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(54) **TAMOXIFENE ET ANALOGUES DE CELUI-CI**
(54) **TAMOXIFEN AND ANALOGUES THEREOF**

(57) On décrit un procédé de préparation d'un isomère géométrique préféré de tamoxifène ou d'un analogue de celui-ci, ce procédé comprenant les étapes consistant à convertir un premier isomère géométrique d'un précurseur en un second isomère géométrique du même précurseur, par mise en contact de ce premier isomère avec du méthanol et/ou de l'isopropanol, puis à former un dérivé à partir du second précurseur afin d'obtenir du tamoxifène ou un analogue anti-oestrogénique de celui-ci.

(57) A method of preparing a preferred geometric isomer of tamoxifen or an analogue comprises converting a first geometric isomer of a precursor to a second geometric isomer of the same precursor by contact with methanol and/or isopropanol and derivatising the second precursor to form tamoxifen or an antiestrogenic analogue thereof.

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(54) Title: TAMOXIFEN AND ANALOGUES THEREOF

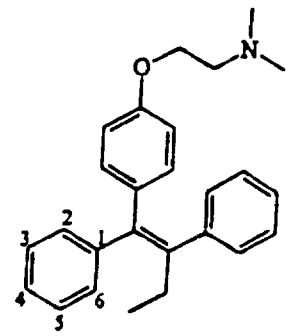
(57) Abstract

A method of preparing a preferred geometric isomer of tamoxifen or an analogue comprises converting a first geometric isomer of a precursor to a second geometric isomer of the same precursor by contact with methanol and/or isopropanol and derivatising the second precursor to form tamoxifen or an antiestrogenic analogue thereof.

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 antioestrogenecity 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

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 a relatively pure isomer of tamoxifen or an analogue thereof 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 converted into another geometric isomer by contacting the isomer with certain solvents.

According to the invention, there is provided a method of preparing a first geometric isomer of tamoxifen or an analogue thereof, the method including selecting a solvent in which a second geometric isomer of tamoxifen or said analogue converts to said first geometric isomer and contacting said second geometric isomer with said solvent in order to cause said conversion.

The conversion of said second isomer to said first isomer can readily be shown using ^{1}H NMR or other analytical techniques. Suitably, the method involves conversion of one geometric isomer to another geometric isomer of the same compound.

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

Preferably, said method includes allowing said first geometric isomer to crystallise in said solvent. The

method may include separating the crystallised product from the remainder.

Various solvents or mixtures of solvents may be selected for use in the method.

Preferably, the solvent is an organic solvent with polar organic solvents being preferred.

Said solvent is preferably a protic solvent.

Preferably, the solvent includes at least one, preferably only one, -OH group.

Said solvent is preferably an alcohol, preferably an aliphatic alcohol. An aliphatic alcohol may be a C_1 to C_{12} alcohol, preferably a C_1 to C_6 alcohol, more preferably a C_1 to C_4 alcohol.

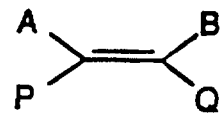
Preferably, the solvent is selected from methanol and propanol, especially iso-propanol. A mixture of methanol and propanol has been found to be particularly advantageous.

The method may be carried out at a temperature of less than 100°C, preferably less than 60°C, more preferably less than 30°C. Advantageously, the method may be carried out at ambient temperature or below.

Preferably, the method is carried out at a temperature of at least -10°C and, more preferably, at least 0°C.

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



(I)

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

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 substituents generally used to affect the activity of drugs for oral administration. In relation to alkyl, alkenyl, alkynyl and phenyl groups, preferred optional substituents include halogen atoms and a hydroxy group and optionally-substituted alkylcarboxy, alkoxy, phenoxy, alkylamino and alkylcarbonyl groups.

Preferred alkyl, alkenyl and alkynyl groups may have 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 alkyl group is a C_1 to C_4, more preferably a C_1 to C_2, alkyl group. Q preferably represents an ethyl group.

Preferably, groups A, B and P independently represent an unsubstituted or monosubstituted phenyl group. Where a group A, B or P is substituted, it is preferably substituted in the 3- or, more preferably, the 4-position.

Preferably, group B is unsubstituted.

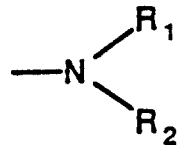
Group P is preferably unsubstituted or substituted by a halogen atom or hydroxy, optionally-substituted alkoxy or phenoxy, groups. Where group P is substituted, it is preferably substituted in the 4-position.

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

$$—O—(CH_2)_n—X \qquad (II)$$

wherein n represents an integer preferably in the range 1 to 8, more preferably 1 to 4; and

X represents a leaving group, for example a halogen, especially a chlorine, atom, or a group of general formula



(III)

wherein R^1 and R^2 independently represent a hydrogen atom or an optionally-substituted, preferably unsubstituted, alkyl group.

