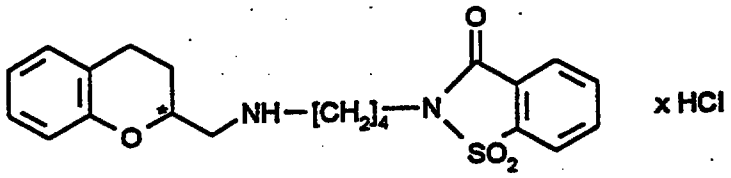
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☑ Drawing(s) : paged ...15... to paged ...15....
☑ Abstract : paged ...16... to paged ...17....
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Crystalline hydrochloride of (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman

The invention relates to the crystalline form of the hydrochloride of the compound (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman, processes for the preparation and the use in medicaments, in particular in medicaments having a neuroprotective action.

The hydrochloride of the compound (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman has the formula (I)



and is designated below as DBCH. The compound of the formula (I) is disclosed, for example, in European Patent Specification EP 352 613 as Example 92 H and, owing to its properties as a 5-HT_{1A} agonist, is proposed, inter alia, as a neuroprotective active substance in medicaments, in particular for the treatment and prevention of neuronal degenerations due to ischaemic effects, such as a stroke.

In the patent specification mentioned, the preparation of DBCH is also described. It is carried out in general by reacting the optically active 2-aminomethylchroman with N-4-bromobutylsaccharin in an inert solvent in the presence of a base. In this way, the compound DBCH is obtained in a crystalline modification (referred to below as modification II). The melting point is stated as 192-194°C.

It has been found that modification II is metastable and undergoes partial conversion at high humidity (85% relative humidity, room temperature). For this reason, it is only

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of limited suitability for use in pharmaceutical formulations.

Surprisingly, a crystalline form of the hydrochloride of (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}chroman (referred to below as modification V), which does not have these disadvantages, has now been found. This crystalline form of DBCH is thermodynamically stable and does not undergo conversion even at high atmospheric humidity (85% relative humidity, room temperature). For this reason, it is particularly suitable for solid medicament formulations.

The crystalline form (modification V), according to the invention, of DBCH is defined by the following physicochemical parameters:

1. The melting point of the crystalline form according to the invention cannot be determined experimentally since a solid-solid phase transition takes place on heating at about 60°C to give modification I (endothermic peak in DSC thermogram, Fig. 1). The heat of transition is 24 J/g.

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2. X-Ray diffraction pattern (cf. Figure 2):

Mod. V [2 Theta]	Mod. V [2 Theta]	Mod. V [2 Theta]	Mod. V [2 Theta]
9.7	22.5	28.4	35.1
11.5	22.6	27.7	35.3
12.3	23.2	29.2	35.7
12.6	24.0	29.3	36.2
13.4	24.4	29.8	36.4
14.5	24.7	30.1	36.7
15.7	24.9	31.1	37.0
16.8	25.8	31.8	37.4
16.9	26.0	32.6	37.6
17.5	26.3	33.9	
18.3	26.9	34.1	
19.4	27.4	34.3	
20.4	27.9	34.7	

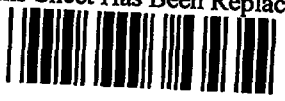
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3. IR spectrum (Figure 3):

Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]
621	1010	1373	2847
672	1021	1408	2873
680	1044	1445	2899
716	1059	1458	2930
731	1106	1488	2949
743	1137	1585	2961
752	1153	1603	2993
783	1179	1690	3025
800	1197	1733	3073
835	1213	2389	3097
849	1242	2424	3189
876	1242	2448	3444
897	1248	2541	
910	1288	2571	
927	1305	2673	
940	1320	2701	
987	1348	2785	

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4. Solid-state ^{13}C-NMR spectrum (Figure 4)

Mod. V [ppm]	Mod. V [ppm]	Mod. V [ppm]	Mod. V [ppm]
159	128	72	26
158	126	55	25
153	121	54	23
137	120	50	
135	118	49	
134	117	40	
133	116	39	
130	115	27	

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5. FIR spectrum (cf. Figure 5)

Mod. V [cm^{-1}]
105
121
152
169
195
224
247
286
300
335
345
391
410
420
426
455
485

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6. Raman spectrum (cf. Figure 6)

Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]
9	644	1379	3044
105	680	1394	3061
119	739	1411	3082
142	763	1433	
174	988	1462	
234	1016	1476	
286	1033	1600	
309	1062	1613	
348	1158	1736	
393	1181	2869	
419	1223	2900	
487	1245	2933	
513	1288	2963	
587	1307	2983	
595	1321	2991	
623	1351	3028	

The modification V differs substantially from the modification II in its physicochemical parameters (DSC melting behaviour, X-ray diffraction pattern, IR spectrum, solid-state ^{13}C-NMR spectrum, FIR spectrum and Raman spectrum (cf. Figures 1 to 6)). The melting point of the modification II is 195°C (DSC, heating rate 10 K/minute).

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The preparation of the crystalline form according to the invention (modification V of DBCH) is carried out in general by suspending DBCH of modification II in water or inert organic substances, for example lower alcohols, ketones or alkanes, until the desired degree of transformation is reached, particularly preferably until quantitative transformation into modification V. As a rule, this transition takes place at temperatures of 0°C to 35°C, preferably at 30°C. The resulting crystals of modification V are separated off and, in order to remove solvent present, are dried at room temperature in vacuo or at elevated temperature until the weight remains constant.

The crystalline modification V, according to the invention, of DBCH can be converted in a known manner into the customary formulations, formulations in which the crystalline active substance is present in solid form, such as, for example, tablets, sugar-coated tablets, pills, granular aerosols, suppositories and suspensions, being suitable. Here, the active substance is converted into the suitable formulation using inert nontoxic pharmaceutically suitable excipients and carriers.

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Experimental part:

Preparation of seed crystals of modification V

0.5 g of DBCH of modification II is suspended in 8 ml of acetone:methanol (7:1) and stirred for 5 days at room temperature. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The IR spectrum is recorded in order to check for quantitative transformation.

Preparation of modification II

The active substance in the form of modification II is obtained in the synthesis of the active substance by the addition of about 1.5 mol equivalents of hydrochloric acid. Modification II is precipitated from ethanol at about 5-50°C, filtered off, then washed with ethanol and dried in vacuo at 95-100°C.

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Examples

Example 1

0.5 g of DBCH of modification II is suspended in 7 ml of acetone:ethanol (6:1). The suspension is seeded with the modification V and stirred for 5 days at 0°C. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The DSC thermogram is recorded in order to check for quantitative transition.

Example 2

0.5 g of DBCH of modification II is suspended in 6 ml of acetone:ethanol (2:1). The suspension is seeded with the modification V and stirred for 5 days at room temperature. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The IR spectrum is recorded in order to check for quantitative transition.

Example 3

1.7 g of DBCH of modification II are suspended in 14 ml of acetone:ethanol (6:1). The suspension is seeded with the modification V and stirred for 6 days at room temperature. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The X-ray diffraction pattern is recorded in order to check for quantitative transition.

Example 4

0.4 g of DBCH of modification II is suspended in 7 ml of acetone:ethanol (6:1). The suspension is seeded with the modification V and stirred for one week at 30°C. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The DSC thermogram is recorded in order to check for quantitative

transformation.

Example 5

0.5 g of DBCH of modification II is suspended in 10 ml of iso-propanol. The suspension is seeded with the modification V and stirred for 6 h at room temperature. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The DSC thermogram is recorded in order to check for quantitative transition.

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Patent Claims

1. Crystalline form of (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman hydrochloride.

2. Crystalline hydrochloride according to Claim 1, which undergoes a transition at about 60°C with a heat of transition of 24 J/g.

3. Crystalline hydrochloride according to Claim 1 or 2, characterized by the following X-ray diffraction data.

Mod. V [2 Theta]	Mod. V [2 Theta]	Mod. V [2 Theta]	Mod. V [2 Theta]
9.7	22.5	28.4	35.1
11.5	22.6	27.7	35.3
12.3	23.2	29.2	35.7
12.6	24.0	29.3	36.2
13.4	24.4	29.8	36.4
14.5	24.7	30.1	36.7
15.7	24.9	31.1	37.0
16.8	25.8	31.8	37.4
16.9	26.0	32.6	37.6
17.5	26.3	33.9	
18.3	26.9	34.1	
19.4	27.4	34.3	
20.4	27.9	34.7	

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4. Crystalline hydrochloride according to any of Claims 1 to 3, characterized by the following IR spectral data:

Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]
621	1010	1373	2847
672	1021	1408	2873
680	1044	1445	2899
716	1059	1458	2930
731	1106	1488	2949
743	1137	1585	2961
752	1153	1603	2993
783	1179	1690	3025
800	1197	1733	3073
835	1213	2389	3097
849	1242	2424	3189
876	1242	2448	3444
897	1248	2541	
910	1288	2571	
927	1305	2673	
940	1320	2701	
987	1348	2785	

5. Crystalline hydrochloride according to any of Claims 1 to 4, characterized by the following solid-state ^{13}C-NMR spectral data:

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Mod. V [ppm]	Mod. V [ppm]	Mod. V [ppm]	Mod. V [ppm]
159	128	72	26
158	126	55	25
153	121	54	23
137	120	50	
135	118	49	
134	117	40	
133	116	39	
130	115	27	

6. Crystalline hydrochloride according to any of Claims 1 to 5, characterized by the following FIR spectral data:

Mod. V [cm^{-1}]
105
121
152
169
195
224
247
286
300

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* C L M S *

Mod. V [cm^{-1}]
335
345
391
410
420
426
455
485

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7. Crystalline hydrochloride according to any of Claims 1 to 6, characterized by the following Raman spectral data:

Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]
9	644	1379	3044
105	680	1394	3061
119	739	1411	3082
142	763	1433	
174	988	1462	
234	1016	1476	
286	1033	1600	
309	1062	1613	
348	1158	1736	

Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]
393	1181	2869	
419	1223	2900	
487	1245	2933	
513	1288	2963	
587	1307	2983	
595	1321	2991	
623	1351	3028	

8. Process for the preparation of crystalline hydrochloride according to Claim 7, characterized in that DBCH of modification II is suspended in water or inert organic substances and quantitatively converted into modification V according to any of Claims 1 to 7.

9. Medicament containing the crystalline hydrochloride according to any of Claims 1 to 7.

10. Use of the crystalline hydrochloride according to any of Claims 1 to 6 for the preparation of medicaments.

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Crystalline hydrochloride of (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman

Abstract

The invention relates to the crystalline form of the hydrochloride of the compound (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman, which is present as a stable form at room temperature. The crystalline modification V of the hydrochloride is suitable in particular for the preparation of solid medicaments, in particular of medicaments for the treatment of neuronal degenerations.

