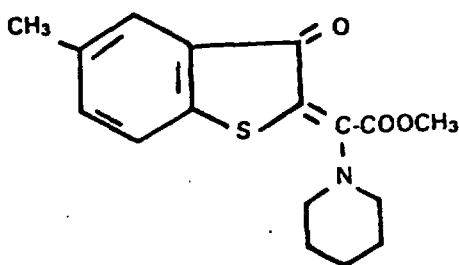


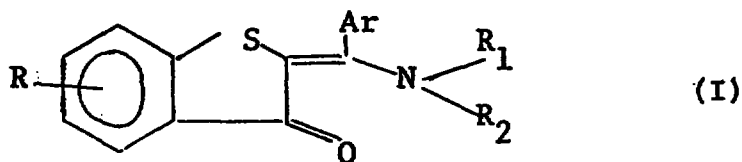
New vinylogous carboxamides, pharmaceutical compositions containing these compounds and processes for their preparation

DE-A-2 804 842 describes, inter alia, the compound 2-(α -piperidino-methoxycarbonylmethylene)-5-methyl[2H]benzothiophen-3-one of formula



(see page 20) which has antiallergic properties.

It has now been found that the new vinylogous carboxamides of general formula



have valuable pharmacological properties, particularly powerful anticonvulsive properties.

This invention thus relates to the new compounds of general formula I, processes for preparing them and pharmaceutical compositions containing these compounds.

In general formula I above:

Ar is a phenyl radical, which can be substituted by 1 or 2 halogen atoms, by alkyl groups with 1 to 3 carbon atoms or by an amino, nitro, cyano or trifluoromethyl group, or is a pyridinyl radical,

R is a hydrogen or chlorine atom or a methyl or methoxy group,

R₁ is a hydrogen atom or a methyl group,

R₂ is a hydrogen atom; a straight-chained or branched alkyl with a maximum of 6 carbon atoms: a 2-propenyl or 2-propynyl group; a cycloalkyl radical with from 3 to a maximum of 8 carbon atoms optionally substituted by a methyl group; or a radical -A-R₄ in which

A is an alkylene group with 2 or 3 carbon atoms and

R₄ is a hydroxy group or a methylamino, dimethylamino, N-methyl-ethylamino, diethylamino, pyrrolidino, piperidino, hexamethyleneimino, morpholino or 4-methyl-1-piperazinyl radical.

In order to illustrate the object of the invention, the following compounds given as examples may be mentioned:

- (E)-2-[(amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one,
(E)-2-[(methylamino)phenylmethylene]-benzo[b]thiophen-3(2H)-one,
(E)-2-[(dimethylamino)phenylmethylene]-benzo[b]thiophen-
5 3(2H)-one,
(E)-2-[(amino)-(2-fluorophenyl)methylene]-benzo[b]thiophen-3(2H)-one,
(E)-2-[(amino)-(2-chlorophenyl)methylene]-benzo[b]thiophen-3(2H)-one,
10 (E)-2-[[[2-(dimethylamino)ethyl]amino]phenylmethylene]-benzo[b]thiophen-3(2H)-one,
(E)-2-[[[2-(hydroxyethyl)amino]phenylmethylene]-benzo[b]thiophen-3(2H)-one,
(E)-2-[(amino)-(2-methylphenyl)methylene]-benzo[b]thiophen-
15 3(2H)-one,
(E)-2-[(ethylamino)phenylmethylene]-benzo[b]thiophen-3(2H)-one,
(E)-2-[(amino)-(2-bromophenyl)methylene]-benzo[b]thiophen-3(2H)-one,
(E)-2-[(amino)-(2-iodophenyl)methylene]-benzo[b]thiophen-
20 3(2H)-one,
(E)-2-[(amino)-(2-ethylphenyl)methylene]-benzo[b]thiophen-3(2H)-one,
(E)-2-[(amino)-(2-propylphenyl)methylene]-benzo[b]thiophen-3(2H)-one,
25 (E)-2-[(amino)-(4-chlorophenyl)methylene]-benzo[b]thiophen-3(2H)-one,
(E)-2-[(amino)-(4-methylphenyl)methylene]-benzo[b]thiophen-3(2H)-one,
(E)-2-[(amino)-(3,4-dichlorophenyl)methylene]-benzo[b]thiophen-
30 3(2H)-one,
(E)-2-[(amino)-(4-fluorophenyl)methylene]-benzo[b]thiophen-3(2H)-one,

- (E)-2-[(amino)-(4-pyridinyl)methylene]-benzo[b]thiophen-3(2H)-one,
(E)-2-[(amino)-(3-pyridinyl)methylene]-benzo[b]thiophen-3(2H)-one,
5 (E)-2-[(amino)phenylmethylene]-5-chlorobenzo[b]thiophen-3(2H)-one,
(E)-2-[(amino)phenylmethylene]-6-chlorobenzo[b]thiophen-3(2H)-one,
(E)-2-[(amino)-(2-chlorophenyl)methylene]-5-chlorobenzo-
10 [b]thiophen-3(2H)-one,
(E)-2-[(amino)-(2-pyridinyl)methylene] benzo[b]thiophen-3(2H)-one,
(E)-2-[(amino)-(2-fluorophenyl)methylene]-5-chlorobenzo-
[b]thiophen-3(2H)-one,
15 (E)-2-[[2-(propenyl)amino]phenylmethylene]-benzo[b]thiophen-3(2H)-one,
(E)-2-[[[3-(dimethylamino)propyl]amino]phenylmethylene]-benzo[b]thiophen-3(2H)-one,
(E)-2-[[[2-(dimethylamino)propyl]amino]phenylmethylene]-
20 benzo[b]thiophen-3(2H)-one,
(E)-2-[[[3-(dimethylamino)-2-propyl]amino]phenylmethylene]-benzo[b]thiophen-3(2H)-one,
(E)-2-[[[2-(N-methyl-ethylamino)ethyl]amino]phenylmethylene]-benzo[b]thiophen-3(2H)-one,
25 (E)-2-[[[2-(diethylamino)ethyl]amino]phenylmethylene]-benzo[b]thiophen-3(2H)-one,
(E)-2-[[[2-(1-pyrrolidinyl)ethyl]amino]phenylmethylene]-benzo[b]thiophen-3(2H)-one,
(E)-2-[[[2-(1-piperidinyl)ethyl]amino]phenylmethylene]-
30 benzo[b]thiophen-3(2H)-one,
(E)-2-[[[2-(hexahydro-1-azepinyl)ethyl]amino]phenylmethylene]-benzo[b]thiophen-3(2H)-one,

- (E)-2-[[[2-(4-morpholinyl)ethyl] amino] phenylmethylene] -benzo -
[b] thiophen-3(2H)-one,
(E)-2-[(propylamino)phenylmethylene] -benzo[b] thiophen-
3(2H)-one,
5 (E)-2-[(butylamino)phenylmethylene] -benzo[b] thiophen-3(2H)-one,
(E)-2-[[[2-propyl)amino] phenylmethylene] -benzo[b] thiophen-
3(2H)-one,
(E)-2-[[[2-methylpropyl)amino] phenylmethylene] -benzo[b]-
thiophen-3(2H)-one,
10 (E)-2-[[[1,1-dimethylethyl)amino] phenylmethylene] -benzo[b]-
thiophen-3(2H)-one,
(E)-2-[[[3-hydroxypropyl)amino] phenylmethylene] -benzo[b]-
thiophen-3(2H)-one,
(E)-2-[(amino)-(3-methylphenyl)methylene] -benzo[b] thiophen-
15 3-(2H)-one,
(E)-2-[(methylamino)-(2-ethylphenyl)methylene] -benzo[b]-
thiophen-3(2H)-one,
(E)-2-[(ethylamino)-(2-ethylphenyl)methylene] -benzo[b]-
thiophen-3(2H)-one,
20 (E)-2-[(amino)-(2-nitrophenyl)methylene] -benzo[b] thiophen-
3(2H)-one,
(E)-2-[(amino)-(2-aminophenyl)methylene] -benzo[b] thiophen-
3(2H)-one,
(E)-2-[(amino)-(2-cyanophenyl)methylene] -benzo[b] thiophen-
25 3(2H)-one,
(E)-2-[(amino)phenylmethylene] -6-methylbenzo[b] thiophen-
3(2H)-one,
(E)-2-[(amino)phenylmethylene] -5-methylbenzo[b] thiophen-
3(2H)-one
30 and
(E)-2-[(amino)phenylmethylene] -6-methoxybenzo[b] thiophen-
3(2H)-one.

However, particularly preferred compounds of the above general formula I are those in which

Ar is a phenyl radical, which can optionally be substituted in the o-position by fluorine, chlorine, bromine, ethyl or methyl,

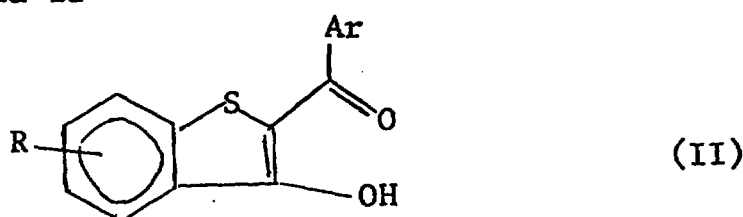
R is a hydrogen atom,

R₁ is a hydrogen atom or a methyl group and

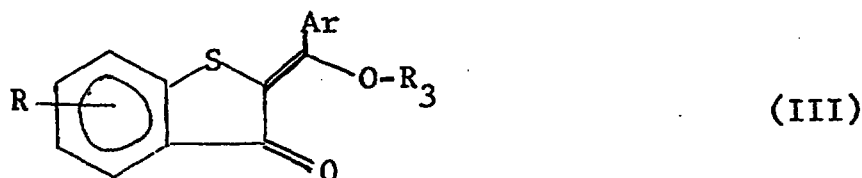
R₂ is a hydrogen atom, a methyl or ethyl group or a 2-hydroxyethyl or 2-(dimethylamino)-ethyl group.

According to the invention, the compounds of the above general formula I are prepared by the following processes:

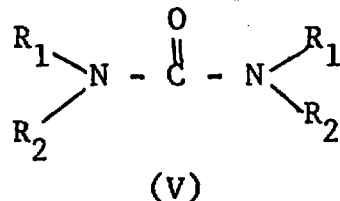
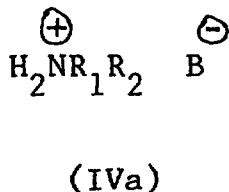
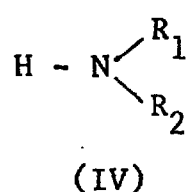
1. By reacting 2-acyl-benzo[b]thiophen-3-ols of general formula II



or enol ethers of general formula III



with amines of general formula IV or with ammonium salts of general formula IVa or with ureas of general formula V:

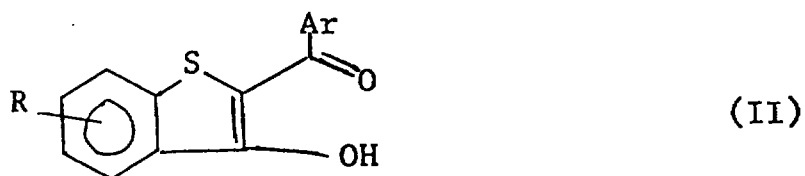


In general formulae II, III, IV, IVa and V, Ar, R, R₁ and R₂ have the meanings defined hereinbefore; R₃ is an alkyl or alkenyl group or a phenylalkyl radical containing a maximum of 20 carbon atoms and optionally substituted in the benzene nucleus by halogen atoms or nitro or methyl groups; and B^θ is the anion of a mono-basic or polybasic, weak to moderately strong organic or inorganic acid, e.g. boric acid, formic acid, acetic acid, propionic acid, n-butyric acid, benzoic acid, nicotinic acid, carbonic acid, carbamic acid, oxalic acid, succinic acid, citric acid, thiocyanic acid and phosphoric acid.