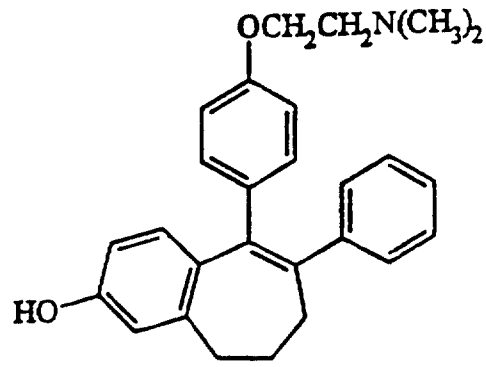
Preferably, n represents 2.

Preferably, said second geometric isomer contacted with solvent in the method is a first analogue of tamoxifen and the method includes the further step of derivatising the first geometric isomer prepared in order to prepare tamoxifen or a second analogue thereof. Thus, preferably the second geometric isomer contacted in the method is a precursor in the preparation of tamoxifen or said second analogue thereof. Preferably, the first analogue of tamoxifen contacted in the method, more preferably said first geometric isomer of said first analogue prepared in the method, has less antiestrogenic activity compared to tamoxifen or said second analogue.

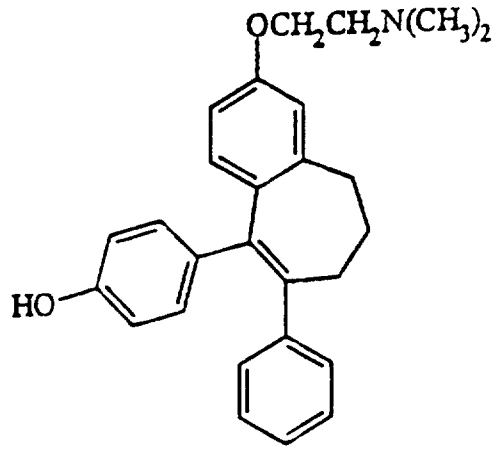
Preferably, said precursor is a compound of general formula I described above wherein B, P and Q are as described above. Preferably, A represents a phenyl group substituted, preferably at the 4-position, by a first moiety which includes an active atom or group which is arranged to react with a second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

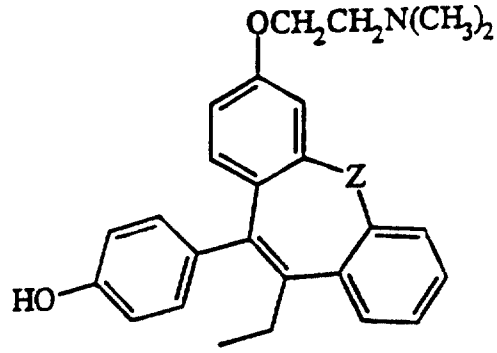
Where a pair of adjacent substituents A, B, P and Q are arranged together to form part of a ring structure, the ring structure may be formed between pairs of substituents A, B, P and Q which are *cis* to one another. Examples of compounds of general formula I which have ring structures as described include:



(IV)



(V)



(VI)

wherein Z represents an oxygen or sulphur atom or a group $-CH_2CH_2-$.

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

The ratio of the volume of the first and/or second isomers to the volume of the solvent used in the method may be in the range 0.1 to 10, preferably in the range 0.5 to 5 and more preferably about 1 to 1. Preferably, sufficient solvent is used to substantially dissolve the first and/or second isomers and thereby define a single-phase solution.

