Organic Process Research & Development

HIGHLIGHTS FROM THE PATENTS

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A Review of U.S. Patents in the Field of Organic Process Development Published During December 2010 and January 2011

SUMMARY

The current selection of patents contains 20 from an original list containing 267 that fitted the selection criteria. Some patents have a considerable amount of experimental detail and space limits the amount that can be included in the review. On the other hand, there are others that have so little detail that it is difficult to accept the claims in the patent. An example is a new process for the preparation of pramipexole, a drug used to treat Parkinson's disease and schizophrenia. The patent claims two novel compounds that are intermediates but provides no physical properties or spectral details for them whatsoever. Another example of lack of detail is in a patent describing a process to prepare pyran compounds that can be used in flavours and perfumes. None of the examples give details of the scale of the experiment nor provide information on the quantities of reagents used; however, there is plenty of spectral data. An example of an abundance of details is a very comprehensive patent on statins that describes several novel intermediates and gives detailed experimental information and spectral details for them all. Two patents from different companies cover novel polymorphs of the antiparasitic agent atovaquone, and it seems that the new polymorphs are all different. A method of improving a process by reducing the number of stages is usually cost-effective but can result in handling problems. For example, a one-step method of making phenothiazine alkylsulfonate derivatives uses very potent carcinogenic sultone compounds. A process that does eliminate the use of hazardous and toxic reagents is exemplified by a patent describing a method to purify ropinirole, another drug used to treat Parkinsonism. The patent describes a means of removing coloured impurities, but it is not clear which reagent is actually used and hence what is the basis of the invention. A process for preparing a high-purity fluoroisoquinoline salt is described that avoids the use of diazonium salts that can be unstable. The removal or minimisation of organic solvents is an area of great activity, and a process for preparing imidazole-2-thiones does not use solvents and generally starts from liquid reagents. In cases where this is not possible or the product is a solid, then a melting point depressant is added to the reaction mixture, and the product yields are very good. A process for producing an enriched mixture of the aroma chemical isopulegol uses the technique of melt crystallisation that also avoids the use of solvents. The purification of an intermediate used to prepare a thiazole pesticide is generally by distillation, but azeotropes can be formed by some reaction impurities. By removing these before distillation the process is improved. Ionic liquids are of interest as reagents and solvents, and a new process claims to produce such compounds with virtually any anion and with very low levels of impurities. Oxycodone is used to relieve severe pain after surgery, and two patents describe methods for removing Michael acceptor impurity levels in the drug. There does appear to be some overlap in the two processes that may result in a legal dispute between the parties. Halogenation reactions can give rise to waste disposal or safety problems, and two patents address such concerns. One replaces 1,2-diiodoethane in an iodination step with F_5C_5I in the synthesis of pyrazole antidepressants, and the other improves the production of dibromodiamantane by using $AlBr_3$ and Br_2. In two separate patents new methods are described for the preparation of the antipsychotic drugs quetiapine and asenapine. A range of sugar derivatives of benzimidazole compounds is described that are antivirals, and a new route for preparing the antiemetic drug dolasteron is disclosed that involves novel intermediates. A number of the patents in this collection describe experiments carried out on a kilo or multikilo scale, and this may suggest an advanced stage of development or even commercial operation. However, there is no legal or commercial significance in the choice of patents in this review. The advantages mentioned herein are those claimed in the patent, unless this reviewer has personal knowledge of the subject.

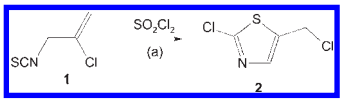
PATENT NO. U.S. 7,846,304

Assignee: Toyo Boseki Kabushiki Kaisha, Osaka, Japan

Title or Subject: Process for Purification of 2-Chloro-5-chloromethyl-1,3-thiazole

The title compound **2** is an intermediate in the production of pesticides that can be purified by vacuum distillation. A recrystallisation process has been proposed elsewhere, but this patent suggests that such a process is not industrially viable. One reason for this is that the crystals melt at 30 °C and the solid is a skin irritant, giving rise to handling and safety problems. Purification by distillation can be problematic because reaction impurities can decompose or form azeotropes with **2** during distillation unless they are removed first. Hence, the patent discloses a process for purifying **2** that removes impurities before distillation of the product. The method involves the treatment of crude **2** with a lower alcohol followed by distillation <200 °C and at a pressure of 3−10 kPa. The patent contains four examples each describing the preparation of 1000 kilo batches of **2** by chlorination of the isocyanate **1** using SO_2Cl_2 as shown in Scheme 1.

Scheme 1[a]



[a] Reagents and conditions: (a) (i) PhMe, 45 °C, 5 h; (ii) 80 °C, 1 h.

After the reaction is complete, most of the PhMe is distilled off and a small amount of MeOH added to the concentrated solution at 39 °C. After heating at 60 °C for 1 h the mixture is distilled to remove the MeOH and PhMe as an azeotrope. The amount of

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MeOH added seems to be enough to remove the remaining PhMe as the MeOH/PhMe azeotrope. The product is recovered by fractional distillation under reduced pressure, and a yield of 78% of **2** is obtained with purity 98.3%.

Advantages. The process improves the recovery and purification of the desired product and is clearly suitable for large-scale production.

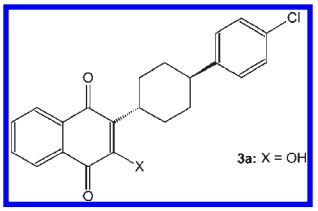
PATENT NO. U.S. 7,847,112

Assignee: Health Science Funding LLC, Morristown, New Jersey, U.S.A.

Title or Subject: Polymorphs of Atovaquone and Process for Its Preparation

Atovaquone **3a** is an antiparasitic agent used in the treatment of pneumonia caused by *Pneumocysis carinii*. It is also used in combination with proguanil for the treatment and prevention of malaria. This is the first of two patents from different companies on this compound, and both patents claim novel but apparently different polymorphs of the drug. This patent states that polymorphs of **3a** have not yet been reported, and it describes three polymorphs designated Forms I, II, and III. **3a** is prepared by the method described in U.S. 4,981,874, and this is referred to as Form I and crystals obtained from a DCM solution by addition of MeOH or *n*-heptane at rt. Form II is obtained from Form I by dissolution in refluxing dioxane followed by cooling to 5 °C. Form III is obtained from Form I by one of three methods; refluxing in Me_2CO followed by addition of H_2O, dissolution in $CHCl_3$ at rt followed by addition of MeOH, or by dissolution in refluxing Pr^i_2O then cooling. The patent provides XRD spectra and DSC thermograms of the three polymorphs, but the patent does not report on the relative thermal stability of the three polymorphs.