The reaction is performed in an excess of the appropriate amine of general formula IV or in a polar protic or aprotic solvent, e.g. in methanol, ethanol, 2-propanol, tetrahydrofuran, dioxan, dimethylformamide, dimethylacetamide, dimethylsulphoxide, hexamethylphosphoric triamide, pyridine, formic acid, acetic acid, propionic acid or isobutyric acid, at temperatures between -20 and 160°C, preferably between 110 and 130°C and optionally at elevated pressure in an autoclave. The compounds of general formulae IV, IVa or V are generally used in an excess of 3 to 10 mol, based on the compound of general formula II or III to be reacted. However, it is also possible to use equimolar quantities of the reactants.

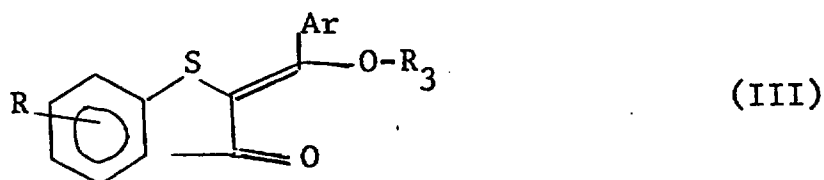
2. For the preparation of compounds of general formula I in which R₁ and R₂ stand for hydrogen atoms:

2.1. By reacting 2-acyl-benzo[b]thiophen-3-ols of general formula II



or enol ethers of general formula III

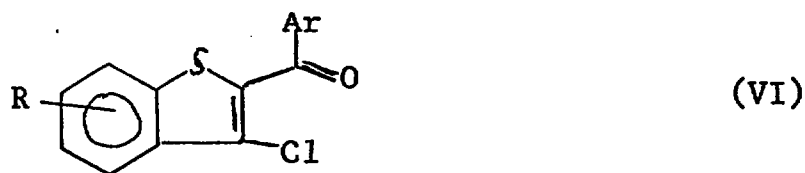
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with formamide, whereby in general formulae II and III, Ar, R and R₃ have the meanings given hereinbefore.

2.2 By reacting 2-acyl-3-chlorobenzo[b]thiophenes of general formula VI

10



with ammonium salts of general formula IVb



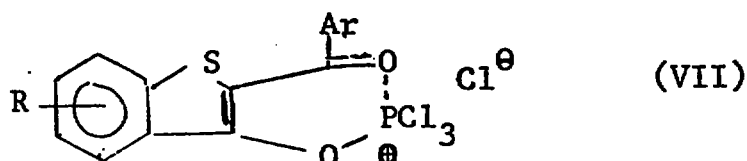
in which Ar, R and B⁻ are as defined hereinbefore.

The reaction is carried out in polar, protic or aprotic solvents, e.g. in methanol, ethanol, 2-propanol, tetrahydrofuran, dioxan, dimethylformamide, dimethylacetamide, pyridine, dimethylsulphoxide or hexamethylphosphoric triamide, but preferably in lower aliphatic carboxylic acids such as formic, acetic, propionic or n-butyric acid, at temperatures between 20 and 160°C,

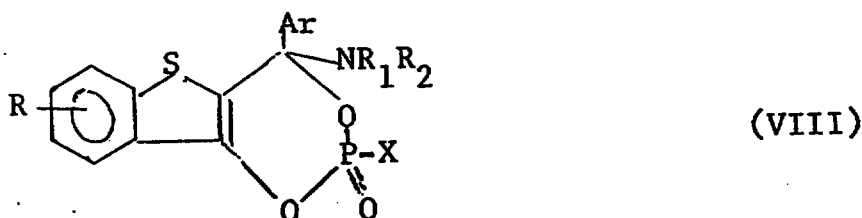
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preferably between 110 and 130°C and optionally at elevated pressure in an autoclave. An excess of formamide or ammonium salt of general formula IVb of up to 10 mol is advantageous with regard to the yield of the compound of general formula I, but it is also possible to use equimolar quantities of the reactants VI and IVb or formamide.

3. By reacting 2-acyl-benzo[b]thiophen-3-ols of general formula II with phosphorus(V) chloride; subsequent aminolysis of the unstable salts obtained of the assumed, but unproven formula VII



with amines of general formula IV whereby, in addition to end products of general formula I, non-stoichiometric phosphorus-containing substances of the possible, but also unproven formula VIII



are obtained, whose hydrolysis with dilute aqueous mineral acids also leads to the desired vinylogous carboxamides of general formula I in the form of the corresponding mineral acid salts.

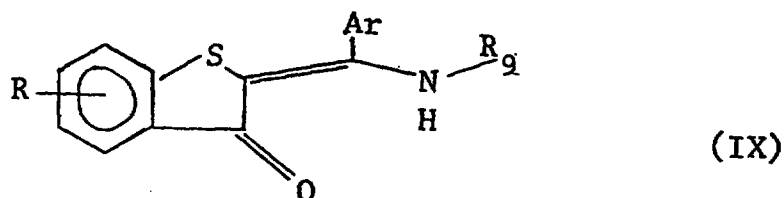
In the hypothetical general formulae VII and VIII Ar, R, R₁ and R₂ have the meanings given hereinbefore

and X stands for chlorine and/or hydroxy and/or a radical $-NR_1R_2$.

The reaction of 2-acyl-benzo[b]thiophen-3-ols of general formula II with phosphorus(V) chloride takes place in inert, hydrocarbon-like solvents, such as petroleum ether, petrol, benzene, toluene, xylene, chlorobenzene or 1,2-dichlorobenzene and at temperatures between 0 and 40°C, preferably between 15 and 25°C. In view of their instability, it is advantageous to quickly further react the salts of the assumed structure VII with amines of general formula IV. The amines of formula IV are preferably used in the form of aqueous solutions, but can also be used as they are. An excess of 2 to 20 mol of the amine of general formula IV is used per mol of the salt complex of general formula VII. However, equimolar quantities of the amine of general formula IV suffice when additional bases such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate or tert. amines such as triethylamine, trimethylamine, 1,5-diazabicyclo[4,3,0]non-5-ene or 1,8-diazabicyclo[5,4,0]undec-7-ene are added. Aminolysis, which is generally performed as a two-phase reaction, takes place at temperatures between 0 and 100°C, preferably between 40 and 60°C.

The nitrogen- and phosphorus-containing compounds of the assumed formula VIII can be converted into the corresponding salts of the desired vinylogous carboxamides of general formula I by treatment with dilute, aqueous mineral acids. Examples of such aqueous mineral

- acids are 1 to 20% aqueous hydrochloric acid, hydrobromic acid or hydriodic acid, as well as 1 to 50% aqueous sulphuric or phosphoric acid. Temperatures between 30 and 100°C, preferably between 50 and 70° C
- 5 are suitable for the hydrolysis reaction. The salts obtained can be converted into the desired end products of general formula I in conventional manner by treatment with bases, e.g. aqueous solutions of sodium hydroxide, potassium hydroxide, calcium hydroxide,
- 10 potassium carbonate, sodium carbonate, sodium hydrogen carbonate, ammonia or amines such as methylamine or triethylamine.
4. For the preparation of compounds of general formula I in which R_1 and R_2 stand for hydrogen atoms:
- 15 By reduction of compounds of general formula IX



- in which Ar and R are as hereinbefore defined and R_9 represents a hydroxy group or a radical $-NR_5R_6$ wherein R_5 and R_6 which may be identical or different each
- 20 represents an alkyl group with 1 to 6 carbon atoms or R_5 can be a hydrogen atom and R_6 a phenyl radical optionally substituted by halogen atoms or alkyl or alkoxy groups with 1 to 3 carbon atoms and R and Ar have the meanings given hereinbefore.
- 25 The following reduction methods are suitable:

- 4.1 Hydrogenation in the presence of catalytically activated metals of the 8th subgroup of the Periodic Table of elements. Palladium and platinum catalysts, for example palladium on animal charcoal or finely divided platinum formed in situ from platinum(IV) oxide, are particularly suitable. Hydrogenation preferably takes place in polar solvents such as glacial acetic acid, propionic acid, methanol, ethanol, dioxan or tetrahydrofuran and optionally in the presence of strong mineral acids such as e.g. perchloric, sulphuric or orthophosphoric acids at temperatures between 0 and 50°C, but preferably at ambient temperature and at a hydrogen pressure of 0.5 to 5 bar. However, it is also possible to use a higher hydrogen pressure. If in a compound of general formula IX, Ar stands for a nitrophenyl radical, then the nitro group is also reduced to an amino group.
- 4.2. Reduction by means of nascent hydrogen and/or tin (II) chloride. Reduction by means of iron powder in the presence of dilute or semi-concentrated mineral acids such as hydrochloric, hydrobromic, sulphuric or phosphoric acids and reduction by means of tin(II) chloride in the presence of concentrated hydrochloric or hydrobromic acid have proved to be particularly suitable. When reducing by means of iron, the preferred solvents are polar, water-miscible organic solvents such as methanol, ethanol, dioxan, tetrahydrofuran or glacial acetic acid. The working temperature is between 10 and 100°C, preference being given to ambient temperature. For the tin(II) chloride method, temperatures between 0

and 40°C, but preferably ambient temperature are used and the aforementioned additional solvents are employed. If in a compound of general formula IX, Ar stands for a nitrophenyl radical, the nitro group is also reduced.

- 5 4.3. Reduction with complex alkali metal aluminium hydrides, preferably lithium aluminium hydride or sodium bis-(2-methoxyethoxy)-aluminium hydride using anhydrous ethers, e.g. diethyl ether, dioxan, tetrahydrofuran, 1,2-dimethoxyethane, diethylene glycol dimethyl ether, triethylene glycol dimethyl ether
10 as solvents, at temperatures between -20 and 100°C, preferably +20 to +50°C. If in a compound of general formula IX, Ar stands for a nitrophenyl radical the nitro group is also reduced to an amino group.
- 15 4.4. Reduction with sodium dithionite in aqueous solution or suspension in the presence of excess alkali metal hydroxide. The reaction can take place with or without additional solvents such as e.g. methanol, ethanol, dioxan, tetrahydrofuran, 1,2-ethane-diol,
20 1,2-dimethoxy-ethane or 2-ethoxy-ethanol. The reaction temperature can be 60 to 120°C, but the boiling point of water is preferred. If in a compound of general formula IX, Ar stands for a nitrophenyl radical, the nitro group is also reduced to an amino group.
- 25 4.5. Reduction with iron(II) hydroxide in aqueous solution or suspension at temperatures between 0 and 100°C, preferably between 15 and 50°C. The reaction can be performed with or without additional solvents such as e.g. methanol, ethanol, dioxan, tetrahydrofuran,
30 1,2-ethanol, 1,2-dimethoxy-ethane or 2-ethoxy -

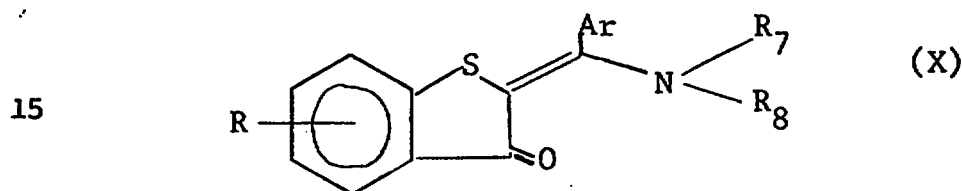
ethanol. Iron(II) hydroxide is preferably formed in situ from suitable iron (II) salts, e.g. from iron (II) sulphate heptahydrate, iron(II) chloride, iron (II) chloride tetrahydrate or iron(II) nitrate

5 hexahydrate by adding bases, preferably an aqueous ammonia solution.

If in a compound of general formula IX Ar stands for a nitrophenyl radical, the nitro group is also reduced to an amino group.