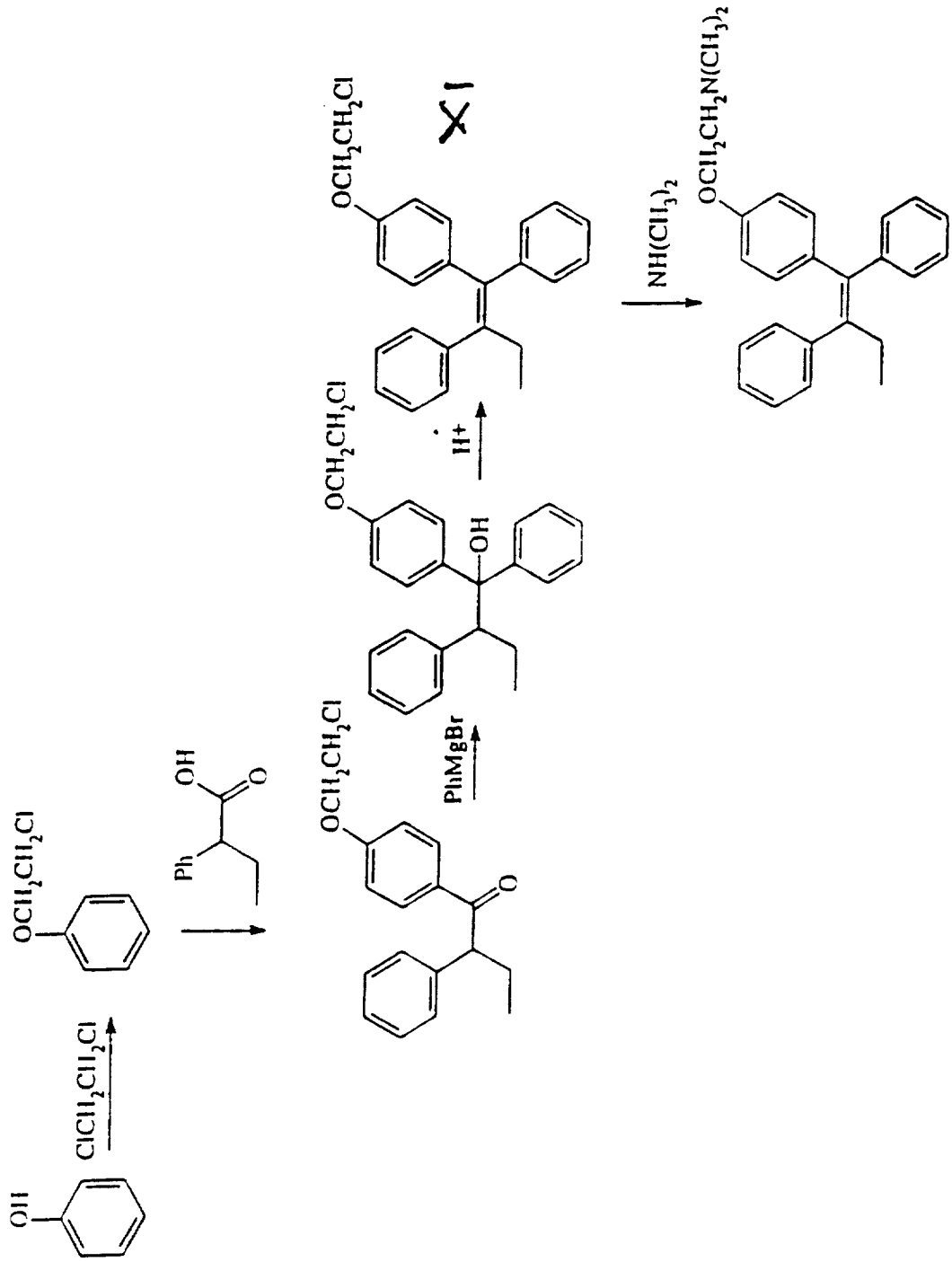
When the method involves contacting a mixture which comprises first and second isomers, the mixture used may be prepared by known routes to tamoxifen and its analogues, for example as described in J.Chem. Research, 1985(S) 116, (M) 1342 and 1986 (S) 58, (M) 0771.

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

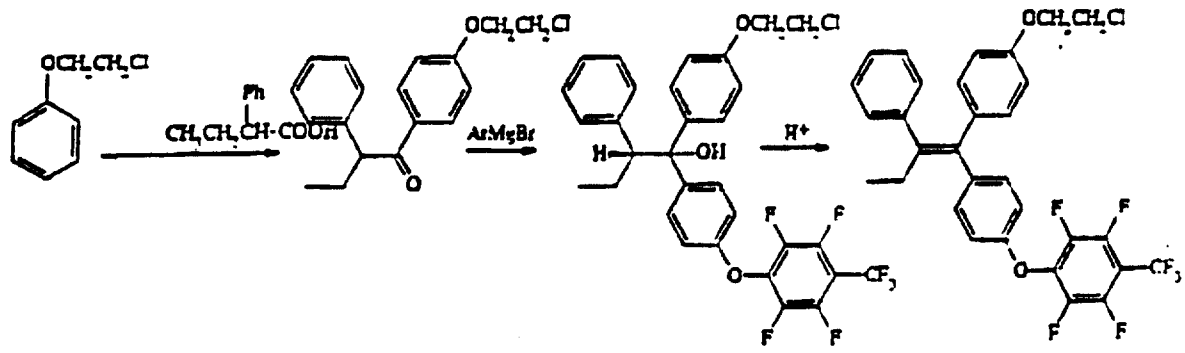
Referring to Scheme I, preferably, the alkene derivative of formula XI is contacted with said solvent prior to the reaction with trimethylamine. In one embodiment, it is found that, after contacting a mixture

of geometric isomers of said compound XI with methanol, tamoxifen can be produced which contains over 98 wt% of the desired Z isomer (which has the stereochemical configuration of compound XI shown in Scheme I) and 1-2 wt% of the undesired E isomer. Thus, in general terms, the method described above may be used to prepare tamoxifen or an analogue which includes greater than 95 wt% and preferably greater than 98 wt% of said first geometric isomer.

Scheme 1


OH
ClCH2CH2Cl
OCH2CH2Cl
Ph
OH
O
OCH2CH2Cl
PhMgBr
OCH2CH2Cl
OH
H+
XI
OCH2CH2Cl
NH(CH3)2
OCH2CH2N(CH3)2

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



(VII) (VIII) (IX) (X)

The invention extends to a method of preparing tamoxifen or an antiestrogenic analogue thereof, the method including the steps of contacting a precursor of tamoxifen or said analogue with a solvent in which a second geometric isomer of said precursor can convert to a first geometric isomer thereof and derivatising said precursor in order to produce said tamoxifen or said analogue.

The invention extends to the use of a solvent for converting a second geometric isomer of tamoxifen or an analogue thereof into a first geometric isomer.