Atovaquone



Advantages. The process gives novel polymorphs of this important drug that can be used in preparation of pharmaceutical formulations.

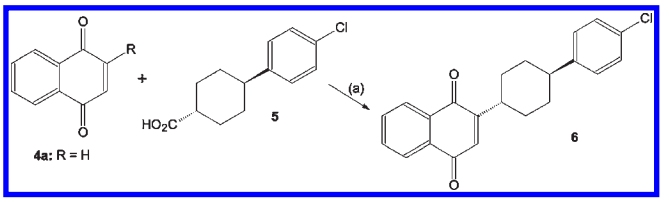
PATENT NO. U.S. 7,847,127

Assignee: IPCA Laboratories Ltd., Mumbai, India

Title or Subject: Process for Preparation of Atovaquone and Novel Intermediates Thereof

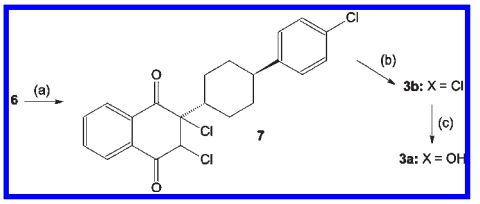
This is the second patent covering **3a** that also describes novel polymorphs and in addition contains synthetic details for the preparation of novel intermediates. This patent states that there are only a few reports of alternative methods for preparing **3a** that are apparently based on decarboxylative condensation processes and give very poor yields of 3−5%. This patent refers to the PCT publication (WO/2006/008752) as being the first to identify the existence of three polymorphs of **3a**. An objective of this work is to develop a form of **3a** that has increased bioavailability and solubility. The synthesis of **3a** is outlined in Schemes 2 and 3. The first stage is the preparation of **6** by condensation of **4a** and **5** in the presence of $AgNO_3$ and a persulphate. The yield of **6** after

Scheme 2[a]



[a] Reagents and conditions: (a) (i) $AgNO_3$, H_2O, MeCN, reflux; (ii) $(NH_4)_2S_2O_8$, H_2O, reflux, 2 h; (iii) cool <5 °C, extract in DCM, wash; (iv) evaporate; (v) add MeCN, filter, crystallise.

Scheme 3[a]



[a] Reagents and conditions: (a) (i) Cl_2, HOAc, 20 °C; (ii) H_2O, filter, dry. (b) (i) NaOAc, HOAc, reflux, 1 h; (ii) cool, add H_2O, filter. (c) (i) MeOH, add aq NaOH, 20 min; (ii) reflux, 45 min; (iii) cool <5 °C, filter; (iv) 50% HCl, filter.

crystallisation from MeCN is 20%, and although low, this is an improvement compared to alternative methods that involve the reaction of **5** with the chlorosubstituted compound **4b** (R = Cl).

In the next stage **6** is chlorinated using Cl_2 gas to form **7** in 95% isolated yield, and dehydrochlorination of **7** forms **3b** that is isolated in 70% yield after crystallisation. Hydrolysis of **3b** using HCl forms **3a** that, after crystallisation, is isolated in 70% yield.

The crystals obtained by the above method are identified as Form I and are used to prepare a polymorph designated as Form IPCA-ATO. This is done by dissolving in DCM, filtering, and then solidifying the solution using liquid N_2. Such a technique is not likely to be commercially viable although it does demonstrate the existence of the new polymoprh. The material is then said to be lyophilized with DCM, and after removal of the DCM by an unspecified method the novel polymorph is isolated in quantitative yield. The actual claims of this patent cover the novel intermediates compounds **6** and **7**, methods for their preparation, and their use in the synthesis of **3a**. Also covered in the patent is the epimerization of a mixture of **3a** and its *cis*-isomer using 90% H_2SO_4. The result was **3a** in 99.8% purity. The patent provides XRD and IR spectra and a DSC thermogram of the new polymorph as well as ^1H and ^{13}C NMR data for the novel intermediates.

Advantages. The process gives an improved yield of the desired drug molecule, a novel polymorph, and a method of recovering any *cis*-isomer that is formed.

PATENT NO. U.S. 7,855,287

Assignee: Cyanagen Srl, Bologna, Italy

Title or Subject: Preparation of High-Purity Phenothiazine *N*-Alkylsulfonates and Their use as Chemiluminescent Assays for Measuring Peroxidase Activity

Water-soluble phenothiazine alkylsulfonate derivatives are used in detergents as accelerators of peroxidases and in solar

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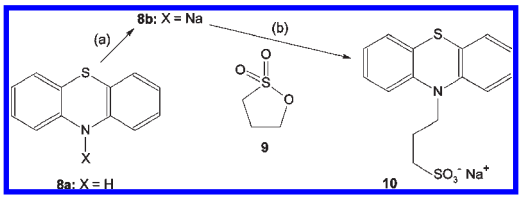
Scheme 4[a]



[a] Reagents and conditions: (a) (i) NaH, THF, rt, 1 h; (ii) 50 °C, 0.5 h. (b) (i) THF, 0 °C, 0.5 h; (ii) rt, 0.5 h; (iii) filter, wash in THF then Et_2O, dry.

energy conversion systems. Current methods of making such compounds are said to be expensive; hence, alternative processes are desired. The patent states that the literature method requires two steps, whereas the new process only needs one, and this is shown in Scheme 4. The reaction is shown as two stages, but the anion **8b** is not isolated. After formation of **8b** the solution is orange, and after the addition of **9** it immediately changes to clear yellow, and this fades to colourless. During this time the salt precipitates from solution, and after washing **10** is isolated in 92.9% yield and said to be of high purity containing <0.0002 mol % of **8a**. It can be recrystallised from EtOH. The patent also describes the preparation of *n*-butyl analogue of **8b**. Although this synthesis is very efficient, it does involve the use of very potent carcinogenic sultones, and no mention is made of this.