10 5. For the preparation of compounds of general formula I in which R_1 represents a hydrogen atom and R_2 and R are as hereinbefore defined:

By reacting vinylogous carboxamides of general formula X

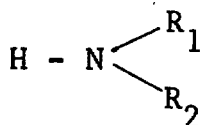


in which R_7 is a hydrogen atom or a methyl group and R_8 is a hydrogen atom; a straight or branched chain alkyl radical with up to 6 carbon atoms; a 2-propenyl or 2-propynyl group; a cycloalkyl radical with from 3 to 8 carbon atoms optionally substituted by a methyl group; or a radical $-A-R_4$

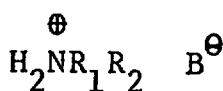
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in which Ar, R, A and R₄ are as hereinbefore defined,
with amines of general formula IV or with ammonium
salts of general formula IVa or with ureas of general
formula V

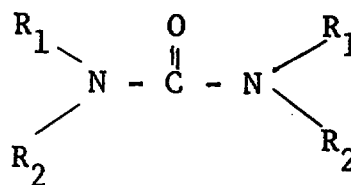
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(IV)



(IVa)



(V)

in which R₁ represents a hydrogen atom and R₂ is as
hereinbefore defined, and B[⊖] is the anion of a monobasic
or polybasic weak to moderately strong organic or inorganic
10 acid, e.g. boric acid, formic acid, acetic acid, propionic
acid, n-butyric acid, benzoic acid, nicotinic acid,
carbonic acid, carbamic acid, oxalic acid, succinic
acid, citric acid, thiocyanic acid or phosphoric acid.

The reaction is performed in an excess of the particular
15 amine of general formula IV or in a polar protic
or aprotic solvent, e.g. in methanol, ethanol, 2-propanol,
tetrahydrofuran, dioxan, dimethylformamide, dimethyl-
acetamide, dimethylsulphoxide, hexamethylphosphoric
triamide, pyridine, formic acid, acetic acid, propionic
20 acid or isobutyric acid, at temperatures between -20

and 160°C and preferably between 110 and 130°C and optionally at elevated pressure in an autoclave. The compounds of general formulae IV, IVa or V are generally used in an excess of 3 to 10mol, based on the substrate of general formula X to be reacted, but it is also possible to use equimolar quantities of the reactants.

The compounds of general formula II used as starting materials are in part known from the literature or can be prepared in accordance with processes known from the literature (K. Görlitzer, Arch. Pharm, 307, 523 [1974]). For example, the following 2-acyl-benzo[b]thiophen-3-ols were obtained from the corresponding methyl thiosalicylates appropriately substituted in the benzene nucleus and appropriate 2-chloro or 2-bromo-1-aryl-ethanones.

15 2-(4-chlorobenzoyl)-benzo[b]thiophen-3-ol, m.p. 124-125°C
(petroleum ether/ethyl acetate 1:1)
2-(4-methylbenzoyl)-benzo[b]thiophen-3-ol, m.p. 100-101°C
(petroleum ether/ethyl acetate 1:1)
2-(3,4-dichlorobenzoyl)-benzo[b]thiophen-3-ol, m.p. 176-178°C
20 (ethyl acetate)
2-(4-fluorobenzoyl)-benzo[b]thiophen-3-ol, m.p. 118-120°C
(ethyl acetate)
(3-hydroxy-benzo[b]thien-2-yl)-4-pyridinyl-methanone,
m.p. 139-140°C (methanol)
25 2-benzoyl-5-chlorobenzo[b]thiophen-3-ol, m.p. 129-132°C
(methanol)
2-benzoyl-6-chlorobenzo[b]thiophen-3-ol, m.p. 160-162°C
(methanol/ethyl acetate 1:1)
2-(2-fluorobenzoyl)-benzo[b]thiophen-3-ol, m.p. 99-100°C,
30 (petroleum ether/ethyl acetate) 1:1

- 2-(2-chlorobenzoyl)-benzo[b]thiophen-3-ol, m.p. 86-88°C,
(methanol)
- (3-hydroxy-benzo[b]thiophene-2-yl)-2-pyridinyl-methanone,
m.p. 167-168°C (ethyl acetate)
- 5 2-(2-chlorobenzoyl)-5-chlorobenzo[b]thiophen-3-ol,
m.p. 136-138°C (ethyl acetate/methanol 1:1)
- 2-(2-methylbenzoyl)-benzo[b]thiophen-3-ol, m.p. 126-127°C,
(ethyl acetate/methanol 1:1)
- 2-(3-methylbenzoyl)-benzo[b]thiophen-3-ol, m.p. 89-92°C
- 10 (petroleum ether/ethyl acetate 1:1)
- 2-(2-ethylbenzoyl)-benzo[b]thiophen-3-ol, m.p. 39-40°C
(methanol)
- 2-(2-nitrobenzoyl)-benzo[b]thiophen-3-ol, m.p. 151-153°C
(ethyl acetate)
- 15 2-(2-bromobenzoyl)-benzo[b]thiophen-3-ol, m.p. 108-110°C
(methanol)
- 2-(2-trifluoromethyl-benzoyl)-benzo[b]thiophen-3-ol,
m.p. 91-92°C, (methanol),
- 2-benzoyl-5-methylbenzo[b]thiophen-3-ol, m.p. 109-111°C,
- 20 (methanol/ethyl acetate 1:1)
- 2-(2-aminobenzoyl)-benzo[b]thiophen-3-ol, m.p. 129-131°C
(ethyl acetate),
- 2-benzoyl-6-methylbenzo[b]thiophen-3-ol, m.p. 100-102°C
(methanol/ethyl acetate 1:1)
- 25 2-benzoyl-6-methoxybenzo[b]thiophen-3-ol, m.p. 138-139°C,
(methanol),
- 2-benzoyl-4-methylbenzo[b]thiophen-3-ol, m.p. 122-123°C
(methanol/ethyl acetate 1:1).

The starting materials of general formula III, which are new, are obtained according to the aforementioned process 3 by using, in place of amines of general formula IV, a mixture of an alcohol of general formula R_3-OH with a tertiary amine, preferably triethylamine. In this way, for example, the following were prepared:

(E)-2-[(methoxy)phenylmethylene]-benzo[b]thiophen-3(2H)-one, m.p. 136-138°C (diisopropyl ether/petroleum ether 1:1)
 10 $C_{16}H_{12}O_2S$ (268.33)
 Calc. C 71.62 H 4.51 S 11.95
 Found: 71.46 4.83 11.98
 IR(CH_2Cl_2): 2845 (OCH_3), C = 0 1670 cm^{-1}
 UV (ethanol); λ_{max} (neutral) 255 (E= 0.74), 299 (E=0.68),
 15 414 (E=0.25) nm
 λ_{max} (alkaline) 257 (E=0.69), 300 (E=0.42),
 413 (E=0.15) nm
 Concentration: 50 $\mu g/ml$; layer thickness 0.2cm)
 ^1H-NMR ($CDCl_3$; 80MHz): δ 8.2- 7.0 (9H-m; ar.H);
 20 3.69 (3H-s; -O- CH_3)
 MS: $\frac{m}{e}$ 268(s), 254, 239, 237, 197, 176(s), 165, 126.5, 121,
 105, 77(s), 51, 28(s).

The starting materials of general formulae IV and V are known from the literature and are, in general, commercially available. The starting materials of general formulae IVa and IVb can easily be prepared by reacting corresponding amines of general formula IV with appropriate acids.

The starting materials of general formula VI are known from the literature (T. Higa and A.H. Krubsack, J. Org. Chemistry 41, 3399 [1976]) or are obtained from the unstable salts of general formula VII after prolonged storage at ambient temperature or after gentle heating to temperatures between 30 and 80°C. Thus, for example, may be obtained:

2-Benzoyl-3-chlorobenzo[b]thiophen, m.p. 71-73°C (cyclohexane).

The starting materials of general formula IX are partly known (S. B. Arwad and N. F. Abdul-Malik, Austr. J. Chem, 28, 601-5 [1975]) or can be prepared from the compounds of general formula II according to the aforementioned process 3 by replacing the amines of general formula IV with compounds of general formula H_2NR_4 , or, where R_4 represents a hydroxy group, they can easily be obtained from compounds of general formula II by boiling with hydroxyamine hydrochloride in a mixture of pyridine and ethanol. In this way, for example, the following compounds may be prepared:

(E)-2-[(2-phenylhydrazino)phenylmethylene]-benzo[b]thiophen-3(2H)-one,

m.p. 168°C (methanol/acetone 1:1);

(E)-2-[(hydroxyamino)phenylmethylene]-benzo[b]thiophen-3(2H)-one,

m.p. 128-130°C (petroleum ether/ethyl acetate 1:1)

$C_{15}H_{11}NO_2S$ (269.32)

Calc:	C66.90	H4.12	N5.20	S11.90
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Found:	66.90	4.06	5.14	12.06
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IR (CH₂Cl₂): OH 3550; associated N-H, O-H 3400 to 2500;
C=O 1595; C=C 1610, 1570 cm⁻¹

UV (ethanol): λ_{max} (neutral 257 (E=0.70); 304-316 (E=0.34);
330 (E=0.32)nm;

5 λ_{max} (alkaline) 220 (E=0.86); 275 (E=0.47);
405 (E=0.33)m,;

(Concentration: 50μg/ml; layer thickness 0.2 cm).

The starting materials of general formula X can be prepared analogously.

10 As already stated hereinbefore, the novel compounds of general formula I have valuable pharmacological properties, acting especially on the central nervous system and in particular having an anticonvulsant activity.

15 For example, the anticonvulsant activity of the following compounds was investigated:

A= (E)-2-[(amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

B= (E)-2-[(methylamino)phenylmethylene]-benzo[b]thiophen-3-(2H)-one

20 C= (E)-2-[(amino)-(2-chlorophenyl)methylene] benzo[b]thiophen-3(2H)-one

D= (E)-2-[[(2-hydroxyethyl)amino] phenylmethylene]-benzo[b]-thiophen-3(2H)-one

E= (E)-2-[(amino)-(2-methylphenyl)methylene]-benzo[b]-
25 thiophen-3(2H)-one

F= (E)-2-[(ethylamino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

1. Anticonvulsant activity in mice

The anticonvulsant activity was tested as the inhibition of the tonic extensor spasm of the rear legs of male mice under maximum electric shock.

5 Method

The test animals were male SPF mice (Chbb: NMRI) weighing 20 to 26g which, up to one hour before oral administration of the test compound, had access to standard feed and drinking water.

10 The test procedure was based on that of SWINYARD BROWN and GOODMAN (J.Pharmacol, exp. Ther. 106, 319, [1952]). The electric shock equipment was manufactured in accordance with information provided by WOODBURY and DAVENPORT (Arch. int. Pharmacodyn, 92, 97, [1952]). The
15 electrical stimuli were applied to the heads of the animals above the eyes using chamois-covered steel ball electrodes moistened with a 0.9% NaCl solution. The stimulus lasted 0.2 sec. using alternating current of 50Hz and 50mA. There was a clonic and then a tonic
20 stretching spasm of the extremities in the case of all the controls. The tonic stretching spasm did not occur in the case of animals protected by anticonvulsants.

The substances to be tested were suspended in 1%
25 tylose mucilage and administered orally in a volume of 0.1ml/10g of mouse to 10 mice/dose. The animals were subject to shock treatment 30, 140 and 300 minutes after administering the substance and the ED₅₀ values

were determined as the dosages sufficient to protect 50% of the animals against the tonic stretching spasm of the rear extremities either graphically or by the method of LITCHFIELD and WILCOXON (J. Pharmacol. exp. Ther. 5 96. 99, [1949]).

Result

Substance	ED ₅₀ mg/kg p.o.		
	30	150	300 minutes
A	12.8	37	46
B	90	38	49
C	7.0	4.4	5.0
D	33	41	42.5
E	22.8	13.3	15.7
F	22.5	54.5	79

2. Acute toxicity

The orienting acute toxicity of the substances were determined after administering a dose to a group of, in each case, 6 or 10 mice with body weights between 20 and 26g (observation period: 7 days).