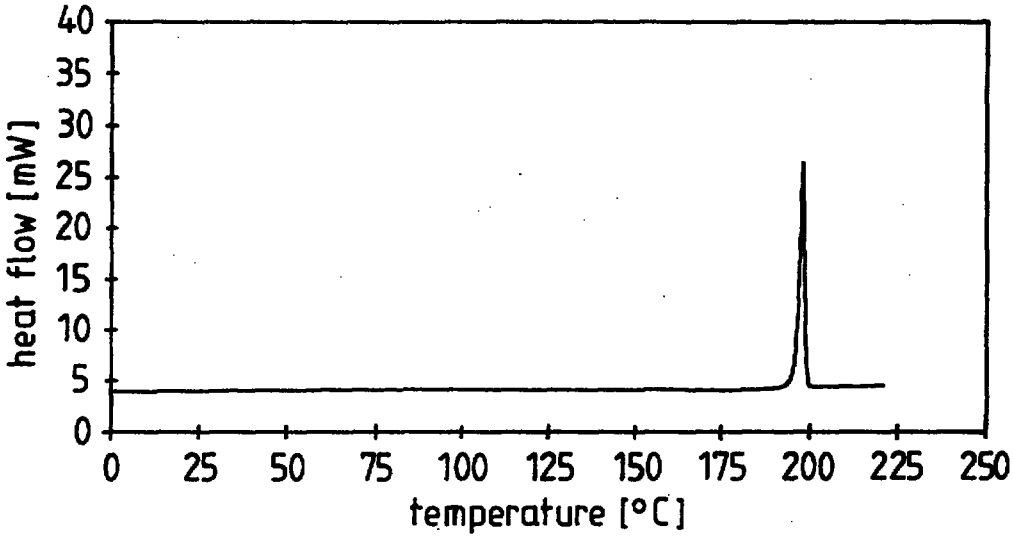
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Fig. 1

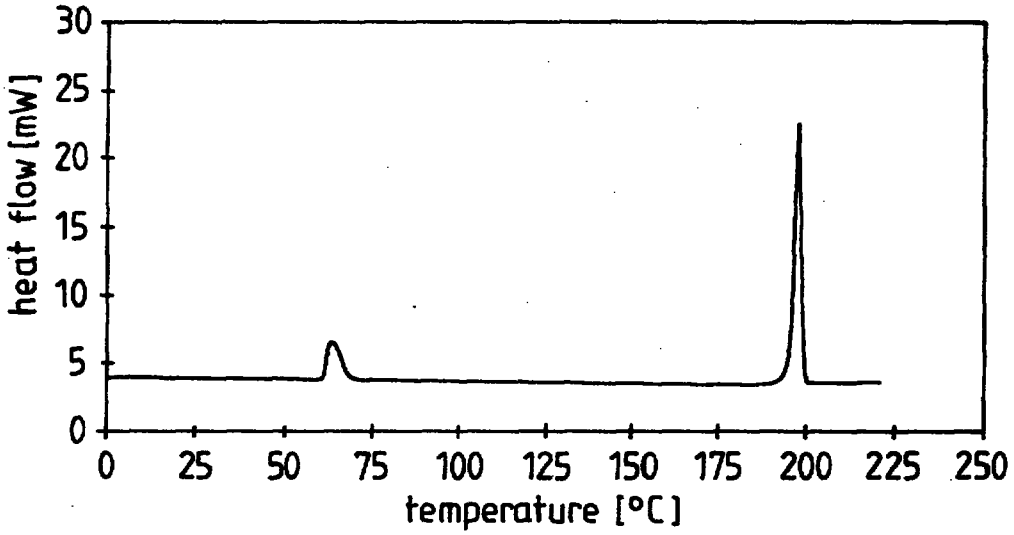
DSC-thermograms of DBCH

Modification II.



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Modification V.

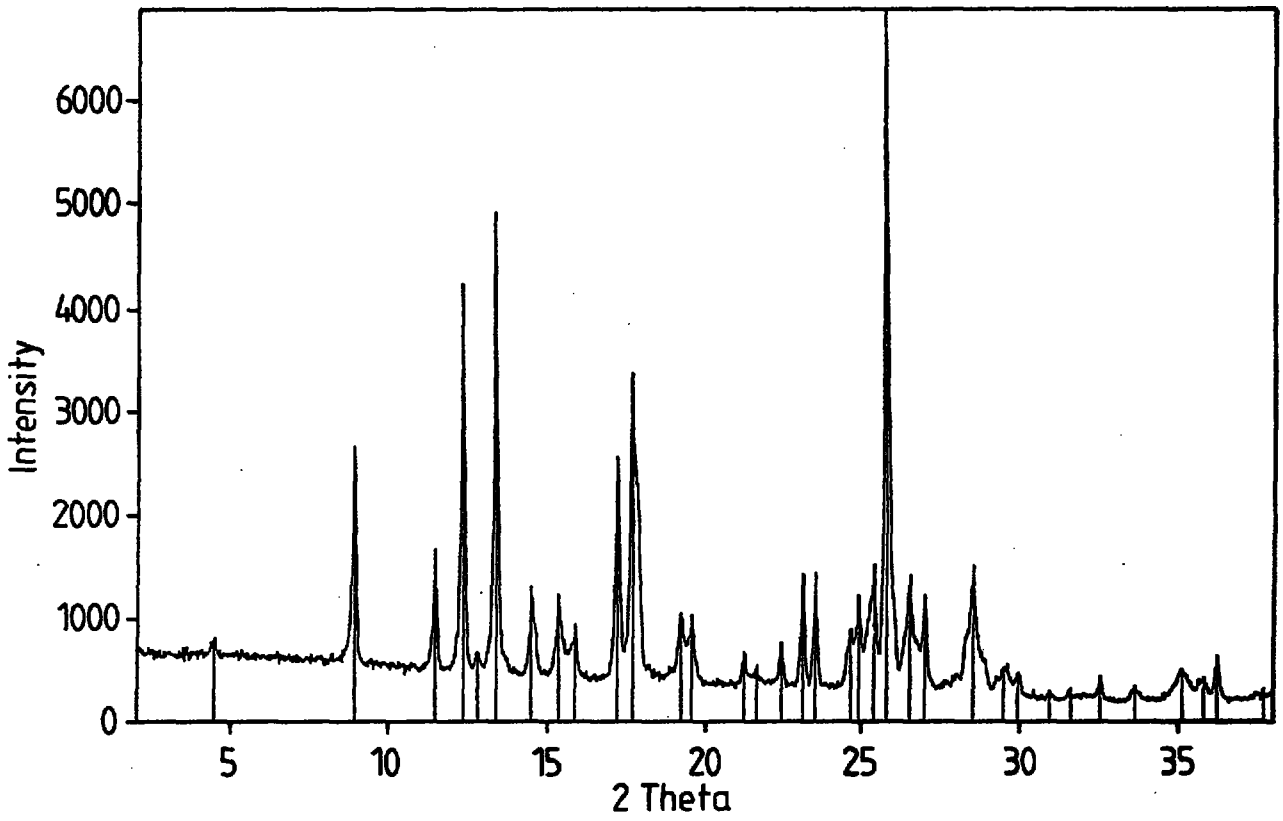


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Fig. 2

X-ray pattern of DBCH

Modification II.



Modification V.

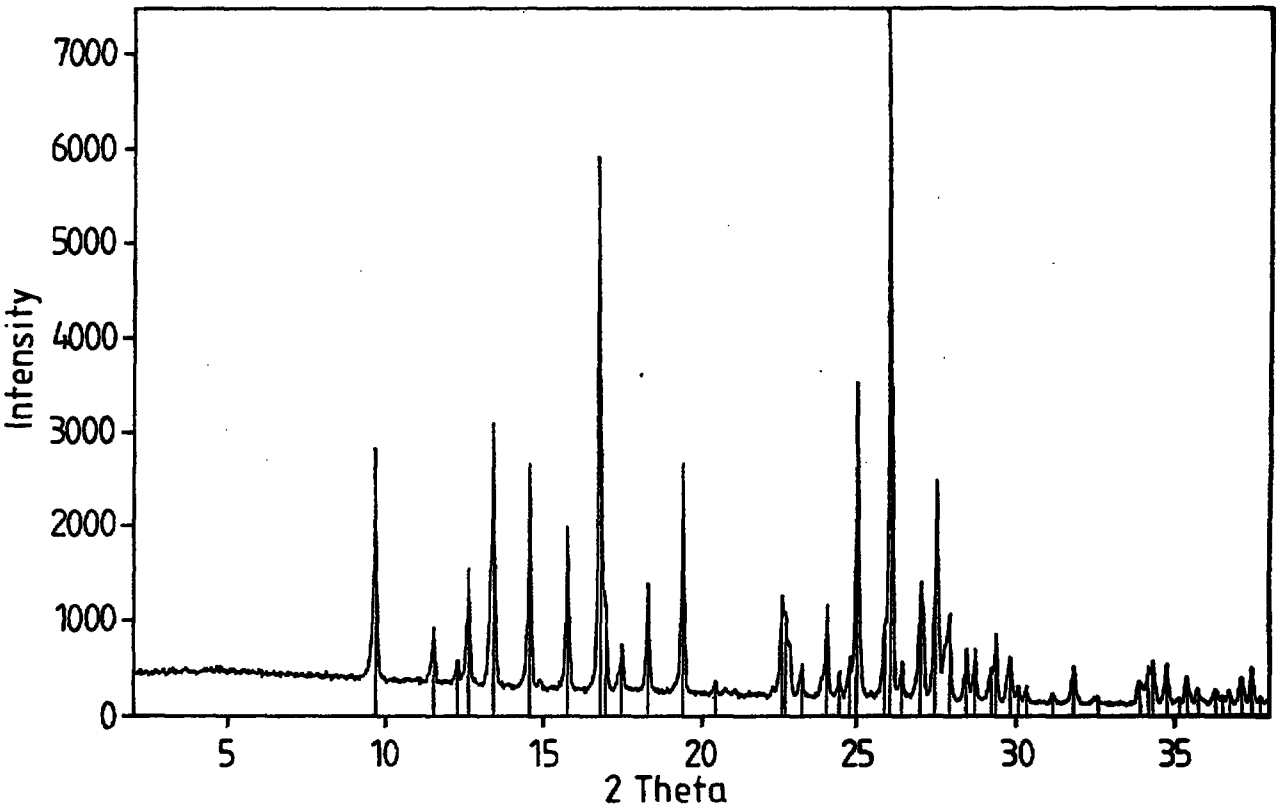
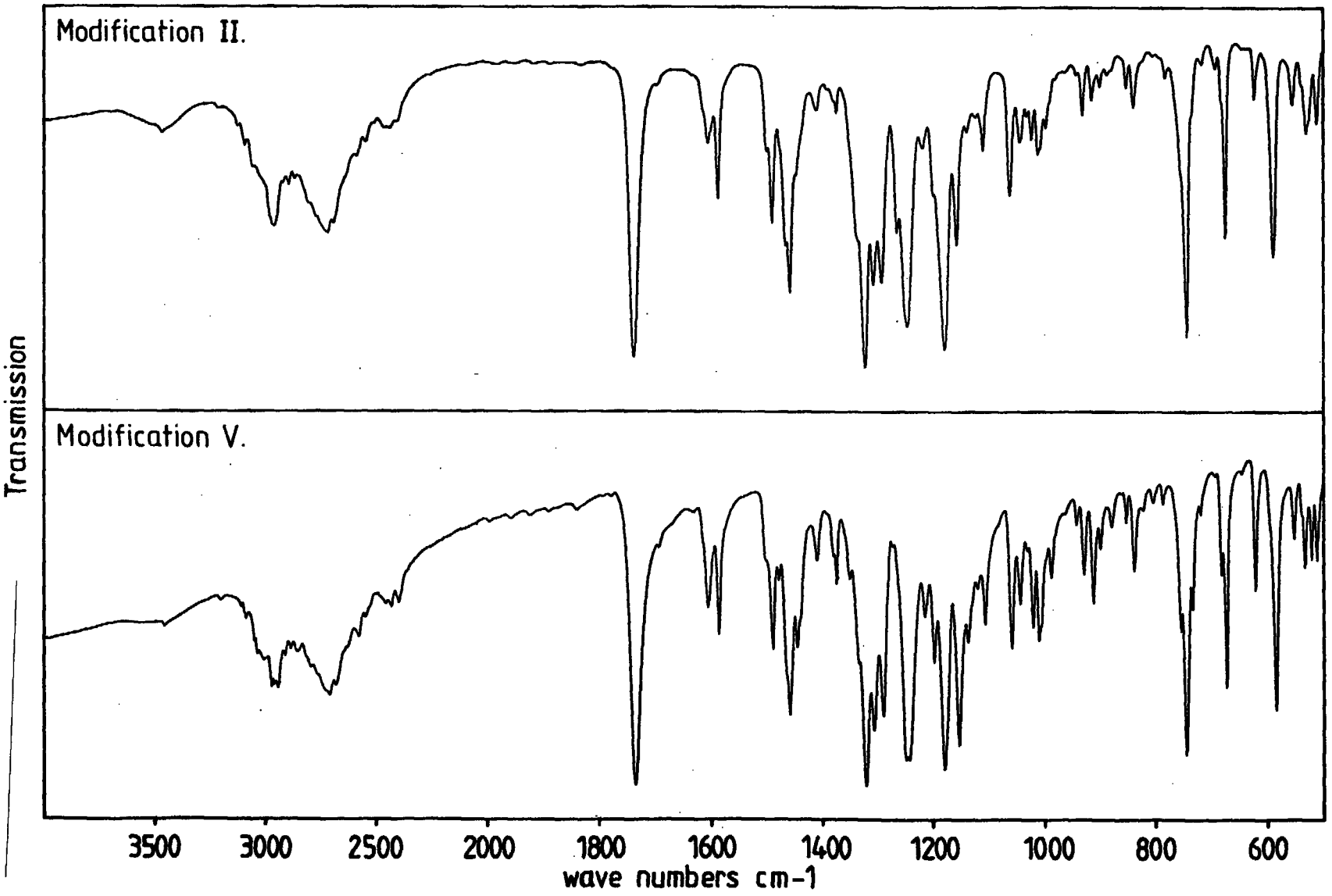