Advantages. The patent claims that the procedure is simple and gives a product of extraordinary purity. Chemically the process may indeed be simple, but handling such dangerous materials may not.

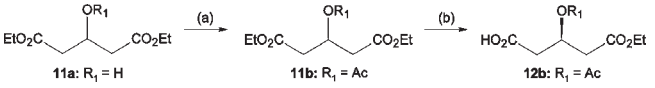
PATENT NO. U.S. 7,855,302

Assignee: Ciba Specialty Chemicals Corp., Tarrytown, New York, U.S.A.

Title or Subject: Process for the Preparation of 7-Amino-3,5-dihydroxyheptanoic Acid Derivatives, Intermediates in the Synthesis of Statins

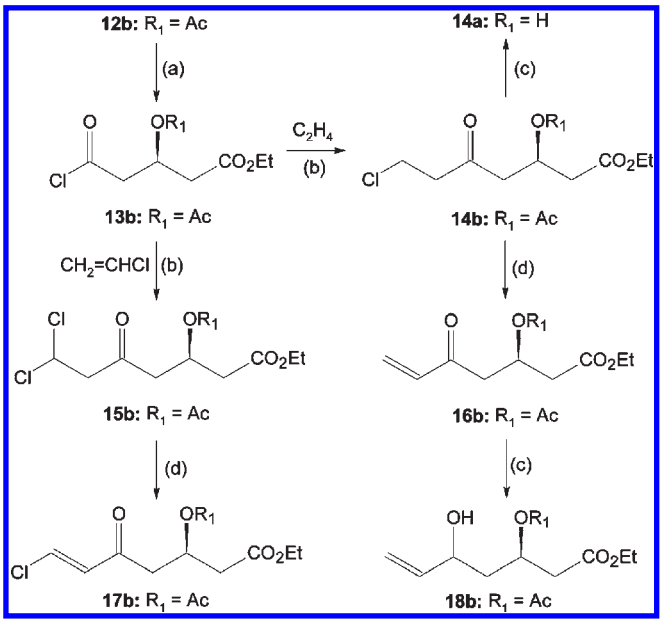
Improvements in the synthesis of statins for controlling blood cholesterol levels are regularly reported and have been recently reviewed (*Org. Process Res. Dev.* **2011**, *15*, 10). The current patent describes a range of novel compounds that can be used in the synthesis of statins, and the claims cover these compounds that are exemplified by **12b**. The patent contains a complex series of reaction schemes and has a substantial amount of experimental information that can only be covered in a cursory manner. The interested reader is recommended to consult the patent for further details. The synthesis of **12b** is shown in Scheme 5 and begins with acetylation of **11a** to form **11b** in 98.8% isolated yield and is described as pure by NMR. The acetate is stereoselectively

Scheme 5[a]



[a] Reagents and conditions: (a) (i) Ac_2O, pyridine, rt, 12 h; (ii) EtOAc; (iii) wash in HCl, $NaHCO_3$, brine; (iv) dry, evaporate. (b) (i) α-Chymotrypsin, H_2O, buffer at pH 7, rt; (ii) 0.5 M NaOH to give pH 7.8, rt; (iii) extract in EtOAc, evaporate.

Scheme 6[a]



[a] Reagents and conditions: (a) (i) $(COCl)_2$/DMF, DCM, <5 °C, 0.5 h; (ii) rt, 1.5 h. (b) $AlCl_3$, EDC, 40 °C. (c) (i) PLE, KH_2PO_4, EtOH, pH 7 (ii) 0.5 M NaOH, pH 7, rt. (d) Et_3N, Et_2O, rt.

hydrolysed in the presence of α-chymotrypsin, giving **12b** in 97% isolated yield (purity not reported).

The patent describes a complex series of reactions involving **12b** and its derivatives. Scheme 6 outlines a selection of these, but space limitations preclude the inclusion of the workup procedures. Chlorination of **12b** using $(COCl)_2$ and DMF gives **13b** that is isolated in quantitative yield in pure form (by NMR). Treatment of **13b** with gaseous C_2H_4 in the presence of $AlCl_3$ produces **14b** that is isolated as an oil in virtually quantitative yield. The acetate can be stereoselectively hydrolysed to **14a** in the presence of pig's liver esterase (PLE). Treatment of **13b** with vinyl chloride produces **15b** that is isolated as a brown oil, purified by column chromatography (ColC), and isolated in 91% yield. This can be dehydrochlorinated with Et_3N to give **17b** that is isolated as a dark-red oil in 71% yield that is pure enough for further reactions but can be purified by ColC. This chloro compound can be converted to the iodo analogue by treatment with NaI in Me_2CO. The chloroketone **14b** is used to prepare **16b** by dehydrochlorination with Et_3N, and the product is isolated in 71% yield after purification by ColC. Hydrolysis of **16b** in the presence of PLE gives **18b** in 26.5% yield.

The patent describes a further series of reactions of **14b** and derivatives that are shown in Scheme 7. The first reaction is formation of the azide **19b** by reaction of **14b** with NaN_3 in the presence of 18-crown-6. The azide is isolated in 82% yield, and then the acetate group is hydrolysed using Chirazyme E1 to give **19a** in 86% yield after ColC. The ketone group in **19a** is then reduced using Et_3B and $NaBH_4$ and **21a** is isolated as an oil in 71% in yield. Acid-catalysed reaction of **21a** with $(MeO)_2CMe_2$ produces **20a** that is isolated in 85% yield as an oil, and the azide group is then catalytically reduced, giving **20b** in 93% yield.