Substance	Orienting acute toxicity (LD ₅₀)
A	2,400 mg/kg p.o.
B	> 1,000 mg/kg p.o.
C	500 to 1,000 mg/kg p.o.
D	> 1,000 mg/kg p.o.
E	> 1,000 mg/kg p.o.
F	> 1,000 mg/kg p.o.

The novel compounds of general formula I prepared in accordance with the invention are especially suitable for the treatment of spastic states and epilepsy and for pharmaceutical use, optionally
5 combined with other active substances, can be incorporated into conventional pharmaceutical preparations such as tablets; coated tablets, powders, suppositories or suspensions. For humans, the single dose is appropriately 50 to 300mg, but preferably 50
10 to 200mg.

The following examples serve to further illustrate the invention.

Example 1

(E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

50.86g (0.2mol) of 2-benzoyl-benzo[b]thiophen-3-ol
are dissolved in 600cc of toluene in a 1 litre separating
5 funnel and after adding 42.0g (0.2mol) of phosphorus(V)
chloride mechanical stirring takes place for 5 minutes
at room temperature. The suspension of the resulting red
complex is subsequently introduced whilst vigorously
stirring into 150cc (approx. 2 mol) of concentrated
10 ammonia, the reaction temperature being regulated to 40
to 50°C by external cooling, with water. Heating to 50°C
takes place for 1 hour, followed by cooling, the addition
of hydrochloric acid to give a pH of 1 and refluxing until
the yellow starting spot can no longer be detected by thin
15 layer chromatography (silica gel pre-prepared thin layer
chromatography plates F₂₅₄ Merck; 1,2-dichloroethane/
ethyl acetate/glacial acetic acid 100:30:3). This is
followed by cooling to +10°C, filtering with suction after
standing for 1 hour at this temperature, washing of the
20 precipitate with a little toluene and then thoroughly
with water to remove inorganic salts.

The orange toluene phase is separated from the combined
filtrates, is washed once with 500cc of water and is concen-
trated by evaporation. The resulting, partly crystalline
25 residue is boiled twice with on each occasion 20cc of
methanol and is then cooled on each occasion to +10°C. (E)-
2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one
hydrochloride is dissolved, whilst the unreacted starting
substance remains undissolved.

30 The methanol solutions obtained are combined with the
solution of the above-obtained crystalline precipitate in
25cc of methanol, mixed with 25cc of ammonia and subsequently

the desired product is precipitated in the form of yellow crystals.

This is followed by filtering with suction, drying of the precipitate in a vacuum drier, the dissolving of the product in 70cc of ethyl acetate, the addition of just enough petroleum ether to ensure that no precipitate forms (approx. 40cc), the addition of 4 g of activated charcoal, boiling and filtering hot. By adding 100cc of petroleum ether and cooling to +10°C, the pure end product is obtained from the cooled filtrate. After standing for two hours, filtering with suction takes place and the precipitate is thoroughly washed with approximately 40cc of petroleum ether. After concentrating the combined mother liquors to approx. 50cc total volume, further product with the same quality can be obtained. After drying in vacuo, the yellow crystals melt at 121.6-122.5°C. Yield: 35.6g (70% of theory).

TLC detection:

Stationary phase: silica gel pre-prepared thin layer chromatography plates (F₂₅₄ Merck)

20 Mobile phase: a) 1,2-dichloroethane: R_F starting material 0.7
R_F product 0.15

b) 1,2-dichloroethane/ethyl acetate/glacial acetic acid (100:30:3):

25 R_F starting material 0.9
R_F product 0.4

C₁₅H₁₁NOS (253.32):

Calc: C 71.12 H 4.38 N 5.53 S 12.66

Found: 71.20 4.59 5.59 12.52

IR(KBr): N-H 3475, C=O 1600 cm⁻¹

30 UV(ethanol): λ_{max} 184, 317, 430 nm, shoulder at 270 nm

¹H-NMR(CDCl₃): δ 11.0 (1H, wide, internal H bridge);

8.01 (1H-dd, J=7.6 and 2Hz, ar.H);

7.9-7.1 (8H-m, ar.H); 5.78 (1H-s, exchangeable H)

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^{13}C -NMR(CDCl_3); 22.63MHz): δ 103.66; 185.55(C=O); 131.28;
123.48; 131.80; 124.20; 144.80; 136.87;
160.07; 134.53; 127.97; 129.40; 125.82;

In the same way as the above-obtained ^{15}N labelled
5 compound, the signal for the carbon adjacent to ^{15}N
splits:

δ 160.59 (d, $J^{15}\text{N-C}$ 14.71 Hz).

Example 2

(E)-2-[(Methylamino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

10 Prepared in the same way as in Example 1 from 2-benzoyl-
benzo[b]thiophen-3-ol, phosphorus(V) chloride and 40%
aqueous methylamine solution in a yield of 43% of theory.
mp. 155-156°C (methanol)

$\text{C}_{16}\text{H}_{13}\text{NOS}$ (267.34)

15	Calc.	C 71.88	H 4.90	N 5.24	S 11.99	.
	Found:	72.10	4.75	5.21	12.20	

Example 3

(E)-2-[(Amino)-(4-chlorophenyl)methylene]-benzo[b]thiophen-3(2H)-one

20 Prepared as in Example 1 from 2-(4-chlorobenzoyl)-benzo-
[b] thiophen-3-ol, phosphorus(V) chloride and concentrated
aqueous ammonia in a yield of 55% of theory.
mp. 182-183°C (benzene)

$\text{C}_{15}\text{H}_{10}\text{ClNOS}$ (287.77)

25	Calc.	C 62.61	H 3.50	Cl 12.32	N 4.87	S 11.14
	Found:	62.90	3.62	12.55	4.76	11.18

Example 4

(E)-2-[(Dimethylamino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

Prepared as in Example 1 from 2-benzoyl-benzo[b]thiophen-3-ol, phosphorus(V) chloride and 40% aqueous dimethylamine solution in a yield of 7% of theory.

m.p. 178-180°C (ethyl acetate/petroleum ether 1:1)

C₁₇H₁₅NOS (281.38)

Calc. C 72.57 H 5.37 N 4.98 S 11.39

10 Found: 72.17 5.33 4.80 11.37

IR(CH₂Cl₂): C=O 1610 cm⁻¹

UV(ethanol): λ max 270 to 290 (E=0.43), 332 (E=0.42) and 454 (E=0.37) nm

(layer thickness 0.2cm; concentration 50 µg/ml)

15 ¹H-NMR (CDCl₃; 80 MHz): δ 7.99 (1H-dd, I=7 and 2Hz; ar.H); 7.7-7.2 (8H-m ar.H); 3.28 (6H-s)

Example 5

(E)-2-[(Amino)-(4-methylphenyl)methylene]-benzo[b]thiophen-3(2H)-one

20 Prepared as in Example 1 from 2-(4-methylbenzoyl)-benzo[b]thiophen-3-ol, phosphorus(V) chloride and concentrated ammonia in a yield of 62% theory.

m.p. 147°C (ethyl acetate/petroleum ether 1:1)

C₁₆H₁₃NOS (267.34)

25 Calc. C 71.88 H 4.90 N 5.24 S 11.99

Found: 71.38 4.82 5.14 12.58

Example 6

(E)-2-[(Amino)-(3,4-dichlorophenyl)methylene]-benzo[b]-thiophen-3(2H)-one

Prepared as in Example 1 from 2-(3,4-dichlorobenzoyl)-
5 benzo[b] thiophen-3-ol, phosphorus(V) chloride and
concentrated ammonia in a yield of 50% of theory;
m.p. 169-170°C (ethyl acetate)

C₁₅H₉Cl₂NOS (322.21)

Calc. C 55.92 H 2.82 Cl 22.01 N 4.35 S 9.95

10 Found: 55.81 3.06 22.45 4.47 10.10

Example 7

(E)-2-[(Amino)-(4-fluorophenyl)methylene]-benzo[b]thiophen-3(2H)-one

Prepared as in Example 1 from 2-(4-fluorobenzoyl)-benzo
15 [b]thiophen-3-ol, phosphorus(V) chloride and concentrated
ammonia in a yield of 63% of theory. Yellow, felt-like
crystals of m.p. 158°C (methanol)

C₁₅H₁₀FNOS (271.31)

Calc. C 66.41 H 3.72 N 5.16 S 11.82

20 Found: 66.51 4.00 5.23 11.92

IR(CH₂Cl₂): N-H 3465, C=O 1610 cm⁻¹

UV (ethanol): λ max 282, 315, 428nm; shoulder at 260nm

¹H-NMR (CDCl₃): δ 11.07 (1H, wide, internal H-bridge);

8.08 (1H-dd), J=7.5 and 2Hz; ar. H);

25 7.95 - 7.1 (7H-m; ar.H); 5.86 (1H, broad,
exchangeable H).

Example 8

(E)-2-[(Amino)-(4-pyridinyl)methylene]-benzo[b]thiophen-3(2H)-one

Prepared as in Example 1 from (3-hydroxybenzo[b]thien-
5 2-yl)-4-pyridinyl-methanone, phosphorus(V) chloride and
25% aqueous ammonia solution in a yield of 6% of theory.
m.p. 198-200°C (methanol)

C₁₄H₁₀N₂OS (254.30)

Calc. C 66.12 H 3.96 N 11.02 S 12.61

10 Found: 65.99 3.92 10.80 12.30

IR(KBr): N-H broad 3470 to 2800; C=O 1620 cm⁻¹

UV (ethanol): λ_{max} 275-281 (E=0.50), 310 (E=0.45), 431 (E=0.43)nm
after adding alkali

λ_{max} 285 (E=0.80), 395 (E=0.33)nm

15 (Concentration: 50μg/ml; layer thickness 0.2 cm)

¹H-NMR (CDCl₃/CD₃OD); 80 Mhz): δ 8.86 (2H-dd, J=5Hz and 2Hz;

α-pyridyl-H); 8.07 (1H-dd, J=7 and 2Hz; ar. H);

7.85-7.2 (5H-m; ar.H); 2 exchangeable hydrogen atoms.

Example 9

20 (E)-2-[(Amino)phenylmethylene]-5-chlorobenzo[b]thiophen-3(2H)-one

Prepared as in Example 1 from 2-benzoyl-5-chlorobenzo[b]-
thiophen-3-ol, phosphorus(V) chloride and concentrated
ammonia in a yield of 57% of theory.

m.p. 172-173°C (ethyl acetate)

25 C₁₅H₁₀ClNOS (287.77)

Calc. C 62.61 H 3.50 Cl 12.32 N 4.87 S 11.14

Found: 62.39 3.47 12.31 4.77 11.45

IR(KBr): N-H (or O-H) 3450, 3330, 3140; C=O 1625 cm⁻¹

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UV(ethanol): $\lambda_{\max}$ 258 (E=0.42), 287 (E=0.53), 322 (E=0.48),
 λ 4.34 (E= 0.49) nm

after adding alkali:

5 $\lambda_{\max}$ 286 (E=0.62); 320 shoulder (E=0.23);
393 (E=0.30); 434 shoulder.
(Concentration: 50 μ g/ml; layer thickness 0.2cm)

Example 10

(E)-2-[(Amino)phenylmethylene]-6-chlorobenzo[b]thiophen-
3(2H)-one

Prepared as in Example 1 from 2-benzoyl-6-chlorobenzo [b]-
10 thiophen-3-ol, phosphorus(V) chloride and concentrated
ammonia in a yield of 27% theory. m.p. 191-192°C (ethyl
acetate).

C₁₅H₁₀ClNOS (287.77)

Calc. C 62.61 H 3.50 Cl 12.32 N 4.87 S 11.14

15 Found: 62.80 3.50 12.40 5.11 11.08

IR(KBr): N-H 3470 and broad bands at 3220 and 3120; C=O 1600 cm⁻¹

UV(ethanol): $\lambda_{\max}$ (neutral) 286 (E=0.64), 309 (E=0.54), 425 (E=0.55) nm

$\lambda_{\max}$ (alkaline) 284 (E=0.67), 308 shoulder (E=0.33),
405 (E=0.33), 428 (shoulder) nm.

