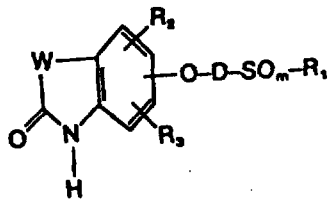
New carbostyril derivatives, their preparation and pharmaceutical compositions containing these compounds

It is known from DE-A-2 453 113 that 5-(2-hydroxy-3-tert.-butylamino-propoxy)-3,4-dihydrocarbostyril has antithrombotic properties. Moreover, DE-A-2 527 937 describes hydroxycarbonylalkoxy-carbostyrils and the esters thereof which also have antithrombotic properties.

Furthermore, Japanese Offenlegungsschrift 21176/78 of 27th February describes carbostyril derivatives which are substituted by a 3-(ethylthio)-propoxy, 3-(ethylsulphonyl)-propoxy or 2-(n-butylthio)-ethoxy group and which also have antithrombotic properties.

It has now been found that the new carbostyril derivatives of general formula



(I)

have, in addition to a positive inotropic activity, in particular antithrombotic or superior antithrombotic properties.

The present invention thus relates to the new carbostyril derivatives of general formula I, the pharmaceutical compositions containing them and processes for preparing them.

In general formula I above,

W represents a vinylene group (optionally substituted by a methyl group) or an ethylene group;

m is 0, 1 or 2;

D represents a straight-chained or branched alkylene group containing from 2 to 6 carbon atoms, whilst there must be at least 2 carbon atoms between the oxygen atom and the SO_m group, or a xylylene group;

R_1 represents a cycloalkyl group containing from 3 to 6 carbon atoms; an aryl group containing from 6 to 10 carbon atoms, an aralkyl group containing from 7 to 11 carbon atoms, whilst the abovementioned aromatic nuclei may be monosubstituted by an alkyl group containing 1 to 4 carbon atoms or by a hydroxy, methoxy, amino, acetylamino, nitro, carboxyl, cyclohexyl or phenyl group or by a halogen atom and, in addition, the abovementioned monosubstituted phenyl group may be mono- or disubstituted by alkyl groups containing from 1 to 4 carbon atoms and/or halogen atoms (whilst the substituents of the phenyl nucleus may be the same or different), an N-methyl-cyclohexylamino-carbonylmethyl, amino-iminomethylene, pyridyl, pyridylmethyl, furfuryl, benzimidazolyl, benzothiazolyl, pyrimidyl, quinolyl, quinazolin-4-onyl, 4,5-bis-(p-chlorophenyl)-oxazol-2-yl, pyridyl-oxide, triazolyl, methylpyridyl, methoxypyridyl, fluoropyridyl, chloro-pyridyl, aminopyridyl, acetylaminopyridyl or triphenyl-methyl group or a tert.butyl group, if

m represents the number 1,

R_2 and R_3, which may be the same or different, each represents a hydrogen or halogen atom, an alkyl group containing from 1 to 4 carbon atoms or an amino, acetylamino or nitro group.

In the definitions of the groups R_1, R_2 and R_3, the term "halogen atom" refers more particularly to a fluorine, chlorine, bromine or iodine atom; thus, as examples of the definitions given for the groups D, R_1, R_2 and R_3 hereinbefore

D may represent an ethylene, n-propylene, n-butylene, n-pentylene, n-hexylene, 1-methylethylene,

2-methylethylene, 1-methyl-n-propylene, 2-methyl-n-propylene, 3-methyl-n-propylene, 1-methyl-n-butylene, 2-methyl-n-butylene, 3-methyl-n-butylene, 4-methyl-n-butylene, 1-methyl-n-pentylene, 2-methyl-n-pentylene, 3-methyl-n-pentylene, 4-methyl-n-pentylene, 5-methyl-n-pentylene, 1,1-dimethylethylene, 1,2-dimethylethylene, 2,2-dimethylethylene, 1,1-dimethyl-n-propylene, 2,2-dimethyl-n-propylene, 3,3-dimethyl-n-propylene, 1,2-dimethyl-n-propylene, 1,3-dimethyl-n-propylene, 1,1-dimethyl-n-butylene, 2,2-dimethyl-n-butylene, 3,3-dimethyl-n-butylene, 4,4-dimethyl-n-butylene, 1,2-dimethyl-n-butylene, 1,4-dimethyl-n-butylene, 2,3-dimethyl-n-butylene, 1-ethylethylene, 2-ethylethylene, 1-ethyl-n-propylene, 2-ethyl-n-propylene, 3-ethyl-n-propylene, 1-ethyl-n-butylene, 2-ethyl-n-butylene, 3-ethyl-n-butylene, 4-ethyl-n-butylene, 1-methyl-2-ethyl-ethylene, 1-methyl-2-ethyl-n-propylene, 1-methyl-3-ethyl-n-propylene, 1-methyl-2-propyl-ethylene, 1-propylethylene, 1-butylethylene, 1-propyl-n-propylene, p-xylylene, o-xylylene or m-xylylene group,

R_1 may represent a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, benzyl, phenylethyl, naphthyl, naphthylmethyl, cyclohexylphenyl, biphenyl, triphenylmethyl, N-methylcyclohexylaminocarbonylmethyl, amino-iminomethyl, pyridyl, pyridylmethyl, furfuryl, benzimidazolyl, benzthiazolyl, pyrimidyl, quinolyl, quinazolin-4-on-yl, 4,5-bis-(p-chlorophenyl)-oxazol-2-yl, pyridyl-oxide, methylphenyl, dimethylphenyl, tert.-butylphenyl, methyl-tert.-butylphenyl, methyl-pyridyl, methoxyphenyl, dimethoxyphenyl, methoxypyridyl, hydroxyphenyl, dihydroxyphenyl, fluorophenyl, difluoro-phenyl, trifluorophenyl, 1,2,4-triazolyl, fluoropyridyl, chlorophenyl, dichlorophenyl, trichlorophenyl, chloropyridyl, bromophenyl, dibromophenyl, aminophenyl, acetylaminophenyl, aminopyridyl, acetylaminopyridyl, nitrophenyl, carboxyphenyl, hydroxy-dichlorophenyl,

hydroxy-dibromophenyl, amino-dichlorophenyl, amino-dibromophenyl, hydroxy-di-tert.-butylphenyl, methoxy-fluorophenyl, methoxy-chlorophenyl, methoxy-bromophenyl, fluoromethylphenyl, chloromethylphenyl or bromomethylphenyl group,

R_2 and R_3, which may be the same or different, may represent a hydrogen, fluorine, chlorine, bromine or iodine atom or a methyl, ethyl, propyl, isopropyl, butyl, tert.-butyl, nitro, amino or acetylamino group.

The application thus relates particularly to those compounds of general formula I wherein W, D and m are as hereinbefore defined, R_1 represents a cyclohexyl, benzyl, naphthyl, pyridyl, pyrimidyl, 1,2,4-triazolyl, pyridyl-oxide, furfuryl, triphenylmethyl, quinolyl, benzimidazolyl, benzthiazolyl, quinazolin-4-on-yl, 4,5-bis-(p-chlorophenyl)-oxazol-2-yl, N-methylcyclohexylaminocarbonylmethyl or amino-iminomethyl group; a phenyl group optionally substituted by a carboxyl, hydroxy, methoxy, amino, acetylamino, nitro, cyclohexyl or phenyl group; a phenyl group substituted by one or two substituents selected from halogen atoms and alkyl groups each containing from 1 to 4 carbon atoms; or a hydroxyphenyl, halophenyl or aminophenyl group substituted by two halogen atoms or by two alkyl groups each containing from 1 to 4 carbon atoms, R_2 represents a hydrogen, chlorine or bromine atom or a methyl, amino, acetylamino or nitro group, and R_3 represents a hydrogen atom.

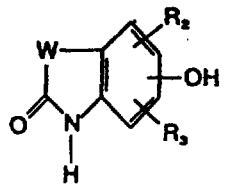
However, the preferred compounds of general formula I above are those wherein W represents a vinylene group (optionally substituted by a methyl group) or an ethylene group; m represents 0, 1 or 2, D represents an alkylene group containing from 2 to 5 carbon atoms, whilst there must be at least 2 carbon atoms between the oxygen atom and the SO_m group,

R_1 represents a cyclohexyl, phenyl, benzyl, naphthyl, biphenyl-cyclohexylphenyl, pyridyl, methylphenyl, methoxyphenyl, fluorophenyl, chlorophenyl, dichlorophenyl, trichlorophenyl, bromophenyl, dibromophenyl, bromomethylphenyl, amino-dibromophenyl or hydroxy-di-tert.-butylphenyl group; and R_2 and R_3 represent hydrogen atoms.

The particularly preferred compounds of general formula I, however, are those wherein W represents an ethylene, vinylene or 2-methylvinylene group; m represents 1 or 2; R_2 and R_3 each represents a hydrogen atom; R_1 represents a cyclohexyl, phenyl, benzyl, naphth-2-yl, 2-methoxyphenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 2,5-dichlorophenyl, 4-hydroxy-3,5-di-tert.-butylphenyl or pyrid-2-yl group, and D represents an ethylene, n-propylene or n-butylene group.

According to the invention, the new compounds of general formula I are obtained by the following processes:

a) Reaction of a hydroxy compound of general formula



(II)

(wherein R_2, R_3 and W are as hereinbefore defined), or a salt thereof with an inorganic or tertiary organic base, with a compound of formula III,

$$Z - D - SO_m - R_1 \qquad \text{(III)}$$

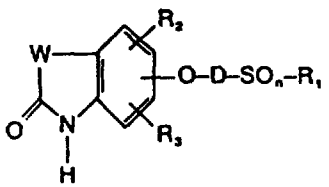
(wherein D, R_2 and m are as hereinbefore defined) and Z represents a nucleophilically exchangeable

group, for example a halogen atom or a sulfonic acid ester group, e.g. a chlorine, bromine or iodine atom or a p-toluenesulfonyloxy or methanesulfonyloxy group).

The reaction is conveniently carried out in a suitable solvent such as e.g. dioxan, tetrahydrofuran, chloroform or toluene, but preferably, however, in an anhydrous aprotic solvent such as, for example, acetone, dimethylformamide or dimethylsulfoxide. The reaction may optionally be effected in the presence of an alkali metal base, e.g. sodium carbonate, potassium carbonate or sodium hydroxide. Suitable temperatures for the reaction are generally from 0°C to the boiling temperature of the reaction mixture, for example at temperatures of from 0 to 100°C, preferred temperatures being however, from 10 to 50°C. The reaction may, if desired, be carried out in the absence of a solvent.

b) for the preparation of compounds of general formula I wherein m is 1 or 2:

Oxidation of a compound of formula



(IV)

wherein R_1 to R_3, D and W are as hereinbefore defined and n represents 0 or 1.

The oxidation is preferably carried out in the presence of a solvent, e.g. water, aqueous pyridine, ethanol, methanol, acetone, formic acid, glacial acetic acid, dilute sulfuric acid or trifluoroacetic acid. Suitable temperatures are generally from -80 to +100°C depending on the oxidising agent

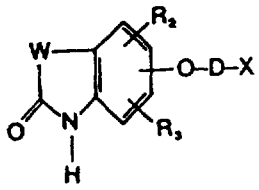
used.

When preparing compounds of general formula I wherein m is 1, the oxidation is most conveniently effected with one equivalent of an oxidising agent. Oxidation may, for example be effected with hydrogen peroxide in glacial acetic acid or formic acid at 0 to 20°C or in acetone at 0 to 60°C; with a peracid such as e.g. performic acid in glacial acetic acid or trifluoroacetic acid at 0 to 50°C; with sodium metaperiodate in aqueous methanol or ethanol at 15 to 25°C; with N-bromo-succinimide in ethanol; with tert.-butyl hypochlorite in methanol at -80 to -30°C; with iodobenzene dichloride in aqueous pyridine at 0 to 50°C; with nitric acid in glacial acetic acid at 0 to 20°C; with chromic acid in glacial acetic acid or in acetone at 0 to 20°C; with chromic acid in glacial acetic acid or in acetone at 0 to 20°C; or with sulfuryl chloride in methylene chloride at -70°C, the thioether chlorine complex thus formed being appropriately hydrolysed with aqueous ethanol.