The patent also contains examples describing the formation of analogues of **12b** in which R_1 = $MeOCH_2CH_2$ or $MeOCH_2$, and the products are then used in reactions analogous to those described above. The preparation of a number of Bu^t ester analogues is also described. The patent reports that the amine

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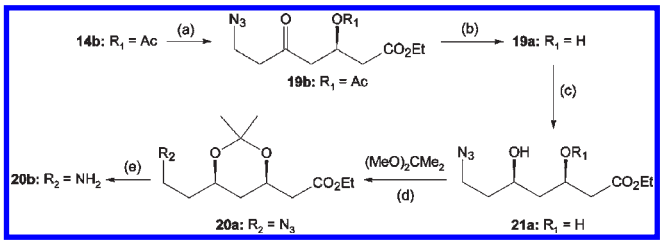
Scheme 7[a]



[a] Reagents and conditions: (a) 18-crown-6, NaN_3, DMF, rt. (b) Chirazyme E1, KH_2PO_4, EtOH, pH 7; (ii) 0.5 M NaOH, pH 7, rt. (c) (i) Et_3B, MeOH, THF, rt, 1 h; (ii) $NaBH_4$, −65 °C, 1.5 h. (d) TsOH, THF, rt, 2.5 h. (e) Pd/C, EtOH, H_2, 10 bar, 30 °C, 1 h.

20b is used to prepare atorvastatin and cerivastatin, but no details are provided. ^{1}H NMR data are provided for all the novel compounds.

Advantages. The patent reports the synthesis of a range of novel compounds that can be used in the preparation of a number of statins.

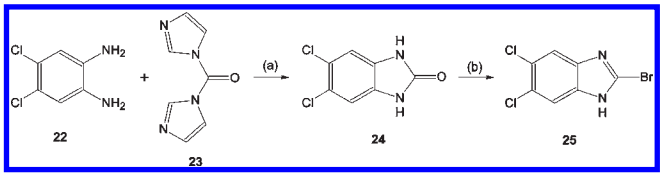
PATENT NO. U.S. 7,858,773

Assignee: GlaxoSmithKline LLC, Philadelphia, Pennsylvania, U.S.A.

Title or Subject: Process for Preparing Substituted Benzimidazole Compounds

This patent has a single, very comprehensive claim that covers the preparation of a wide range of the title compounds. The compounds covered are sugar derivatives such as pyranosides or furanosides that have antiviral activity. These are made from the bromo-derivative **25** that is obtained by the method outlined in Scheme 8. The first stage is cyclisation of the diamine **23** with the diimidazole **22** to form **24**. The reaction is carried out at rt in THF, and either **22** is added to **23** in THF or vice versa. The yield is >95% in both cases, and the product is then brominated using $POBr_3$ to give **25**. The crude product is isolated in 77% yield, and after crystallisation from hot EtOAc a 34% yield of purified product is obtained.

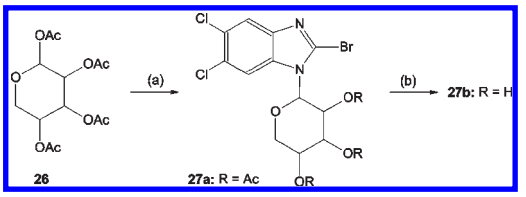
Scheme 8[a]



[a] Reagents and conditions: (a) (i) THF, rt; (ii) add H_2O, cool, filter, wash, dry. (b) (i) $POBr_3$, EtOAc, reflux, 29 h; (ii) cool 20 °C, add H_2O; (iii) separate, H_2O wash, active C, evaporate; (iv) EtOAc/isooctane, filter, dry.

The bromo compound **25** is then used to prepare a series of derivatives such as **27a** and **27b**. The first stage is silylation of **25** using $Me_3SiOC(Me)=NSiMe_3$ and $TfOSiMe_3$. The appropriate acetylated sugar derivative such as the β-D-ribopyranose **26** is then added to form **27a**. The OAc leaving group of the sugar molecule is in the α- or β-position. The patent also describes the preparation of the β-L-ribofuranose analogue of **27a**. The acetyl groups in **27a** are then removed by base hydrolysis using LiOH to form **27b**. The crude product is isolated and then purified by ColC to give **27b** in 56% yield (Scheme 9). The Br in **27b** can be

Scheme 9[a]



[a] Reagents and conditions: (a) (i) $Me_3SiOC(Me)=NSiMe_3$, EDC, reflux, 0.5 h; (ii) $TfOSiMe_3$, rt; (iii) **25**, reflux, 0.5 h; (iv) aq NaHCO3, extract in DCM, dry, evaporate. (b) 1 M LiOH, dioxane, <5 °C; (ii) rt, 1 h; (iii) buffer to give pH 7, extract in EtOAc; (iv) dry, evaporate.

converted to NH_2 by reaction with an amine such as Pr^iNH_2, or cyclopentylamine in refluxing EtOH, and the product is isolated in a yield of around 60%.

^{1}H NMR data are given for **27a** and **27b** and for the furanose analogues.

Advantages. The patent describes new methods for preparing compounds that have antiviral activity.

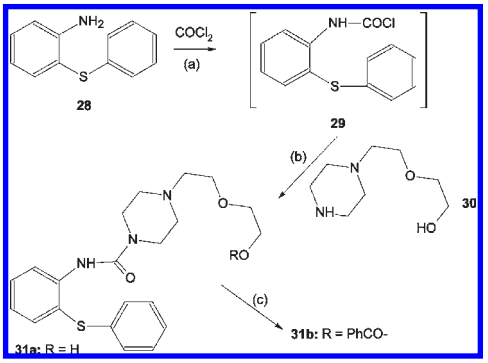
PATENT NO. U.S. 7,858,777

Assignee: Fermion Oy, Espoo, Finland

Title or Subject: Method for the Preparation of Quetiapine

Quetiapine **32a** (R = H), is an antipsychotic agent used in the treatment of schizophrenia and is available as Seroquel. A patent describing its preparation was reviewed recently (*Org. Process Res. Dev.* **2010**, *14*, 759), and the current patent provides an alternative two-stage process for preparing **32a** . The first stage, shown in Scheme 10, is to prepare the amide **31a** by reaction of **28** with $COCl_2$ to form the intermediate **29** that is not isolated but treated with **30** to give the amide that is isolated in 79% yield. The next step is protection of the OH group by treatment of **31a** with PhCOCl to form **31b** that is isolated in 97% yield.

Scheme 10[a]



[a] Reagents and conditions: (a) (i) Et_3N, PhMe, −50 °C, 5 min; (ii) rt, 1.5 h. (b) (i) Et_3N, PhMe, −10 °C; (ii) rt, 1.5 h; (iii) filter, wash, dry. (c) PhCOCl, PhMe, <10 °C; (ii) 20 °C, 16 h; (iii) 1 M NaOH, H_2O, 20 °C, 20 min; (iv) separate, wash, dry.