20 (Concentration: 50 μ g/ml; layer thickness : 0.2cm)

Example 11

(E)-2-[(Amino)-(2-fluorophenyl)methylene]-benzo[b]thiophen-
3(2H)-one

Prepared as in Example 1 from 2-(2-fluorobenzoyl)-benzo[b]-
25 thiophen-3-ol, phosphorus(V) chloride and concentrated
ammonia, but using a mixture of toluene and petroleum
ether in a volume ratio of 2:1 in place of pure toluene,
giving a yield of 50% of theory. Yellow crystals of m.p.
156-158°C (ethyl acetate/petroleum ether 1:1).

C₁₅H₁₀FNOS (271.31)

Calc. C 66.41 H 3.72 N 5.16 S 11.82

Found: 66.11 3.61 5.25 12.57

IR(KBr): N-H 3475, as well as associated N-H; C=O 1600 cm⁻¹

- 5 UV(ethanol): λ_{max} (neutral) 258 (shoulder), 281, 312, 424nm;
λ_{max} (alkaline) 281, 310(shoulder), 388,
422 (shoulder) nm.

Example 12

- 10 (E)-2-[(Amino)-(2-chlorophenyl)methylene]-benzo[b]thiophen-3(2H)-one

Prepared as in Example 1 from 2-(2-chlorobenzoyl)-benzo[b]-thiophen-3-ol, phosphorus(V) chloride and concentrated ammonia in a yield of 33% of theory; m.p. 167-168°C (ethyl acetate)

- 15 C₁₅H₁₀ClNOS (287.77)

Calc. C 62.61 H 3.50 Cl 12.32 N 4.87 S 11.14

Found: 63.10 3.70 12.95 4.84 11.78

IR(KBr): N-H 3470 (as well as associated N-H); C=O 1600 cm⁻¹

- 20 UV(ethanol): λ_{max} (neutral) 260 shoulder (E=0.41); 283
(E=0.51); 310 (E=0.49); 422
(E=0.46)nm;

λ_{max} (alkaline) 283 (E=0.60); 308 shoulder
(E=0.11); 380-385 (E=0.32)nm;

(Concentration: 50μg/ml; layer thickness: 0.2cm)

- 25 Example 13

(E)-2-[(Amino)-(2-pyridinyl)methylene]-benzo[b]thiophen-3(2H)-one

- 30 Prepared as in Example 1 from (3-hydroxybenzo[b]thien-2-yl)-2-pyridinyl-methanone, phosphorus(V) chloride and concentrated ammonia in a yield of 27% of theory.

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m.p. 128-130°C (ethyl acetate)

C₁₄H₁₀N₂OS (254.30)

Calc. C 66.12 H 3.96 N 11.02 S 12.61

Found: 66.34 4.09 11.45 12.70

5 IR(KBr): N-H or associated N-H 3290; C=O approx. 1600 cm⁻¹

UV(ethanol): λ max (neutral) 250 shoulder (E=0.39); 274

(E=0.58); 329 (E=0.49) and <390nm;

λ max (alkaline) 286 (E=0.65); 325 shoulder

10 (E=0.30); <390nm;

(Concentration: 50μg/l; layer thickness 0.2cm)

Example 14

(E)-2-[(Amino)-(2-chlorophenyl)methylene]-5-chlorobenzo[b]-thiophen-3(2H)-one

15 Prepared as in Example 1 from 2-(2-chlorobenzoyl)-5-chlorobenzo[b]thiophen-3-ol, phosphorus(V) chloride and concentrated aqueous ammonia in a yield of 40% of theory; m.p. 199-201°C (ethyl acetate)

C₁₅H₉Cl₂NOS (322.21)

20 Calc. C 55.92 H 2.82 Cl 22.01 N 4.35 S 9.95

Found: 55.67 3.09 21.70 4.22 10.30

IR(CH₂Cl₂): N-H 3475 (as well as associated N-H) C=O 1610 cm⁻¹

UV(ethanol): λ max (neutral) 260 (E=0.34); 293 (E=0.52);

314 (E=0.44); 432 (E=0.44)nm

25 λ max (alkaline) 293 (E=0.64); 320 shoulder

(E=0.16); 390 (E=0.32)nm

(Concentration: 50μg/ml; layer thickness: 0.2cm)

Example 15

(E)-2-[[(2-Propenyl)amino]phenylmethylene]-benzo[b]thiophen-3(2H)-one

30 Prepared as in Example 1 from 2-benzoyl-benzo[b]thiophen-3-ol, phosphorus(V) chloride and a solution of 1 part by

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volume of allylamine in 2 parts by volume of water in a yield of 43% of theory. m.p. 104-106°C (ethyl acetate).

$C_{18}H_{15}NOS$ (293.39)

Calc: C 73.69 H 5.15 N 4.77 S 10.93

5 Found: 73.48 5.22 4.78 11.18

IR(CH_2Cl_2): C=C 1645, C=O approx. 1600 cm^{-1}

UV(ethanol): λ_{max} (neutral) 265 shoulder (E=0.42); 286 (E=0.52);
320 (E=0.56); 431 (E=0.60);

no change on adding alkali

10 (Concentration 50 $\mu g/ml$; layer thickness 0.2cm)

1H -NMR($CDCl_3$): δ 12.0 (1H, broad, internal H bridge);

8.05 (1H-dd), J=7 and 2Hz ar.H);

7.7-7.15 (8H-m; ar.H); 6.15-5.6 (1H-m);

olefinic H); 5.45-5.05 (2H-m; olefin. H);

15 4.0-3.7 (2H-m aliph. CH_2).

Example 16

(E)-2-[[[2-(Dimethylamino)ethyl]amino]phenylmethylene]-benzo-
[b] thiophen-3(2H)-one

Prepared as in Example 1 from 2-benzoyl-benzo[b]thiophen-

20 3-ol, phosphorus(V) chloride and a solution of 2 volumes of N,N-dimethylethylenediamine in 3 volumes of water in a yield of 42% of theory. Orange yellow crystals of m.p. 123-125°C (ethyl acetate).

$C_{19}H_{20}N_2OS$ (324.44)

Calc: C 70.34 H 6.21 N 8.63 S 9.88

Found: 70.16 6.11 8.65 10.17

IR(CH_2Cl_2): NH associated; C=O 1600 cm^{-1}

UV(ethanol): λ_{max} (neutral) 287 (E=0.44), 322 (E=0.44), 431
(E=0.49)nm

No change on adding alkali.

(Concentration 50 $\mu g/ml$; layer thickness 0.2cm).

Example 17

(E)-2-[[[3-(Dimethylamino)propyl]amino]phenylmethylene]-benzo[b]thiophen-3(2H)-one

Prepared as in Example 1 from 2-benzoyl-benzo[b]-thiophen-3-ol, phosphorus(V) chloride and an aqueous solution of 3-(dimethylamino)-propylamine (prepared from 51g of diamine and 70cc of water) in a yield of 26% of theory.

m.p. 90-91°C (ethyl acetate/petroleum ether 1:1).

$C_{20}H_{22}N_2OS$ (338.47)

10 Calc. C 70.97 H 6.55 N 8.28 S 9.47

Found: 70.83 6.67 8.31 9.29

Example 18

(E)-2-[[(2-Hydroxyethyl)amino]phenylmethylene]-benzo[b]thiophen-3(2H)-one

15 Prepared as in Example 1 from 2-benzoyl-benzo[b]thiophen-3-ol, phosphorus(V) chloride and a 40% aqueous ethanolamine solution in a yield of 13% of theory.

m.p. 122-123°C (ethyl acetate /petroleum ether 1:1)

$C_{17}H_{15}NO_2S$ (297.38)

20 Calc. C 68.66 H 5.08 N 4.71 S 10.78

Found: 68.65 4.89 4.71 11.00

IR(CH_2Cl_2): O-H 3620, N-H or O-H (associated), 3340 broad, C=O approx. 1600 cm^{-1}

UV(ethanol): λ max (neutral) 226 (E=0.58); 2.63 (E=0.68);

25 336 (E=0.86); 4.60 (E=0.50)nm

λ max (alkaline) 257-261 (E=0.60), 336 (E=0.63);

4.59 (E=0.36)nm

Example 19

(E)-2-[(Amino)-(2-methylphenyl)methylene]-benzo[b]thiophen-3(2H)-one

Prepared as in Example 1 from 2-(2-methylbenzoyl)-benzo-
5 [b]-thiophen-3-ol, phosphorus(V) chloride and concentrated aqueous ammonia in a yield of 50% of theory.

m.p. 143-144°C (ethyl acetate/petroleum ether 1:1)

C₁₆H₁₃NOS (267.34)

Calc: C 71.88 H 4.90 N 5.24 S 11.99

10 Found: 72.23 5.04 5.27 11.70

IR(CH₂Cl₂): 3480 (N-H), O-H associated or NH associated;
approx. 1600 cm⁻¹ (C=O)

UV(ethanol): λ max (neutral) 260 shoulder (E=0.48); 285 (E=0.59);
311 (E=0.57); 4.22 (E=0.59)nm

15 λ max (alkaline) 285 (E=0.64); 310 (E=0.45);
421 (E=0.42); shoulder at 404
(E=0.40)nm.

(Concentration: 50μg/ml; layer thickness 0.2cm)

Example 20

20 (E)-2-[[(Ethyl)amino]phenylmethylene]-benzo[b]thiophen-3-(2H)-one

Prepared as in Example 1 from 2-benzoyl-benzo[b]thiophen-3-ol, phosphorus(V) chloride and 30% aqueous ethylamine solution in a yield of 56% of theory. m.p. 115-116°C
25 (ethyl acetate/petroleum ether 1:1).

C₁₇H₁₅NOS (281.38)

Calc: C 72.57 H 5.37 N 4.98 S 11.39

Found: 72.43 5.53 4.89 11.65

Example 21

(E)-2- [[(Methylethyl)amino]phenylmethylene]-benzo[b]-thiophen-3(2H)-one

Prepared as in Example 1 from 2-benzoyl-benzo[b]thiophen-3-ol, phosphorus(V) chloride and 38.5% aqueous ethylamine solution in a yield of 54% of theory: m.p. 112-113°C (ethyl acetate/petroleum ether 1:1).

C₁₈H₁₇NOS (295.40)

Calc. C 73.19 H 5.80 N 4.74 S 10.85

10 Found: 73.15 5.99 4.61 10.80

IR(CH₂C₁₂): C=O approx. 1590 cm⁻¹

UV(ethanol): λ_{max} (neutral, 286, 321, 429, shoulder at 260nm; no displacement on adding alkali

15 ¹H-NMR (CDCl₃, 80MHz): δ 11.88 (1H, broad, internal H bridge);
7.95 (1H-dd, J=7Hz and 2Hz; ar. H);
7.7-7.15 (8H-m; ar. H);
3.9-3.4 (1H-m >CH);
1.24 (6H-d; J=6Hz; (CH₃)₂)

Example 22

20 (E)-2-[(Amino)(3-methylphenyl)methylene]-benzo[b]thiophen-3(2H)-one

Prepared as in Example 1 from 2-(3-methylbenzoyl)-benzo[b]thiophen-3-ol, phosphorus(V) chloride and concentrated ammonia in a yield of 36% of theory: m.p. 114-115°C (ethyl acetate/petroleum ether 1:1)

C₁₆H₁₃NOS (267.34)

Calc. C 71.88 H 4.90 N 5.24 S 11.99

Found: 71.95 4.91 5.56 12.17

Example 23

(E)-2-[(Amino)-(2-ethylphenyl)methylene]-benzo[b]thiophen-3(2H)-one

Prepared as in Example 1 from 2-(2-ethylbenzoyl)-benzo[b]-
5 thiophen-3-ol, phosphorus(V) chloride and concentrated
ammonia in a yield of 46% of theory; m.p. 132-133°C
(ethyl acetate/petroleum ether 1:1)

C₁₇H₁₅NOS (281.38)

Calc: C 72.57 H 5.37 N 4.98 S 11.39

10 Found: 72.95 5.58 5.05 11.56

IR(KBr): 3500 - 3000 N-H associated, approx. 1600 cm⁻¹ C=O

UV(ethanol): λ_{max} (neutral) 260-274 (E=0.42); 284 (E=0.52);

312 (E=0.51); 422 (E=0.53);

shoulder at 410nm

15 λ_{max} (alkaline) 284 (E=0.56); 312 (E=0.41);

422 (E=0.41);

shoulders at 260 (E=0.37) and 404 (E=0.38)nm

(Concentration: 50 µg/ml; layer thickness: 0.2cm)

Example 24

20 (E)-2-[[(Methyl)amino]-2-ethylphenyl)methylene]-benzo[b]-
thiophen-3(2H)-one

Prepared as in Example 1 from 2-(2-ethylbenzoyl)-benzo[b]-
thiophen-3-ol, phosphorus(V) chloride and 25% aqueous
methylamine solution in a yield of 42% of theory;

25 m.p. 126-127°C (ethyl acetate/petroleum ether 1:1)

C₁₈H₁₇NOS (295.40)

Calc. C 73.19 H 5.80 N 4.74 S 10.85

Found: 73.30 5.67 4.85 10.89

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IR(CH₂Cl₂): C=O approx. 1600 cm⁻¹

UV(ethanol): λ max (neutral) 266-274, 289, 318, 429,
a shoulder at 412nm; no change on adding alkali.