When preparing compounds of general formula I wherein m is 2, the oxidation is conveniently effected with one or with two or more equivalents of the oxidising agent used. Oxidation may, for example be carried out with hydrogen peroxide in glacial acetic acid or formic acid at 20 to 100°C or in acetone at 0 to 60°C; with a peracid such as e.g. performic acid or m-chloroperbenzoic acid in glacial acetic acid, trifluoroacetic acid or chloroform at temperatures of from 0 to 50°C; with nitric acid in glacial acetic acid at 0 to 20°C; or with chromic acid or potassium permanganate in glacial acetic acid, aqueous sulfuric acid or in acetone at 0 to 20°C. Thus, if n represents 0 in a compound of general formula IV, the reaction is preferably carried out with two or more equivalents

of the oxidising agent, and accordingly with at least one equivalent if n represents 1.

In order to prepare a compound of general formula I wherein m is 0, reaction of a compound of formula



(V)

wherein R_2, R_3, D and W are as hereinbefore defined, with a compound of formula

$$Y - R_1 \qquad \text{(VI)}$$

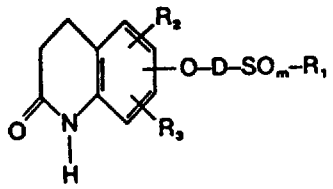
wherein R_1 is as hereinbefore defined and either one of X and Y in the compounds of general formulae V and VI represents a mercapto group whilst the other of X and Y represents a nucleophilically exchangeable group such as, for example, a halogen atom or a sulfonic acid ester group, e.g. a chlorine, bromine or iodine atom or a p-toluenesulfonyloxy or methanesulfonyloxy group.

The reaction is conveniently carried out in a suitable solvent such as e.g. dioxan, tetrahydrofuran, chloroform or toluene, but preferably, however, in an anhydrous aprotic solvent such as e.g. acetone, dimethylformamide or dimethylsulfoxide. The reaction may, if desired, be effected in the presence of an alkali metal base such as e.g. sodium carbonate, potassium carbonate or sodium hydroxide. Suitable reaction temperatures are generally from 0°C to the boiling temperature of the reaction mixture e.g. at temperatures of from 0 to 100°C. Preferred

temperatures are, however, from 10 to 50°C. The reaction may, if desired, be carried out in the absence of a solvent.

d) For the preparation of a carbostyril of general formula I wherein W represents a vinylene group;

Dehydrogenation of a 3,4-dihydrocarbostyril of general formula



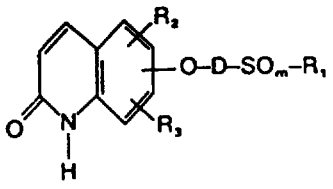
(VII)

wherein R_1-R_3, D and m are as hereinbefore defined.

Dehydrogenation is carried out in the presence of a dehydrogenating agent, e.g. an oxidising agent such as 2,3-dichloro-5,6-dicyano-benzoquinone, chloranil or a noble metal catalyst such as e.g. palladium/charcoal, preferably in an inert solvent such as dioxan or mesitylene, at elevated temperatures, e.g. at temperatures of from 100 to 200°C, preferably at the boiling temperature of the solvent used.

e) for the preparation of a carbostyril of general formula I wherein W represents an ethylene group and m is 0 or 2:

Hydrogenation of a carbostyril of general formula



(VIII)

wherein R_1-R_3, D and m are as hereinbefore defined.

The hydrogenation is preferably carried out in the presence of a solvent such as ethanol, ethyl acetate, glacial acetic acid or dioxan with catalytically activated hydrogen, e.g. with hydrogen in the presence of a hydrogenation catalyst such as e.g. palladium/charcoal, platinum, Raney nickel, Raney cobalt or dirhenium heptasulfide, preferable at a hydrogen pressure of from 1 to 5 bar. Suitable temperatures for the hydrogenation are generally from 0 to 50°C, preferred temperatures being ambient temperatures.

The compounds of general formulae II to VIII used as starting materials are either known from the literature or they can be obtained according to known processes. For example a 6-, 7- or 8-hydroxy-3,4-dihydro-carbostyril of formula II can be obtained by acylation of a corresponding aniline derivative with an appropriate β-halocarboxylic acid derivative and subsequent cyclisation according to the method described by Friedel-Crafts (see J. chem. Soc. 1955, 743-744; Chem. Pharm. Bull. 1961, 970 - 975 and Ber. dtsch. Chem. Ges. 60, 858 (1927)). A 5-hydroxy-3,4-dihydrocarbostyril of formula II can be obtained by cyclisation of a corresponding 2-(β-cyanoethyl)-cyclohexane-1,3-dione derivative and subsequent aromatisation, for example with N-bromo-succinimide (see Chem. and Ind. 1970, 1435).

The preparation of the corresponding hydroxycarbostyrils of general formula II is known from the literature (see for example J. Amer. chem. Soc. 72, 346 (1950) and ibid 76, 2402 (1954) or J. Org. Chem. 33, 1089 (1968) and ibid 36, 3493 (1971)). Furthermore, the preparation of 5-hydroxyoxindole is described in J. chem. Soc. 1961, 2723.

The compounds of general formulae IV, V, VII and VIII useful as starting materials can be

obtained by alkylation of a corresponding hydroxy derivative, optionally followed by oxidation.

As already mentioned above, the compounds of general formula I prepared according to the invention possess interesting pharmacological properties, not only a positive inotropic activity but also antithrombotic activity. Moreover, the thioethers of general formula I are valuable intermediates for preparing the sulphoxides and sulphones of general formula I. For example the following compounds were tested with regard to their biological properties:

A = 6-(4-Phenylmercapto-butoxy)-3,4-dihydro-carbostyril,

B = 6-(4-Phenylsulfinylbutoxy)-3,4-dihydro-carbostyril,

C = 6-(4-Phenylsulfonylbutoxy)-3,4-dihydro-carbostyril,

D = 6-[4-(2-Pyridylmercapto)-butoxy]-3,4-dihydrocarbostyril,

E = 6-[4-(2-Pyridylsulfinyl)-butoxy]-3,4-dihydrocarbostyril,

F = 6-[4-(2-Pyridylsulfonyl)-butoxy]-3,4-dihydrocarbostyril,

G = 6-(2-Phenylsulfinyl-ethoxy)-3,4-dihydro-carbostyril,

H = 6-(4-Benzylsulfinyl-butoxy)-3,4-dihydro-carbostyril,

I = 6-[4-(4-Chlorophenylsulfinyl)-butoxy]-3,4-dihydrocarbostyril,

K = 6-(4-Cyclohexylsulfinyl-butoxy)-3,4-dihydro-carbostyril,

L = 6-[4-(2-Naphthylsulfinyl)-butoxy]-3,4-dihydrocarbostyril,

M = 6-[4-(2-Methoxyphenylsulfinyl)-butoxy]-3,4-dihydrocarbostyril,

N = 6-(4-Phenylsulfinyl-butoxy)-carbostyril,

O = 6-[4-(4-Hydroxy-3,5-di-tert.-butyl-phenyl-

sulfinyl)-butoxy]carbostyril,

P = 6-[4-(3,4-Dichlorophenylsulfinyl)-butoxy]-carbostyril,

Q = 4-Methyl-6-(4-phenylsulfinyl-butoxy)-carbostyril,

R = 6-[4-(3,4-Dichlorophenylsulfonyl)-butoxy]-3,4-dihydrocarbostyril,

S = 6-[4-(2,5-Dichlorophenylsulfinyl)-butoxy]-3,4-dihydrocarbostyril,

T = 6-[4-(Pyrid-2-yl-sulfonyl)-butoxy]carbostyril

and U = 6-[4-(3,4-Dichlorophenylsulfinyl)-butoxy]-3,4-dihydrocarbostyril.

1. Determination of the thrombocyte aggregation according to the method of Born and Cross (J. Physiol. 170, 397 (1964):

The thrombocyte aggregation was measured in the platelet-rich plasma of healthy human donors. The decrease in optical density was measured and recorded photometrically after the addition of adenosine diphosphate or collagen. From the angle of inclination of the density curve, the velocity of aggregation was estimated (Vmax). The optical density was taken as the point on the curve where the most light was transmitted (O.D.). The ED_{50} data in the Table relate to the optical density.

Small doses of collagen were chosen, but sufficient to give irreversible aggregation. To provoke maximum aggregation, about 0.01 ml of the collagen solution was added to 1 ml of platelet-rich plasma. (Commercial collagent of Messrs. Hormonchemie, Munich). The adenosine diphosphate (ADP) doses were chosen to give only the first phase of the BORN curve. The necessary amount of ADP was about 1.10^{-6} mol/l. Commercial ADP of Messrs. Boehringer Mannheim was used.

The dosage of the test compounds which provoked a 50% inhibition of the thrombocyte aggregation

was determined graphically (ED_{50}).

Compound	ED_{50} 10^{-6} mol/l	
	Collagen	ADP
A	50	>100
B	4	20
C	5	15
D	45	>100
E	6.5	25
F	20	20
G	3.5	17
H	2.5	14
I	4	10
K	4.5	12
L	1	10
M	4	22
N	0.6	3
O	0.2	0.5
P	0.2	1.8
Q	3.6	40
R	1.5	25
S	1.0	10
T	0.1	6
U	4	15

2. Determination of the positive inotropic activity:

Rats were narcotized with ether and subsequently killed by a blow behind the neck. After opening the thorax the heart was removed and both auricles were isolated. The auricles were placed into an organ bath of 100 ml. The bath had been filled with a tyrode solution at a temperature of 30°C. The tyrode solution was infused with carbogen (95% of O_2 and 5% of CO_2). The spontaneous contractions of the auricles were registered isometrically.

The auricles were charged with 1 g. The test compounds were tested on 4 auricles each in a concentration of 1 x 10^{-5} g/ml. The variation in the contraction force was registered in % from the starting values.

The following table gives the results obtained.

Compound	Increase in contraction force in %
B	30
C	35
I	52
L	63
M	65
Q	58
S	83
T	32

3. Acute toxicity:

The acute toxicity of the test compounds was determined in groups of 10 mice each after oral administration of a single dose of 1 000 mg/kg (observation time: 14 days).

Compound	acute toxicity per os
A	>1 000 mg/kg (0 out of 10 animals died)
B	>1 000 mg/kg (0 out of 10 animals died)
C	>1 000 mg/kg (0 out of 10 animals died)
D	>1 000 mg/kg (0 out of 10 animals died)
E	>1 000 mg/kg (0 out of 10 animals died)
F	>1 000 mg/kg (0 out of 10 animals died)
G	>1 000 mg/kg (0 out of 10 animals died)
H	>1 000 mg/kg (0 out of 10 animals died)
I	>1 000 mg/kg (0 out of 10 animals died)
K	>1 000 mg/kg (0 out of 10 animals died)
L	>1 000 mg/kg (0 out of 10 animals died)
M	>1 000 mg/kg (0 out of 10 animals died)
P	>1 000 mg/kg (0 out of 10 animals died)
Q	>1 000 mg/kg (0 out of 10 animals died)
R	>1 000 mg/kg (0 out of 10 animals died)
S	>1 000 mg/kg (0 out of 10 animals died)
U	>1 000 mg/kg (0 out of 10 animals died)

In view of their pharmacological properties, the new compounds of general formula I are suitable for the prophylaxis of thrombo-embolic diseases such as coronary infarct, cerebral infarct, so-called transient ischaemic attacks and amaurosis fugax and for the prophylaxis of arteriosclerosis, and for this purpose they may be formulated, optionally together with other active substances, into conventional pharmaceutical preparations such as plain tablets, coated tablets, capsules, suppositories or suspensions.

The individual dosage is 50 to 100 mg, two to three times a day, and the daily dosage is thus 100-300 mg.

The following Examples serve to illustrate the present invention.

Example 1

6-[4-(2-Pyridylmercapto)-butoxy]-3,4-dihydrocarbostyril

14.4 g (0.13 mol) of 2-mercaptopyridine and 17.9 g (0.13 mol) of potassium carbonate were stirred in 360 ml of dimethylsulfoxide, dried over a molecular sieve, and 36 g (0.12 mol) of 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C, prepared from 6-hydroxy-carbostyril and 1,4-dibromobutane) were added to this mixture. After stirring for 15 hours at approx. 25°C, the reaction mixture was poured into 3.6 l of water and again stirred for 30 minutes. The precipitated product was suction filtered, well washed with water, dried and recrystallized from xylene by addition of charcoal. Yellow crystals of m.p. 123 - 124.5°C were obtained.
Yield: 32 g (81.2 % of theory).