Fig. 3

IR-spectra of DBCH

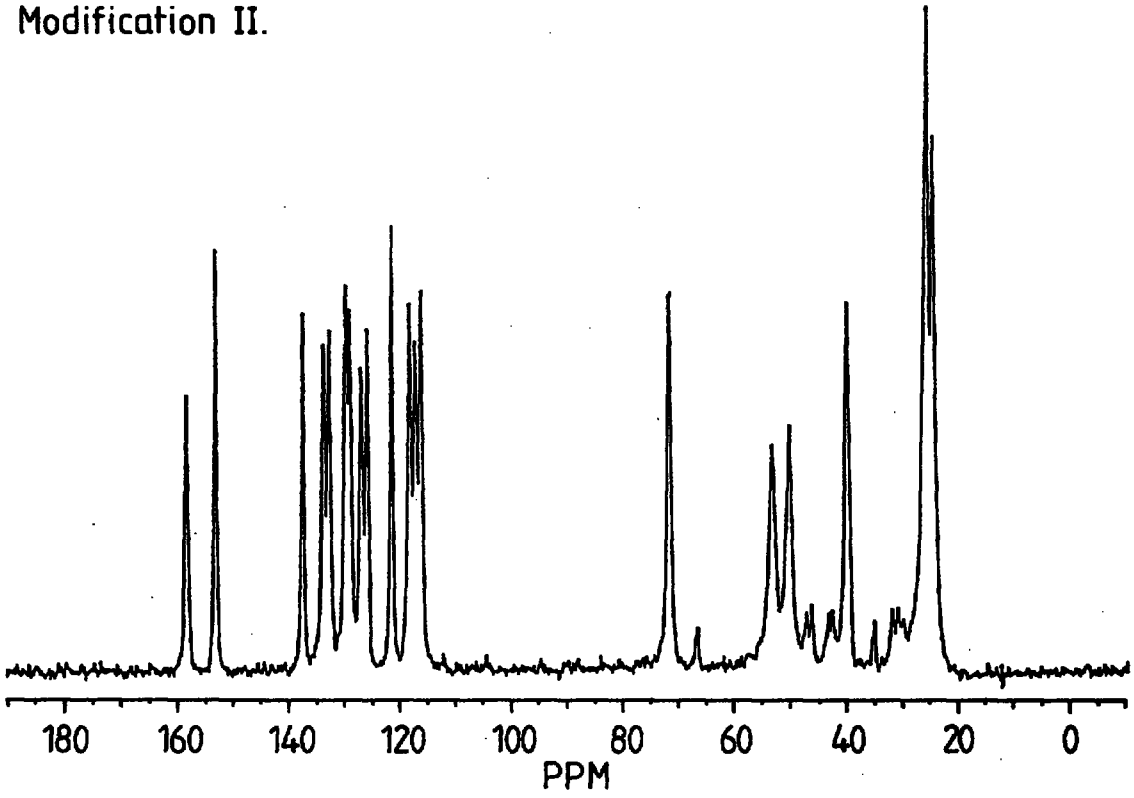


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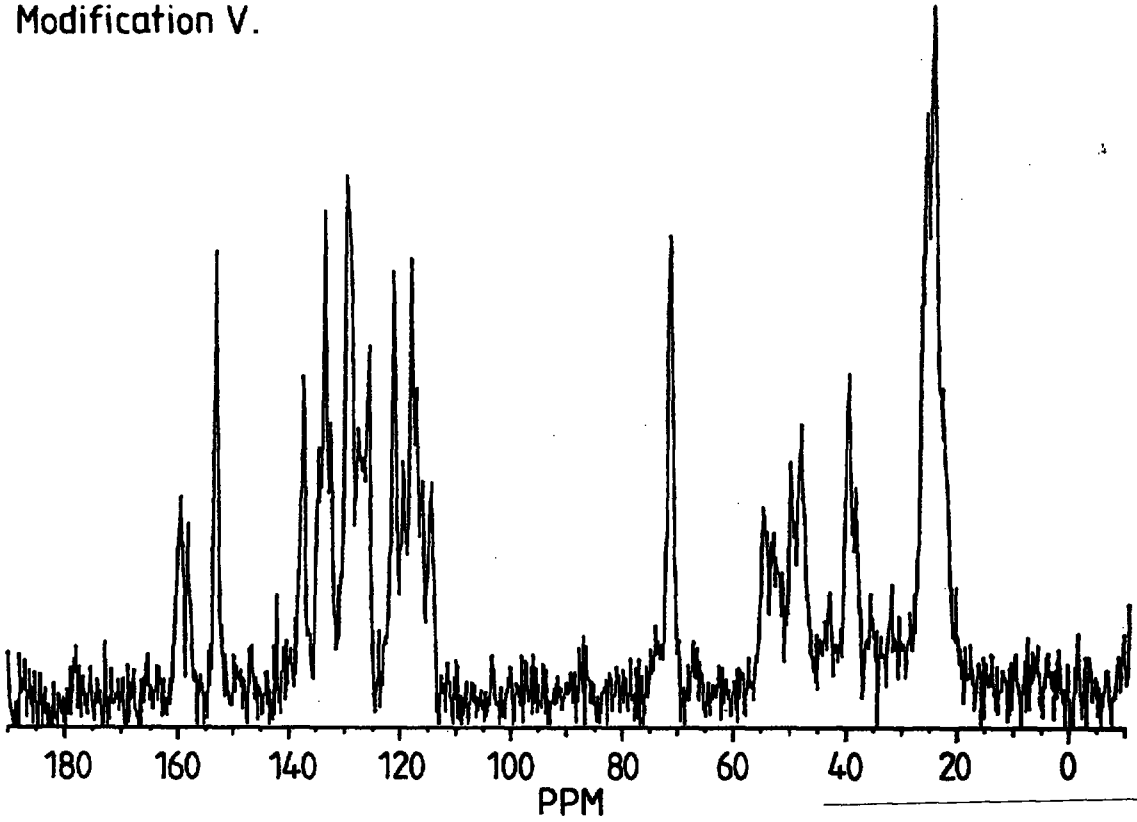
Fig. 4

^{13}C-solid state NMR spectra of DBCH

Modification II.



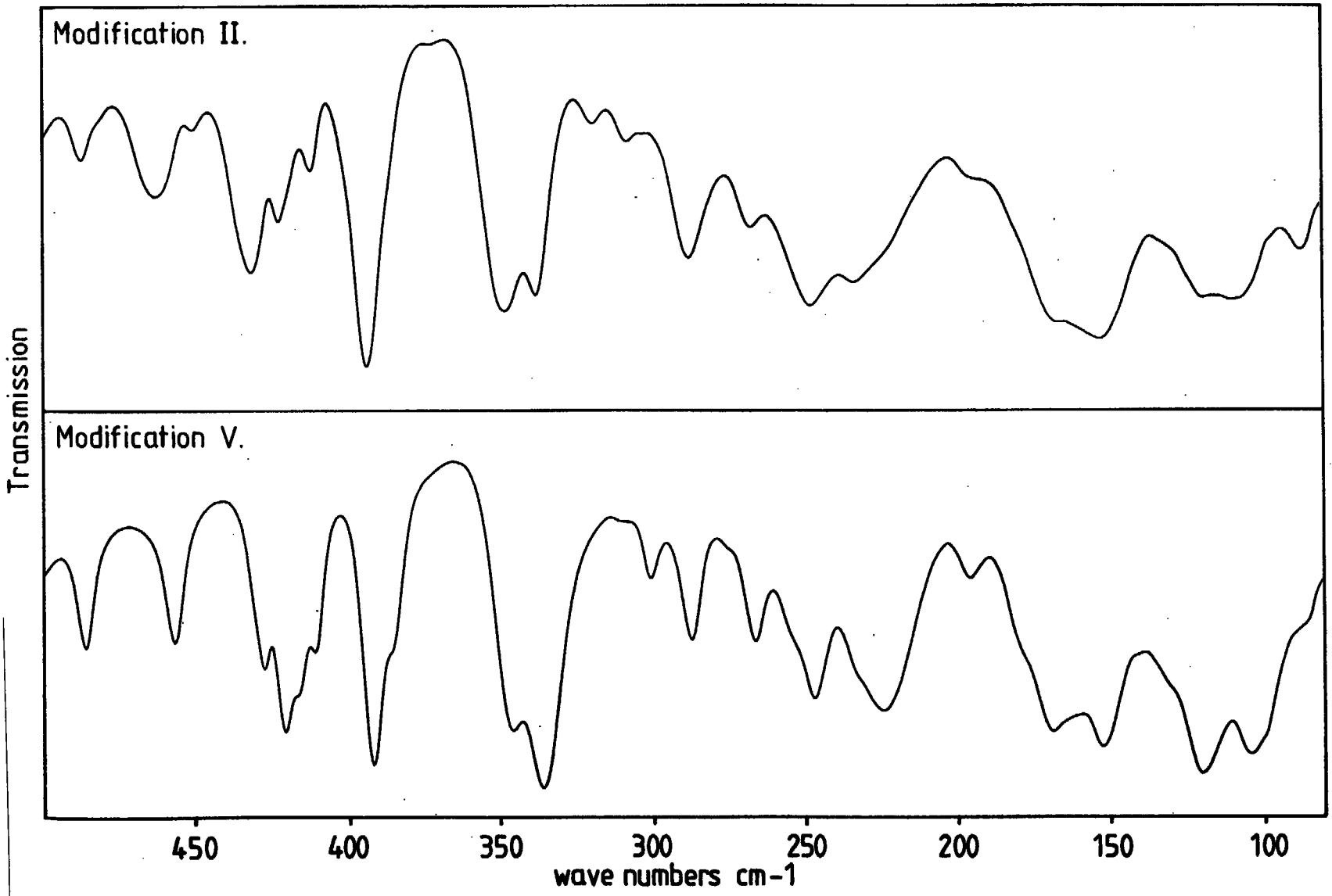
Modification V.



