preparing 4-hydroxytamoxifen involves derivatising compound X prepared according to the reaction scheme provided below.

25



- 15 -

The invention extends to pharmaceutically acceptable forms, for example salts of tamoxifen or analogues thereof.

5 The invention extends to a method of preparing tamoxifen or a derivative, especially an antiestrogenic derivative, thereof, the method including the steps of allowing a first geometric isomer of a precursor of
10 tamoxifen or said derivative to crystallise in a solvent and derivatising said precursor in order to produce said tamoxifen or said derivative.

 The invention extends to the use of a solvent for removing predominantly a first geometric isomer of
15 tamoxifen or an analogue thereof from a mixture of isomers.

 The invention extends to a method of preparing an antiestrogenic isomer of tamoxifen or an analogue thereof
20 in purity of at least 99%, suitably at least 99.5%, preferably at least 99.7%, more preferably at least 99.8%, especially at least 99.9%, most preferably at least 99.95%, the method using a solvent as described herein.

25 The invention extends to the product of any process described herein.

 Any feature of any aspect or embodiment described herein may be combined with any feature of any other
30 aspect or embodiment described herein.

 The invention will now be described, by way of example, with reference to the accompanying figures wherein:

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Figure 1 is a ^1H NMR spectrum for a mixture of isomers of a tamoxifen precursor, prepared in Example 1;

Figures 2 to 4 provide further detail for the spectrum of Figure 1;

Figure 5 is a ^1H NMR spectrum for the product obtained in Example 1 after washing with methanol.

Figure 6 is an ^1H NMR spectrum of the material referred to in figure 5, after recrystallisation from hexanol in the dark;

Figure 7 is a ^1H NMR spectrum of the material referred to in figure 5, after recrystallisation from methanol in the dark; and

Figure 8 is an HPLC analysis on the product of figure 7.

Example 1

Preparation of Z isomer of Tamoxifen

A solution of bromobenzene (3.92g, 25mmol) in ether (5ml) containing a crystal of iodine was added dropwise to a suspension of magnesium turnings (0.63g, 26mmol) in ether (5ml) at reflux. After the addition was complete, the reaction mixture was cooled to room temperature and a solution of 1-[4-(2-chloroethoxy)phenyl]-2-phenyl-1-butanone (3.75g, 12.4mmol) in ether (15ml) was added over 1 hour. The resulting mixture was refluxed for 16 hours, then poured into dilute hydrochloric acid (50ml) and extracted with ether (3x40ml). The combined ether layers were concentrated, the residual oil was dissolved in ethanol (10ml) and refluxed with concentrated hydrochloric

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acid (5ml) for 4 hours. The organic phase was separated, dried (Na_2SO_4) and evaporated to dryness to give a yellow oil, which upon standing at room temperature for 5 minutes became a pale yellow solid (4.99 g, 111% - n.b. this yield suggests the presence of impurities). ^1H NMR (see Figures 1 to 4 and discussion below) showed this to be a 2:1 mixture of the Z and E isomers. The solid was then covered with methanol and stirred at room temperature until a fine suspension formed. The suspension was filtered to give a pure white solid (3.82 g, 85%) which was a 3.2:1 mixture of Z:E isomers (see Figure 5). The pure solid from above was dissolved in hot hexanol (100°C) and left to crystallise at ambient temperature. A 22:1 mixture of Z:E isomers (2.11 g, 47% (see Figure 6)) was produced, and this product was in turn recrystallised from methanol by dissolving the material in the minimum amount of boiling methanol to give pure (as confirmed by ^1H NMR and HPLC - see Figures 7 and 8) Z isomer of 2-chloroethoxy tamoxifen (1.55 g, 34.6% yield). M.p. $107-109^\circ\text{C}$, m/z 362/364 (chlorine atom present). δ_{H} 0.92 (3H, t, $J = 7.33$ Hz, CH_3), 2.46 (2H, q, $J = 7.33$ Hz, CH_2CH_3), 3.72 (2H, t, $J = 5.86$ Hz, $\text{OCH}_2\text{CH}_2\text{Cl}$), 4.09 (2H, t, $J = 5.86$ Hz, $\text{OCH}_2\text{CH}_2\text{Cl}$), 6.55 (2H, d, $J = 8.79$ Hz, aromatic protons ortho to $\text{OCH}_2\text{CH}_2\text{Cl}$), 6.79 (2H, d, $J = 8.79$ Hz, aromatic protons meta to $\text{OCH}_2\text{CH}_2\text{Cl}$), 7.10-7.38 (10H, m, the two remaining C_6H_5 's) (see Figure 5). The 2-chloroethoxy tamoxifen was reacted with dimethylamine in ethanol, under reflux, to produce the desired Z isomer of tamoxifen.

30 Analysis of ^1H NMR data

Figures 1 to 4 represent a mixture of the E- and Z-forms of compound XI described above in Scheme I.

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The expansion of the region δ 0.80 to 1.05 shows two overlapping triplets corresponding to the CH_3 groups in the Z- and E- derivatives respectively. The critical point is the ratio of the heights of the peaks at 0.92 (for the Z) and 0.94 (for the E), which is approximately 2:1.

The expansion of the 4.00 to 4.35 region reveals similar information where ratios are 10:6.4 and 5.56:3.43. Similarly expansion of the region 3.6 to 3.9 shows the ratio to be 2.46:1. All of these measurements suggest an approximate 2:1 ratio. The discussion with reference to figure 1 also applies to the spectra of figures 6 and 7 referred to below.