Example 2

6-[4-(2-Pyridylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

32.8 g (0.1 mol) of 6-[4-(2-pyridylmercapto)-butoxy]-3,4-dihydrocarbostyril were dissolved in 330 ml of glacial acetic acid and 10.2 g (0.105 mol) of 35 % hydrogen peroxide were added. The solution was stirred for 15 hours at approx. 20°C. The glacial acetic acid was distilled off at 60°C in vacuo, the residue was washed with ether and the thus obtained crude product was recrystallized twice from xylene by addition of charcoal. Colourless crystals of m.p. 144.5 - 146°C were obtained.
Yield: 27.5 g (79.8 % of theory).

Example 3

6-/4-(2-Pyridylsulfonyl)-butoxy/-3,4-dihydrocarbostyril

5 g (0.015 mol) of 6-/4-(2-pyridylmercapto)-butoxy/-3,4-dihydrocarbostyril were dissolved in 50 ml of glacial acetic acid and 4.5 g (0.045 mol) of 35 % hydrogen peroxide were added. After stirring for 40 hours at approx. 25°C, the glacial acetic acid was distilled off at 60°C in vacuo. The solid residue was washed with ether and recrystallized from xylene by addition of charcoal. Colourless crystals of m.p. 123.8 - 125°C were obtained.
Yield: 3.8 g (70.3 % of theory).

Example 4

6-(4-Phenylsulfinylbutoxy)-3,4-dihydrocarbostyril

32.6 g (0.2 mol) of 6-hydroxy-3,4-dihydrocarbostyril (see F. F. Mayer et al. in Ber. dtsch. chem. Ges. 60, 858 (1927)) and 27.6 g (0.2 mol) of potassium carbonate were stirred for 5 minutes in 600 ml of dimethylsulfoxide, dried over a molecular sieve, and subsequently 52.2 g of 4-phenylsulfinylbutylbromide (0.2 mol) (prepared from thiophenol and 1,4-dibromobutane and subsequent oxidation with hydrogen peroxide in glacial acetic acid analogously to example 2; oily substance, solidified whilst standing in the refrigerator) were added. After stirring for 15 hours at 25°C the reaction mixture was poured into 6 l of water. After stirring for further 30 minutes the precipitated product was suction filtered and well washed with water. After drying the residue was recrystallized from 600 ml (approx.) of xylene by addition of charcoal. White crystals of m.p. 144.5 - 145.5°C were obtained.
Yield: 49 g (71.3 % of theory).

Example 5

6-(4-Phenylmercapto-butoxy)-3,4-dihydro-carbostyril

Prepared analogously to Example 4 from 6-hydroxy-3,4-dihydro-carbostyril and 4-(phenylmercapto)-butylbromide (b.p. $_{0.02}$: 96 - 103°C, prepared from thiophenol and 1.4-dibromobutane).
M.p.: 121.5 - 123°C
Yield: 75.6 % of theory.

Example 6

6-(4-Phenylsulfonyl-butoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 4 from 6-hydroxy-3,4-dihydro-carbostyril and 4-phenyl-sulfonyl-butylbromide (prepared from 4-(phenylmercapto)-butylbromide by oxidation analogously to Example 3).
M.p.: 157.5 - 158°C
Yield: 65.1 % of theory.

Example 7

6-/4-(4-Fluorophenylmercapto)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C) and 4-fluoro-thiophenol .
M.p.: 139 - 140°C
Yield: 93.1 % of theory.

Example 8

6-/4-(4-Fluorophenylsulfinyl)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-/4-(4-fluorophenyl-mercapto)-butoxy7-3,4-dihydrocarbostyril.
M.p.: 184.5 - 186°C
Yield: 88 % of theory.

Example 9

6-/4-(4-Methylphenyl-mercapto)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-chlorobutoxy)-3,4-dihydrocarbostyril (m.p. 147 - 148°C) and 4-methylthiophenol .
M.p.: 120 - 121°C
Yield: 91 % of theory.

Example 10

6-/4-(4-Methylphenyl-sulfinyl)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-/4-(4-methylphenyl-mercapto)-butoxy7-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 149.5 - 150°C
Yield: 97 % of theory.

Example 11

6-/4-(3-Methylphenylmercapto)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-chlorobutoxy)-3,4-dihydrocarbostyril (m.p. 147 - 148°C) and 3-methylthiophenol .

M.p.: 95 - 96°C
Yield: 91 % of theory.

Example 12

6-[4-(3-Methylphenylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-[4-(3-methylphenylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
Wax-like resin.
Yield: 95 % of theory.
R_f-value: 0.48 (thin-layer chromatogram on silica gel - eluent: benzene/ethanol/conc. ammonia = 75/25/1).

Example 13

6-[4-(4-Chlorophenylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-chlorobutoxy)-3,4-dihydrocarbostyril (m.p. 147 - 148°C) and 4-chlorothiophenol.
M.p.: 144 - 146°C
Yield: 88 % of theory.

Example 14

6-[4-(4-Chlorophenylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-[4-(4-chlorophenylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 148 - 149.5°C
Yield: 70 % of theory.

Example 15

6-[4-(3,4-Dichlorophenylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-chlorobutoxy)-3,4-dihydrocarbostyril (m.p. 147 - 148°C) and 3,4-dichlorothiophenol .
M.p.: 116.5 - 118°C
Yield: 87 % of theory.

Example 16

6-[4-(3,4-Dichlorophenylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-[4-(3,4-dichlorophenylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 106.5 - 108°C
Yield: 74 % of theory.

Example 17

6-[4-(2-Methoxyphenylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p. 142 - 147°C) and 2-methoxythiophenol .
M.p.: 130.5 - 133°C
Yield: 74 % of theory.

Example 18

6-[4-(2-Methoxyphenylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-[4-(2-methoxyphenylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.

M.p.: 162 - 163°C
Yield: 62 % of theory.

Example 19

6-[4-(3-Methoxyphenylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p. 142 - 147°C) and 3-methoxy-thiophenol.
M.p.: 93.5 - 97°C
Yield: 61 % of theory.

Example 20

6-[4-(3-Methoxyphenylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-[4-(3-methoxyphenyl-mercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 147 - 148°C
Yield: 49 % of theory.

Example 21

6-[4-(4-Methoxyphenylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p. 142 - 147°C) and 4-methoxy-thiophenol.
M.p.: 130.5 - 133°C
Yield: 82 % of theory.

Example 22

6-[4-(4-Methoxyphenylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-[4-(4-methoxyphenylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 132 - 133°C
Yield: 71 % of theory.

Example 23

6-[4-(3,4-Dimethoxyphenylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 3,4-dimethoxythiophenol and 6-(4-chlorobutoxy)-3,4-dihydrocarbostyril [prepared from 6-hydroxy-carbostyril (see F. Mayer et al. in Ber. dtsch. chem. Ges. 60, 858 (1927) and 4-chlorobutyl benzenesulfonate].

M.p.: 117 - 119°C
Yield: 73 % of theory.

Example 24

6-[4-(3,4-Dimethoxyphenylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-[4-(3,4-dimethoxyphenylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 145 - 147°C
Yield: 79 % of theory.

Example 25

6-[4-(3,4-Dimethoxyphenylsulfonyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 3 from 6-[4-(3,4-dimethoxyphenylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 158 - 160°C
Yield: 62 % of theory.

Example 26

6-[4-(4-Biphenylylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 4-phenylthiophenol and 6-(4-bromobutoxy)-3,4-dihydrocarbostyril.
M.p.: 179.5 - 181°C
Yield: 74 % of theory.

Example 27

6-[4-(4-Biphenylylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-[4-(4-biphenylylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 192 - 192.5°C.
Yield: 86 % of theory.

Example 28

6-[4-(2-Naphthylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 2-naphthylmercaptane and 6-(4-bromobutoxy)-3,4-dihydrocarbostyril.
M.p.: 108.5 - 109.5°C
Yield: 48 % of theory.

Example 29

6-/4-(2-Naphthylsulfinyl)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-/4-(2-naphthylmercapto)-butoxy7-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 147.5 - 148.5°C
Yield: 57 % of theory.

Example 30

6-/5-(2-Pyridylsulfinyl)-pentoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-/5-(2-pyridylmercapto)-pentoxy7-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 116 - 118°C
Yield: 69 % of theory.

Example 31

6-/5-(2-Pyridylsulfonyl)-pentoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 3 from 6-/5-(2-pyridylmercapto)-pentoxy7-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 113.5 - 115.0°C
Yield: 71 % of theory.

Example 32

7-(4-Phenylsulfonyl-butoxy)-carbostyril

Prepared analogously to Example 3 from 7-(4-phenylmercapto-butoxy)-carbostyril and hydrogen peroxide.
M.p.: 199 - 201°C
Yield: 85 % of theory.

Example 33

6-(4-Cyclohexylmercaptobutoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from cyclohexylmercaptane and 6-(4-chlorobutoxy)-3,4-dihydrocarbostyril (m.p.: 147 - 148°C).
M.p.: 114 - 115°C
Yield: 80 % of theory.

Example 34

6-(4-Cyclohexylsulfinyl-butoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-(4-cyclohexylmercapto-butoxy)-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 153 - 155.5°C
Yield: 63 % of theory.

Example 35

6-(4-Benzylmercapto-butoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from benzylmercaptane and 6-(4-chlorobutoxy)-3,4-dihydrocarbostyril.
M.p.: 77.5 - 78.5°C
Yield: 90 % of theory.

Example 36

6-(4-Benzylsulfinyl-butoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-(4-benzylmercapto-butoxy)-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 141.5 - 142°C
Yield: 95 % of theory.

Example 37

6-/4-(2-Furylmethylmercapto)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 2-furfurylmercaptane and 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C).
M.p.: 79 - 80°C
Yield: 64 % of theory.

Example 38

6-[4-(2-Furylmethylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-[4-(2-furylmethylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 135 - 136°C
Yield: 60 % of theory.

Example 39

6-[4-(2-Pyrimidyl-mercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-chlorobutoxy)-3,4-dihydrocarbostyril (m.p.: 147 - 148°C) and 2-mercaptopyrimidine.
M.p.: 154 - 156°C
Yield: 79 % of theory.

Example 40

6-[4-(2-Pyrimidylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-[4-(2-pyrimidyl-mercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 154 - 156°C
Yield: 36 % of theory.

Example 41

6-[4-(4-Pyridylmercapto)-butoxy]-3,4-dihydrocarbostyril

To a solution of 1.3 g of 4-mercaptopyridine, 2.3 g of 30 % sodium methoxide solution and of 15 ml of methanol, 3.0 g of 6-(4-bromobutoxy)-3,4-dihydrocarbostyril were added and stirred for 14 hours at room temperature. Subsequently the solution was diluted with 20 ml of water and the resulting precipitate was recrystallized from ethanol.
M.p.: 128 - 129°C
Yield: 1.6 g (49 % of theory).

Example 42

6-[4-(2-Benzimidazolylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-chlorobutoxy)-3,4-dihydrocarbostyril (m.p.: 147 - 148°C) and 2-mercapto-benzimidazole.
M.p.: 100 - 103°C
Yield: 45 % of theory.

Example 43

6-/4-(2-Benzimidazolylsulfinyl)-butoxy/-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-/4-(2-benzimidazolyl-mercapto)-butoxy/-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 180 - 182°C
Yield: 36 % of theory.

Example 44

6-/4-(2-Benzthiazolyl-mercapto)-butoxy/-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-chlorobutoxy)-3,4-dihydrocarbostyril (m.p.: 147 - 148°C) and 2-mercapto-benzthiazole.
M.p.: 157 - 158°C
Yield: 70 % of theory.

Example 45

6-/4-(2-Benzthiazolylsulfinyl)-butoxy/-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-/4-(2-benzthiazolyl-mercapto)-butoxy/-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 183 - 184°C
Yield: 69 % of theory.

Example 46

6-(2-Phenylmercapto-ethoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from thiophenol and 6-(2-chloroethoxy)-3,4-dihydrocarbostyril (m.p.: 152.5 to 153.5°C).

M.p.: 132 - 133.5°C
Yield: 91 % of theory.

Example 47

6-(2-Phenylsulfinyl-ethoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-(2-phenylmercapto-ethoxy)-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 171 - 172°C
Yield: 84 % of theory.

Example 48

6-(2-Phenylsulfonyl-ethoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 3 from 6-(2-phenylmercapto-ethoxy)-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 185 - 186°C
Yield: 94 % of theory.