The next stage of the synthesis is the cyclisation of **31b** to form **32b**, and this is carried out by treatment with $POCl_3$ and P_2O_5 as shown in Scheme 11. **32b** is obtained in 79% yield, and then the protective group is removed by treatment with NaOH giving **32a** that is isolated in 81.6% yield.

^{1}H NMR data are given for all isolated intermediates.

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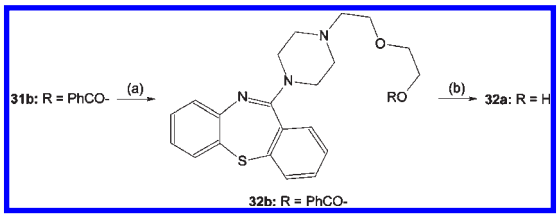
Scheme 11[a]



[a] Reagents and conditions: (a) (i) $POCl_3$, P_2O_5, 90 °C. 19 h; (ii) evaporate; (iii) DCM, ice/H_2O, 0 °C, $NaHCO_3$ to give pH 8; (iv) separate, wash, dry evaporate; (b) (i) 50% aq NaOH, EtOH, 80 C, 2 h; (ii) evaporate; (iii) EtOAc, brine, 50% NaOH to give pH 12; (iv) extract in EtOAc, wash, dry, evaporate.

Advantages. The process provides an alternative synthesis of the desired API via novel intermediates.

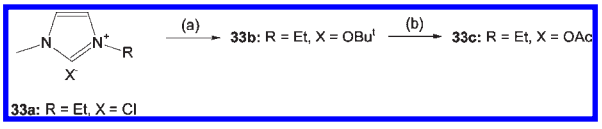
PATENT NO. U.S. 7,858,802

Assignee: BASF SE, Ludwigshafen, Germany

Title or Subject: Method of Preparing Ionic Liquids

The interest in ionic liquids has increased significantly in the past few years. A patent from BASF, covering the use of imidazolium ionic liquids as entrainers in the separation of azeotropic mixtures, has been previously reviewed (*Org. Process Res. Dev.* **2009**, *13*, 371). Alternative methods of preparing ionic liquids are summarised, and it is claimed that they can result in products containing high residual levels of impurities. The current patent is very wide ranging and claims that ionic liquids can be made containing virtually any anion. The cation of the ionic liquids is an imidazolium group, and examples are given for the preparation of ionic liquids with the anions AcO^-, TsO^-, $H_2PO_4^-$, $H_2BO_3^-$, cyanurate, and saccharinate. Two methods are described for preparing the liquids that are termed the alkoxide or the barium methods. Scheme 12 shows the alkoxide method used to prepare **33c**. Using solid Bu^tOK, a solution of the alkoxide in Bu^tOH is prepared, and molten **33a** is added to form the butoxide salt **33b**. This is treated with HOAc to form the desired ionic liquid **33c** that is isolated as an oil in 95.2% yield, containing 0.52% Cl and 0.04% H_2O. **33c** may also be prepared in 90% yield by intermediate formation of the ethoxide salt. The butylmethylimidazolium acetate is also prepared by the same procedure.

Scheme 12[a]



[a] Reagents and conditions: (a) (i) Bu^tOK, Bu^nOH, rt, 3 h; (ii) filter, wash in Bu^nOH. (b) (i) HOAc, rt; (ii) evaporate, extract with EtOAc, dry.

The barium method for preparing **33c** and related compounds starts from the imidazolium HSO_4 salts and uses hydrated $Ba(OH)_2$. The patent does not describe the preparation of the imidazolium HSO_4 salt that still contains excess H_2SO_4. The reactions take place in H_2O, and in one example **33c** is isolated in 88% yield containing 180 ppm Cl, 160 ppm S, 650 ppm Ba, and 0.68% H_2O.

Advantages. The process provides an effective method of preparing a wide range of these salts that have useful applications.

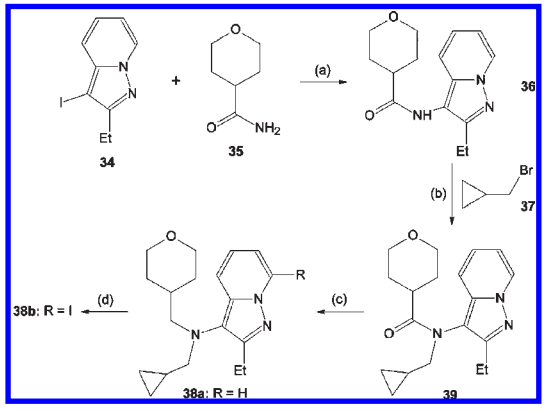
PATENT NO. U.S. 7,858,809

Assignee: Eisai R&D Management Co. Ltd., Tokyo, Japan

Title or Subject: Process for Production of Pyrazole-Fused Ring Derivatives

The claims of this comprehensive patent cover the novel iodopyrazole compound **38b** that is an intermediate in the synthesis of pyrazole antidepressants. In the synthesis of the phenylpyrazole derivatives the patent states that there is a generally an iodination step and an amine group is introduced. It is stated that iodination using 1,2-diiodoethane is not suitable on an industrial scale and the introduction of the amine group gives low yields. Scheme 13 outlines the new route for the

Scheme 13[a]



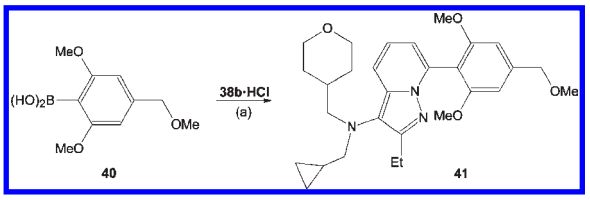
[a] Reagents and conditions: (a) (i) CuI, CHD, K_3PO_4, xylene, 120 °C, 6 h; (ii) Cool to 61.5 °C, add hot H_2O; (iii) NH_3, 1 h, filter; (iv) wash, dry. (b) (i) Bu^tOK, DME, 40 °C, 4 h; (ii) PhMe, H_2O; (iii) wash, evaporate. (c) (i) $BH_3 \cdot THF$, THF, 55 °C, 2 h; (ii) cool, 2 M HCl; (iii) 50 °C, 1 h; (iv) cool, 5 M NaOH to give pH 8, separate; (v); PhMe, H_2O, evaporate. (d) (i) Bu^nLi, THF, −73 °C, 1 h; (ii) F_5C_5I, −73 °C, 80 min; (iii) H_2O, THF, heptane; (iv) separate, H_2O wash; (v) 5 M HCl, separate; (vi) 5 M NaOH; (vii) extract in PhMe, wash, evaporate, dry.

