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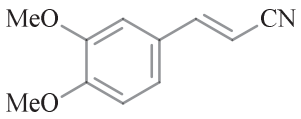
(54) Benevnelse **Novel method for synthesising (2E)-3-(3,4-dimethhoxyphenyl)prop-2-enenitrile and use for synthesising ivabradine and the added salts thereof with a pharmaceutically acceptable acid**

(56) Anførte publikasjoner

EP-A1- 0 534 859
WO-A1-2011/138625
DE-A1- 2 303 919
SPENCER A: "A HIGHLY EFFICIENT VERSION OF THE PALLADIUM-CATALYSED ARYLATION OF ALKENES WITH ARYL BROMIDES", JOURNAL OF ORGANOMETALLIC CHEMISTRY, ELSEVIER-SEQUOIA S.A. LAUSANNE, CH, vol. 258, 1 janvier 1983 (1983-01-01), pages 101-108, XP001205429, ISSN: 0022-328X, DOI: 10.1016/0022-328X(83)89511-4
KAMETANI TETSUJI ET AL: "Syntheses of (+-)-tetrahydropalmatine and spirobenzylisoquinolines by thermolysis of benzocyclobutene derivatives", JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, CHEMICAL SOCIETY, LETCHWORTH; GB, no. 10, 1 janvier 1985 (1985-01-01), pages 2151-2154, XP008162620, ISSN: 0300-922X, DOI: 10.1039/P19850002151
ZHAO SHENG YIN ET AL: "A practical synthesis of 1-cyano-4,5-dimethoxybenzocyclobutene", JOURNAL OF CHEMICAL RESEARCH, SCIENCE REVIEWS LTD, GB, no. 7, 1 janvier 2009 (2009-01-01), pages 420-422, XP008162622, ISSN: 0308-2342

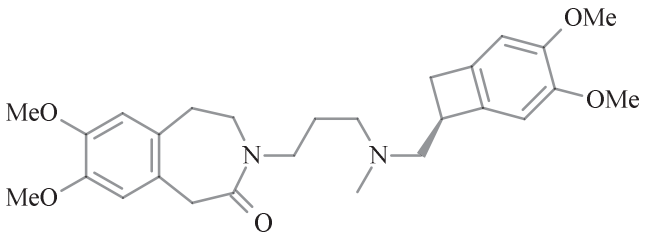
The present invention relates to a process for the synthesis of (2*E*)-3-(3,4-dimethoxyphenyl)prop-2-enenitrile of formula (I):



(I)

and to the application thereof in the synthesis of ivabradine and addition salts thereof with a pharmaceutically acceptable acid.

The compound of formula (I) obtained in accordance with the process of the invention is useful in the synthesis of ivabradine of formula (II):



(II),

or 3-{3-[{[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}(methyl)amino]propyl}-7,8-dimethoxy-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one,

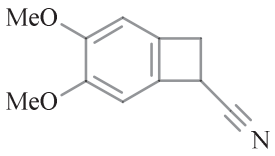
which may be converted into an addition salt thereof with a pharmaceutically acceptable acid selected from hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, benzenesulphonic acid and camphoric acid, and into hydrates thereof.

Ivabradine, and its addition salts with a pharmaceutically acceptable acid, and more especially its hydrochloride, have very valuable pharmacological and therapeutic properties, especially bradycardic properties, making those compounds useful in the treatment or prevention of various clinical situations of myocardial ischaemia such as angina pectoris, myocardial infarction and associated rhythm disturbances, and also in

various pathologies involving rhythm disturbances, especially supraventricular rhythm disturbances, and in heart failure.

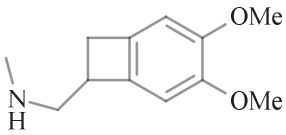
The preparation and therapeutic use of ivabradine and its addition salts with a pharmaceutically acceptable acid, and more especially its hydrochloride, have been described in the European patent specification EP 0 534 859.