Example 49

6-(3-Phenylmercapto-propoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(3-bromopropoxy)-3,4-dihydrocarbostyril (m.p.: 111 - 118°C) and thiophenol .
M.p.: 111 - 112°C
Yield: 77 % of theory.

Example 50

6-(3-Phenylsulfinyl-propoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-[3-(phenylmercapto)-propoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 131.5 - 133.5°C
Yield: 67 % of theory.

Example 51

6-(6-Phenylmercapto-hexoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(6-bromohexoxy)-3,4-dihydrocarbostyril (m.p.: 107.5 - 108°C) and thiophenol.
M.p.: 112.5 - 113°C
Yield: 34 % of theory.

Example 52

6-(6-Phenylsulfinyl-hexoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-(6-phenylmercapto-hexoxy)-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 119.5 - 121.5°C
Yield: 35 % of theory.

Example 53

7-(4-Phenylmercaptobutoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 4 from 7-hydroxy-3,4-dihydrocarbostyril (N. Shigematsu et al. in Chem. Pharm. Bull. 1961, 970 - 975) and 4-phenylmercapto-butylbromide (bp.$_{0.02}$: 96 to 103°C).
M.p.: 121 - 123°C
Yield: 72 % of theory.

Example 54

7-(4-Phenylsulfinyl-butoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 4 from 7-hydroxy-3,4-dihydrocarbostyril (N. Shigematsu et al. in Chem. Pharm. Bull. 1961, 970 - 975) and 4-phenylsulfinylbutylbromide.
M.p.: 134 - 136°C
Yield: 80 % of theory.

Example 55

7-(4-Phenylsulfonyl-butoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 4 from 7-hydroxy-3,4-dihydrocarbostyril (N. Shigematsu et al. in Chem. Pharm. Bull. 1961, 970 - 975) and 4-phenylsulfonylbutylbromide.
M.p.: 178.5 - 179.5°C
Yield: 74 % of theory.

Example 56

8-(4-Phenylmercaptobutoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 4 from 8-hydroxy-3,4-dihydrocarbostyril (J. D. Loudon et al. in J. Chem. Soc. 1955, 743 - 744) and 4-phenylmercapto-butylbromide ($bp._{0.02}$: 96 - 103°C).
M.p.: 101 - 102°C
Yield: 75 % of theory.

Example 57

8-(4-Phenylsulfinyl-butoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 4 from 8-hydroxy-3,4-dihydrocarbostyril (J. D. Loudon et al. in J. Chem. Soc. 1955, 743 - 744) and phenylsulfinylbutylbromide.
Colourless resin was obtained.
Yield: 60 % of theory.
R_f-value: 0.60 (thinlayer chromatogram on silica gel - eluent: benzene/ethanol/conc. ammonia = 75/25/1).

Example 58

8-(4-Phenylsulfonyl-butoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 3 from 8-(4-phenylmercapto-butoxy)-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 114.5 - 115°C
Yield: 60 % of theory.

Example 59

6-/4-(2-Benzthiazolyl-sulfonyl)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-/4-(2-benzthiazolyl-mercapto)-butoxy7-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 146 - 149°C
Yield: 61 % of theory.

Example 60

6-/4-(2-Quinolylmercapto)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p. 142 - 147°C) and 2-mercapto-quinoline.
M.p.: 115°C
Yield: 64 % of theory.

Example 61

6-/4-(2-Quinazolin-4-on-yl-mercapto)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C) and 2-mercaptoquinazolin-4-one.
M.p.: 184.5 - 188°C
Yield: 63 % of theory.

Example 62

6-(4-Triphenylmethylmercapto-butoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C) and triphenylmethylmercaptan.
M.p.: 169 - 170°C
Yield: 89 % of theory.

Example 63

6-/2-(2-Naphthylmercapto)-ethoxy/-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-chloroethoxy)-3,4-dihydrocarbostyril (m.p.: 147 - 148°C) and 2-naphthylmercaptan.
M.p.: 147.5 - 147.8°C
Yield: 77 % of theory.

Example 64

6-/2-(2-Naphthylsulfinyl)-ethoxy/-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-/2-(2-naphthylmercapto)-ethoxy/-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 186.5 - 187.5°C
Yield: 88 % of theory.

Example 65

6-/2-(4-Biphenylylmercapto)-ethoxy/-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(2-chloroethoxy)-3,4-dihydrocarbostyril (m.p.: 152.5 - 153.5°C) and 4-mer-

captobiphenyl.
M.p.: 192 - 194°C
Yield: 92 % of theory.

Example 66

6-[2-(4-Biphenylyl-sulfinyl)-ethoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-[2-(4-biphenylylmercapto)-ethoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 195 - 196°C
Yield: 66 % of theory.

Example 67

6-[3-(2-Pyridylmercapto)-propoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(3-bromopropoxy)-3,4-dihydrocarbostyril and 2-mercaptopyridine.
M.p.: 108 - 108.5°C
Yield: 42 % of theory.

Example 68

6-(4-Phenylsulfinyl-butoxy)-3,4-dihydrocarbostyril

1.6 g of 6-(4-phenylmercapto-butoxy)-3,4-dihydrocarbostyril were dissolved in 50 ml of methanol and 0.9 g of N-bromo-succininimide were added. After stirring for 15 hours at room temperature, the mixture was diluted with 500 ml of hot water (80°C) and decanted from the firstly oily residue, whereby after a while crystals were formed. After re-crystallization from xylene white crystals of m.p. 144 to 145°C were obtained.
Yield: 1.2 g (66 % of theory).

Example 69

6-(4-Phenylsulfinyl-butoxy)-3,4-dihydrocarbostyril

3.3 g of 6-(4-phenylmercapto-butoxy)-3,4-dihydrocarbostyril were dissolved in 50 ml of methylene chloride, cooled to -70°C and a solution of 1.5 g of sulfuryl chloride in 5 ml of methylene chloride was added dropwise. After 15 hours 20 ml of 95 % ethanol were added and the mixture was heated to room temperature by removing of the cooling bath, neutralized with aqueous sodium carbonate solution, the methylene chloride phase was dried with sodium sulfate and the solvent was removed. The residue was recrystallized from toluene.
M.p.: 143 - 145°C
Yield: 2.8 g (81 % of theory).

Example 70

5-(4-Phenylmercapto-butoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 4 from 5-hydroxy-3,4-dihydrocarbostyril and 4-phenylmercaptobutylbromide.
M.p.: 155 - 157°C
Yield: 64 % of theory.

Example 71

5-(4-Phenylsulfinyl-butoxy)-3,4-dihydro carbostyril

Prepared analogously to Example 4 from 5-hydroxy-3,4-dihydrocarbostyril and 4-phenylsulfinylbutylbromide.
M.p.: 136 - 138°C
Yield: 64 % of theory.

Example 72

5-(4-Phenylsulfonyl-butoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 4 from 5-hydroxy-3,4-dihydrocarbostyril and 4-phenylsulfonylbutylbromide.
M.p.: 187 - 189°C
Yield: 73 % of theory.

Example 73

6-[4-(2-Naphthylsulfonyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 3 from 6-[4-(2-naphthylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 173 - 175°C
Yield: 95 % of theory.

Example 74

6-[4-(4-Biphenylylsulfonyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 3 from 6-[4-(4-biphenylylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 232 - 234.5°C
Yield: 83 % of theory.

Example 75

6-(4-Phenylsulfonyl-butoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 3 from 6-(4-phenylsulfinyl-butoxy)-3,4-dihydrocarbostyril and hydrogen peroxide.

M.p.: 157 - 158°C
Yield: 88 % of theory.

Example 76

6-/4-(2-Pyridylsulfonyl)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 3 from 6-/4-(2-pyridylsulfinyl)-butoxy7-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 123.8 - 125°C
Yield: 76 % of theory.

Example 77

5-(4-Phenylsulfonyl-butoxy)-carbostyril

1.87 g of 2,3-dichloro-5,6-dicyano-benzoquinone were added to 1.8 g of 5-(4-phenylsulfonyl-butoxy)-3,4-dihydrocarbostyril, dissolved in 45 ml of dioxane. The solution was heated for 2.5 hours in an oil bath. The reaction mixture was hot filtered and the insoluble residue, which was formed during the reaction, was washed out with hot dioxane. The combined filtrates were diluted with 100 ml of chloroform and extracted several times with altogether 150 ml of 2N-sodium hydroxide. After drying the chloroform extracts with sodium sulfate and filtering in the presence of activated charcoal the residue was evaporated and ethyl acetate was added until white crystals were precipitated.
M.p.: 182 - 183°C
Yield: 850 mg (47 % of theory).

Example 78

5-(4-Phenylmercapto-butoxy)-carbostyril

Prepared analogously to Example 77 from 5-(4-phenylmercapto-butoxy)-3,4-dihydrocarbostyril and 2,3-dichloro-5,6-dicyano-benzoquinone.
M.p.: 185 - 187°C
Yield: 40 % of theory.

Example 79

5-(4-Phenylsulfinyl-butoxy)-carbostyril

0.165 ml of 30 % hydrogen peroxide, dissolved in 8 ml of glacial acetic acid, were added to 0.56 g of 5-(4-phenylmercapto-butoxy)-carbostyril . The mixture was diluted with water and extracted with chloroform twice. The chloroform extract was washed with dilute sodium carbonate solution , with water, dried over magnesium sulfate and evaporated. The residue was mixed with ethyl acetate and colourless crystals of m.p. 155 - 157°C were obtained.
Yield: 389 mg (65 % of theory).

Example 80

6-(4-Phenylmercapto-butoxy)-carbostyril

Prepared analogously to Example 77 from 6-(4-phenylmercapto-butoxy)-3,4-dihydrocarbostyril and 2,3-dichloro-4,5-dicyano-benzoquinone.
M.p.: 162 - 164°C
Yield: 35 % of theory.

Example 81

6-(4-Phenylsulfinyl-butoxy)-carbostyril

Prepared analogously to Example 77 from 6-(4-phenylsulfinyl-butoxy)-3,4-dihydrocarbostyril and 2,3-dichloro-5,6-dicyano-benzoquinone. For purification the mixture was chromatographed on a silica gel column with a mixture of benzene/ethanol/conc. ammonia = 75/25/3.
M.p.: 181 - 182.5°C
Yield: 48 % of theory.
From the first fractions of the column chromatography 6-(4-phenylmercapto-butoxy)-carbostyril of m.p. 162 - 164°C was isolated in a yield of 15 % of theory.

Example 82

6-(4-Phenylsulfonyl-butoxy)-carbostyril

Prepared analogously to Example 77 from 6-(4-phenylsulfonyl-butoxy)-3,4-dihydrocarbostyril and 2,3-dichloro-5,6-dicyano-benzoquinone. Purification was carried out by column chromatography on silica gel (grain size: 0.2 - 0.5 mm) with chloroform/methanol/ethyl acetate = 4/1/1.
M.p.: 212 - 213°C
Yield: 54 % of theory.

Example 83

5-(4-Phenylmercapto-butoxy)-carbostyril

49 g of 4-phenylmercaptobutylbromide were added to a mixture of 32.3 g of 5-hydroxycarbostyril, 30 g of potassium carbonate and 650 ml of dimethylsulfoxide, dried over a molecular sieve. The mixture was stirred for 20 hours at 25°C, diluted with 3 l of water and the crystallized reaction product was suction filtered.

M.p.: 185 - 187°C (from toluene)
Yield: 45.0 g (70 % of theory).

Example 84

5-(4-Phenylsulfonyl-butoxy)-carbostyril

Prepared analogously to Example 79 from 5-(4-phenylmercapto-butoxy)-carbostyril and 4 moles of hydrogen peroxide at a temperature of 60°C and a reaction time of 14 hours.
M.p.: 182 - 183°C
Yield: 73 % of theory.

Example 85

6-(4-Phenylmercapto-butoxy)-carbostyril

Prepared analogously to Example 83 from 6-hydroxycarbostyril and 4-phenylmercaptobutylbromide.
M.p.: 161 - 163°C
Yield: 78 % of theory.

Example 86

6-(4-Phenylsulfinyl-butoxy)-carbostyril

Prepared analogously to Example 79 from 6-(4-phenylmercapto-butoxy)-carbostyril and hydrogen peroxide.
M.p.: 181 - 182°C
Yield: 68 % of theory.

Example 87

6-(4-Phenylsulfinyl-butoxy)-carbostyril

Prepared analogously to Example 83 from 6-hydroxycarbostyril and 4-phenylsulfinylbutylbromide.
M.p.: 181 - 182°C
Yield: 71 % of theory.