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 aspect or embodiment described herein.

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

Figure 1 is a ^{1}H NMR spectrum for a mixture of isomers of a tamoxifen precursor, prepared in Example 3;

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

Figure 5 is a ^{1}H NMR spectrum for the product obtained in Example 3 after treatment with methanol.

Example 1

Preparation of 4-Hydroxytamoxifen

A solution of 1,2-dibromoethane (1.41g, 7.5mmol) in ether (5ml) was added dropwise with stirring to a boiling solution of 2,3,5,6-tetrafluoro-1-(4'-bromophenoxy)-4-(trifluoromethyl)benzene (3.89g), 10mmol) in ether (3ml) containing magnesium turnings (486mg, 20mmol) under dried nitrogen in order to prepare a Grignard reagent. When the addition was complete, a solution of 1-[4-(2-chloroethoxy)phenyl]-2-phenyl-1-butanone (compound VIII) (3.02g, 10mmol) in ether was added. The resulting mixture was stirred at room temperature for 20 hours. The solution was then poured into dilute hydrochloric acid (75ml) and extracted with ether (3x50ml). The combined ether extracts were dried, concentrated, redissolved in absolute alcohol (10ml) and refluxed with concentrated hydrochloric acid (3ml) for 4 hours. The solution was then poured into water (25ml) and extracted with ether (3x20ml). The organic extracts were dried and concentrated to give a light brown oil (about 7ml) which was dissolved in the same volume of methanol and left for 96 hours in a stoppered flask.

Crystals of E isomer of compound X separated out of solution. M.p. 114-117°C (lit. 116-118°C), m/z 594, δ_H 0.92 (3H, t, J = 7.51 Hz, CH_3), 2.45 (2H, q, J = 7.51 Hz, CH_2CH_3), 3.73 (2H, t, J = 5.86 Hz, OCH_2CH_2Cl), 4.10 (2H, t, J = 5.86 Hz, OCH_2CH_2Cl), 6.57 (2H, d, J = 8.8 Hz, aromatic protons ortho to OCH_2CH_2Cl), 6.77 (2H, d, J = 8.8 Hz, aromatic protons meta to OCH_2CH_2Cl), 6.98 (2H, d, J = 8.61 Hz, aromatic protons ortho to OC_7F_7), 7.09-7.18 (5H, m, C_6H_5), 7.22 (2H, d, J = 8.61 Hz, aromatic protons meta to OC_7F_7). It was observed that recrystallisation of the E isomer from methanol was not possible. A typical yield for the E isomer starting from the ketone of formula VIII was 41%. The isolated E isomer of compound X can readily be converted to the desired oestrogenic isomer of 4-hydroxytamoxifen as described in, for example, J. Chem. Research, 1985 (S) 116, (M) 1342 and 1986 (S) 58, (M) 0771.

Example 2

Preparation of Z isomer of 4-Hydroxytamoxifen

The procedure of Example 1 was followed except that the oil produced was dissolved in a 2:1 mixture of methanol and i-propanol. It was observed that a 41% yield of the desired E isomer was obtained in 4 hours.

Example 3

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, under nitrogen. 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 acid (5ml) for 4 hours. The organic phase was separated, dried (Na_2SO_4) and evaporated to dryness to give a yellow oil. ^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 oil was then dissolved in warm methanol (about 40°C) and allowed to cool to room temperature. The colourless crystals formed proved to be pure Z isomer of 2-chloroethoxy tamoxifen (4.12g, 11.4mmol, 92% yield). M.p. 107-109°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, OCH_2CH_2Cl), 4.09 (2H, t, J = 5.86 Hz, OCH_2CH_2Cl), 6.55 (2H, d, J = 8.79 Hz, aromatic protons ortho to OCH_2CH_2Cl), 6.79 (2H, d, J = 8.79 Hz, aromatic protons meta to OCH_2CH_2Cl), 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.

Analysis of ^1H NMR data

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

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.

Referring to Figure 5, this shows almost pure Z-isomer. It should be noted that there is 660 mg of this from an original mixture of a 2:1 ratio mixture of 780 mg which would contain only 520 mg of the Z-isomer.

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 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 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 stated otherwise. Thus, unless expressly stated otherwise, 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

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.

CLAIMS

1. A method of preparing a first geometric isomer of tamoxifen or an analogue thereof, the method including selecting a solvent from which the first geometric isomer can be crystallized; contacting a mixture which comprises first and second geometric isomers of tamoxifen or an analogue with said solvent; and allowing said first geometric isomer to crystallise in said solvent.

2. A method according to claim 1, wherein the solvent is an organic solvent.

3. A method according to claim 1 or claim 2, wherein the solvent is a polar organic solvent.

4. A method according to any preceding claim, wherein the solvent is a protic solvent.

5. A method according to any preceding claim, wherein said solvent is an alcohol.

6. A method according to any preceding claim, wherein the solvent is selected from methanol and/or propanol.

7. A method according to any preceding claim, carried out at a temperature of less than 100°C.

8. A method according to any preceding claim, wherein said analogues of tamoxifen include optionally substituted triphenylalkyl or triphenylalkylene compounds.