¹H-NMR (CDCl₃; 80MHz): δ 11.73 (1H, broad, internal H bridge);
5 7.97 (1H-d, broadened, J=6.5 Hz, ar. H);
7.7-7.0 (7H-m; ar. H);
2.83 (3H-d. J=2.5 Hz; N-CH₃);
2.64 (2H-q, J=7.2 Hz; -CH₂-);
1.19 (3H-t; J=7.2 Hz; C-CH₃).

10 Example 25

(E)-2-[(Ethyl)amino]-(2-ethylphenyl)methylene]-benzo[b]-
thiophen-3(2H)-one

Prepared as in Example 1 from 2(2-ethylbenzoyl)-benzo[b]-
thiophen-3-ol, phosphorus(V) chloride and 25% aqueous
15 ethylamine solution in a yield of 2% of theory: m.p.
76-77°C (diisopropyl ether/petroleum ether 1:2).

C₁₉H₁₉NOS (309.43)

Calc: C 73.75 H 6.19 N 4.53 S 10.36

Found: 74.05 6.16 4.58 10.35

20 Example 26

(E)-2-[(Amino)-(2-nitrophenyl)methylene]-benzo[b]thiophen-
3(2H)-one

Prepared as in Example 1 from 2-(2-nitrobenzoyl)-benzo[b]-
thiophen-3-ol, phosphorus(V) chloride and concentrated
25 aqueous ammonia in a yield of 21% of theory; m.p. 185-186°C
(ethyl acetate).

C₁₅H₁₀N₂O₃S (298.32)

Calc: C 60.39 H 3.38 N 9.39 S 10.75

Found: 60.23 3.42 9.34 10.79

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IR(CH₂Cl₂): N-H 3480 (also N-H associated), C=O approx. 1600, NO₂ 1350 and 1515-1535 cm⁻¹

UV(ethanol): λ max (neutral) 261 (E=0.52); 287 (E=0.51);

313 (E=0.47); 423 (E=0.40) nm

5 λ max (alkaline) 246 (E=0.35); 286 (E=0.64); 312 (E=0.20);

383 (E=0.33) nm;

(concentration: 50μg/ml; layer thickness: 0.2cm)

Example 27

10 (E)-2-[[(1,1-Dimethylethyl)amino]phenylmethylene]-benzo[b]-thiophen-3(2H)-one

Prepared as in Example 1 from 2-benzoyl-benzo[b]thiophen-3-ol, phosphorus(V) chloride and a 40% aqueous solution of 1,1-dimethylethylamine in a yield of 57% of theory; m.p. 131-132°C (ethyl acetate/petroleum ether 1:1)

15 C₁₉H₁₉NOS (309.43)

Calc: C 73.75 H 6.19 N 4.53 S 10.36

Found: 73.40 6.25 4.48 10.34

IR(CH₂Cl₂): N-H associated, C=O approx. 1600, C=C 1610 cm⁻¹

UV(ethanol): λ max (neutral) 264, 288, 324, 416 (shoulder), 432nm;

20 no change on adding alkali

¹H-NMR(CDCl₃, 80MHz): δ 12.35 (1H-s, broad, internal H bridge)

7.96 (1H-dd, J=7Hz and 2Hz; ar.H);

7.65-7.1 (8H-m; ar. H);

1.28 (9H-s; -C(CH₃)₃)

25 Example 28

(E)-2-[(Amino)-(2-bromophenyl)methylene]-benzo[b]thiophen-3(2H)-one

Prepared as in Example 1 from 2-(2-bromobenzoyl)-benzo[b]thiophen-3-ol, phosphorus(V) chloride and concentrated

30 aqueous ammonia in a yield of 42% theory; m.p. 143-144°C

(petroleum ether/ethyl acetate 1:1).

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C₁₅H₁₀BrNOS (332.22)

Calc: C 54.23 H 3.03 Br 24.05 N 4.22 S 9.65

Found: 54.10 3.04 24.25 4.13 9.56

Example 295 (E)-2-[[(2-Propynyl)amino]phenylmethylene]-benzo[b]thiophen-3-(2H)-one

Prepared as in Example 1 from 2-benzoyl-benzo[b]thiophen-3-ol, phosphorus(V) chloride and an aqueous propargylamine solution obtained by reacting a solution of 10g of
 10 propargylamine hydrochloride in 10cc of water with a solution of 10.6g of anhydrous sodium carbonate in 20cc of water, in a yield of 46% of theory; m.p. 126-128°C (ethyl acetate/petroleum ether 1:1).

C₁₈H₁₃NOS (291.37)

15 Calc: C 74.20 H 4.50 N 4.81 S 11.00

Found: 74.04 4.47 4.70 11.05

IR(CH₂Cl₂): -C=C-H 3300, C=O approx. 1600 cm⁻¹; also associated H

UV(ethanol): λ max (neutral) 266-276 (E=0.45); 286 (E=0.48);

319 (E=0.56); 434 (E=0.54);

20 λ max (alkaline) 255 (E=0.70); 313 (E=0.34); 434 (E=0.22).

(concentration: 50μg/ml: layer thickness 0.2cm)

1H-NMR(CDCl₃, 80MHz): δ 11.75 (1H, broad, internal H bridge);

7.95 (1H-dd, J=7Hz and 2Hz; ar. H);

7.7-7.1 (8H-m; ar.H); 3.94 (2H-dd, J=6Hz

25 and 2.5Hz; -CH₂-); 2.32(1H-t; J=2.5Hz).Example 30(E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

A mixture of 10.0g (0.0393mol) of 2-benzoyl-benzo[b]-thiophen-3-ol, 60cc of concentrated aqueous ammonia and
 30 250cc of ethanol was heated for 20 hours at a temperature of 120°C after contacting with 5bar of ammonia gas. After cooling

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the mixture was stirred in 1.5 litres of water, the precipitated pale yellow reaction product was filtered with suction, washed thoroughly several times with on each occasion 50cc of water and dried in air. 4.23g (42% of theory) of yellow crystals of m.p. 121-122°C were obtained (after twice recrystallizing from petroleum ether/ethyl acetate 1:1 using activated carbon) and were found to be completely identical with the product obtained in Example 1 on the basis of elementary analysis, the IR and UV spectra.

On keeping the above reaction mixture for 15 hours at 150°C, the yield is 5% of theory; on keeping for 15 hours at 80°C, the yield drops to 22% of theory and after heating for 15 hours at 40°C and then heating for 10 hours at 60°C, the yield is 31% of theory.

Example 31

(E)-2-[(Amino)phenylmethylene]-benzo[b]-thiophen-3(2H)-one
35.1g (0.138 mol) of 2-benzoyl-benzo[b]thiophen-3-ol are dissolved in 35cc of glacial acetic acid, followed by the addition of 39.0g (0.506 mol) of ammonium acetate and refluxing for 2½ hours. The still warm mixture is stirred into 300cc of ice water and a reddish product is precipitated. The solid is filtered off, dried in air and recrystallized once from 60cc of toluene. For further purification, it is dissolved in 30cc of ethyl acetate and just enough petroleum ether is added to ensure that no further precipitate forms (approx. 20cc), after which 20g of activated carbon is added, followed by boiling and hot filtering. The pure end product is obtained from the cool filtrate by cooling to +10°C and adding 60cc of petroleum ether. Filtering with suction takes place after leaving to stand for 2 hours. By concentrating the mother liquors to a

volume of 30cc and prolonged cooling to +10°C a further 2.0g of the desired product with a good quality can be obtained. The combined crystalline product is thoroughly washed with a total of 20cc of petroleum ether and freed from solvents in a circulating air drier at +70°C. 23.0g (66% of theory) of egg yellow crystals are obtained of m.p. 121.6-122.5°C and are found to be identical with the product of Example 1 on the basis of elementary analysis and the IR and UV spectra.

10 Example 32

(E)-2-[[(Cyclohexyl)amino]phenylmethylene]-benzo[b]thiophen-3(2H)-one

Prepared as in Example 31 with a yield of 56% of theory from 2-benzoyl-benzo[b]thiophen-3-ol and cyclohexylamine.

15 Lemon-yellow crystals are obtained of m.p. 122-123°C (petroleum ether/ethyl acetate 85:15).

$C_{21}H_{21}NOS$ (335.46)

Calc: C 75.19 H 6.31 N 4.18 S 9.56

Found: 74.93 6.27 4.17 9.54

20 IR(CH_2Cl_2): C=O approx. 1600 cm^{-1} , C=C 1610 cm^{-1}

UV(ethanol): λ_{max} (neutral) 288 (E=0.47), 323 (E=0.46);

432 (E=0.50); no displacement after adding alkali;

1H -NMR ($CDCl_3$; 80MHz): δ 12.3-11.8 (H-m, broad, internal H bridge);

7.93 (1H-dd, J=7Hz and 2Hz; ar.H); 7.7-7.1 (8H-m. ar.H);

25 3.6-3.1 (1H-m; γ CH)); 2.1-1.0 (10H-m; cyclohexyl).

Example 33

(E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

Prepared as in Example 31, but using (E)-2-[(methoxy)phenylmethylene]-benzo[b]thiophen-3(2H)-one instead of

30 2-benzoyl-benzo[b]thiophen-3-ol and reduction of the reaction time to 10 minutes, in a yield of 72% of theory.

50

Egg yellow crystals of m.p. 121-122°C found to be completely identical with the product of Example 1 on the basis of TLC, mixed melting point, elementary analysis and IR spectrum.

5 Example 34

(E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

A mixture of 10.0g (0.0373 mol) of (E)-2-[(methoxy)phenylmethylene]-benzo[b]thiophen-3(2H)-one, 75cc of concentrated ammonia and 250cc of methanol is refluxed
10 for 10 minutes, the mixture is stirred after cooling into 1.5 litres of ice-water, the precipitated reaction product is filtered with suction, washed thoroughly with water and dried in air. For purification purposes, the crude product is dissolved in 100cc of ethyl acetate, followed
15 by the addition of ethereal hydrochloric acid until no further precipitate forms, followed by filtering and washing of the filter residue with ethyl acetate. The solid is suspended in 100cc of water and adjusted ammoniacal, after which filtering with suction is again per-
20 formed. After drying and recrystallizing from petroleum ether/ethyl acetate 4.7g (50% of theory) of the title compound are obtained of m.p. 121-122°C, found to be identical with the product obtained in Example 1 on the basis of TLC, mixed melting point and elementary analysis.