Example 88

7-(4-Phenylsulfinyl-butoxy)-carbostyril

Prepared analogously to Example 77 from 7-(4-phenylsulfinyl-butoxy)-3,4-dihydrocarbostyril.
M.p.: 193 - 194°C
Yield: 51 % of theory.

Example 89

8-(4-Phenylmercapto-butoxy)-carbostyril

Prepared analogously to Example 77 from 8-(4-phenylmercapto-butoxy)-3,4-dihydrocarbostyril and 2,3-dichloro-5,6-dicyano-benzoquinone.
M.p.: 119 - 120°C
Yield: 40 % of theory.

Example 90

8-(4-Phenylsulfinyl-butoxy)-carbostyril

Prepared analogously to Example 79 from 8-(4-phenylmercapto-butoxy)-carbostyril by oxidation with hydrogen peroxide.

M.p.: 125.5 - 126.5°C
Yield: 60 % of theory.

Example 91

5-(4-Phenylsulfonyl-butoxy)-carbostyril

100 mg of 5-(4-phenylsulfonyl-butoxy)-3,4-dihydrocarbostyril were refluxed with 30 mg of palladium/charcoal and 1 ml of mesitylene. After 3.5 hours a further 30 mg of palladium/charcoal were added and the mixture was heated for further 9 hours. Subsequently the reaction mixture was hot filtered, the filtrate was evaporated and the residue was chromatographed on a silica gel column with a mixture of benzene/ethanol/conc. ammonia = 75/25/3. Besides the starting material, which did not change during the reaction, 9 mg of 5-(4-phenylsulfonyl-butoxy)-carbostyril were obtained.
M.p.: 182 - 183°C

Example 92

6-(4-Amino-iminomethylmercapto-butoxy)-3,4-dihydrocarbostyril

18 g of 6-(4-bromobutoxy)-3,4-dihydrocarbostyril, 5 g of thiourea and 250 ml of water were heated up to boiling until a solution was obtained (approx. 4 hours). After cooling the impurities were extracted with chloroform and the residue was made alkaline by means of ammonia. The precipitated crystals were suction filtered and dried.
M.p.: 140 - 141.8°C
M.p. of the hydrochloride: 208 - 211°C
Yield: 90 % of theory.

Example 93

6-(4-Phenylsulfonyl)-butoxy-3,4-dihydrocarbostyril

107 mg of 6-(4-phenylsulfonyl)-butoxy-carbostyril were suspended in 15 ml of methanol, mixed with 40 mg of palladium/charcoal and hydrogenated at 50°C and at a hydrogen pressure of 2.5 bar for 14 hours. After filtering off the catalyst and evaporating the clear solution, the residue was obtained as colourless crystals.
M.p.: 153 - 154°C
Yield: 89 mg (83 % of theory).

Example 94

6-(4-Benzylmercapto-butoxy)-3,4-dihydrocarbostyril

2.5 g of 6-(4-mercaptobutoxy)-3,4-dihydrocarbostyril, dissolved in 25 ml of dimethylsulfoxide, were mixed whilst stirring with 1.4 g of potassium carbonate and subsequently with 1.3 ml of benzylchloride. After stirring for 15 hours at room temperature the reaction mixture was diluted with 200 ml of water, the precipitated oily substance was separated and recrystallized from ethyl acetate.
M.p.: 76 - 78°C
Yield: 2.8 g (82 % of theory).

Example 95

6-(5-Phenylmercaptopentoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(5-bromopentoxy)-3,4-dihydro-carbostyril and thiophenol .
M.p.: 117 - 119°C
Yield: 71 % of theory.

Example 96

6-(5-Phenylsulfinyl-pentoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-(5-phenylmercapto-pentoxy)-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 104 - 109.5°C
Yield: 66 % of theory.

Example 97

6-(5-Phenylsulfinyl-pentoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 3 from 6-(5-phenylmercapto-pentoxy)-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 136.5 - 137.8°C
Yield: 62 % of theory.

Example 98

6-/5-(2-Pyridyl-mercapto)-pentoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(5-bromopentoxy)-3,4-dihydrocarbostyril and 2-mercaptopyridine.
M.p.: 113 - 114.8°C
Yield: 76 % of theory.

Example 99

6-/4-(4-Hydroxyphenylmercapto)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril and 4-hydroxythiophenol.
M.p.: 191.5 - 193.0°C
Yield: 83 % of theory.

Example 100

6-/4-(4-Hydroxyphenylsulfinyl)-butoxy/-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-/4-(4-hydroxyphenylmercapto)-butoxy/-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 206 - 207.8°C
Yield: 84 % of theory.

Example 101

6-/4-(4-Hydroxyphenylsulfonyl)-butoxy/-3,4-dihydrocarbostyril

Prepared analogously to Example 3 from 6-/4-(4-hydroxyphenylmercapto)-butoxy/-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 219 - 219.5°C
Yield: 78 % of theory.

Example 102

6-/4-(4-Acetaminophenyl mercapto)-butoxy/-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril and 4-acetaminothiophenol.
M.p.: 162.5 - 163.0°C
Yield: 65 % of theory.

Example 103

6-/4-(4-Acetaminophenylsulfinyl)-butoxy/-3,4-dihydrocarbostyril

Prepared analogously to Example 2 from 6-/4-(4-acetaminophenylmercapto)-butoxy/-3,4-dihydrocarbostyril and hydrogen peroxide.

M.p.: 202.0 - 203.8°C
Yield: 55 % of theory.

Example 104

6-/4-(4-Acetaminophenylsulfonyl)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 3 from 6-/4-(4-acetaminophenyl-mercapto)-butoxy7-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 143.5 - 147.0°C
Yield: 88 % of theory.

Example 105

6-/4-(4,5-Di-p-chlorophenyl-oxazole-2-yl-mercapto)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 1 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril and 2-mercapto-4,5-di-p-chlorophenyl-oxazole.
M.p.: 110 - 115°C
Yield: 70 % of theory.

Example 106

6-/4-(2-Pyridylsulfinyl)-butoxy7-carbostyril

Prepared analogously to Example 77 from 6-/4-(2-pyridylsulfinyl)-butoxy7-3,4-dihydrocarbostyril and 2,3-dichloro-5,6-dicyano-benzoquinone.
M.p.: 152 - 154°C
Yield: 48 % of theory.

Example 107

6-(4-Phenylmercapto-butoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 93 from 6-(4-phenylmercapto-butoxy)-carbostyril by catalytic hydrogenation with rhenium-VII-sulfide as catalyst.
M.p.: 121 - 122°C
Yield: 67 % of theory.

Example 108

8-(4-Phenylsulfonyl-butoxy)-carbostyril

Prepared analogously to Example 77 from 8-(4-phenylsulfonyl-butoxy)-3,4-dihydrocarbostyril and 2,3-dichloro-5,6-dicyano-benzoquinone.
M.p.: 146 - 147°C
Yield: 41 % of theory.

Example 109

7-(4-Phenylmercapto-butoxy)-carbostyril

Prepared analogously to Example 77 from 7-(4-phenylmercapto-butoxy)-3,4-dihydrocarbostyril and 2,3-dichloro-5,6-dicyano-benzoquinone.
M.p.: 157.5 - 158.5°C
Yield: 54 % of theory.

Example 110

6-/4-(2,5-Dichlorophenylmercapto)-butoxy7-3,4-dihydrocarbostyril

8.94 g (0.03 mol) of 6-(bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C) were added to a mixture of 2.21 g (0.0315 mol) of potassium methoxide, 5.76 g (0.0315 mol) of 98 % 2,5-dichlorothiophenol and of 54 ml of methanol.

The reaction mixture was refluxed whereby at first a clear solution was obtained. After 5 minutes sufficient crystalline reaction product had precipitated, so that the reaction mixture was hardly stirrable. After one hour the mixture was cooled to room temperature, suction filtered and recrystallized from ethanol. Colourless crystals of m.p. 133 - 134°C were obtained. Yield: 10.60 g (89.1 % of theory).

Example 111

6-/4-(2,5-Dichlorophenylsulfinyl)-butoxy7-3,4-dihydrocarbostyril

5.55 g (0.014 mol) of 6-/4-(2,5-dichlorophenylmercapto)-butoxy7-3,4-dihydrocarbostyril, suspended in 40 ml of glacial acetic acid, were mixed with 1.19 ml of a 40.06 % aqueous solution of hydrogen peroxide (0.014 mol), dissolved in 1.5 ml of glacial acetic acid, and stirred at room temperature. The suspension was allowed to clear and an almost clear solution was obtained. After 70 hours white crystals were precipitated which were suction filtered and recrystallized from ethanol.

M.p.: 185 - 186°C

Yield: 5.43 g (94.1 % of theory).

Example 112

6-[4-(2,5-Dichlorophenylsulfonyl)-butoxy]-3,4-dihydrocarbostyril

2.97 g (0.0075 mol) of 6-[4-(2,5-dichlorophenylmercapto)-butoxy]-3,4-dihydrocarbostyril were added to 15 ml of ice-cooled formic acid and mixed with 1.49 ml of 40.08 % hydrogen peroxide (0.0175 mol). After stirring for 2.5 hours the mixture was diluted with three times the amount of water. The precipitated crystals were recrystallized from ethanol.
M.p.: 174.5 - 175.5°C
Yield: 1.99 g (61.9 % of theory).

Example 113

6-[4-(3,4-Dichlorophenylsulfonyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 112 from 6-[4-(3,4-dichlorophenylmercapto)-butoxy]-3,4-dihydrocarbostyril (m.p.: 116.5 - 118°C) and hydrogen peroxide.
M.p.: 172 - 173°C
Yield: 96 % of theory.

Example 114

6-[4-(4-Hydroxy-3,5-di-tert.-butyl-phenylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C) and 4-hydroxy-3,5-di-tert.-butylthiophenol.
M.p.: 146 - 147°C
Yield: 68.8 % of theory.

Example 115

6-[4-(4-Hydroxy-3,5-di-tert.-butyl-phenylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 111 from 6-[4-(4-hydroxy-3,5-di-tert.-butyl-phenylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 170 - 171°C
Yield: 80.7 % of theory.

Example 116

6-[4-(4-Hydroxy-3,5-di-tert.-butyl-phenylsulfonyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 112 from 6-[4-(4-hydroxy-3,5-di-tert.-butyl-phenylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 165 - 167°C
Yield: 97.6 % of theory.

Example 117

6-[4-(2-Carboxyphenylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril and 2-thiobenzoic acid.
M.p.: 176 - 179°C
Yield: 57.5 % of theory.

Example 118

6-[4-(2-Carboxy-phenylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 111 from 6-[4-(2-carboxy-phenylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 194 - 196°C
Yield: 77.2 % of theory.

Example 119

6-[4-(4-Pyridylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril and 4-mercaptopyridine and subsequent oxidation of the obtained 6-[4-(4-pyridylmercapto)-butoxy]-3,4-dihydrocarbostyril (m.p.: 128 - 133°C) with hydrogen peroxide analogously to Example 123.
M.p.: 154°C
Yield: 57 % of theory.

Example 120

6-[4-(4-Pyridylsulfonyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 112 from 6-[4-(4-pyridylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 179 - 183°C
Yield: 35.9 % of theory.

Example 121

6-(3-Benzylmercapto-propoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 110 from 6-(3-bromopropoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C) and benzyl mercaptane.
M.p.: 97.5 - 99.0°C
Yield: 58 % of theory.

Example 122

6-(3-Benzylsulfinyl-propoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 111 from 6-(3-benzylmercapto)-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 144.5 - 147.0°C
Yield: 51 % of theory.

Example 123

6-/4-(2-Pyridyl-sulfonyl)-butoxy/-carbostyril

Prepared analogously to Example 112 from 6-/4-(2-pyridyl-sulfinyl)-butoxy/-carbostyril and hydrogen peroxide.
M.p.: 179 - 180°C
Yield: 65.8 % of theory.

Example 124

4-Methyl-6-(4-phenylmercapto-butoxy)-carbostyril

5.25 g (0.03 mol) of 4-methyl-6-hydroxycarbostyril (m.p.: 326 - 330°C, see R. R. Holmes et al. in J. Amer. Chem. Soc. 76, 2404 (1954)), 8.09 g (0.033 mol) of 4-phenylmercaptobutyl-bromide and 6.22 g (0.045 mol) of potassium carbonate were stirred at room temperature for 16 hours in 70 ml dimethylsulfoxide. Subsequently the mixture was diluted with water and the precipitated crystals were recrystallized from toluene after drying.
M.p.: 148 - 150°C
Yield: 6.2 g (61.2 % of theory).