9. A method according to any preceding claim, wherein said first and second isomers contacted with solvent in the method are first analogues of tamoxifen and the method

includes a further step of derivatising the first geometric isomer prepared in order to prepare tamoxifen or a second analogue thereof.

10. A method of preparing tamoxifen or an antiestrogenic analogue thereof, the method including the steps of contacting a precursor of tamoxifen or said analogue with a solvent and derivatising said precursor in order to produce tamoxifen or said analogue.

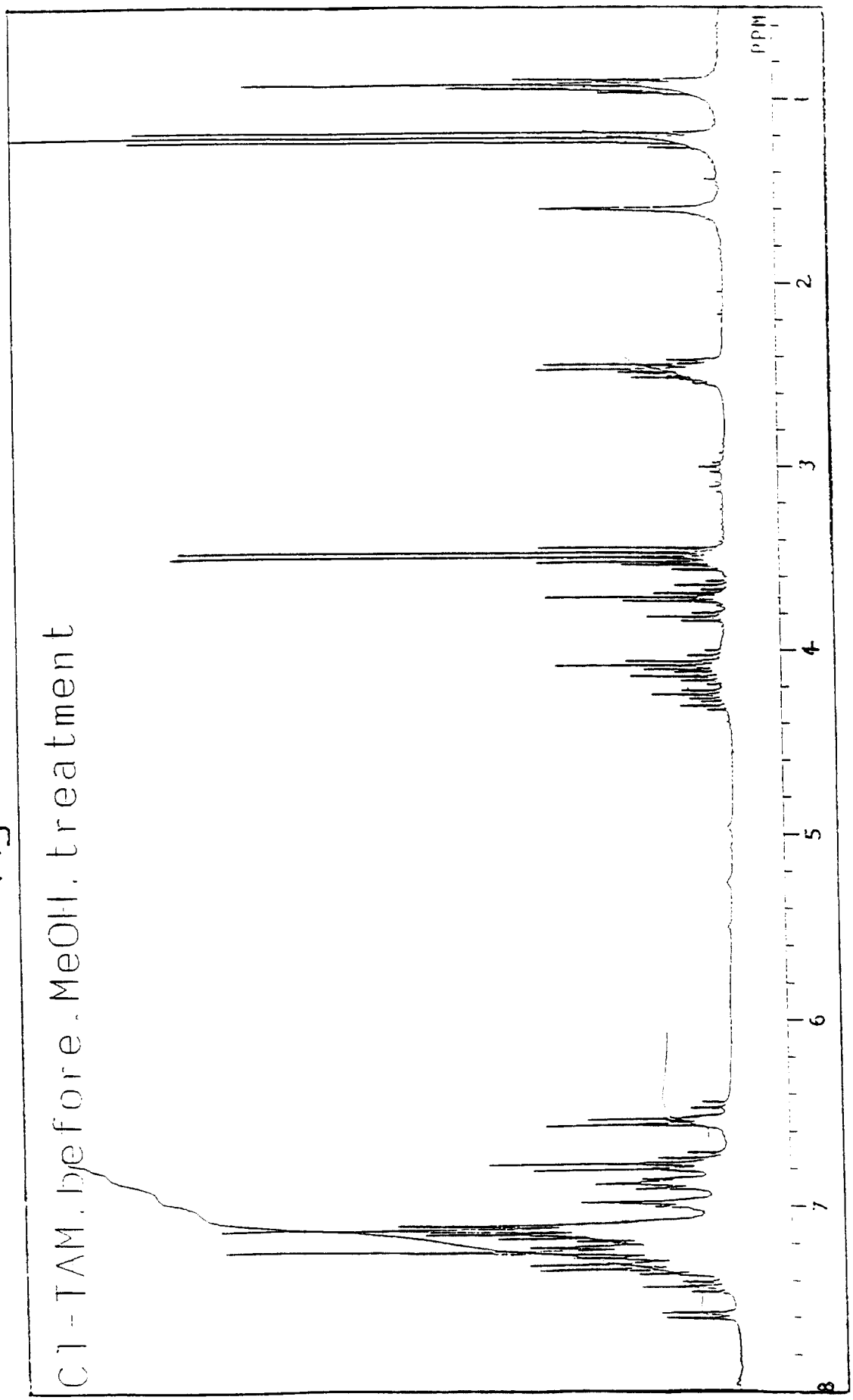


Fig. 1.