That patent specification describes the preparation of ivabradine starting from 3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile of formula (III):



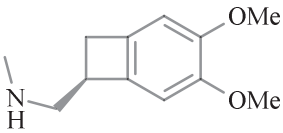
(III),

which is converted into the compound of formula (IV):



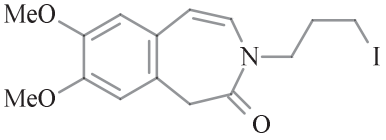
(IV),

which is resolved to yield the compound of formula (V):



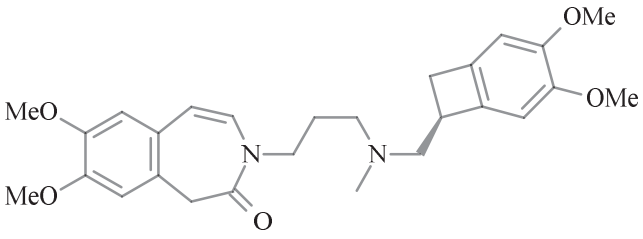
(V),

which is reacted with the compound of formula (VI):



(VI)

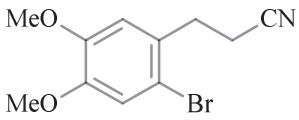
to yield the compound of formula (VII):



(VII),

the catalytic hydrogenation of which yields ivabradine, which is then converted into its hydrochloride.

The preparation of the compound of formula (III) starting from (3-(2-bromo-4,5-dimethoxyphenyl)propanenitrile of formula (VIII) is described in *Tetrahedron* **1973**, 29, pp 73-76:



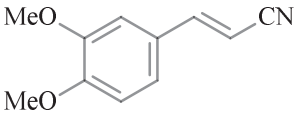
(VIII).

The compound of formula (I), a precursor of the compound of formula (VIII), is accordingly a key intermediate in the synthesis of ivabradine.

The patent application DE 2 303 919 describes the preparation of the compound of formula (I), starting from 3,4-dimethoxybenzaldehyde, with a yield of 74 %.

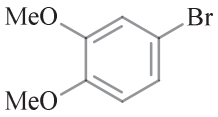
In view of the industrial value of ivabradine and its salts, it has been imperative to find an effective process allowing (2*E*)-3-(3,4-dimethoxyphenyl)prop-2-enenitrile of formula (I) to be obtained in an excellent yield.

The present invention relates to a process for the synthesis of the compound of formula (I):



(I),

characterised in that the compound of formula (IX):



(IX)

is subjected to a coupling reaction with acrylonitrile in the presence of a palladium catalyst, a ligand, a base and a phase transfer agent in an organic solvent to yield the compound of formula (I).

Among the palladium catalysts that may be used to carry out the conversion of the compound of formula (IX) into the compound of formula (I), there may be mentioned, without implying any limitation, palladium diacetate, palladium on carbon, and palladium dichloride.

The palladium catalyst preferably used to carry out the conversion of the compound of formula (IX) into the compound of formula (I) is palladium on carbon.

Among the ligands that may be used to carry out the conversion of the compound of formula (IX) into the compound of formula (I), there may be mentioned, without implying any limitation, triphenylphosphine and tri(*o*-tolyl)phosphine.

The ligand preferably used to carry out the conversion of the compound of formula (IX) into the compound of formula (I) is tri(*o*-tolyl)phosphine.

Among the bases that may be used to carry out the conversion of the compound of formula (IX) into the compound of formula (I), there may be mentioned, without implying any limitation, triethylamine, sodium acetate, sodium carbonate and potassium carbonate.

The base preferably used to carry out the conversion of the compound of formula (IX) into the compound of formula (I) is sodium acetate.

Among the phase transfer agents that may be used to carry out the conversion of the compound of formula (IX) into the compound of formula (I), there may be mentioned, without implying any limitation, tetrabutylammonium bromide and tetrabutylammonium chloride.

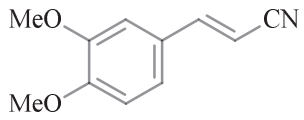
The phase transfer agent preferably used to carry out the conversion of the compound of formula (IX) into the compound of formula (I) is tetrabutylammonium bromide.