Example 125

4-Methyl-6-(4-phenylsulfinyl-butoxy)-carbostyril

Prepared analogously to Example 124 from 4-methyl-6-hydroxy-carbostyril (m.p.: 326 - 330°C) and 4-phenylsulfinylbutyl-bromide.
M.p.: 167 - 168°C
Yield: 47.3 % of theory.

Example 126

4-Methyl-6-(4-phenylsulfonyl-butoxy)-carbostyril

Prepared analogously to Example 124 from 4-methyl-6-hydroxy-carbostyril (m.p.: 326 - 330°C) and 4-phenylsulfonylbutyl-bromide.
M.p.: 217 - 219°C
Yield: 66.6 % of theory.

Example 127

4-Methyl-6-/4-(2-pyridylmercapto)-butoxy/-carbostyril

Prepared analogously to Example 110 from 4-methyl-6-(4-bromo-butoxy)-carbostyril (m.p.: 217 - 219°C) and 2-mercaptopyridine.
M.p.: 149 - 151°C
Yield: 85.7 % of theory.

Example 128

4-Methyl-6-/4-(2-pyridylsulfinyl)-butoxy/-carbostyril

Prepared analogously to Example 111 from 4-methyl-6-/4-(2-pyridylmercapto)-butoxy/carbostyril and hydrogen peroxide.
M.p.: 167 - 169°C
Yield: 61.8 % of theory.

Example 129

4-Methyl-6-/4-(2-pyridylsulfonyl)-butoxy/-carbostyril

Prepared analogously to Example 112 from 4-methyl-6-/4-(2-pyridylmercapto)-butoxy/carbostyril and hydrogen peroxide.

M.p.: 195 - 197°C
Yield: 29.5 % of theory.

Example 130

4-Methyl-6-[4-(2-quinolylmercapto)-butoxy]-carbostyril

Prepared analogously to Example 110 from 4-methyl-6-(4-bromo-butoxy)-carbostyril and 2-mercaptoquinoline.
M.p.: 162 - 163°C
Yield: 81.9 % of theory.

Example 131

4-Methyl-6-[4-(2-quinolylsulfinyl)-butoxy]-carbostyril

Prepared analogously to Example 111 from 4-methyl-6-[4-(2-quinolylmercapto)-butoxy]carbostyril and hydrogen peroxide.
M.p.: 189 - 190°C
Yield: 47.5 % of theory.

Example 132

4-Methyl-6-[4-(2-quinolylsulfonyl)-butoxy]carbostyril

Prepared analogously to Example 112 from 4-methyl-6-[4-(2-quinolylmercapto)-butoxy]carbostyril and hydrogen peroxide.
M.p.: 199 - 203°C
Yield: 31.5 % of theory.

Example 133

4-Methyl-6-/4-(4-biphenylylsulfinyl)-butoxy/carbostyril

Prepared analogously to Example 111 from 4-methyl-6-/4-(4-biphenylylmercapto)-butoxy/carbostyril (m.p.: 174 - 176° C) and hydrogen peroxide.
M.p.: 161 - 162°C
Yield: 59 % of theory.

Example 134

6-/4-(4-Chlorophenylmercapto)-butoxy/carbostyril

Prepared analogously to Example 110 from 6-(4-chlorobutoxy) carbostyril (m.p.: 206 - 208°C) and 4-chlorothiophenol.
M.p.: 168 - 170°C
Yield: 85 % of theory.

Example 135

6-/4-(4-Chlorophenylsulfinyl)-butoxy/carbostyril

Prepared analogously to Example 111 from 6-/4-(4-chlorophenylmercapto)-butoxy/carbostyril and hydrogen peroxide.
M.p.: 157 - 158°C
Yield: 81 % of theory.

Example 136

6-/4-(4-Chlorophenylsulfonyl)-butoxy/carbostyril

Prepared analogously to Example 112 from 6-/4-(4-chlorophenylmercapto)-butoxy/carbostyril and hydrogen peroxide.

M.p.: 197 - 199°C
Yield: 99 % of theory.

Example 137

6-/4-(3,4-Dichlorophenylmercapto)-butoxy/carbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-carbostyril (m.p.: 198 - 199°C) and 3,4-dichlorothiophenol .
M.p.: 149 - 152°C
Yield: 60 % of theory.

Example 138

6-/4-(3,4-Dichlorophenylsulfinyl)-butoxy/carbostyril

Prepared analogously to Example 111 from 6-/4-(3,4-dichlorophenylmercapto)-butoxy/carbostyril and hydrogen peroxide.
M.p.: 191 - 196°C
Yield: 87 % of theory.

Example 139

6-/4-(3,4-Dichlorophenylsulfonyl)-butoxy/carbostyril

Prepared analogously to Example 112 from 6-/4-(3,4-dichlorophenylmercapto)-butoxy/carbostyril and hydrogen peroxide.
M.p.: 188 - 190°C
Yield: 83 % of theory.

Example 140

6-/4-(2,5-Dichlorophenylmercapto)-butoxy/carbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-carbostyril and 2,5-dichlorothiophenol .
M.p.: 175 - 176°C
Yield: 85 % of theory.

Example 141

6-/4-(2,5-Dichlorophenylsulfinyl)-butoxy/carbostyril

Prepared analogously to Example 111 from 6-/4-(2,5-dichlorophenylmercapto)-butoxy/carbostyril and hydrogen peroxide.
M.p.: 200 - 202°C
Yield: 75 % of theory.

Example 142

6-/4-(2,5-Dichlorophenylsulfonyl)-butoxy/carbostyril

Prepared analogously to Example 112 from 6-/4-(2,5-dichlorophenylmercapto)-butoxy/carbostyril and hydrogen peroxide in formic acid.
M.p.: 203 - 205°C
Yield: 79 % of theory.

Example 143

6-/4-(4-Fluorophenylmercapto)-butoxy/carbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-carbostyril and 4-fluorothiophenol .
M.p.: 149 - 150°C
Yield: 85 % of theory.

Example 144

6-[4-(4-Fluorophenylsulfinyl)-butoxy]carbostyril

Prepared analogously to Example 111 from 6-[4-(4-fluorophenylmercapto)-butoxy]carbostyril and hydrogen peroxide.
M.p.: 164 - 165°C
Yield: 50 % of theory.

Example 145

6-[4-(4-Fluorophenylsulfonyl)-butoxy]carbostyril

Prepared analogously to Example 112 from 6-[4-(4-fluorophenylmercapto)-butoxy]carbostyril and hydrogen peroxide in formic acid.
M.p.: 209 - 211°C
Yield: 59 % of theory.

Example 146

6-[4-(4-Hydroxy-3,5-di-tert.-butyl-phenylmercapto)-butoxy]-carbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-carbostyril (m.p.: 198 - 199°C) and 4-hydroxy-3,5-di-tert.-butyl-thiophenol (m.p.: 84.5 - 86.0°C).
M.p.: 172 - 173°C
Yield: 77 % of theory.

Example 147

6-[4-(4-Hydroxy-3,5-di-tert.-butylphenylsulfinyl)-butoxy]-carbostyril

Prepared analogously to Example 111 from 6-[4-(4-hydroxy-3,5-di-tert.-butylphenylmercapto)-butoxy]carbostyril and hydrogen peroxide.
M.p.: 192 - 194°C
Yield: 83 % of theory.

Example 148

6-[4-(4-Hydroxy-3,5-di-tert.-butylphenylsulfonyl)-butoxy]-carbostyril

Prepared analogously to Example 112 from 6-[4-(4-hydroxy-3,5-di-tert.-butylphenylmercapto)-butoxy]carbostyril and hydrogen peroxide in formic acid.
M.p.: 242 - 244°C
Yield: 92 % of theory.

Example 149

6-[4-(4-Biphenylylmercapto)-butoxy]carbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-carbostyril (m.p.: 198 - 199°C) and 4-biphenyl mercaptan.
M.p.: 191 - 192°C
Yield: 82 % of theory.

Example 150

6-/4-(4-Biphenylylsulfinyl)-butoxy7carbostyril

Prepared analogously to Example 111 from 6-/4-(4-biphenylylmercapto)-butoxy7carbostyril and hydrogen peroxide.
M.p.: 196 - 197°C
Yield: 80 % of theory.

Example 151

6-/4-(4-Biphenylylsulfonyl)-butoxy7carbostyril

Prepared analogously to Example 112 from 6-/4-(4-biphenylylmercapto)-butoxy7carbostyril and hydrogen peroxide.
M.p.: 213 - 215°C
Yield: 73 % of theory.

Example 152

6-/4-(4-Nitro-phenylmercapto)-butoxy7carbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-carbostyril (m.p.: 198 - 199°C) and 4-nitrothiophenol .
M.p.: 184 - 185°C
Yield: 96 % of theory.

Example 153

6-/4-(4-Nitro-phenylsulfinyl)-butoxy7carbostyril

Prepared analogously to Example 111 from 6-/4-(4-nitrophenylmercapto)-butoxy7carbostyril and hydrogen peroxide.

M.p.: 183 - 184°C
Yield: 77 % of theory.

Example 154

6-[4-(4-Nitro-phenylsulfonyl)-butoxy]carbostyril

Prepared analogously to Example 112 from 6-[4-(4-nitro-phenylsulfinyl)-butoxy]carbostyril and hydrogen peroxide in formic acid.
M.p.: 230 - 232°C
Yield: 70 % of theory.

Example 155

6-[4-(2-Quinolylmercapto)-butoxy]carbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-carbostyril (m.p.: 132°C) and 2-mercaptoquinoline.
M.p.: 132°C
Yield: 99 % of theory.

Example 156

6-[4-(2-Quinolylsulfinyl)-butoxy]carbostyril

Prepared analogously to Example 111 from 6-[4-(2-quinolyl-mercapto)-butoxy]carbostyril and hydrogen peroxide.
M.p.: 161 - 162°C
Yield: 66 % of theory.

Example 157

6-/4-(2-Quinolylsulfonyl)-butoxy/carbostyril

Prepared analogously to Example 112 from 6-/4-(2-quinolylsulfinyl)-butoxy/carbostyril and hydrogen peroxide in formic acid.
M.p.: 197 - 198°C
Yield: 58 % of theory.

Example 158

6-/2-(Phenylsulfinylmethyl)-benzyloxy/-3,4-dihydro-carbostyril

A mixture of 67.1 g of phthalide, 51.3 ml of thiophenol, 35.1 g of potassium methoxide and 250 ml of methanol was refluxed. Subsequently the resulting 2-phenylmercaptomethylbenzoic acid (yield: 78 % of theory, m.p.: 108 - 110°C) was

esterified with methanol/thionylchloride whilst standing at -40°C. After standing over night at room temperature methyl 2-phenylmercaptomethyl-benzoate (yield: 89 % of theory, b.p.$_{0.07}$: 145°C) was obtained, which was converted to the 2-phenylmercaptomethyl-phenylcarbinole (yield: 97 % of theory, m.p.: 64 - 65°C) by means of reduction with lithiumaluminium hydride in diethyl ether. This compound was converted to 2-phenylmercaptomethyl-phenylmethyl-p-toluenesulfonate by the addition of p-toluenesulfonyl chloride. (Thin-layer chromatogram: silica gel; eluent: chloroform/ethyl acetate = 1 : 1; R_f-value = 0.8. Yield: 55 % of theory). This ester was converted into 6-[2-(phenylmercaptomethyl)-benzyloxy]-3,4-dihydrocarbostyril analogously to Example 140 with 6-hydroxy-3,4-dihydrocarbostyril (thin-layer chromatogram: silica gel; eluent: chloroform/ethyl acetate = 1 : 1; R_f-value = 0.35; Yield: 64 % of theory).
This substance was oxidised analogously to Example 111 to 6-[2-(phenylsulfinylmethyl)-benzyloxy]-3,4-dihydrocarbostyril by means of hydrogen peroxide.
M.p.: 133 - 135°C
Yield: 64 % of theory.