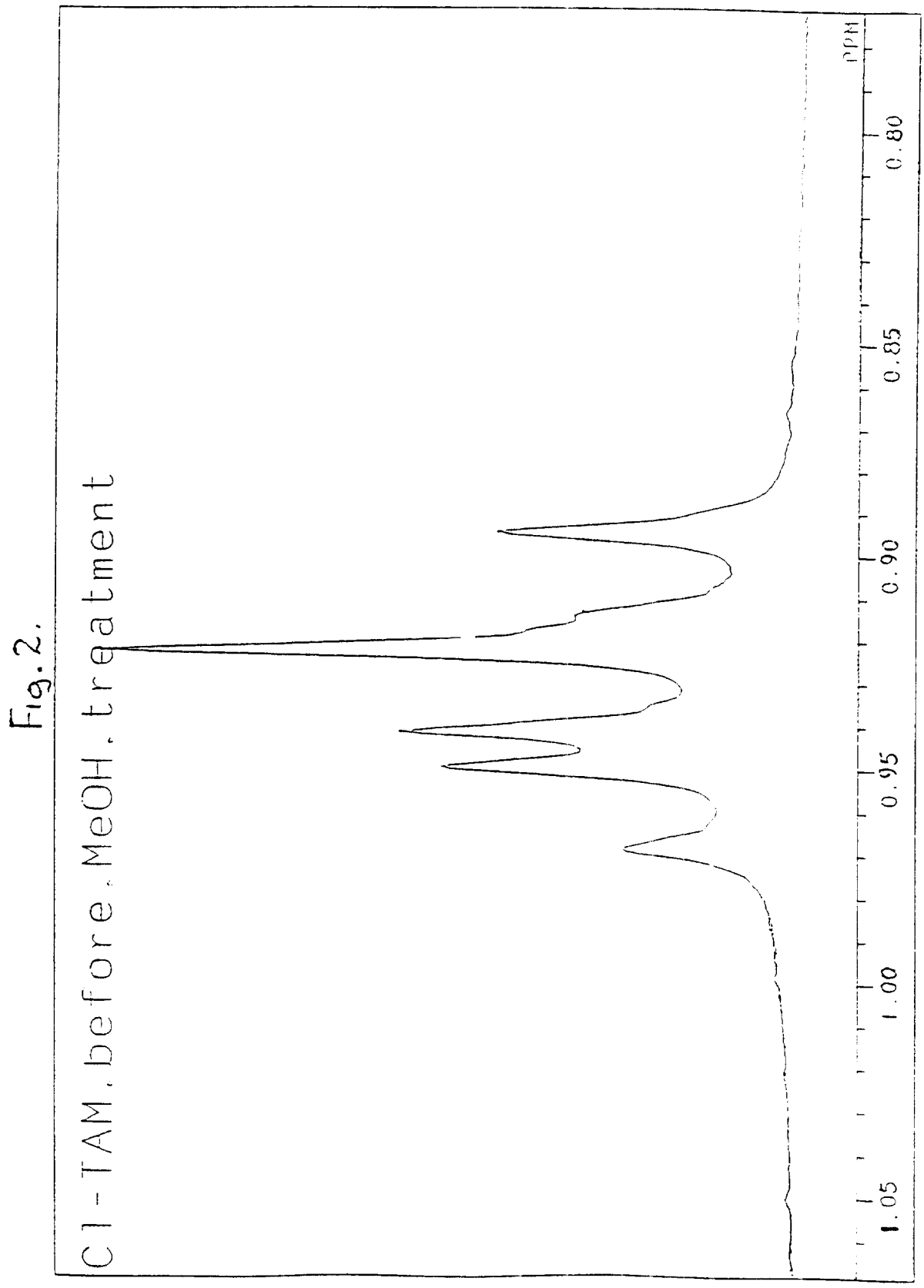


Fig. 2.