Among the organic solvents that may be used to carry out the conversion of the compound of formula (IX) into the compound of formula (I), there may be mentioned, without implying any limitation, *N*,*N*-dimethylacetamide and *N*,*N*-dimethylformamide.

The solvent preferably used to carry out the conversion of the compound of formula (IX) into the compound of formula (I) is *N*,*N*-dimethylacetamide.

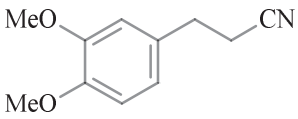
The conversion of the compound of formula (IX) into the compound of formula (I) is carried out at a temperature preferably between 100°C and 170ºC, inclusive.

The present invention relates also to a process for the synthesis of the compound of formula (VIII) starting from the compound of formula (I), prepared according to the process described hereinbefore, characterised in that said compound of formula (I):



(I)

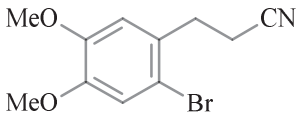
is converted into the compound of formula (X):



(X)

by a reduction reaction,

which compound is converted into the compound of formula (VIII):



(VIII)

by a bromination reaction.

The reduction reaction performed on the compound of formula (I) may be carried out under the conditions described for the corresponding brominated compound in the patent application CN 101 407 474 and in the publication *J. Chem. Res.* **2009** (7), 420-422.

The bromination reaction performed on the compound of formula (X) may be carried out under the conditions described for similar compounds in the publications *J. Chem. Soc., Perkin Trans I* **1985**, 2151-2154 and *J. Chem. Soc., Perkin Trans I* **1991**, 1749-1754.

Also, the preparation of the compound of formula (VIII) by a bromination reaction performed on the compound of formula (X), in the presence of dibromine in acetic acid, has been described in *J. Org. Chem* **1972**, vol. 37, no. 21, pp 3374-3376, with a yield of 48 %.

The present invention relates also to a process for the synthesis of ivabradine starting from the compound of formula (I) prepared in accordance with the process of the invention and converted into the compound of formula (VIII) in accordance with the reaction sequence described hereinbefore. The compound of formula (VIII) is then converted into the compound of formula (III) following the teaching of the prior art (*Tetrahedron* **1973**, 29, pp 73-76) by an intramolecular cyclisation reaction in a basic medium, said compound of formula (III) then being converted into ivabradine in accordance with the process described in EP 0 534 859.

The Examples that follow illustrate the invention.

The melting points were measured using a BÜCHI B-545 Melting Point Apparatus (Volt. 230VAC, Freq. 50/60 Hz, Power max. 220W).

List of abbreviations used

DMAC: *N*,*N*-dimethylacetamide
m.p: melting point
THF: tetrahydrofuran

Example 1: (2*E*)-3-(3,4-dimethoxyphenyl)prop-2-enenitrile

A mixture of 5 g of 4-bromo-1,2-dimethoxybenzene (3.31 mL, 23 mmoles), 3.2 g of acrylonitrile (3.9 mL, 60 mmoles, 2.6 eq.), 2.3 g of sodium acetate (27.6 mmoles, 1.2

eq.), 7.4 g of tetrabutylammonium bromide (23 mmoles, 1 eq.), 0.7 g of tri(o-tolyl)phosphine (2.3 mmoles, 0.1 eq.) and 4.9 g of palladium 5% on carbon (2.3 mmoles, 0.1 eq.) in 25 mL of DMAC is prepared. The black suspension is stirred at reflux for 12 hours. The reaction mixture is brought back to ambient temperature and filtered. The solid residue is rinsed twice with toluene. The filtrates are combined and evaporated under reduced pressure. The crude reaction product is purified on a silica column (eluant: methylcyclohexane:ethyl acetate 6:4) to yield 1.4 g of the expected product.