Example 159

6-[4-(Phenylmercaptomethyl)-benzyloxy]-3,4-dihydrocarbostyril

p-Xylylenedichloride was reacted with thiophenol in a 1:1 molar ratioin the presence of excess potassium carbonate in dimethylsulfoxide. The obtained 4-phenylmercaptomethyl-benzylchloride (control: thin-layer chromatogram) was further reacted with 6-hydroxy-3,4-dihydrocarbostyril analogously to Example 140 without isolation.
M.p.: 139 - 141°C
Yield: 52 % of theory.

Example 160

6-[4-(Phenylsulfinylmethyl)-benzyloxy -3,4-dihydrocarbostyril

Prepared analogously to Example 111 from 6-[4-(phenylmercaptomethyl)-benzyloxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 179 - 181°C
Yield: 61 % of theory.

Example 161

6-(4-Cyclohexylmercapto-butoxy)-carbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-carbostyril (m.p.: 198 - 199°C) and cyclohexyl mercaptan.
M.p.: 153 - 159°C
Yield: 89 % of theory.

Example 162

6-(4-Cyclohexylsulfinyl-butoxy)-carbostyril

Prepared analogously to Example 111 from 6-(4-cyclohexylmercapto-butoxy)-carbostyril and hydrogen peroxide.
M.p.: 169 - 170°C
Yield: 57 % of theory.

Example 163

6-[4-(4-Bromophenylmercapto)-butoxy]carbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-carbostyril (m.p.: 198 - 199°C) and 4-bromothiophenol .

M.p.: 156 - 158°C
Yield: 53 % of theory.

Example 164

6-/4-(4-Bromophenylsulfinyl)-butoxy7carbostyril

Prepared analogously to Example 111 from 6-/4-(4-bromophenylmercapto)-butoxy7carbostyril and hydrogen peroxide.
M.p.: 168 - 170°C
Yield: 65 % of theory.

Example 165

6-/4-(3-Methyl-4-bromo-phenylmercapto)-butoxy7carbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-carbostyril (m.p.: 189 - 199°C) and 3-methyl-4-bromo-thiophenol .
M.p.: 167 - 169°C
Yield: 76 % of theory.

Example 166

6-/4-(3-Methyl-4-bromo-phenylsulfinyl)-butoxy7-carbostyril

Prepared analogously to Example 111 from 6-/4-(3-methyl-4-bromo-phenylmercapto)-butoxy7carbostyril and hydrogen peroxide.
M.p.: 169 - 172°C
Yield: 79 % of theory.

Example 167

6-/4-(3-Methyl-4-bromo-phenylsulfonyl)-butoxy/carbostyril

Prepared analogously to Example 112 from 6-/4-(3-methyl-4-bromo-phenylmercapto)-butoxy/carbostyril and hydrogen peroxide.
M.p.: 163 - 167°C
Yield: 57 % of theory.

Example 168

6-/4-(1,2,4-Triazole-3-yl-mercapto)-butoxy/carbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-carbostyril and 3-mercapto-1,2,4-triazole.

Yield: 82 % of theory.

Example 169

6-/4-(2,4,5-Trichlorophenylmercapto)-butoxy/carbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-carbostyril (m.p.: 198 - 199°C) and 2,4,5-trichlorothiophenol .
M.p.: 177 - 178°C
Yield: 83 % of theory.

Example 170

6-/4-(2,4,5-Trichlorophenylsulfinyl)-butoxy/carbostyril

Prepared analogously to Example 111 from 6-/4-(2,4-5-trichlorophenylmercapto)-butoxy/carbostyril and hydrogen peroxide.

M.p.: 206 - 208°C
Yield: 98 % of theory.

Example 171

6-[4-(3,5-Dibromo-4-amino-phenylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 1[10] from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C) and 3,5-dibromo-4-amino-thiophenol.
M.p.: 90 - 92°C
Yield: 89 % of theory.

Example 172

6-[4-(3,5-Dibromo-4-amino-phenyl-sulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 111 from 6-[4-(3,5-dibromo-4-amino-phenylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 144 - 146°C
Yield: 76 % of theory.

Example 173

6-[4-(3,5-Dibromo-4-amino-phenylsulfonyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 112 from 6-[4-(3,5-dibromo-4-aminophenylsulfinyl)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 157 - 159°C
Yield: 87 % of theory.

Example 174

6-/4-(3,5-Dibromo-4-amino-phenylmercapto)-butoxy/carbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-carbostyril (m.p.: 198 - 199°C) and 3,5-dibromo-4-amino-thiophenol.
M.p.: 153 - 155°C
Yield: 86 % of theory.

Example 175

6-/4-(3,5-Dibromo-4-amino-phenylsulfinyl)-butoxy/carbostyril

Prepared analogously to Example 111 from 6-/4-(3,5-dibromo-4-amino-phenylmercapto)-butoxy/carbostyril and hydrogen peroxide.
M.p.: 205 - 207°C
Yield: 79 % of theory.

Example 176

6-/4-(3,5-Dibromo-4-amino-phenylsulfonyl)-butoxy/carbostyril

Prepared analogously to Example 112 from 6-/4-(3,5-dibromo-4-amino-phenylmercapto)-butoxy/carbostyril and hydrogen peroxide in formic acid.
M.p.: 238 - 241°C
Yield: 87 % of theory.

Example 177

6-[4-(4-Bromo-3-methyl-phenylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C) and 4-bromo-3-methyl-thiophenol.
M.p.: 104 - 109°C
Yield: 81 % of theory.

Example 178

6-[4-(4-Bromo-3-methyl-phenylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 111 from 6-[4-(4-bromo-3-methyl-phenylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 129 - 130°C
Yield: 75 % of theory.

Example 179

6-[4-(2,5-Dibromo-phenylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C) and 2,5-dibromo-thiophenol.
M.p.: 127 - 129°C
Yield: 75 % of theory.

Example 180

6-/4-(2,5-Dibromo-phenylsulfinyl)-butoxy/-3,4-dihydrocarbostyril

Prepared analogously to Example 111 from 6-/4-(2,5-dibromo-phenylmercapto)-butoxy/-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 182 - 184°C
Yield: 84 % of theory.

Example 181

6-/4-(2,5-Dibromo-phenylmercapto)-butoxy/carbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-carbostyril (m.p.: 198 - 199°C) and 2,5-dibromo-thiophenol.
M.p.: 178 - 185°C
Yield: 67 % of theory.

Example 182

6-/4-(2,5-Dibromo-phenylsulfinyl)-butoxy/carbostyril

Prepared analogously to Example 111 from 6-/4-(2,5-dibromo-phenylmercapto)-butoxy/carbostyril and hydrogen peroxide.
M.p : 187 - 189°C
Yield: 45 % of theory.

Example 183

6-/3-(3,4-Dichloro-phenylmercapto)-propoxy/-3,4-dihydrocarbostyril

Prepared analogously to Example 110 from 6-(3-bromopropoxy)-3,4-dihydrocarbostyril (m.p.: 111 - 118°C) and 3,4-dichloro-thiophenol.

M.p.: 106 - 107°C
Yield: 76 % of theory.

Example 184

6-/3-(3,4-Dichloro-phenylsulfinyl)-propoxy7-3,4-dihydrocarbostyri

Prepared analogously to Example 111 from 6-/3-(3,4-dichloro-phenylmercapto)-propoxy7-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 170 - 172°C
Yield: 84 % of theory.

Example 185

6-/4-(4-Cyclohexyl-phenylmercapto)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C) and 4-cyclohexyl-thiophenol.
M.p.: 118 - 120°C
Yield: 68 % of theory.

Example 186

6-/4-(4-Cyclohexyl-phenylsulfinyl)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 111 from 6-/4-(4-cyclohexyl-phenylmercapto)-butoxy7-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 155 - 157°C
Yield: 65 % of theory.

Example 187

6-/4-(4-Cyclohexyl-phenylsulfonyl)-butoxy/-3,4-dihydrocarbostyril

Prepared analogously to Example 1[12] from 6-/4-(4-cyclohexyl-phenylmercapto)-butoxy/-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 172 - 174°C
Yield: 52 % of theory.

Example 188

6-/4-(4-Cyclohexyl-phenylmercapto)-butoxy/carbostyril

Prepared analogously to Example 1[10] from 6-(4-bromobutoxy)-carbostyril (m.p.: 188 - 189°C) and 4-cyclohexylthiophenol.
M.p.: 165 - 167°C
Yield: 64 % of theory.

Example 189

6-/4-(4-Cyclohexyl-phenylsulfinyl)-butoxy/carbostyril

Prepared analogously to Example 1[11] from 6-/4-(4-cyclohexyl-phenylmercapto)-butoxy/carbostyril and hydrogen peroxide.
M.p.: 188 - 190°C
Yield: 64 % of theory.

Example 190

6-/4-(4-Cyclohexyl-phenylsulfonyl)-butoxy/carbostyril

Prepared analogously to Example 1[12] from 6-/4-(4-cyclohexyl-phenylmercapto)-butoxy/carbostyril and hydrogen peroxide.

M.p.: 185 - 186°C
Yield: 87 % of theory.

Example 191

6-/4-(4-tert.-Butyl-phenylmercapto)-butoxy7-3,4-dihydrocarbostyri

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C) and 4-tert.-butyl-thiophenol.
M.p.: 126 - 127°C
Yield: 86 % of theory.

Example 192

6-/4-(4-tert.-Butyl-phenylsulfinyl)-butoxy7-3,4-dihydrocarbostyri

Prepared analogously to Example 111 from 6-/4-(4-tert.-butyl-phenylmercapto)-butoxy7-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 121 - 123°C
Yield: 67 % of theory.

Example 193

6-/4-(4-tert.-Butyl-phenylsulfonyl)-butoxy7-3,4-dihydrocarbostyri

Prepared analogously to Example 112 from 6-/4-(4-tert.-butyl-phenylmercapto)-butoxy7-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 198 - 200°C
Yield: 83 % of theory.

Example 194

6-/4-(4-tert.-Butyl-phenylmercapto)-butoxy7carbostyril

(Starting compound for Examples 192 and 193)

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-carbostyril (m.p.: 198 - 199 °C) and 4-tert.-butylthiophenol.

M.p.: 156 - 158°C

Yield: 63 % of theory.

Example 195

6-/4-(4-tert.-Butyl-phenylsulfinyl)-butoxy7carbostyril

Prepared analogously to Example 111 from 6-/4-(4-tert.-butyl-phenylmercapto)-butoxy7carbostyril and hydrogen peroxide.

M.p.: 164 - 166°C

Yield: 74 % of theory.

Example 196

6-/4-(4-tert.-Butyl-phenylsulfonyl)-butoxy7carbostyril

Prepared analogously to Example 111 from 6-/4-(4-tert.-butyl-phenylmercapto)-butoxy7carbostyril and hydrogen peroxide.

M.p.: 203 - 205°C

Yield: 56 % of theory.

Example 197

6-/4-(2-Quinolylsulfinyl)-butoxy7-3,4-dihydrocarbostyril

Prepared analogously to Example 111 from 6-/4-(2-quinolyly-mercapto)-butoxy7-3,4-dihydrocarbostyril and hydrogen peroxide.

M.p.: 154 - 157°C
Yield: 79 % of theory.

Example 198

6-[4-(2-Quinolylsulfonyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 112 from 6-[4-(2-quinolylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
R_f-value: 0.50 (silica gel fluorescent plate; eluent: benzene/ethanol/conc. ammonia = 75/25/2).
Yield: 72 % of theory.

Example 199

6-[2-(N-Methyl-N-cyclohexyl-carbamidomethylmercapto)-ethoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 110 from 6-(2-chloroethoxy)-3,4-dihydrocarbostyril (m.p.: 152.5 - 153.5°C) and N-methyl-N-cyclohexyl-thioglycolic acid amide.
R_f-value: 0.46 (silica gel fluorescent plate; eluent: ethylenechloride/methanol = 95/5).
Yield: 63 % of theory.

Example 200

6-[2-(N-Methyl-N-cyclohexyl-carbamidomethylsulfinyl)-ethoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 111 from 6-[2-(N-methyl-N-cyclohexylcarbamidomethylmercapto)-ethoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.

R_f-value: 0.34 (silica gel fluorescent plate; eluent: ethylene chloride/methanol = 95/5).
M.p.: 143 - 146°C
Yield: 48 % of theory.

Example 201

6-[2-(N-Methyl-N-cyclohexyl-carbamidomethylsulfonyl)-ethoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 112 from 6-[2-(N-methyl-N-cyclohexylcarbamidomethylmercapto)-ethoxy]-3,4-dihydrocarbostyril and hydrogen peroxide in formic acid.
R_f-value: 0.48 (silica gel fluorescent plate; eluent: ethylene chloride/methanol = 95/5)
M.p.: 110 - 111°C
Yield: 45 % of theory.