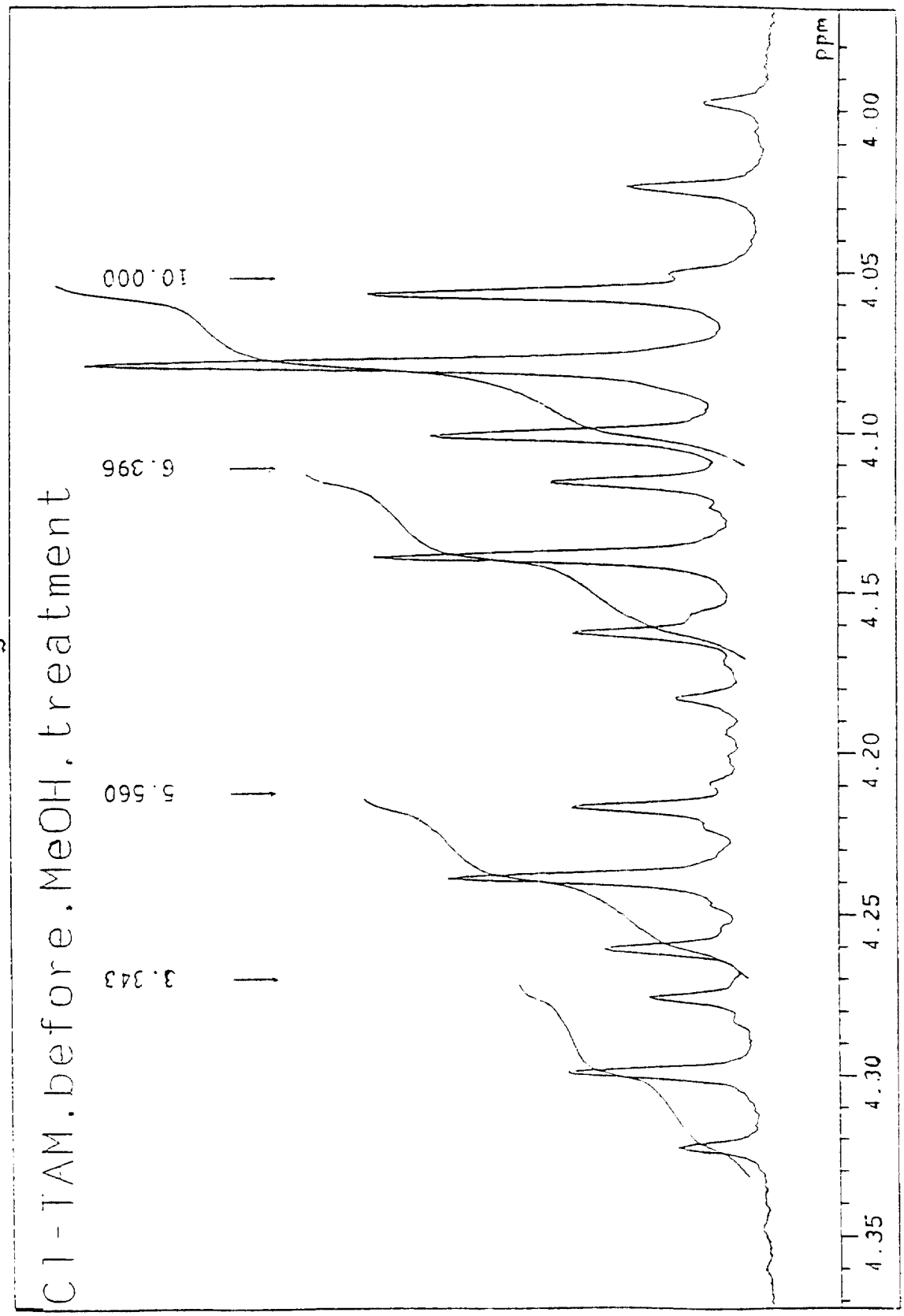
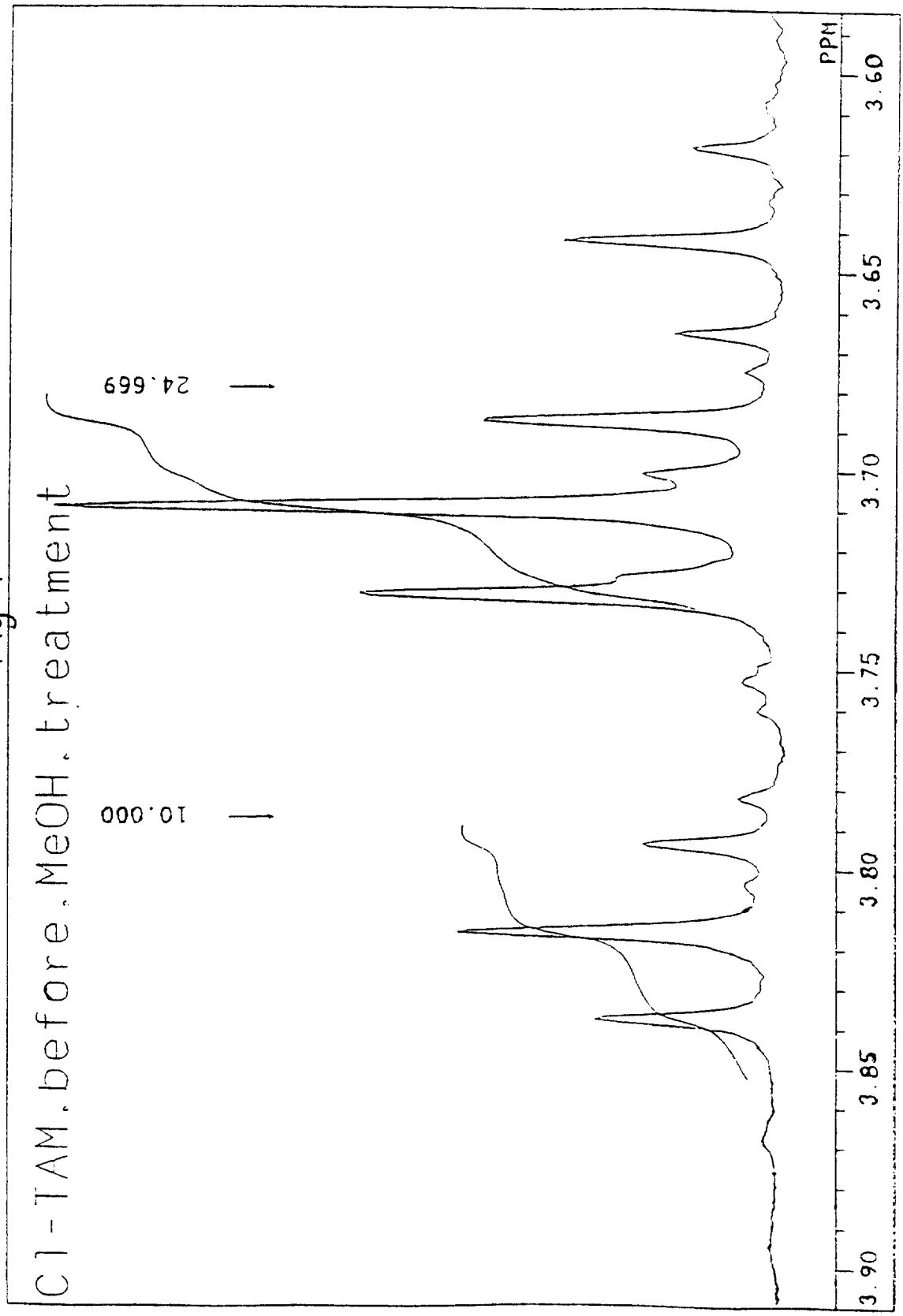