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Fig. 5

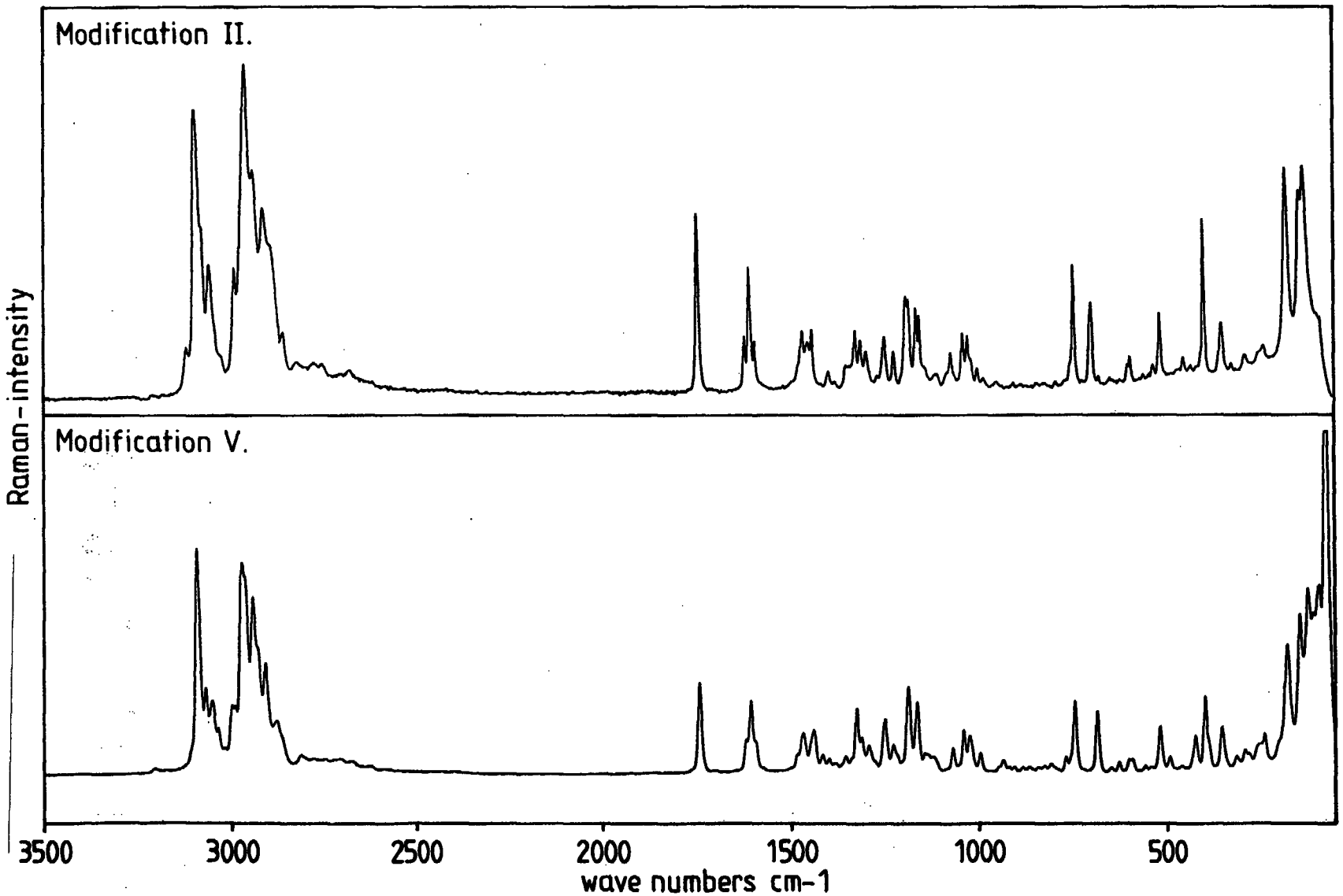
FIR-spectra of DBCH



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Fig. 6

Raman-spectra of DBCH



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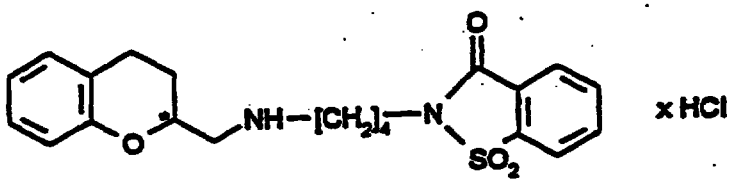
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Crystalline hydrochloride of (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman

The invention relates to the crystalline form of the hydrochloride of the compound (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman, processes for the preparation and the use in medicaments, in particular in medicaments having a neuroprotective action.

The hydrochloride of the compound (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman has the formula (I)



and is designated below as DBCH. The compound of the formula (I) is disclosed, for example, in European Patent Specification EP 352 613 as Example 92 H and, owing to its properties as a 5-HT_{1A} agonist, is proposed, inter alia, as a neuroprotective active substance in medicaments, in particular for the treatment and prevention of neuronal degenerations due to ischaemic effects, such as a stroke.

In the patent specification mentioned, the preparation of DBCH is also described. It is carried out in general by reacting the optically active 2-aminomethylchroman with N-4-bromobutylsaccharin in an inert solvent in the presence of a base. In this way, the compound DBCH is obtained in a crystalline modification (referred to below as modification II). The melting point is stated as 192-194°C.

It has been found that modification II is metastable and undergoes partial conversion at high humidity (85% relative humidity, room temperature). For this reason, it is only

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of limited suitability for use in pharmaceutical formulations.

Surprisingly, a crystalline form of the hydrochloride of (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}chroman (referred to below as modification V), which does not have these disadvantages, has now been found. This crystalline form of DBCH is thermodynamically stable and does not undergo conversion even at high atmospheric humidity (85% relative humidity, room temperature). For this reason, it is particularly suitable for solid medicament formulations.

The crystalline form (modification V), according to the invention, of DBCH is defined by the following physicochemical parameters:

1. The melting point of the crystalline form according to the invention cannot be determined experimentally since a solid-solid phase transition takes place on heating at about 60°C to give modification I (endothermic peak in DSC thermogram, Fig. 1). The heat of transition is 24 J/g.

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2. X-Ray diffraction pattern (cf. Figure 2):

Mod. V [2 Theta]	Mod. V [2 Theta]	Mod. V [2 Theta]	Mod. V [2 Theta]
9.7	22.5	28.4	35.1
11.5	22.6	27.7	35.3
12.3	23.2	29.2	35.7
12.6	24.0	29.3	36.2
13.4	24.4	29.8	36.4
14.5	24.7	30.1	36.7
15.7	24.9	31.1	37.0
16.8	25.8	31.8	37.4
16.9	26.0	32.6	37.6
17.5	26.3	33.9	
18.3	26.9	34.1	
19.4	27.4	34.3	
20.4	27.9	34.7	

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3. IR spectrum (Figure 3):

Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]
621	1010	1373	2847
672	1021	1408	2873
680	1044	1445	2899
716	1059	1458	2930
731	1106	1488	2949
743	1137	1585	2961
752	1153	1603	2993
783	1179	1690	3025
800	1197	1733	3073
835	1213	2389	3097
849	1242	2424	3189
876	1242	2448	3444
897	1248	2541	
910	1288	2571	
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4. Solid-state ^{13}C-NMR spectrum (Figure 4)

Mod. V [ppm]	Mod. V [ppm]	Mod. V [ppm]	Mod. V [ppm]
159	128	72	26
158	126	55	25
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135	118	49	
134	117	40	
133	116	39	
130	115	27	

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5. FIR spectrum (cf. Figure 5)

Mod. V [cm^{-1}]
105
121
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6. Raman spectrum (cf. Figure 6)

Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]
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348	1158	1736	
393	1181	2869	
419	1223	2900	
487	1245	2933	
513	1288	2963	
587	1307	2983	
595	1321	2991	
623	1351	3028	

The modification V differs substantially from the modification II in its physicochemical parameters (DSC melting behaviour, X-ray diffraction pattern, IR spectrum, solid-state ^{13}C-NMR spectrum, FIR spectrum and Raman spectrum (cf. Figures 1 to 6)). The melting point of the modification II is 195°C (DSC, heating rate 10 K/minute).

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The preparation of the crystalline form according to the invention (modification V of DBCH) is carried out in general by suspending DBCH of modification II in water or inert organic substances, for example lower alcohols, ketones or alkanes, until the desired degree of transformation is reached, particularly preferably until quantitative transformation into modification V. As a rule, this transition takes place at temperatures of 0°C to 35°C, preferably at 30°C. The resulting crystals of modification V are separated off and, in order to remove solvent present, are dried at room temperature in vacuo or at elevated temperature until the weight remains constant.

The crystalline modification V, according to the invention, of DBCH can be converted in a known manner into the customary formulations, formulations in which the crystalline active substance is present in solid form, such as, for example, tablets, sugar-coated tablets, pills, granular aerosols, suppositories and suspensions, being suitable. Here, the active substance is converted into the suitable formulation using inert nontoxic pharmaceutically suitable excipients and carriers.

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Experimental part:

Preparation of seed crystals of modification V

0.5 g of DBCH of modification II is suspended in 8 ml of acetone:methanol (7:1) and stirred for 5 days at room temperature. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The IR spectrum is recorded in order to check for quantitative transformation.