25 Example 35

(E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

A mixture of 35.0g (0.138 mol) of 2-benzoyl-benzc[b]-thiophen-3-ol, 24.0g (0.311mol) of ammonium acetate and 25cc of dimethylsulphoxide is stirred for 1 hour at a
30 reaction temperature of 125°C. The cooled reaction mixture

is stirred into a mixture of 150cc of petroleum ether and 300cc of ice water. The suspension obtained is then filtered with suction and the filter residue is thoroughly washed with water. For purification purposes, the dried
5 crude product is taken up in 40cc of ethyl acetate and just enough petroleum ether is added to ensure that no further precipitate forms (approx. 20cc). 5g of activated carbon are added, followed by boiling and filtering hot. The pure product is obtained from the crude filtrate by
10 adding 60cc of petroleum ether and cooling to +10°C. Further product with the same quality can be obtained by concentrating the mother liquor to approximately 30cc total volume. The combined crystalline product is washed with petroleum ether and dried in vacuo and 25.2g (72% of theory)
15 of the desired product are obtained of m.p. 121.6-122.5°C, which is found to be identical with that of Example 1 on the basis of its thin layer chromatogram, mixed melting point and IR spectrum.

Example 36

20 (E)-2-[[[2-(4-Morpholinyl)ethyl]amino]phenylmethylene]-benzo-[b]thiophen-3(2H)-one

Prepared as in Example 35 from 2-benzoyl-benzo[b]thiophen-3-ol and 2-(4-morpholinyl)-ethylamine instead of ammonium acetate in a yield of 62% of theory.

25 $C_{21}H_{22}N_2O_2S$ (366.48)

Calc: C 68.83 H 6.05 N 7.64 S 8.75

Found: 68.60 6.20 7.70 8.80

IR(CH₂Cl₂): N-H associated 3200-3600, C=O approx. 1600 cm⁻¹

UV(ethanol): λ_{max} (neutral) 275 (shoulder), 288, 322, 433nm;

30 no displacement on adding alkali.

5

(E)-2-[[(Propyl)amino]phenylmethylene]-benzo[b]thiophen-3-
(2H)-one

10

Calc: C 73.19 H 5.80 N 4.74 S 10.85

15

Prepared as in Example 35 from 2-benzoyl-benzo[b]thiophen-

3-ol and n-butylammonium acetate in a yield of 64% of

20

Found: 73 40 6 13 4 64 10 44

(E)-2-[[(2-Methylpropyl)amino]phenylmethylene]-benzo[b]-

25

3-ol and (2-methylpropyl)ammonium acetate in a yield of

30

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Calc: C 73.75 H 6.19 N 4.53 S 10.36

Found: 76.60 6.21 4.68 10.30

IR(CH₂Cl₂): N-H associated 3200-3600; C=O approx. 1600 cm⁻¹

UV(ethanol): λ_{max} (neutral) 270 (shoulder), 288, 323, 432nm;

5 no displacement on adding alkali.

¹H-NMR (CDCl₃/D₂O; 80MHz); 7.94 (1H-dd, J=6.5 and 2Hz; ar.H);

7.7-7.1 (8H-m; ar.H)

3.05(2H-d; J=6.5Hz; N-CH₂-C);

2.1-1.5 (1H-m; -C-CH₂-C);

10 0.95(6H-d; J=6.5Hz; -C(CH₃)₂).

Example 40

(E)-2-[(Dimethylamino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

Prepared as in Example 31 from 2-benzoyl-benzo[b]thiophen-
15 3-ol and dimethylammonium acetate in a yield of 18% of theory; m.p. 179-180°C (ethyl acetate / petroleum ether 1:2)
The product is identical to that prepared according to Example 4 on the basis of the thin layer chromatogram, elementary analysis and IR spectrum.

20 Example 41

(E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

5.0g (0.0197mol) 2-benzoyl-benzo[b]thiophen-3-ol, 12.0g (0.156mol) of ammonium acetate and 5cc of 1,2-ethanediol are heated for 2 hours at 130°C, accompanied by stirring.
25 The cooled mixture is stirred into 50cc of iced water, followed by filtering with suction and the column chromatographic purification of the filter residue on silica gel, using 1,2-dichloroethane for eluting. At the end of recrystallization from petroleum ether/ethylene acetate (2:1) 2.5g (50%
30 of theory) of egg yellow crystals are obtained of m.p. 121-122°C which, on the basis of TLC, mixed melting point

and elementary analysis are identical to the product of Example 1.

Example 42

(E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

- 5 Prepared as in Example 41 from 2-benzoyl-benzo[b]thiophen-3-ol, but using urea instead of ammonium acetate, in a yield of 55% of theory; m.p. 121-122°C (petroleum ether/ethyl acetate 2:1). The product is identical with that of Example 1 on the basis of the TLC, mixed melting point
10 and IR spectrum.

Example 43

(E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

- 5.0g (0.0186 mol) of (E)-2-[(methoxy)phenylmethylene]-benzo[b]-thiophen-3(2H)-one and 10.0g (0.167 mol) of urea are
15 thoroughly triturated and heated for 10 minutes at a temperature between 125 and 130°C. The cold product is column chromatographically purified as described in Example 41 and 3.84 (81% of theory) of egg yellow crystals are obtained of m.p. 121-122°C (petroleum ether/ethyl acetate
20 2:1), which are identical to the product of Example 1 on the basis of the TLC, mixed melting point, elementary analysis and IR spectrum.

Example 44

(E)-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

- 25 On reacting 2-benzoyl-benzo[b]thiophen-3-ol with the following reagents in place of ammonium acetate under the conditions of Example 35, the title compound is obtained, defined in each case by the thin layer chromatogram, mixed melting point, elementary analysis and IR
30 spectrum in the yields shown to the right below:

	Ammonium oxalate	42% of theory
	Ammonium carbonate	64% of theory
	Ammonium formate	74% of theory
	Ammonium propionate	66% of theory
5	Ammonium carbamate	59% of theory
	Diammonium hydrogen citrate	61% of theory

Example 45

(E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

On reacting 2-benzoyl-benzo[b]thiophen-3-ol with the
10 following reagents in the case of ammonium acetate under
the conditions of Example 31, the title compound of
m.p. 121-122°C (petroleum ether/ethyl acetate 2:1) is
obtained with the yields given to the right below:

	Ammonium formate	78% of theory
15	Formamide	70% of theory
	Ammonium thiocyanate	33% of theory
	Triammonium phosphate	27% of theory

Example 46

(E)-2-[(Methylamino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

20 Prepared as in Example 31 from 2-benzoyl-benzo[b]thiophen-
3-ol, but using N,N'-dimethylurea in place of ammonium
acetate, in a yield of 66% of theory; m.p. 156-157°C
(ethyl acetate). On the basis of the thin layer chromatogram,
mixed melting point, elementary analysis and IR spectrum,
25 the product is identical to that of Example 2.

Example 47

(E)-2-[(Amino)-(2-bromophenyl)methylene]-benzo[b]thiophen-3(2H)-one

Prepared as in Example 31 from 2-(2-bromobenzoyl)-benzo-
 5 [b]thiophen-3-ol and formamide in place of ammonium
 acetate in a yield of 10% of theory; m.p. 143-144°C
 (petroleum ether/ethyl acetate 1:1). The thin layer
 chromatogram, mixed melting point, elementary analysis
 and IR spectrum show it to be identical with the product
 10 of Example 28.

Example 48

(E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

Prepared as in Example 35, but using 2-benzoyl-3-chlorobenzo-
 [b]thiophene in place of 2-benzoyl-benzo[b]thiophen-3-ol
 15 in a yield of 9% of theory; m.p. 120-121°C (ethyl acetate/
 petroleum ether 1:2). The TLC, IR and UV spectra show
 it to be identical with the product of Example 1.

Example 49

(E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

20 0.5g (0.00186mol) of (E)-2-[(hydroxyamino)phenylmethylene]-
 benzo[b]thiophen-3(2H)-one dissolved in 10cc of glacial
 acetic acid are catalytically hydrogenated for 2½ hours
 at a hydrogen pressure of 5 bar in the presence of 0.2g
 of platinum(IV) oxide. At the end of the hydrogen uptake,
 25 the catalyst-free solution is stirred into 100cc of water,
 exhaustively extracted with ether, the combined ether
 extracts are successively washed with water, saturated
 aqueous sodium hydrogen carbonate solution and then again
 with water, followed by drying over sodium sulphate. The
 30 crystalline residue left behind after expelling the solvent

is recrystallized twice using activated carbon from a mixture of petroleum ether and ethyl acetate (2:1). 0.37g (79% of theory) of egg yellow crystals of m.p. 121-122°C are obtained which, on the basis of the thin layer chromatogram, mixed melting point and IR spectrum are found to be identical with a product obtained according to Example 1.

Example 50

(E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

Prepared as in Example 49 from[(E)-2-[(2-phenylhydrazino)phenylmethylene]-benzo[b]thiophen-3(2H)-one in a yield of 48% of theory; m.p. 121-122°C (ethyl acetate/petroleum ether 1:2). The thin layer chromatogram, mixed melting point and IR spectrum show the product to be identical with that of Example 1.

Example 51

(E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

0.5g(0.00145mol) of (E)-2-[(2-phenylhydrazino)phenylmethylene]-benzo[b]thiophen-3(2H)-one (of m.p. 168°C after recrystallizing from methanol/acetone 1:1) are suspended in 5cc of 2% aqueous caustic soda solution, 1.0g (0.00476 mol) of sodium dithionite dihydrate is added, followed by refluxing for 2 hours. After cooling, the mixture is extracted with 1,2-dichloroethane, the organic solvent is expelled and the remaining residue is purified by column chromatography on silica gel using 1,2-dichloroethane for eluting. After the final recrystallization from petroleum ether/ethyl acetate(2:1) 0.22g (54% of theory) of bright yellow crystals is obtained of m.p. 121-122°C which, on the basis of the TLC, mixed melting point and IR spectrum are identical with the product of Example 1.

Example 52

(E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

Prepared as in Example 51, but using (E)-2-[(hydroxyamino)-phenylmethylene]-benzo[b]thiophen-3(2H)-one as the
5 starting substance in a yield of 47%, m.p. 121-122°C (petroleum ether/ethyl acetate 2:1). According to the thin layer chromatogram, melting point and IR spectrum, the product is identical with that of Example 1.

Example 53

10 (E)-2-[(Amino(phenylmethylene)-benzo[b]thiophen-3(2H)-one

0.5g (0.00145mol) of (E)-2-[(2-phenylhydrazino)phenylmethylene]-benzo[b]thiophen-3(2H)-one is dissolved in 10cc of glacial acetic acid and 5cc of 20% hydrochloric acid and 1.0g of iron powder are added. The maintenance
15 of a reaction temperature of 15 to 23°C is ensured by external cooling with water. After 1 hour, the mixture is worked up as in Example 49. 0.33g (90% of theory) of the title compound of m.p. 121-122°C (petroleum ether/ethyl acetate 2:1) is obtained which, according to the TLC,
20 mixed melting point and elementary analysis is identical with the product of Example 1.

Example 54

(E)-2-[(Amino)-(2-trifluoromethylphenyl)methylene]-benzo-
[b]thiophen-3(2H)-one

Prepared as in Example 1 from 2-(2-trifluoromethyl-
5 benzoyl)-benzo[b]thiophen-3-ol, phosphorus(V) chloride
and concentrated ammonia in a yield of 6% of theory;
m.p. 148-149°C (petroleum ether/ethyl acetate 2:1).

C₁₆H₁₀F₃NOS (321.31)

Calc: C 59.81 H 3.14 N 4.36

10 Found: 59.99 3.49 4.27

Example 55

(E)-2-[(Amino)-(2-aminophenyl)methylene]-benzo[b]thiophen-
3(2H)-one

0.5g (0.00168mol) of (E)-2-[(amino)-(2-nitrophenyl)
15 methylene]-benzo[b]thiophen-3(2H)-one are dissolved in a
mixture of 10cc of methyl acetate and 10cc of tetrahydro-
furan. After adding 0.5g of Raney nickel at ambient
temperature and with a hydrogen pressure of 5 bar,
hydrogenation takes place until hydrogen uptake is at
20 an end. Filtration from the catalyst is then carried out,
followed by evaporation of the solvent at reduced pressure
and recrystallization of the remaining residue twice using

activated charcoal from tetrahydrofuran/petroleum ether (1:1).
330mg (73% of theory) of yellow crystals are obtained of m.p.
186-187°C (petroleum ether/tetrahydrofuran 1:1).