Cl-TAM.before.MeOH.treatment
10.000
6.396
5.560
3.343
ppm
4.00
4.05
4.10
4.15
4.20
4.25
4.30
4.35

Fig.3.


Cl-TAM.before.MeOH.treatment
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10.000
PPM
3.60
3.65
3.70
3.75
3.80
3.85
3.90

Fig. 4.

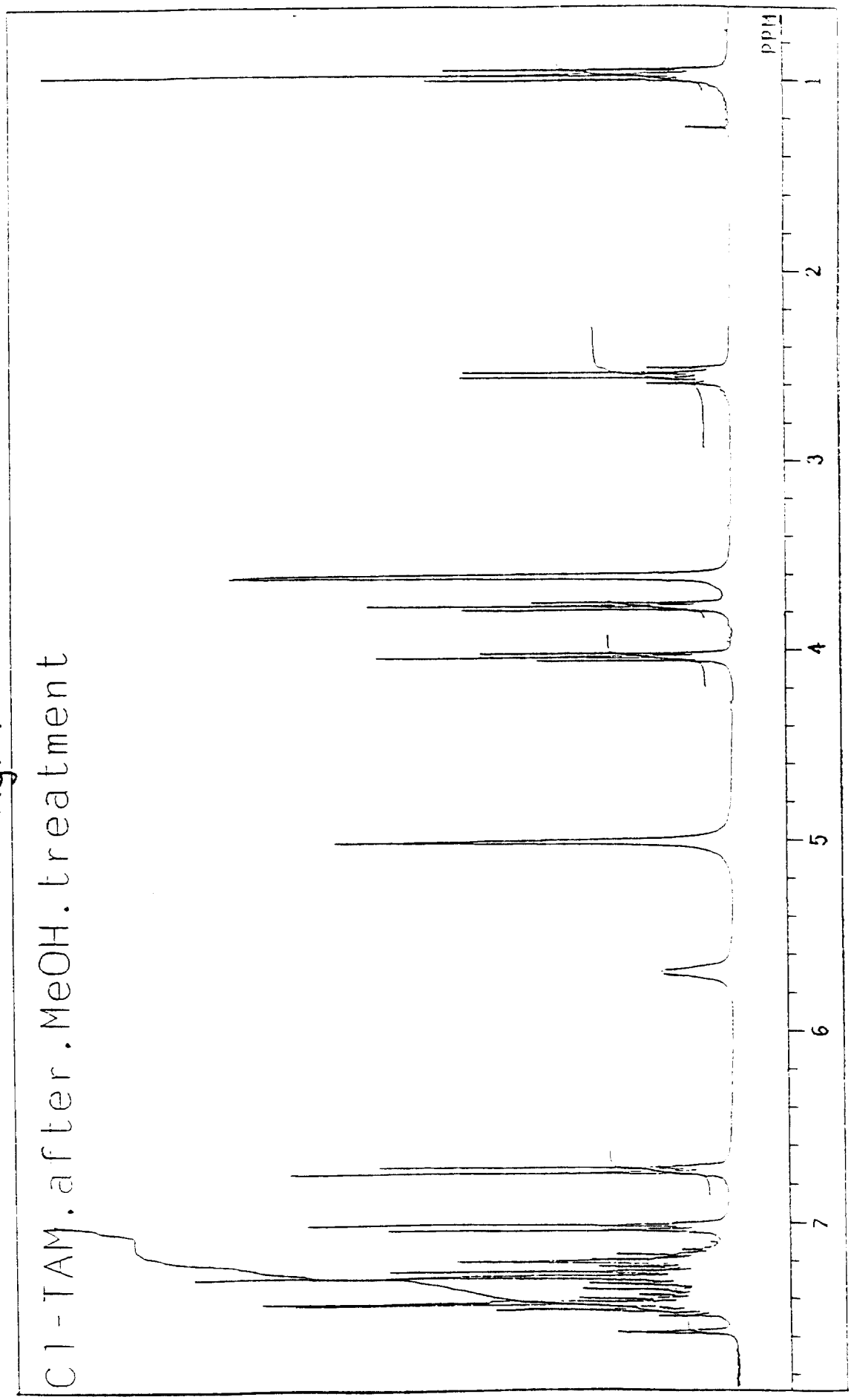

Fig.5.