Preparation of modification II

The active substance in the form of modification II is obtained in the synthesis of the active substance by the addition of about 1.5 mol equivalents of hydrochloric acid. Modification II is precipitated from ethanol at about 5-50°C, filtered off, then washed with ethanol and dried in vacuo at 95-100°C.

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Examples

Example 1

0.5 g of DBCH of modification II is suspended in 7 ml of acetone:ethanol (6:1). The suspension is seeded with the modification V and stirred for 5 days at 0°C. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The DSC thermogram is recorded in order to check for quantitative transition.

Example 2

0.5 g of DBCH of modification II is suspended in 6 ml of acetone:ethanol (2:1). The suspension is seeded with the modification V and stirred for 5 days at room temperature. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The IR spectrum is recorded in order to check for quantitative transition.

Example 3

1.7 g of DBCH of modification II are suspended in 14 ml of acetone:ethanol (6:1). The suspension is seeded with the modification V and stirred for 6 days at room temperature. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The X-ray diffraction pattern is recorded in order to check for quantitative transition.

Example 4

0.4 g of DBCH of modification II is suspended in 7 ml of acetone:ethanol (6:1). The suspension is seeded with the modification V and stirred for one week at 30°C. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The DSC thermogram is recorded in order to check for quantitative

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transformation.

Example 5

0.5 g of DBCH of modification II is suspended in 10 ml of iso-propanol. The suspension is seeded with the modification V and stirred for 6 h at room temperature. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The DSC thermogram is recorded in order to check for quantitative transition.

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Patent Claims

1. Crystalline form of (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman hydrochloride.

2. Crystalline hydrochloride according to Claim 1, which undergoes a transition at about 60°C with a heat of transition of 24 J/g.

3. Crystalline hydrochloride according to Claim 1 or 2, characterized by the following X-ray diffraction data.

Mod. V [2 Theta]	Mod. V [2 Theta]	Mod. V [2 Theta]	Mod. V [2 Theta]
9.7	22.5	28.4	35.1
11.5	22.6	27.7	35.3
12.3	23.2	29.2	35.7
12.6	24.0	29.3	36.2
13.4	24.4	29.8	36.4
14.5	24.7	30.1	36.7
15.7	24.9	31.1	37.0
16.8	25.8	31.8	37.4
16.9	26.0	32.6	37.6
17.5	26.3	33.9	
18.3	26.9	34.1	
19.4	27.4	34.3	
20.4	27.9	34.7	

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4. Crystalline hydrochloride according to any of Claims 1 to 3, characterized by the following IR spectral data:

Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]
621	1010	1373	2847
672	1021	1408	2873
680	1044	1445	2899
716	1059	1458	2930
731	1106	1488	2949
743	1137	1585	2961
752	1153	1603	2993
783	1179	1690	3025
800	1197	1733	3073
835	1213	2389	3097
849	1242	2424	3189
876	1242	2448	3444
897	1248	2541	
910	1288	2571	
927	1305	2673	
940	1320	2701	
987	1348	2785	

5. Crystalline hydrochloride according to any of Claims 1 to 4, characterized by the following solid-state ^{13}C-NMR spectral data:

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Mod. V [ppm]	Mod. V [ppm]	Mod. V [ppm]	Mod. V [ppm]
159	128	72	26
158	126	55	25
153	121	54	23
137	120	50	
135	118	49	
134	117	40	
133	116	39	
130	115	27	

6. Crystalline hydrochloride according to any of Claims 1 to 5, characterized by the following FIR spectral data:

Mod. V [cm^{-1}]
105
121
152
169
195
224
247
286
300

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Mod. V [cm^{-1}]
335
345
391
410
420
426
455
485

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7. Crystalline hydrochloride according to any of Claims 1 to 6, characterized by the following Raman spectral data:

Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]
9	644	1379	3044
105	680	1394	3061
119	739	1411	3082
142	763	1433	
174	988	1462	
234	1016	1476	
286	1033	1600	
309	1062	1613	
348	1158	1736	

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Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]
393	1181	2869	
419	1223	2900	
487	1245	2933	
513	1288	2963	
587	1307	2983	
595	1321	2991	
623	1351	3028	

8. Process for the preparation of crystalline hydrochloride according to Claim 7, characterized in that DBCH of modification II is suspended in water or inert organic substances and quantitatively converted into modification V according to any of Claims 1 to 7.

9. Medicament containing the crystalline hydrochloride according to any of Claims 1 to 7.

10. Use of the crystalline hydrochloride according to any of Claims 1 to 6 for the preparation of medicaments.

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Crystalline hydrochloride of (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman

Abstract

The invention relates to the crystalline form of the hydrochloride of the compound (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman, which is present as a stable form at room temperature. The crystalline modification V of the hydrochloride is suitable in particular for the preparation of solid medicaments, in particular of medicaments for the treatment of neuronal degenerations.

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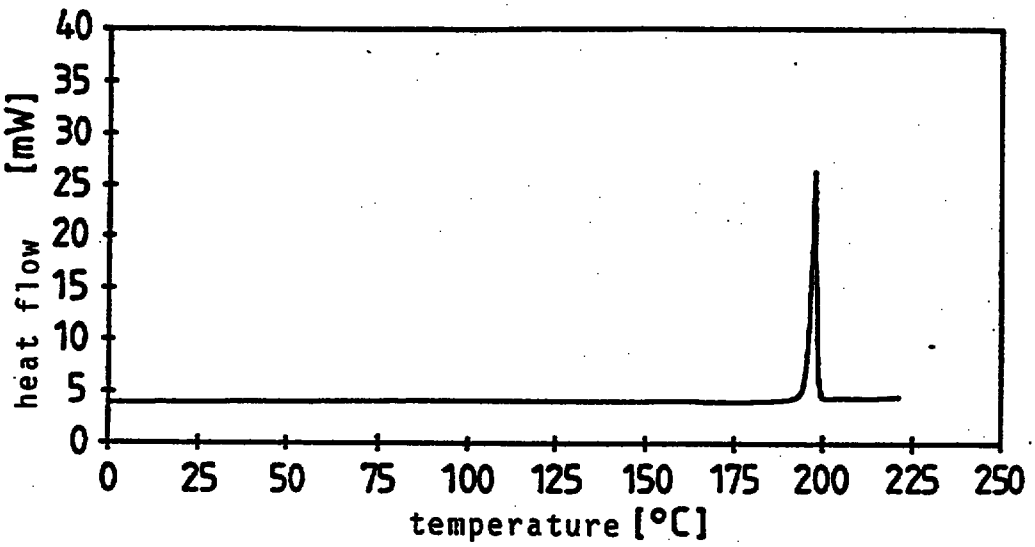
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Fig. 1

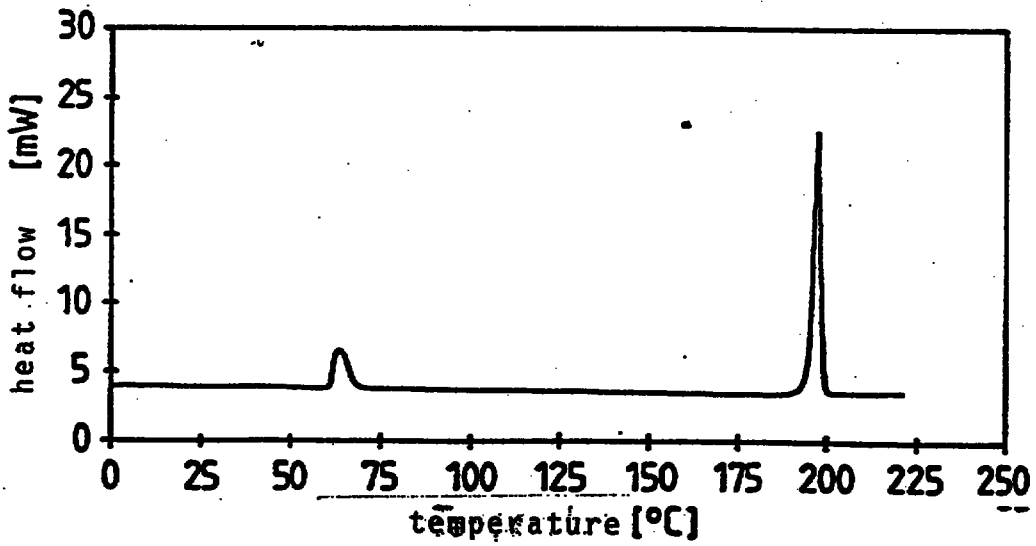
DSC- thermograms of DBCH

Modification II.



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Modification V.