Figure 5 shows the ^1H NMR spectrum of the pure solid obtained after the methanol washing of the crude reaction product. Figure 6 shows the ^1H NMR spectrum of the solid obtained following the recrystallisation from hexanol of the product shown in Figure 5, and Figures 7 and 8 respectively show the ^1H NMR and the HPLC analyses of the pure Z isomer obtained following the second recrystallisation, this time from methanol. The HPLC analysis we carried out under the following conditions: Hypersil ODS 5 mm, 250 x 4.0 mm column and 50% MeOH : 30%; MeCN : 20%; H_2O mobile phase at 1ml/min.

As an alternative to the use of hexanol followed by methanol as described in Example 1, other solvents were tested to assess their ability to predominantly remove the Z isomer of 2-chloroethoxy tamoxifen from a mixture of Z- and E- isomers. The following solvents were found to be effective: methanol, ethanol, propanol, iso-propanol, butanol, pentanol, cyclohexanol, acetonitrile, benzene, toluene, nitromethane, petroleum ether and dioxan.

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The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this
5 specification, and the contents of all such papers and documents are incorporated herein by reference.

All of the features disclosed in this specification (including any accompanying claims, abstract and
10 drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive..

Each feature disclosed in this specification (including any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly
15 stated otherwise. Thus, unless expressly stated otherwise
20 each feature disclosed is one example only of a generic series of equivalent or similar features.

The invention is not restricted to the details of the foregoing embodiment(s). The invention extends to any
25 novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

- 20 -

CLAIMS

1. A method of removing predominantly a first geometric isomer of tamoxifen or an analogue thereof from a mixture
5 comprising said first geometric isomer and a second geometric isomer, the method including the step of allowing the first isomer to crystallise in a solvent.
2. A method according to Claim 1, wherein said solvent
10 is contacted with said mixture at a first temperature which is less than the boiling point of the solvent and recrystallisation is then carried out at a second temperature which is greater than -4°C .
3. A method according to Claim 2, wherein said second
15 temperature is greater than 20°C .
4. A method according to any preceding claim, wherein
said solvent includes a first solvent part which is a
20 polar organic solvent.
5. A method according to Claim 4, wherein said first
solvent part is an alcohol having only one $-\text{OH}$ group.
6. A method according to Claim 4 or Claim 5, wherein
25 said first solvent part is hexanol.
7. A method according to any preceding claim, comprising
allowing the first isomer to crystallise in said solvent
30 (hereinafter "said first solvent") in a first step and subsequently allowing the crystallised product of the first step to crystallise in a solvent (hereinafter "said second solvent") in a second step.



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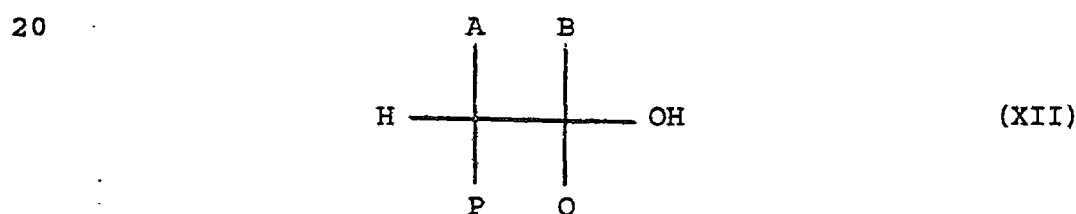
8. A method according to Claim 7, wherein said second solvent has a lower boiling point than said first solvent.

9. A method according to Claim 8, wherein said second
5 solvent comprises methanol.

10. A method according to any preceding claim, wherein
10 said first geometric isomer is crystallised at some stage in said method from a solvent which includes methanol.

11. A method according to any preceding claim, wherein
said first geometric isomer of tamoxifen or an analogue
represents a precursor of tamoxifen or a derivative
thereof which precursor can be converted to tamoxifen or
15 a said derivative thereof.

12. A method according to Claim 11, wherein said
precursor is prepared from a compound of general formula



25 wherein A, B and P independently represent an optionally-substituted phenyl group and Q represents a hydrogen atom or an optionally-substituted alkyl, alkenyl, alkynyl or phenyl group.

30 13. A method according to Claim 11 or Claim 12, wherein said precursor is derivatised using a compound which includes a group of general formula

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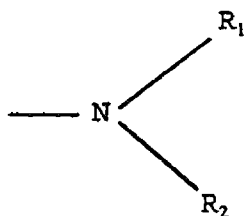


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to convert said precursor to tamoxifen or said derivative, wherein R₁ and R₂ independently represent a hydrogen atom or an optionally-substituted alkyl group.

10

14. A method of preparing tamoxifen or a derivative, especially an antiestrogenic derivative, thereof, the method including the steps of allowing a first geometric isomer of a precursor of tamoxifen or said derivative to crystallise in a solvent and derivatising said isomer in order to produce said tamoxifen or said derivative.

15

15. The use of a solvent for removing predominantly a first geometric isomer of tamoxifen or an analogue thereof from a mixture of isomers.

20

16. A method of preparing an antiestrogenic isomer of tamoxifen or an analogue thereof in purity of at least 99%, the method using a solvent or solvents as described in any preceding claim.

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