Example 202

6-[2-(N-Methyl-N-cyclohexyl-carbamidomethylmercapto)-ethoxy]-carbostyril

Prepared analogously to Example 110 from 6-(2-chloroethoxy)-carbostyril [R_f-value: 0.30 (silica gel fluorescent plate; eluent: ethylene chloride/methanol = 95/5)] and N-methyl-N-cyclohexyl-thioglycolic acid amide.
R_f-value: 0.41 (silica gel fluorescent plate; eluent: ethylene chloride/methanol = 95/5).
Yield: 62 % of theory.

Example 203

6-/2-(N-Methyl-N-cyclohexyl-carbamidomethylsulfinyl)-ethoxy/-carbostyril

Prepared analogously to Example 111 from 6-/2-(N-methyl-N-cyclohexyl-carbamidomercapto)-ethoxy/carbostyril and hydrogen peroxide.
R_f-value: 0.027 (silica gel fluorescent plate; eluent: ethylene chloride/methanol = 95/5).
M.p.: 128 - 130°C
Yield: 65 % of theory.

Example 204

6-/2-(N-Methyl-N-cyclohexyl-carbamidomethylsulfonyl)-ethoxy/-carbostyril

Prepared analogously to Example 112 from 6-/2-(N-methyl-N-cyclohexyl-carbamidomercapto)-ethoxy/carbostyril and hydrogen peroxide.
R_f-value: 0.39 (silica gel fluorescent plate; eluent: ethylene chloride/methanol = 95/5).
Yield: 67 % of theory.

Example 205

6-/3-(3,4-Dichlorophenylsulfonyl)-propoxy/-3,4-dihydrocarbostyril

Prepared analogously to Example 112 from 6-/3-(3,4-dichlorophenylmercapto)-propoxy/-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 187 - 188°C
Yield: 87 % of theory.

Example 206

6-[5-(3,4-Dichlorophenylmercapto)-pentoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 110 from 6-(5-bromopentoxy)-3,4-dihydrocarbostyril (m.p.: 97 - 98°C) and 3,4-dichlorothiophenol.
M.p.: 101 - 104°C
Yield: 69 % of theory.

Example 207

6-[5-(3,4-Dichlorophenylsulfinyl)-pentoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 111 from 6-[5-(3,4-dichlorophenylmercapto)-pentoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 165 - 166°C
Yield: 74 % of theory.

Example 208

6-[5-(3,4-Dichlorophenylsulfonyl)-pentoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 112 from 6-[5-(3,4-dichlorophenylmercapto)-pentoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
M.p.: 176 - 178°C
Yield: 65 % of theory.

Example 209

6-[4-(2-Methyl-4-tert.-butyl-phenylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C) and 2-methyl-4-tert.-butylthiophenol.
M.p.: 81 - 85°C
Yield: 91 % of theory.

Example 210

6-[4-(2-Methyl-4-tert.-butyl-phenylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 111 from 6-[4-(2-methyl-4-tert.-butyl-phenylmercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide. Resinous substance.
R_f-value: 0.54 (silica gel fluorescent plate; eluent: ethylene chloride/methanol = 95/5).

Example 211

6-[4-(3,5-Dichloro-4-hydroxy-phenylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C) and 3,4-dichloro-4-hydroxy-thiophenol under nitrogen as inert gas.
M.p.: 110 - 114°C
Yield: 94 % of theory.

Example 212

5-Bromo-6-(4-phenylmercaptobutoxy)-carbostyril

Prepared analogously to Example 1[10] from 5-bromo-6-(4-bromobutoxy)-carbostyril (prepared by bromination of 6-(4-bromobutoxy)-carbostyril) and thiophenol.
M.p.: 209 - 213°C
Yield: 41 % of theory.

Example 213

5-Nitro-6-(4-phenyl-mercaptobutoxy)-carbostyril

Prepared analogously to Example 1[10] from 5-nitro-6-(4-bromobutoxy)-carbostyril (m.p.: 250°C, prepared by nitration of 6-(4-bromobutoxy)-3,4-dihydrocarbostyril) and thiophenol.
M.p.: 228 - 230°C
Yield: 71 % of theory.

Example 214

5-Nitro-6-(4-phenylsulfinylbutoxy)-carbostyril

Prepared analogously to Example 1[11] from 5-nitro-6-(4-phenylmercaptobutoxy)-carbostyril and hydrogen peroxide.
M.p.: 192 - 194°C
Yield: 91 % of theory.

Example 215

5-Acetamino-6-(4-phenylmercaptobutoxy)-carbostyril

Prepared analogously to Example 1[10] from 5-acetamino-6-(4-bromobutoxy)-carbostyril (prepared by reduction with zinc in acetic acid of 5-nitro-6-(4-bromobutoxy)-carbostyril under addition of acetic anhydride) and thiophenol.

M.p.: 238 - 240°C
Yield: 80 % of theory.

Example 216

5-Acetamino-6-(4-phenylsulfinylbutoxy)-carbostyril

Prepared analogously to Example 111 from 5-acetamino-6-(4-phenylmercapto)-butoxy)-carbostyril and hydrogen peroxide.
M.p.: 213 - 217°C
Yield: 47 % of theory.

Example 217

5-Bromo-6-(4-phenylsulfinylbutoxy)-carbostyril

Prepared analogously to Example 111 from 5-bromo-6-(4-phenylmercaptobutoxy)-carbostyril and hydrogen peroxide.
M.p.: 190 - 191°C
Yield: 82 % of theory.

Example 218

4-Methyl-6-/4-(2-pyridylsulfinyl)-butoxy7carbostyril

0.170 g (0.0005 mol) of 4-methyl-6-/4-(2-pyridylmercapto)-butoxy7carbostyril, dissolved in 5 ml of glacial acetic acid, and 0.107 g (0.0005 mol) of sodium metaperiodate, dissolved in 6 ml of water, were mixed and left to stand at room temperature for 22 hours. Subsequently the solution was diluted with 20 ml of water and the reaction product was extracted with chloroform. The extract was shaken once with sodium bicarbonate solution and dried over anhydrous magnesium sulfate. After evaporating the organic phase the residue was recrystallized from toluene.
M.p.: 166 - 168°C
Yield: 0.04 g (22,5 % of theory).

Example 219

6-(4-tert.-Butylsulfinyl-butoxy)-3,4-dihydrocarbostyril

Prepared analogously to Example 111 from 6-(4-tert.-butylmercapto-butoxy)-3,4-dihydrocarbostyril (m.p.: 117 - 118°C) and hydrogen peroxide.
M.p.: 126 - 128°C
Yield: 62 % of theory.

Example 220

6-[4-(3-Hydroxy-pyrid-2-yl-mercapto)-butoxy -3,4-dihydrocarbostyril
Prepared analogously to Example 110 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C) and 3-hydroxy-2-mercapto-pyridine.
M.p.: 211 - 216°C
Yield: 58 % of theory.

Example 221

6-[4-(1,2,4-Triazole-3-yl-sulfinyl)-butoxy]carbostyril

Prepared analogously to Example 111 from 6-[4-(1,2,4-triazole-3-yl-mercapto)-butoxy]carbostyril and hydrogen peroxide.
R_f-value: 0.12 (silica gel fluorescent plate, eluent: ethylenechloride/methanol = 95/5).

Example 222

6-[4-(1,2,4-Triazole-3-yl-mercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C) and 3-mercapto-1,2,4-triazole.
M.p.: 152 - 154°C
Yield: 82 % of theory.

Example 223

6-[4-(1,2,4-Triazole-3-yl-sulfinyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 111 from 6-[4-(1,2,4-triazole-3-yl-mercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
R_f-value: 0.18 (silica gel fluorescent plate, eluent: ethylenechloride/methanol = 95/5).

Example 224

6-[4-(1,2,4-Triazole-3-yl-sulfonyl)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 112 from 6-[4-(1,2,4-triazole-3-yl-mercapto)-butoxy]-3,4-dihydrocarbostyril and hydrogen peroxide.
R_f-value: 0.22 (silica gel fluorescent plate, eluent: ethylenechloride/methanol = 95/5).
M.p.: 217 - 224°C.

Example 225

6-[4-(2,4,5-Trichlorophenylmercapto)-butoxy]-3,4-dihydrocarbostyril

Prepared analogously to Example 110 from 6-(4-bromobutoxy)-3,4-dihydrocarbostyril (m.p.: 142 - 147°C) and 2,4,5-trichloro-thiophenol.
M.p.: 144 - 145°C
Yield: 87 % of theory.

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Example A

Tablets containing 100 mg of 6-[4-(2-Pyridylsulfinyl)-butoxy]-3,4-dihydrocarbostyril

Composition:

1 tablet contains:

Active ingredient	100.0 mg
Lactose	80.0 mg
Corn starch	34.0 mg
Polyvinylpyrrolidone	4.0 mg
Magnesium stearate	2.0 mg
	220.0 mg

Method of preparation:

The active ingredient, mixed with lactose and corn starch, was homogeneously moistened with an aqueous solution of polyvinylpyrrolidone. The mixture was passed through a screen of 2.0 mm mesh-size, dried at 50°C (in a rack drying chamber), again passed through a screen of mesh-size 1.5 mm and the lubricant was added. Then the mixture was pressed into tablets.

Weight of tablet: 220 mg

Diameter: 10 mm, biplanar with a facet on both sides and a notch on one side.

Example B

Coated tablets containing 50 mg of 6-(4-Phenylsulfinylbutoxy)-3,4-dihydrocarbostyril

1 coated tablet contains:

Active ingredient	50.0 mg
Lactose	40.0 mg
Corn starch	17.0 mg

Polyvinylpyrrolidone	2.0 mg
Magnesium stearate	1.0 mg
	110.0 mg

Method of preparation:

The granulate was prepared analogously to Example A.
The mixture was pressed into coated tablets.
Weight of core: 110 mg
Diameter: 8 mm, biconvex.
The cores were isolated and subsequently covered in a coating vessel according to known processes with pyrrolidone and with a coating consisting essentially of sugar up to 200 mg and subsequently coated with pure sugar syrup to 210 mg.

Example C

Hard gelatine capsules containing 100 mg of 6-[4-(2-Pyridyl-sulfinyl)-butoxy]-3,4-dihydrocarbostyril

1 capsule contains:

Active ingredient		100.0 mg
Corn starch (dried)	approx.	130.0 mg
Lactose (powdered)	approx.	87.0 mg
Magnesium stearate		3.0 mg
		320.0 mg

Method of preparation:

The active ingredient and excipients were mixed together, passed through a screen of 0.75 mm mesh-size and mixed homogeneously with a suitable device. The mixture was filled into hard gelatine capsules of size 1.
Content of capsule: approx. 320 mg
Capsule: hard gelatine size 1

Example D

Suppositories containing 150 mg of 6-(4-Phenylsulfinylbutoxy)-3,4-dihydrocarbostyril

1 suppository contains:

Active ingredient	150.0 mg
Polyethylene glycol 1500	550.0 mg
Polyethylene glycol 6000	460.0 mg
Polyoxyethylene sorbitan monostearate	840.0 mg
	2 000.0 mg

Method of preparation:

After melting the suppository mass, the active ingredient was homogenously dispersed therein and the melt was poured into pre-cooled moulds.

Example E

Suspension containing 50 mg of 6-[4-(2-Pyridylsulfinyl-butoxy]-3,4-dihydrocarbostyril per 5 ml

100 ml of suspension contain:

Active ingredient	1.0 g
Carboxymethyl cellulose-Na-salt	0.1 g
Methyl-p-hydroxybenzoate	0.05 g
Propyl-p-hydroxybenzoate	0.01 g
Cane sugar	10.0 g
Glycerine	5.0 g
Sorbitol solution 70 %	20.0 g
Flavouring	0.3 g
Water dist. ad	100 ml

Method of preparation:

Distilled water was heated to 70°C. Whilst stirring methyl-p-hydroxybenzoate and propyl-p-hydroxybenzoate as well as glycerine and carboxymethyl cellulose sodium salt were dissolved therein. The mixture was cooled to room temperature and whilst stirring the active ingredient was added and the whole was homogenously dispersed. After adding and dissolving the sugar, the sorbitol solution and flavouring the suspension was evacuated whilst stirring in order to eliminate air.

5 ml of suspension contain 50 mg of active ingredient.