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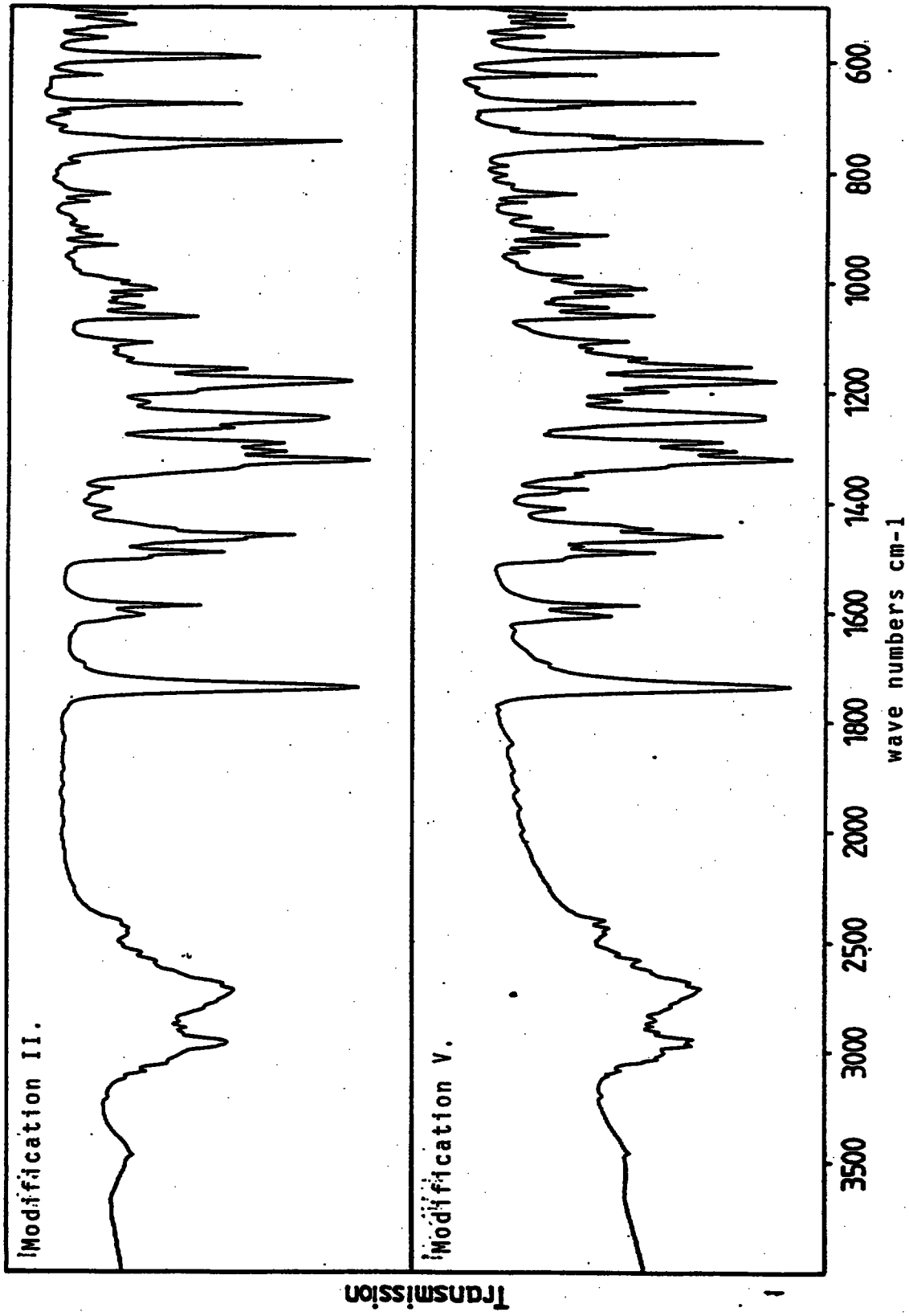
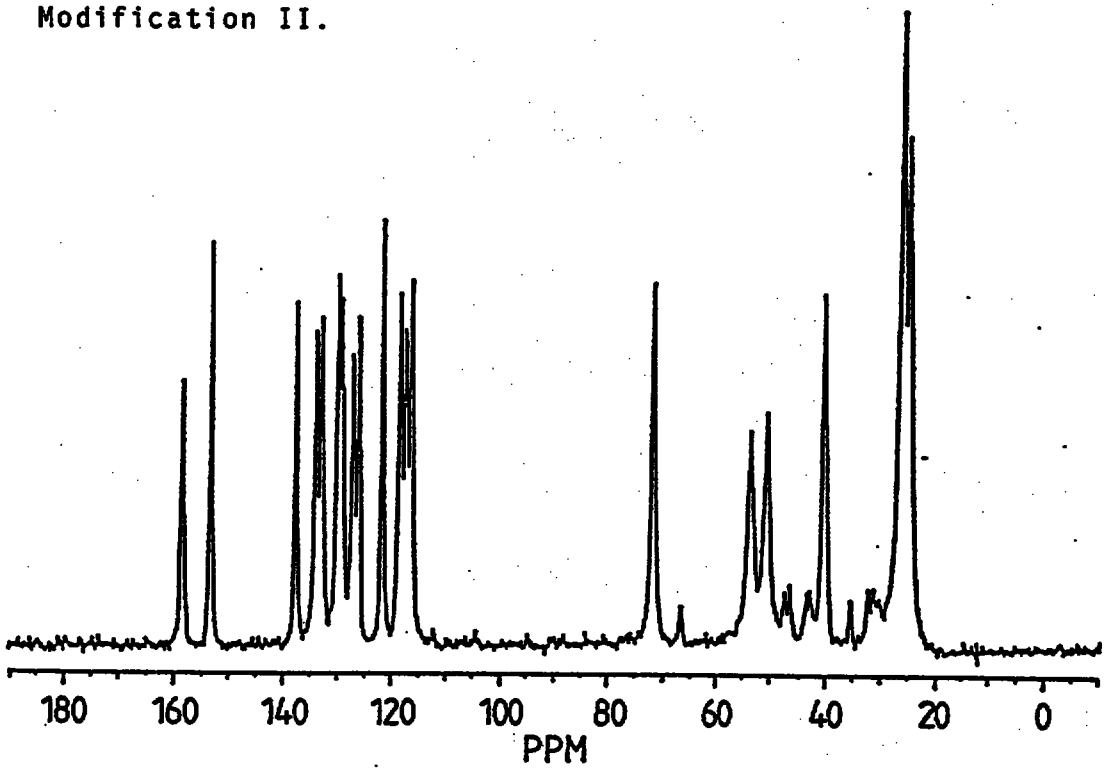


Fig. 3
IR-Spectra of DBCH

Fig. 4

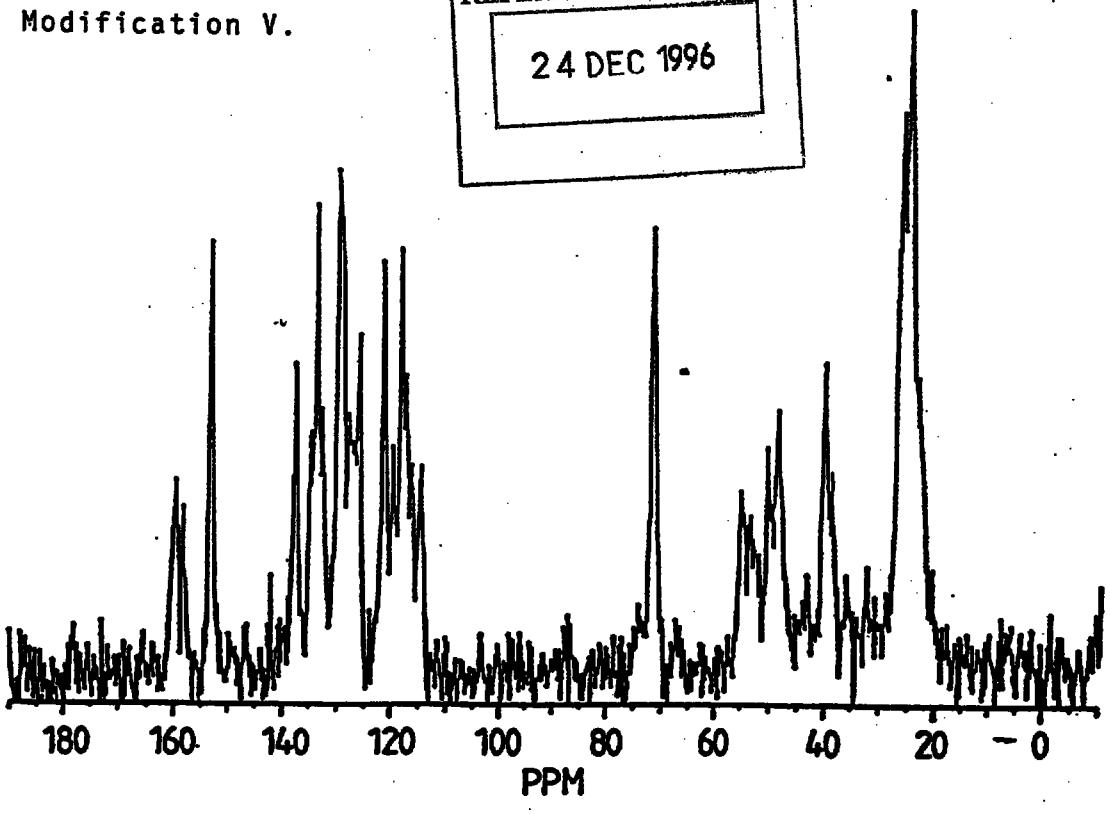
^{13}C- solid state NMR spectra of DBCH

Modification II.



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Modification V.