$C_{15}H_{12}N_2OS$ (268.34)

5 Calc: C 67.14 H 4.51 N 10.44 S 11.95

Found: 66.73 4.84 9.82 11.75

Example 56

(E)-2-[[[(Cyclopropyl)amino]phenylmethylene]-benzo[b]thiophen-3(2H)-one

- 10 Prepared as in Example 31 in a yield of 25% of theory from
2-benzoyl-benzo[b]thiophen-3-ol and cyclopropylamine.
Egg yellow crystals of m.p. 131-132°C (petroleum ether/
ethyl acetate 1:1).

$C_{18}H_{15}NOS$ (293.39)

15 Calc: C 73.69 H 5.15 N 4.77 S 10.93

Found: 73.28 5.38 4.75 11.10

IR(CH_2Cl_2): internal H bridge, C=O 1595 cm^{-1}

UV(ethanol); λ_{max} 266-276 (E=0.44); 286 (E=0.46); 321 (E=0.49);
435 (E=0.54)nm

- 20 (Concentration: 50 μ g/ml; layer thickness 0.2cm)

1H -NMR ($CDCl_3/CD_3OD$; 80MHz): δ 7.96(1H-dd, J=7Hz and 2Hz; ar. H);
7.6-7.1(8H-m; ar. H); 2.8-2.4(1H-m;
N-CH); 0.8-0.5 (4H-m; C $\begin{smallmatrix} CH_2 \\ | \\ CH_2 \end{smallmatrix}$)

Example 57

- 25 (E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

0.5g (0.00186mol) of (E)-2-[(hydroxyamino)phenylmethylene]-
benzo[b]thiophen-3(2H)-one are dissolved in 20cc of
tetrahydrofuran, successively mixed with a solution of
1.05g (0.038mol) of iron(II) sulphate heptahydrate in

- 30 2cc of water and 1 drop of concentrated hydrochloric acid
and with 3cc of concentrated ammonia and stirred for 3 hours

at ambient temperature, followed by heating to 90°C for 5 minutes. The cooled mixture is stirred into 100cc of water and exhaustively extracted with ether. The ether extracts are washed with water, dried over sodium

5 sulphate and the crystalline residue left behind after expelling the solvent is recrystallized twice from a mixture of petroleum ether and ethyl acetate (2:1) using activated charcoal 0.24g (51% of theory) of egg yellow crystals of m.p. 121-122°C is obtained which, 10 according to the thin layer chromatogram, mixed melting point, elementary analysis and IR spectrum is identical with the product of Example 1.

Example 58

(E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

15 0.5g (0.000145 mol) of (E)-2-[(2-phenylhydrazino)-phenylmethylene]-benzo[b]thiophen-3(2H)-one, 1.0g(0.00443 mol) of tin(II) chloride dihydrate and 5cc of concentrated hydrochloric acid are magnetically stirred for 24 hours at room temperature. The clear solution obtained is evaporated 20 in vacuo to a viscous paste, then mixed with 10cc of water and adjusted to pH 7 by the dropwise addition of 10% ammonia solution. The suspension obtained is exhaustively extracted with ethyl acetate, the combined organic extracts are dried over sodium sulphate and concentrated under reduced 25 pressure and the remaining residue is purified column chromatographically on silica gel, using 1,2-dichloroethane for eluting. After finally recrystallizing from petroleum ether/ethyl acetate (2:1) 0.21g (57% of theory) of egg yellow crystals of m.p. 121-122°C are obtained which, on 30 the basis of the TLC, mixed melting point and elementary analysis is identical with the product of Example 1.

Example 59

(E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

- 0.5g (0.00145mol) of (E)-2-[(2-phenylhydrazino)phenylmethylene]-benzo[b]thiophen-3(2H)-one are dissolved in
5 10cc of anhydrous tetrahydrofuran and stirred for 30 minutes at ambient temperature after adding 0.1g (0.00264mol) of lithium tetrahydroaluminate. In order to decompose the excess lithium tetrahydroaluminate, 10 drops of water, 10 drops of 15% aqueous sodium hydroxide solution and
10 then a further 50 drops of water are successively added, followed by boiling, filtering, removing the solvent from the filtrate and purification of the residue as described in Example 58. 0.085g (23% of theory) of egg yellow crystals of m.p. 120-121°C are obtained and the thin
15 layer chromatogram and mixed melting point revealed them to be identical with the product of Example 1.

Example 60

(E)-2-[(Amino)phenylmethylene]-5-methylbenzo[b]thiophen-3-(2H)-one

- 20 Prepared as in Example 35 from 2-benzoyl-5-methylbenzo[b]thiophen-3-ol and ammonium acetate in a yield of 51% of theory.

m.p. 153-154°C (toluene)

$C_{16}H_{13}NOS$ (267.34)

- 25 Calc: C 71.88 H 4.90 N 5.24 S 11.99

Found: 72.10 5.08 5.22 12.15

IR(CH_2Cl_2): NH 3470 C=O 1600 cm^{-1}

UV(ethanol): λ_{max} (neutral) 266-271 (E=0.53), 325 (E=0.58),
435 (E=0.51)nm;

- 30 λ_{max} (alkaline) 279 (E=0.52), 325 (E=0.47),
433 (E=0.38)nm

(Concentration: 50 $\mu g/ml$, layer thickness: 0.2cm)

¹H-NMR(CDCl₃, 80MHz): δ 10.94(1H, broad, internal H-bridge);
7.9-7.15 (8H-m, ar. H). 5.88 (1H, wide,
exchangeable H), 2.46(3H-s).

Example 61

5 (E)-2-[(Amino)phenylmethylene]-6-methylbenzo[b]thiophen-3(2H)-one

Prepared as in Example 31 from 2-benzoyl-6-methylbenzo[b]-thiophen-3-ol and ammonium acetate in a yield of 57% of theory.

10 m.p. 166-167°C (ethyl acetate/petroleum ether 1:1).

C₁₆H₁₃NOS (267.34)

Calc: C 71.88 H 4.90 N 5.24 S 11.99

Found: 71.70 4.94 5.05 11.95

IR(CH₂Cl₂): NH 3470, C=O 1600 cm⁻¹

15 UV(ethanol): λ max (neutral) 283 (E=0.57); 321 (E=0.55);
427 (E=0.51)nm

(Concentration: 50µg/ml; layer thickness: 0.2cm)

Example 62

20 (E)-2-[(Amino)phenylmethylene]-6-methoxybenzo[b]thiophen-3(2H)-one

Prepared as in Example 31 from 2-benzoyl-6-methoxybenzo[b]-thiophen-3-ol and ammonium acetate in a yield of 64% of theory.

m.p. 147-149°C (toluene/petroleum ether 1:1)

25 C₁₆H₁₃NO₂S (283.34)

Calc: C 67.82 H 4.62 N 4.94 S 11.32

Found: 67.77 4.69 5.26 11.85

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Example 63(E)-2-[(Amino)phenylmethylene]-4-methylbenzo[b]thiophen-3(2H)-one

- Prepared as in Example 31 from 2-benzoyl-4-methylbenzo[b]thiophen-3-ol and ammonium acetate in a yield of 50% of theory. m.p. 198-200°C (diisopropyl ether/ethyl acetate 2:1)
- $C_{16}H_{13}NO$ (267.34)
- | | | | | | |
|---------|-------|---|------|---|------|
| Calc: C | 71.88 | H | 4.90 | N | 5.24 |
| Found: | 71.75 | | 5.01 | | 5.23 |
- 10 IR(CH_2Cl_2): NH 3460, C=O 1600 cm^{-1}
- UV(Ethanol): λ max (neutral) 272-275 (E=0.60); 315 (E=0.46); 433 (E=0.59)nm;
- λ max (alkaline) 272-275 (E=0.60); 315 (E=0.44); 433 (E=0.55)nm;
- 15 (Concentration: 50 μ g/ml; layer thickness : 0.2cm)

Example 64(E)-2-[(Methylamino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

- 2.53g (0.01mol) of (E)-2-[(amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one are dissolved in 10ml of glacial acetic acid, followed by the addition of 20.0g (0.22mol) of methylammonium acetate and refluxing for 5 hours. The still warm mixture is stirred into 100ml of iced water and a reddish brown product is precipitated. The solid is filtered off, dried in air and, to separate small quantities of starting
- 25 substance, is column chromatographically purified on silica gel using firstly 1,2-dichloroethane and then 1,2-dichloroethane/acetone (volume ratio 95:5) as the eluants. The egg yellow residue left behind after evaporating the eluates is recrystallized twice from methanol. 2.05g (77% of theory) of
- 30 yellow crystals of m.p. 155-156°C are obtained which are identical with the product according to Example 2 according to the elementary analysis, IR and UV spectra and mixed melting

point.

Example 65

(E)-2-[(Methylamino)phenylmethylene]-benzo[b]thiophen-3(2H)-one

- 5 A mixture of 2.53g (0.01mol) of (E)-2-[(amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one, 40.0g (0.44mol) of methylammonium acetate and 10ml of dimethylsulphoxide are heated for 5 hours to a reaction temperature of 130 to 140°C. Working up is in accordance with Example
- 10 64 and the desired compound of m.p. 154-155°C (methanol) is obtained in a yield of 58% of theory. The product is identical with that of Example 2 according to the elementary analysis and thin layer chromatogram.

Example 66

- 15 (E)-2-[(Amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one
2.67g (0.01mol) of (E)-2-[(methylamino)phenylmethylene]-benzo[b]thiophen-3(2H)-one are dissolved in 10ml of glacial acetic acid, followed by the addition of 25.0g (0.32mol) of ammonium acetate and refluxing for 15 minutes.
- 20 After working up as in Example 65, 1.85g (73% of theory) of yellow crystals of m.p. 121-122°C (petroleum ether/ethyl acetate 2:1) are obtained which, according to the mixed melting point and IR and UV spectra, are identical with the product of Example 1.

25 Example 67

(E)-2-[(Amino)phenylmethylene]benzo[b]thiophen-3(2H)-one

- The procedure is as in Example 66, but 0.32 mol of urea are used instead of ammonium acetate. After corresponding working up, 1.92 (76% of theory) of yellow crystals are
- 30 obtained of m.p. 121-122°C (petroleum ether/ethyl acetate 2:1) which, on the basis of elementary analysis, mixed melting point and thin layer chromatogram are identical with the product of Example 1.

66

The compounds of general formula I can be incorporated into conventional pharmaceutical preparation forms such as tablets and coated tablets. The single dose for adults is 20 to 200mg, preferably 40 to 100mg, whilst the daily dose is generally 40 to 400mg, preferably 80 to 200mg. A number of examples are given hereinafter:

Example I

Tablets containing 50mg of (E)-2-[(amino)phenylmethylene]-benzo[b]thiophen-3(2H)-one.

10 Composition:

Active ingredient	50mg
Lactose	148mg
Potato starch	60mg
Magnesium stearate	<u>2mg</u>
	260mg

15

The active substance and lactose are mixed into a 10% potato starch solution and the mixture is granulated through a sieve of mesh size 1.5mm. The granulate is dried and is again worked through the same sieve. The magnesium stearate is added and the granulate is pressed into tablets. Tablet weight: 260mg.

Example II

Coated tablets containing 50mg of (E)-2-[(methylamino)phenylmethylene]-benzo[b]thiophen-3(2H)-one.

- 25 The granulate is prepared in the same way as in Example I and is pressed into coated tablet cores. The cores are provided with a coating which essentially comprises sugar and talc. The coating is subsequently polished with beeswax.
- Core weight: 260mg
- 30 Coated tablet weight: 300mg.