preparation of **38b** and begins with the reaction of **34** with **35** in the presence of a mixture of CuI, K_3PO_4, and an amine compound that acts as a ligand. In the patent example the amine used is the *cis*/*trans* mixture 1,2-cyclohexanediamine (CHD). The product is said to be a 6:1 mixture of two conformers of **36** in 79.6% isolated yield. In the next step the amine group in **36** is alkylated using **37** in the presence of a base to form **39** that is isolated as an oil in 92.6% yield. The next step is reduction of the amide group with $BH_3 \cdot THF$ giving **38a** in 99.2% isolated yield. The iodination of **39** is a key feature of this patent and is carried out using F_5C_5I. The first stage of this reaction is low-temperature treatment of **38a** with Bu^nLi followed by addition of F_5C_5I. The product **38b** is a deep green oil that is isolated in 87.3% yield, and a crystalline product can be obtained in 63% yield by crystallisation of the crude product from MeCN/H_2O. The HCl salt can be isolated as a solvate of $(MeO)_2CO$ and Pr^iOH in 93.7% yield by treating a solution of **38b** in $(MeO)_2CO$ with concd HCl and Pr^iOH.

The HCl salt of **38b** can be converted to **41** by a Pd-catalysed coupling reaction with **40** (Scheme 14). The patent example describes the use of a ratio of **38b**·**HCl** to **40** of almost 4:1. The crude **41** is obtained as a green solid and is converted to the Ts salt that is isolated in 79.5% yield.

dx.doi.org/10.1021/op200077a |*Org. Process Res. Dev.* 2011, 15, 491–502

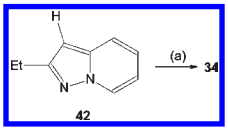
Scheme 14[a]



[a] Reagents and conditions: (a) (i) $Pd(OAc)_2$, PPh_3, K_2CO_3, H_2O, DME, 100 °C, 6 h; (ii) cool rt, extract in PhMe; (ii) wash in HCl; (iv) Pr^iOAc, 5 M NaOH to give pH 14, 0 °C; (v) wash in aq $(H_2NCH_2)_2$, H_2O; (vi) concentrate, wash in EtOH, azeotropic distillation.

The patent describes the preparation of the starting materials **34**, **35**, and **40**. Scheme 15 shows the method used to obtain **34** by treatment of **42** with NaI in the presence of NCS, giving the product in 98.9% yield despite a lengthy workup procedure.

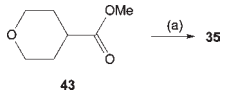
Scheme 15[a]



[a] Reagents and conditions: (a) (i) NCS, NaI, H_2O, EtOAc, 0 °C, 0.5 h; (ii) rt, 140 min; (iii) add H_2O/EtOAc; (iv) extract in EtOAc; (v) wash in $Na_2S_2O_3$, evaporate; (vi) dissolve in hexane, filter, H_2O wash, evaporate; (vii) dissolve in EtOAc, evaporate.

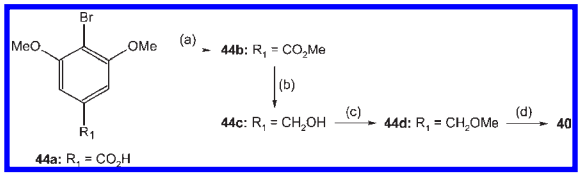
The preparation of **35** by reaction of the methyl ester **43** with NH_3 is shown in Scheme 16 and takes 43.5 h, producing **35** in 74.6% yield.

Scheme 16[a]



[a] Reagents and conditions: (a) (i) rt, 43.5 h; (ii) cool to 0 °C, filter, dry at 40 °C.

Scheme 17[a]



[a] Reagents and conditions: (a) (i) K_2CO_3, MeI, DMF, 0 C; (ii) rt, 17 h. (b) (i) $LiBH_4$, THF, rt; (ii) reflux, 3 h. (c) (i) NaH, rt 10 min; (ii) MeI, DMF, rt, 1 h. (d) (i) Bu^nLi, THF, −78 °C, 20 min; (ii) $(MeO)_3B$, THF, −78 °C.

The phenyl borate compound **40** is obtained by the multistep route shown in Scheme 17. The detailed workup procedures are omitted, and only the main reactions are shown. The procedure starts from **44a** that is reacted with MeI to form the methyl ester **44b** that is isolated in 99% yield. This is then reduced with $LiBH_4$ to give the benzyl alcohol **44c** in 99% yield. The alcohol is converted to the methyl ether **44d** by treatment with NaH followed by MeI, and the crude product is purified by ColC, and **44d** is isolated as a colourless oil in 96% yield. In the final step **44d** is treated with Bu^nLi followed by $(MeO)_3B$ both at −78 °C, and the product is isolated as a white solid in 86% yield after purification by ColC.

^1H NMR data are provided for the vast majority of the compounds prepared, and a number of the examples are carried out on half-kilo scale, thus indicating that the scale-up potential has been investigated.

Advantages. The process provides a novel intermediate for the preparation of the desired iodopyrazole compounds and gives good yields by methods that are industrially viable.