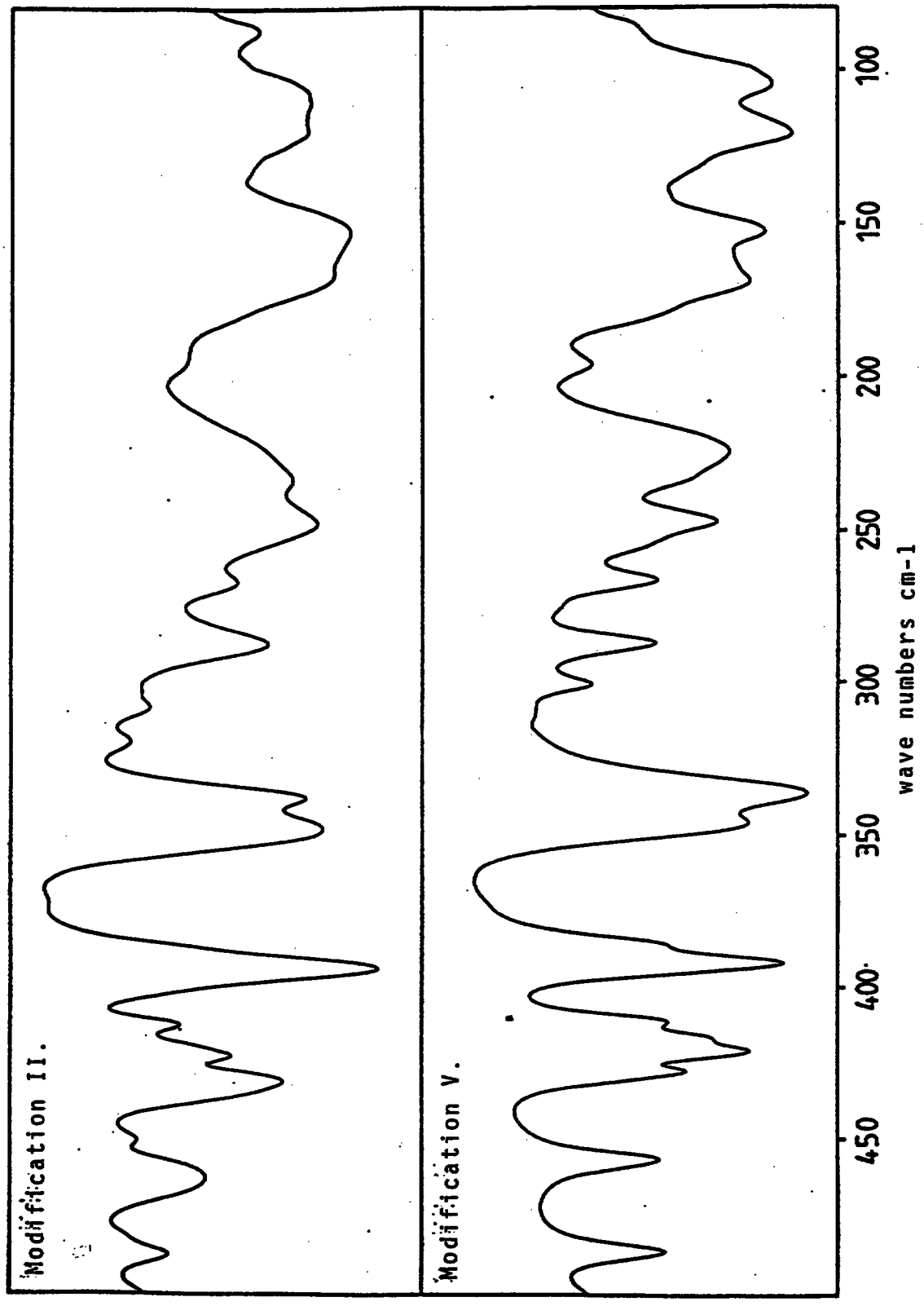


Fig.5
FIR-spectra of DBCH

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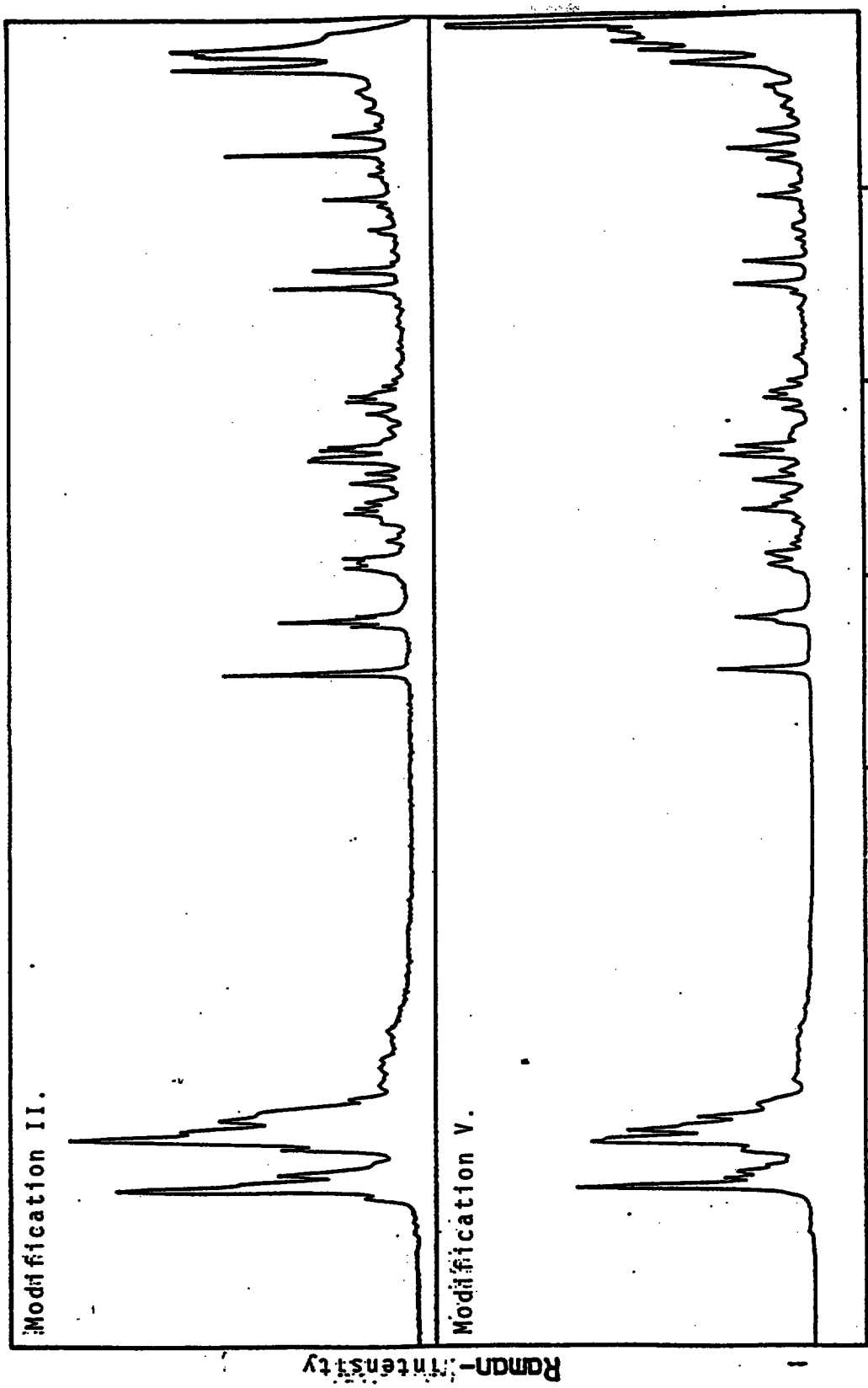


Fig. 6
Raman-Spectra of DBCH

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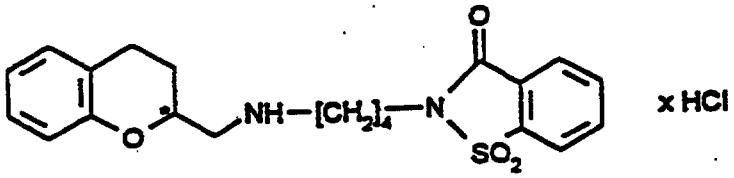
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✓ Description : paged 1... to paged 11..
✓ Claim(s) : paged 12.. to paged 16.
✓ Drawing(s) : paged 17.. to paged ....
✓ Abstract : paged 17.. to paged ....
DATE OF RECEIPT ...7/4/97.....

Crystalline hydrochloride of (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman

The invention relates to the crystalline form of the hydrochloride of the compound (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman, processes for the preparation and the use in medicaments, in particular in medicaments having a neuroprotective action.

The hydrochloride of the compound (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman has the formula (I)



and is designated below as DBCH. The compound of the formula (I) is disclosed, for example, in European Patent Specification EP 352 613 as Example 92 H and, owing to its properties as a 5-HT_{1A} agonist, is proposed, inter alia, as a neuroprotective active substance in medicaments, in particular for the treatment and prevention of neuronal degenerations due to ischaemic effects, such as a stroke.

In the patent specification mentioned, the preparation of DBCH is also described. It is carried out in general by reacting the optically active 2-aminomethylchroman with N-4-bromobutylsaccharin in an inert solvent in the presence of a base. In this way, the compound DBCH is obtained in a crystalline modification (referred to below as modification II). The melting point is stated as 192-194°C.

It has been found that modification II is metastable and undergoes partial conversion at high humidity (85% relative humidity, room temperature). For this reason, it is only

of limited suitability for use in pharmaceutical formulations.

Surprisingly, a crystalline form of the hydrochloride of (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}chroman (referred to below as modification V), which does not have these disadvantages, has now been found. This crystalline form of DBCH is thermodynamically stable and does not undergo conversion even at high atmospheric humidity (85% relative humidity, room temperature). For this reason, it is particularly suitable for solid medicament formulations.

The crystalline form (modification V), according to the invention, of DBCH is defined by the following physicochemical parameters:

1. The melting point of the crystalline form according to the invention cannot be determined experimentally since a solid-solid phase transition takes place on heating at about 60°C to give modification I (endothermic peak in DSC thermogram, Fig. 1). The heat of transition is 24 J/g.

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2. X-Ray diffraction pattern (cf. Figure 2):

Mod. V [2 Theta]	Mod. V [2 Theta]	Mod. V [2 Theta]	Mod. V [2 Theta]
9.7	22.5	28.4	35.1
11.5	22.6	27.7	35.3
12.3	23.2	29.2	35.7
12.6	24.0	29.3	36.2
13.4	24.4	29.8	36.4
14.5	24.7	30.1	36.7
15.7	24.9	31.1	37.0
16.8	25.8	31.8	37.4
16.9	26.0	32.6	37.6
17.5	26.3	33.9	
18.3	26.9	34.1	
19.4	27.4	34.3	
20.4	27.9	34.7	

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3. IR spectrum (Figure 3):

Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]
621	1010	1373	2847
672	1021	1408	2873
680	1044	1445	2899
716	1059	1458	2930
731	1106	1488	2949
743	1137	1585	2961
752	1153	1603	2993
783	1179	1690	3025
800	1197	1733	3073
835	1213	2389	3097
849	1242	2424	3189
876	1242	2448	3444
897	1248	2541	
910	1288	2571	
927	1305	2673	
940	1320	2701	
987	1348	2785	

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4. Solid-state ^{13}C-NMR spectrum (Figure 4)

Mod. V [ppm]	Mod. V [ppm]	Mod. V [ppm]	Mod. V [ppm]
159	128	72	26
158	126	55	25
153	121	54	23
137	120	50	
135	118	49	
134	117	40	
133	116	39	
130	115	27	

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5. FIR spectrum (cf. Figure 5)

Mod. V [cm^{-1}]
105
121
152
169
195
224
247
286
300
335
345
391
410
420
426
455
485

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6. Raman spectrum (cf. Figure 6)

Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]
9	644	1379	3044
105	680	1394	3061
119	739	1411	3082
142	763	1433	
174	988	1462	
234	1016	1476	
286	1033	1600	
309	1062	1613	
348	1158	1736	
393	1181	2869	
419	1223	2900	
487	1245	2933	
513	1288	2963	
587	1307	2983	
595	1321	2991	
623	1351	3028	

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The modification V differs substantially from the modification II in its physicochemical parameters (DSC melting behaviour, X-ray diffraction pattern, IR spectrum, solid-state ^{13}C-NMR spectrum, FIR spectrum and Raman spectrum (cf. Figures 1 to 6)). The melting point of the modification II is 195°C (DSC, heating rate 10 K/minute).

The preparation of the crystalline form according to the invention (modification V of DBCH) is carried out in general by suspending DBCH of modification II in water or inert organic substances, for example lower alcohols, ketones or alkanes, until the desired degree of transformation is reached, particularly preferably until quantitative transformation into modification V. As a rule, this transition takes place at temperatures of 0°C to 35°C, preferably at 30°C. The resulting crystals of modification V are separated off and, in order to remove solvent present, are dried at room temperature in vacuo or at elevated temperature until the weight remains constant.

The crystalline modification V, according to the invention, of DBCH can be converted in a known manner into the customary formulations, formulations in which the crystalline active substance is present in solid form, such as, for example, tablets, sugar-coated tablets, pills, granular aerosols, suppositories and suspensions, being suitable. Here, the active substance is converted into the suitable formulation using inert nontoxic pharmaceutically suitable excipients and carriers.

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Experimental part:

Preparation of seed crystals of modification V

0.5 g of DBCH of modification II is suspended in 8 ml of acetone:methanol (7:1) and stirred for 5 days at room temperature. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The IR spectrum is recorded in order to check for quantitative transformation.

Preparation of modification II

The active substance in the form of modification II is obtained in the synthesis of the active substance by the addition of about 1.5 mol equivalents of hydrochloric acid. Modification II is precipitated from ethanol at about 5-50°C, filtered off, then washed with ethanol and dried in vacuo at 95-100°C.

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Examples

Example 1

0.5 g of DBCH of modification II is suspended in 7 ml of acetone:ethanol (6:1). The suspension is seeded with the modification V and stirred for 5 days at 0°C. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The DSC thermogram is recorded in order to check for quantitative transition.

Example 2

0.5 g of DBCH of modification II is suspended in 6 ml of acetone:ethanol (2:1). The suspension is seeded with the modification V and stirred for 5 days at room temperature. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The IR spectrum is recorded in order to check for quantitative transition.

Example 3

1.7 g of DBCH of modification II are suspended in 14 ml of acetone:ethanol (6:1). The suspension is seeded with the modification V and stirred for 6 days at room temperature. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The X-ray diffraction pattern is recorded in order to check for quantitative transition.