Yield = 33 %

m.p. = 92-99°C

Example 2: 3-(3,4-dimethoxyphenyl)propanenitrile

To a solution of 1 g (5.3 mmoles) of (2*E*)-3-(3,4-dimethoxyphenyl)prop-2-enenitrile in 9.3 mL of pyridine and 2.8 mL of methanol there is added, little by little, 0.24 g of $NaBH_4$ (6.3 mmol, 1.2 eq.). The reaction mixture is heated at reflux for 9 hours. After cooling to ambient temperature, the reaction mixture is added to a solution of 9 mL of hydrochloric acid 37 % in 24 g of ice. The solution is extracted twice with dichloromethane. The organic phases are collected and the solvent is evaporated off under reduced pressure to yield 0.82 g of a red-brown oil which crystallises.

Yield = 82 %

m.p. = 47-48ºC

Example 3: 3-(2-bromo-4,5-dimethoxyphenyl)propanenitrile

Preparation of the title compound is based on the procedure described in the publication *J. Chem. Soc., Perkin Trans I* **1985**, 2151-2154 for preparation of 3-(2-bromo-5,6-dimethoxyphenyl)propanenitrile):

To a mixture of 21 g of 3-(3,4-dimethoxyphenyl)propanenitrile, 10.3 g of sodium acetate and 400 mL of acetic acid there are added 20 g of dibromine in 50 mL of acetic acid. The resulting reaction mixture is stirred overnight and then poured into water and extracted with benzene. The organic phase is washed with aqueous sodium thiosulphate solution and then with water, dried over sodium sulphate and concentrated under reduced pressure. The crude reaction product is purified on a silica column (eluant: benzene), and the product obtained is recrystallised from ethanol to yield 19.3 g of the expected product.

Yield = 65 %

m.p.: 78-80°C

Example 4: 3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile

Based on *Tetrahedron* **1973**, 29, pp 73-76

To a solution of $NaNH_2$, prepared starting from 200 mL of liquid NH_3 and 1 g of Na (catalyst: $FeCl_3$) there are added, in portions, 5.4 g of 3-(2-bromo-4,5-dimethoxyphenyl)propanenitrile and the reaction mixture is stirred at ambient temperature for 2 hours. After evaporating off the excess NH_3, 2 g of NH_4Cl and 200 mL of water are added in portions. The grey crystals formed are collected and recrystallised from ethanol to yield 2.38 g of the expected product.

Yield = 74 %

m.p. = 84-85°C

Example 5: 3,4-dimethoxy-*N*-methylbicyclo[4.2.0]octa-1,3,5-trien-7-amine

Based on EP 0 534 859

Step 1: 3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-amine hydrochloride

312 mL of a molar solution of borane complexed with THF are added dropwise, and whilst stirring at ambient temperature, to a solution of 25 g of 3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile in 250 mL of THF and left in contact for 12 hours; 200 mL of ethanol are then added and stirring is carried out for 1 hour. 100 mL of 3.3N ethereal HCl are added dropwise. 27.7 g of the expected product are obtained.

Yield = 90 %

m.p. = 205°C

Step 2: ethyl (3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)carbamate

1.5 mL of ethyl chloroformate are poured into a suspension of 3.4 g of the compound obtained in Step 1 in 4.5 mL of triethylamine and 50 mL of dichloromethane and left overnight, whilst stirring at ambient temperature; washing with water and with 1N hydrochloric acid is then carried out. Drying is carried out and the solvent is evaporated off to dryness. 3.2 g of an oil corresponding to the expected product are obtained.

Yield = 80 %

Step 3: 3,4-dimethoxy-*N*-methylbicyclo[4.2.0]octa-1,3,5-trien-7-amine

3.2 g of the compound obtained in Step 2 dissolved in 30 mL of THF are added to a suspension of 0.9 g of $LiAlH_4$ in 20 mL of THF. Refluxing is carried out for 1 hour 30 minutes, then hydrolysing using 0.6 ml of water and 0.5 mL of 20 % sodium hydroxide solution and, finally, 2.3 mL of water. The mineral salts are then filtered off, rinsed with THF and then the filtrate obtained is evaporated to dryness. 2.3 g of the expected compound are obtained.