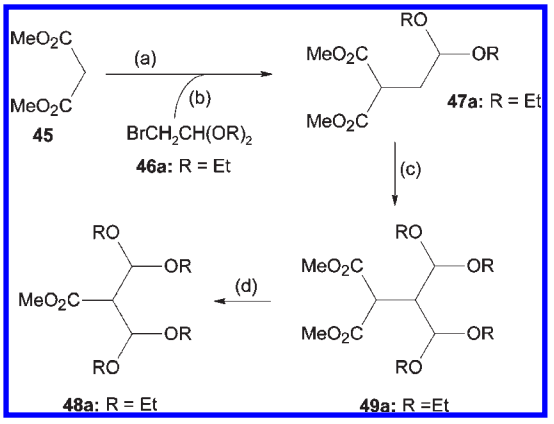
PATENT NO. U.S. 7,858,821

Assignee: INKE SA, Barcelona, Spain

Title or Subject: Intermediate Compounds Useful in the Preparation of Dolasetron

Dolasetron **57b** is an antiemetic, available as Anzemet, and is especially useful to patients receiving chemotherapy. A number of alternative processes for preparing **57b** are summarised and are described as having problems that make them unsuitable for industrial production such as the use of protecting groups or ColC. The patent discloses that the novel esters **48a** (R = Et) and **48b** (R = Me) are particularly useful in the synthesis of **57b**, and these compounds and their synthesis are the subject of the patent and its claims. Scheme 18 outlines the synthesis of **48a** via the

Scheme 18[a]



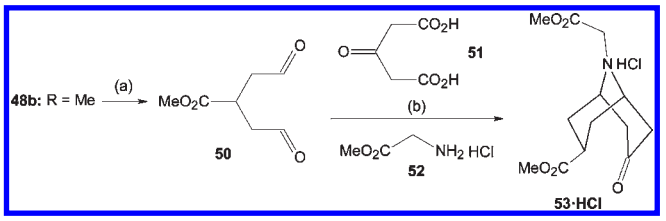
[a] Reagents and conditions: (a) Bu^tOK, DMF, 25 °C. (b) (i) 60 °C; (ii) 90 °C, 8 h; (iii) evaporate at 50 °C; (iv) extract in PhMe; (v) wash in H_2O, evaporate. (c) (i) Same as (a); (ii) **46a**, 60 °C; (iii) 120 °C, 10 h; (iv) same as (b) (iii), (iv), and (v). (d) (i) NaBr, DMF, 150 °C, 12 h; (ii) same as (b) (iii), (iv), and (v).

formation of **47a** and **49a**. The first step is base-catalysed condensation of **45** with **46a** to form **47a** that is obtained as a colourless oil in 75% yield after evaporation of DMF, extraction into PhMe, and then water washing. A further condensation of **46a** with **47a** produces **49a** that is also recovered as an oil in 70% yield. In the final step **49a** is decarboxylated by heating with NaBr in DMF, and **48a** is isolated in 80% yield as a colourless oil. The patent also describes the preparation of **48b** in a one-pot process without isolation of the intermediate **47b**.

The preparation of **57b** from **48b** is described in the patent and takes place in several stages, the first of which is the formation of the HCl salt of **53** as shown in Scheme 19. The first step is acid hydrolysis of **48b** to form **50** that is not isolated but undergoes a

dx.doi.org/10.1021/op200077a |Org. Process Res. Dev. 2011, 15, 491–502

Scheme 19[a]

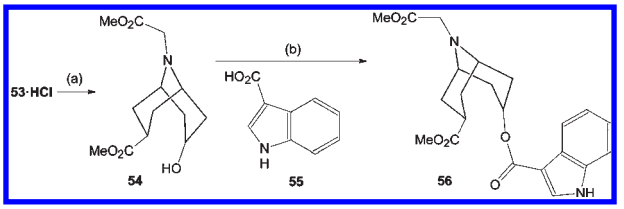


[a] Reagents and conditions: (a) (i) 1 M HCl, rt, 1 h; (ii) citric acid; (iii) NaOH to give pH 2. (b) (i) Na_2HPO_4, 25 °C, 24 h; (ii) HCl to give pH 0.8; (iii) PhMe wash; (iv) 50% K_2CO_3 to give pH 6.8; (v) extract in Pr^iOAc; (vi) aq HCl; (vii) crystallise Pr^iOH/H_2O.

Robinson–Schöpf condensation with **51** and **52** in the presence of Na_2HPO_4 to form **53**. The free base can be isolated by evaporation of the solvent, or the HCl salt is obtained as a monohydrate after crystallisation from Pr^iOH/H_2O. The XRD and IR data for polymorph Form I of this salt are provided, and the salt is said to be a key aspect of the patent.

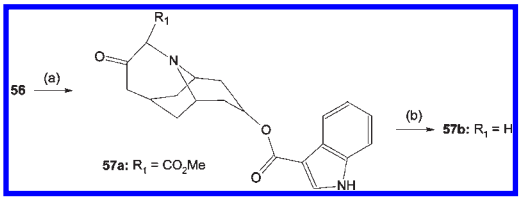
The next stage in the synthesis of **57b** is outlined in Scheme 20 in which **53·HCl** is reduced with $NaBH_4$ to give **54** in 76% isolated yield as a colourless oil. The next step is esterification of **54** with **55** using TFAA and a catalytic amount of DMAP to produce **56**. This is isolated in 89% yield after filtration and drying and used directly in the next step as shown in Scheme 21 although it can be converted to the HCl salt.

Scheme 20[a]



[a] Reagents and conditions: (a) (i) MeOH, Na_2CO_3, 0 °C; (ii) $NaBH_4$, 0 °C, 1 h; (iii) Me_2CO, HCl. (b) (i) TFAA, DMAP, DCM, rt, 4 h; (ii) H_2O, aq $NaHCO_3$, filter; (iii) separate, dry, evaporate.

Scheme 21[a]



[a] Reagents and conditions: (a) (i) Bu^tOK, THF, rt, 3 h; (ii) H_2O, 1 M HCl to give pH 7.5; (iii) extract in DCM, evaporate; (b) (i) LiCl, DMF, 140 °C, 4 h; (ii) cool, evaporate; (iii) DCM, brine wash, dry, evaporate.

In the final stages of the synthesis treatment of **56** with Bu^tOK forms **57a** in a Dieckmann reaction, and heating with LiCl in DMF gives **57b** by dealkoxycarboxylation. The free base **57b** is isolated in 83% yield and can be purified by methods reported in EP 0339669 or is converted to the Ms monohydrate salt that is isolated in 79% yield.

^1H and ^{13}C NMR plus IR data are given for the intermediates and products of all of the ethoxy and methoxy intermediates and final products.