Example 4

0.4 g of DBCH of modification II is suspended in 7 ml of acetone:ethanol (6:1). The suspension is seeded with the modification V and stirred for one week at 30°C. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The DSC thermogram is recorded in order to check for quantitative

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transformation.

Example 5

0.5 g of DBCH of modification II is suspended in 10 ml of iso-propanol. The suspension is seeded with the modification V and stirred for 6 h at room temperature. The residue is filtered off and is dried at room temperature in vacuo until the weight remains constant. The DSC thermogram is recorded in order to check for quantitative transition.

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Patent Claims

1. Crystalline form of (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman hydrochloride.

2. Crystalline hydrochloride according to Claim 1, which undergoes a transition at about 60°C with a heat of transition of 24 J/g.

3. Crystalline hydrochloride according to Claim 1 or 2, characterized by the following X-ray diffraction data.

Mod. V [2 Theta]	Mod. V [2 Theta]	Mod. V [2 Theta]	Mod. V [2 Theta]
9.7	22.5	28.4	35.1
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12.3	23.2	29.2	35.7
12.6	24.0	29.3	36.2
13.4	24.4	29.8	36.4
14.5	24.7	30.1	36.7
15.7	24.9	31.1	37.0
16.8	25.8	31.8	37.4
16.9	26.0	32.6	37.6
17.5	26.3	33.9	
18.3	26.9	34.1	
19.4	27.4	34.3	
20.4	27.9	34.7	

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4. Crystalline hydrochloride according to any of Claims 1 to 3, characterized by the following IR spectral data:

Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]
621	1010	1373	2847
672	1021	1408	2873
680	1044	1445	2899
716	1059	1458	2930
731	1106	1488	2949
743	1137	1585	2961
752	1153	1603	2993
783	1179	1690	3025
800	1197	1733	3073
835	1213	2389	3097
849	1242	2424	3189
876	1242	2448	3444
897	1248	2541	
910	1288	2571	
927	1305	2673	
940	1320	2701	
987	1348	2785	

5. Crystalline hydrochloride according to any of Claims 1 to 4, characterized by the following solid-state ^{13}C-NMR spectral data:

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Mod. V [ppm]	Mod. V [ppm]	Mod. V [ppm]	Mod. V [ppm]
159	128	72	26
158	126	55	25
153	121	54	23
137	120	50	
135	118	49	
134	117	40	
133	116	39	
130	115	27	

6. Crystalline hydrochloride according to any of Claims 1 to 5, characterized by the following FIR spectral data:

Mod. V [cm^{-1}]
105
121
152
169
195
224
247
286
300

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Mod. V [cm^{-1}]
335
345
391
410
420
426
455
485

7. Crystalline hydrochloride according to any of Claims 1 to 6, characterized by the following Raman spectral data:

Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]
9	644	1379	3044
105	680	1394	3061
119	739	1411	3082
142	763	1433	
174	988	1462	
234	1016	1476	
286	1033	1600	
309	1062	1613	
348	1158	1736	

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Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]	Mod. V [cm^{-1}]
393	1181	2869	
419	1223	2900	
487	1245	2933	
513	1288	2963	
587	1307	2983	
595	1321	2991	
623	1351	3028	

8. Process for the preparation of crystalline hydrochloride according to Claim 7, characterized in that DBCH of modification II is suspended in water or inert organic substances and quantitatively converted into modification V according to any of Claims 1 to 7.

9. Medicament containing the crystalline hydrochloride according to any of Claims 1 to 7.

10. Use of the crystalline hydrochloride according to any of Claims 1 to 6 for the preparation of medicaments.

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Crystalline hydrochloride of (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman

Abstract

The invention relates to the crystalline form of the hydrochloride of the compound (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman, which is present as a stable form at room temperature. The crystalline modification V of the hydrochloride is suitable in particular for the preparation of solid medicaments, in particular of medicaments for the treatment of neuronal degenerations.

No suitable figure is suggested

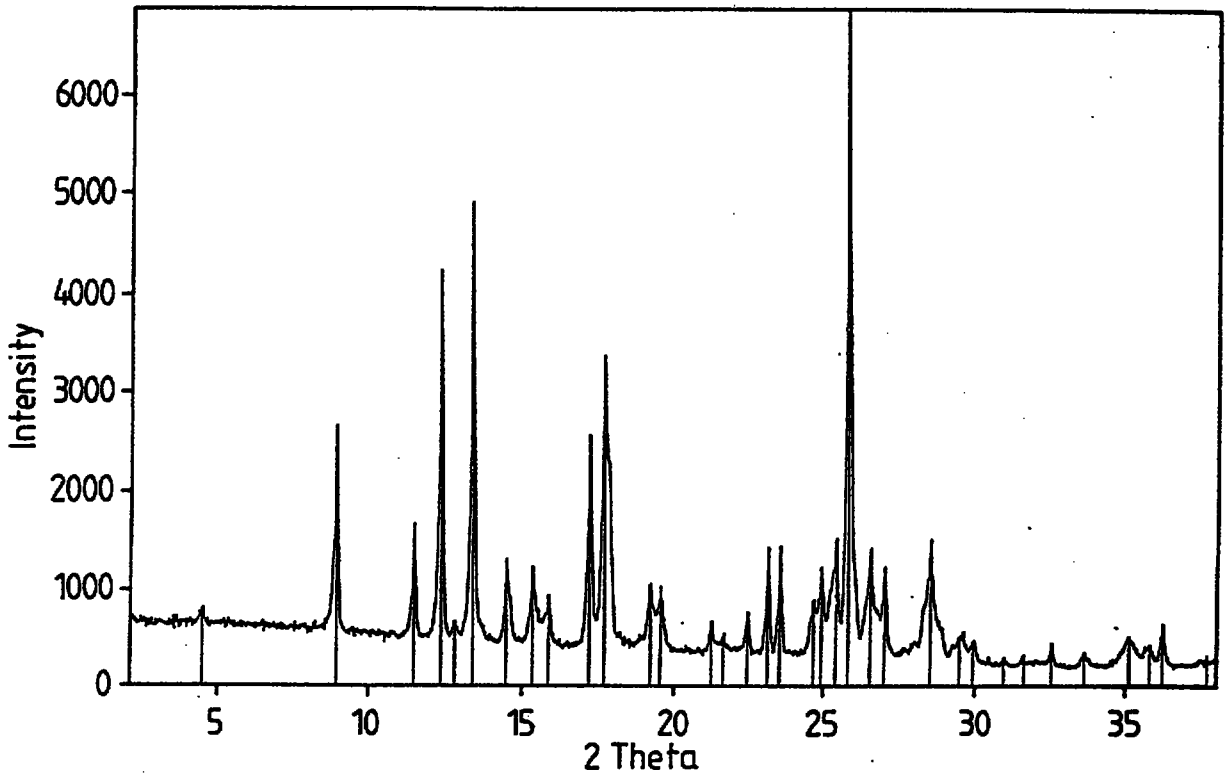
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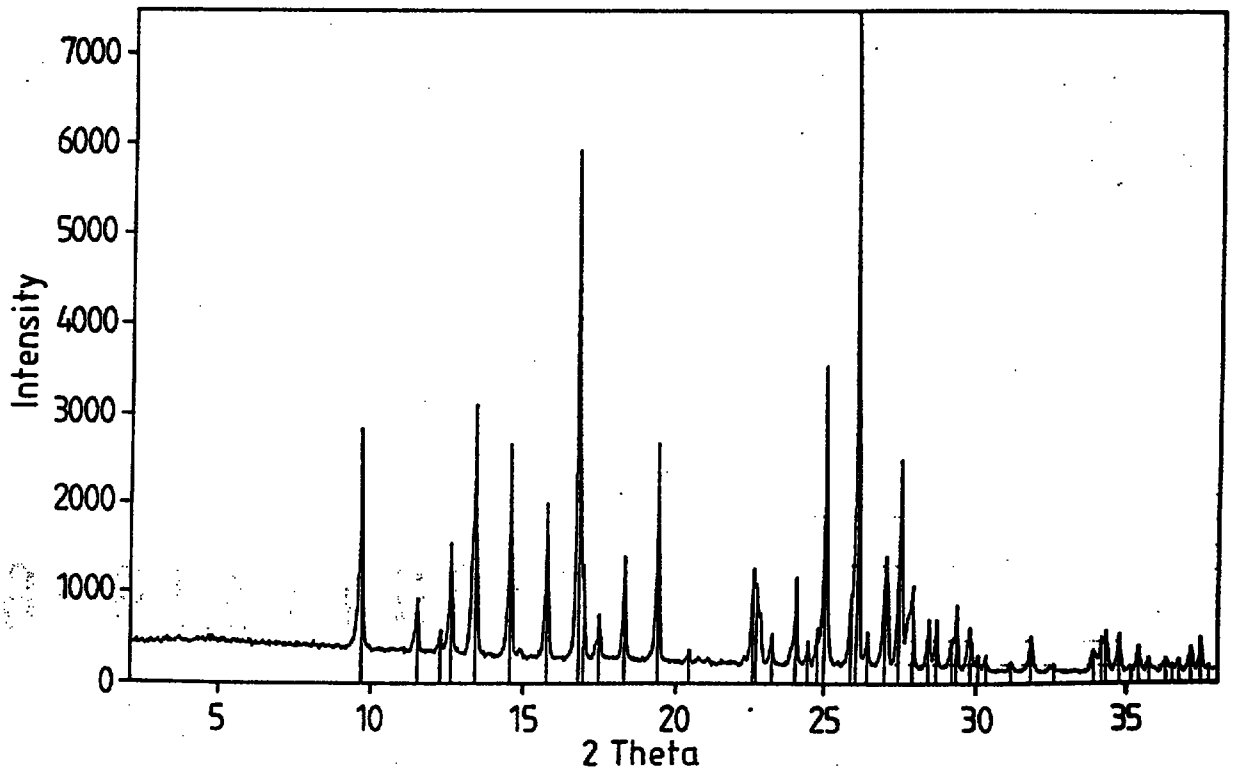
Fig. 2

X-ray pattern of DBCH

Modification II.



Modification V.



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Patent Claims:

1. Crystalline modification V of (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)-butyl]-aminomethyl}-chroman hydrochloride.

2. A composition for the treatment and prevention of neuronal degenerations due to ischemic events comprising an amount effective therefore according to claim 1 and a pharmacologically acceptable diluent.

3. The method for treating and preventing neuronal degenerations due to issemic events in a patient in need thereof which comprises administering such patient an amount effective therefore of the compound according to claim 1.

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Claims

1. Crystalline modification V of (R)-(-)-2-{N-[4-(1,1-dioxido-3-oxo-2,3-dihydrobenzisothiazol-2-yl)-butyl]-aminomethyl}-chroman hydrochloride.

2. A composition for the treatment and prevention of neuronal degenerations due to ischaemic events comprising an amount effective therefore according to claim 1 and a pharmacologically acceptable diluent.

3. A usage of the compound in accordance with claim 1 for treating and preventing neuronal degenerations due to ischaemic events in a patient in need thereof which comprises administering such patient an amount effective therefore.

REPLACEMENT SHEET
22 DEC 1998