Yield = 92 %

Example 6: (7*S*)-3,4-dimethoxy-*N*-methylbicyclo[4.2.0]octa-1,3,5-trien-7-amine

Based on EP 0 534 859

3,4-Dimethoxy-*N*-methylbicyclo[4.2.0]octa-1,3,5-trien-7-amine is reacted with an equimolar amount of (d) camphorsulphonic acid in ethanol. After evaporating off the solvent *in vacuo*, the salt is recrystallised first from ethyl acetate and then from acetonitrile until the target enantiomer is obtained with an optical purity of more than 99 % (evaluated by HPLC on a Chiralcel® OD column).

Example 7: 3-{3-[{[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}(methyl)amino]propyl}-7,8-dimethoxy-1,3-dihydro-2*H*-3-benzazepin-2-one

Based on EP 0 534 859

A solution of the (d) camphorsulphonate salt obtained in Example 6 in ethyl acetate is brought to basic pH using sodium hydroxide and then the organic phase is separated off, washed, dried over Na_2SO_4 and evaporated.

A mixture composed of 5.6 g of potassium carbonate, 2.2 g of the above amine in 100 mL of acetone and 4 g of 3-(3-iodopropyl)-7,8-dimethoxy-1,3-dihydro-2*H*-3-benzazepin-2-one is then refluxed for 18 hours.

The solvent is evaporated off *in vacuo*, and the residue is taken up in ethyl acetate and then extracted with 3N hydrochloric acid.

The aqueous phase separated off is brought to basic pH using sodium hydroxide and is then extracted with ethyl acetate. After washing until neutral and drying over $MgSO_4$,

evaporation *in vacuo* is carried out to obtain 4.5 g of an oil which is purified on a silica column using a mixture of dichloromethane/methanol (90/10) as eluant.

Yield = 64 %

Example 8: 3-{3-[{[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}(methyl)amino]propyl}-7,8-dimethoxy-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one

Based on EP 0 534 859

5 g of 3-{3-[{[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}(methyl)amino]propyl}-7,8-dimethoxy-1,3-dihydro-2*H*-3-benzazepin-2-one in 50 mL of glacial acetic acid are hydrogenated in a Parr apparatus under a hydrogen pressure of 4.9 bar at ambient temperature for 24 hours in the presence of 1 g of palladium hydroxide 10 %. The catalyst is filtered off, the solvent is evaporated off, and then the dry residue is taken up in water and ethyl acetate. The organic phase is dried over anhydrous magnesium sulphate, concentration *in vacuo* is carried out and then the residue is purified on a silica column using a mixture of dichloromethane/methanol (95/5) as eluant.

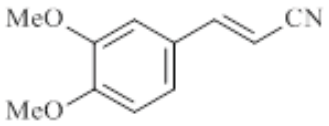
After recrystallisation from ethyl acetate, 2 g of the expected compound are obtained.

Yield = 40 %

m.p. = 101-103°C

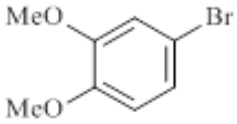
P a t e n t k r a v

1. Fremgangsmåte for syntese av forbindelsen av formel (I):



(I)

karakterisert ved at forbindelsen av formel (IX):



(IX)

underkastes en koblingsreaksjon med akrylonitril ved nærvær av en palladium-katalysator, en ligand, en base og et faseoverføringsmiddel i et organisk oppløsningsmiddel for å gi forbindelsen av formel (I).

2. Fremgangsmåte ifølge krav 1, **karakterisert ved** at palladiumkatalysatoren anvendt for å utføre omdannelsen av forbindelsen av formel (IX) til forbindelsen av formel (I) er valgt fra palladium-diacetat, palladium på karbon og palladiumklorid.

3. Fremgangsmåte ifølge krav 2, **karakterisert ved** at palladiumkatalysatoren som anvendes for å utføre omdannelsen av forbindelsen av formel (IX) til forbindelsen av formel (I), er palladium på karbon.

4. Fremgangsmåte ifølge ethvert av kravene 1 til 3, **karakterisert ved** at liganden som anvendes for å utføre omdannelsen av forbindelsen av formel (IX) til forbindelsen av formel (I), er valgt fra trifenylfosfin og tri(o-tolyl)fosfin.

5. Fremgangsmåte ifølge krav 4, **karakterisert ved** at liganden som anvendes for å utføre omdannelsen av forbindelsen av formel (IX) til forbindelsen av formel (I) er tri(o-tolyl)fosfin.

6. Fremgangsmåte ifølge ethvert av kravene 1 til 5, **karakterisert ved** at basen som anvendes til å utføre omdannelsen av forbindelsen av formel (IX) til forbindelsen av formel (I) er valgt fra trietylamin, natriumacetat, natriumkarbonat og kaliumkarbonat.

7. Fremgangsmåte ifølge krav 6, **karakterisert ved** at basen som anvendes for å utføre omdannelsen av forbindelsen av formel (IX) til forbindelsen av formel (I), er natriumacetat.

8. Fremgangsmåte ifølge ethvert av kravene 1 til 7, **karakterisert ved** at faseoverføringsmiddelet som anvendes for å utføre omdannelsen av forbindelsen av formel (IX) til forbindelsen av formel (I) er valgt fra tetrabutylammoniumbromid og tetrabutylammoniumklorid.

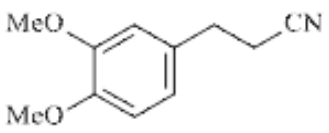
9. Fremgangsmåte ifølge krav 8, **karakterisert ved** at faseoverføringsmiddelet som anvendes for å utføre omdannelsen av forbindelsen av formel (IX) til forbindelsen av formel (I) er terabutylammoniumbromid.

10. Fremgangsmåte ifølge ethvert av kravene 1 til 9, **karakterisert ved** at det organiske oppløsningsmiddelet som anvendes for å utføre omdannelsen av forbindelsen av formel (IX) til forbindelsen av formel (I) er valgt fra N,N-dimetyl-acetamid og N,N-dimetylformamid.

11. Fremgangsmåte ifølge krav 10, **karakterisert ved** at det organiske oppløsningsmiddelet som anvendes for å utføre omdannelsen av forbindelsen av formel (IX) til forbindelsen av formel (I) er N,N-dimetylacetamid.

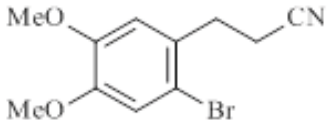
12. Fremgangsmåte ifølge ethvert av kravene 1 til 11, **karakterisert ved** at omdannelsen av forbindelsen av formel (IX) til forbindelsen av formel (I) utføres ved en temperatur mellom 100˚C til og med 170˚C

13. Fremgangsmåte ifølge krav 1, **karakterisert ved** at den fremstilte forbindelsen av formel (I) etterfølgende blir omdannet til forbindelsen av formel (X):



(X)

ved en reduksjonsreaksjon,
hvilken forbindelse omdannes tikl forbindelsen av formel (VIII):



(VIII)

ved en bromineringsreaksjon.

14. Fremgangsmåte for syntese av ivabradine, farmasøytisk akseptable salter derav samt hydrater derav, **karakterisert ved** at:

- forbindelsen av formel (IX) omdannes til forbindelsen av formel (I) i samsvar med fremgangsmåten ifølge krav 1,
- forbindelsen av formel (I) omdannes derpå til forbindelsen av formel (VIII) i samsvar med fremgangsmåten ifølge krav 13,
- forbindelsen av formel (VIII) omdannes derpå til ivabradine, som kan omdannes til addisjonssalter derav med en farmasøytisk akseptabel syre valgt fra saltsyre, hydrobromsyre, svovelsyre, fosforsyre, eddiksyre, trifluoreddiksyre, melkesyre, druesyre, malonsyre, ravsyre, glutarsyre, fumarsyre, vinsyre, eplesyre, sitronsyre, askorbinsyre, oksalsyre, metansulfonsyre, benzensulfonsyre og kamfersyre samt til hydrater derav.