Advantages. The patent provides a novel route to the drug molecule using a route that is claimed to be commercially viable.

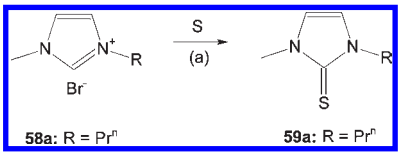
PATENT NO. U.S. 7,868,182

Assignee: Anthony J. Arduengo, III, Coaling, Alabama, U.S.A.

Title or Subject: Solventless One-Step Process for the Production of Imidazole-2-thiones

The use of solvent-free technologies is an area of great interest in the development of ecofriendly chemical processes. The products covered by this patent are used as chemical and pharmaceutical intermediates and as cross-linking catalysts in adhesives and coatings. Methods for preparing the desired compounds invariably use one or more solvents in multistep processes and may also involve protective group strategies. Thus, several steps may be required with the potential for waste production and increased process losses at each step. This new, environmentally friendly method for the production of compounds such as **59a** involves the direct reaction of sulfur with the imidazolium salt **58a** in the presence of a base (Scheme 22). The two reactants are vigorously stirred together and heated at 80–85 °C. The solid base such as K_2CO_3 is then added, and this results in the production of CO_2. After completion of the reaction the mixture is filtered, giving a 96% yield of **59a** as a light-brown oil that is analysed as pure by NMR. Vacuum distillation from KOH gives a colourless oil. Examples are also described using the bases NaH, CaO, and Na_3PO_4, and the product yields are 92%, 83%, and 99% respectively.

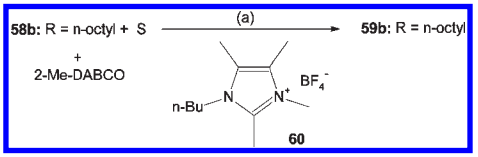
Scheme 22[a]



[a] Reagents and conditions: (a) (i) 80 °C; (ii) K_2CO_3; 80 °C, 20 h; (iii) filter.

The starting material **58a** and product **59a** are both liquid under the preferred reaction conditions, and so the process is relatively easy to perform. In the case of reactants or products that are not liquids, a melting point depressant can be added to the reaction mixture that is referred to as an antifreeze. Examples used are substituted imidazolium salts that have no acidic protons. An example of this is the preparation of **59b** (R = *n*-octyl) from **58b** that is a solid. In this procedure 2-Me-DABCO is used as the base, and the antifreeze is **60** as shown in Scheme 23. The reaction at 80 °C was found to be slow, and so the temperature was increased to 100 °C. After 33 h product is isolated as a yellow oil in 74% yield. The patent provides basic ^1H NMR data for the products **59a** and **59b**.

Scheme 23[a]



[a] Reagents and conditions: (a) (i) 80 °C, 3 h; (ii) 100 °C, 33 h; (iii) cool to 50 °C; (iv) filter, wash in H_2O (× 3), distill.

dx.doi.org/10.1021/op200077a |*Org. Process Res. Dev.* 2011, 15, 491–502

Advantages. The process gives good yields of the products and offers flexibility in the choice of base. Since it does not use solvents, it is considered environmentally friendly.

PATENT NO. U.S. 7,863,462

Assignee: Alembic Limited, Vadodara, India

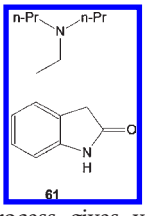
Title or Subject: Process for the Purification of Ropinirole Hydrochloride

Ropinirole **61** is available as Requip in the form of the HCl salt for the treatment of Parkinsonism. The patent reviews several methods for the purification of **61** and concludes that they use very toxic or hazardous reagents such as $HONH_2 \cdot HCl$, H_2NNH_2, $PhNHNH_2$, or $Na_2S_2O_5$. These are all health hazards, and so the objective of the patent is to describe a process for the purification of **61** that does not use such materials and is suitable for industrial-scale production. One problem to overcome is the removal of coloured impurities, and this is done by the use of bleaching agents and active C. There is some confusion in the patent as to the identity of the bleaching agent. It is stated in the text and the claims that sodium dithionate is used, and yet the single example mentions sodium dithionite. The latter is known to be a very strong reducing agent, and logic would suggest that this is probably the compound used. This confusion may be a typographical error but is inexcusable in a legal document. Since the chemical formula of the reagent is not given, it is not possible to state precisely which compound is used and what is the basis of the invention. The various steps of the purification method are as follows:

(1) Add bleaching agent and activated C to a solution of **61·HCl** in MeOH at 25−60 °C for 1 h.
(2) Filter then evaporate to dryness; triturate the residue with EtOH and then filter.
(3) Treat the residue with a base such as Et_3N in DCM and H_2O and isolate the free base.
(4) Treat the free base with a HCl/EtOH solution at <10 °C to form **61·HCl**.
(5) Filter off the solid and dry under vacuum at 75−80 °C.

The yield of **61·HCl** was 80%, and purity was >99.5% (HPLC).

Ropinirole



61

Advantages. The process gives very high-purity product without the necessity of using hazardous reagents.

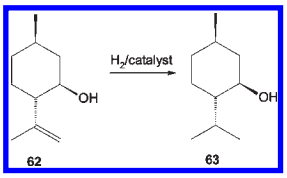
PATENT NO. U.S. 7,868,211

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Method for the Production of Enriched Isopulegol

(−)-Isopulegol **62**, is an aroma chemical that can be hydrogenated to give synthetic menthol **63** for use in flavours and cosmetics (Scheme 24). The patent describes a method of purification of a crude **62** using a technique called melt crystallisation. This a crystallisation process that does not use solvents and is normally applied to purifying compounds that comprise the majority of a mixture and are present at levels of >70%. The technique can be carried out continuously or in batches and

Scheme 24.



involves the melting and subsequent cooling of the mixture whereby the desired solidified compound is collected on the cooled parts of the equipment. Remelting and cooling steps may then be used to remove impurities in the liquid in a process known as sweating. The process can be used to obtain extremely high-purity materials but clearly is only applicable to those compounds that do not decompose at their melting points. It is probably more widely used than many organic chemists may realise. Further details may be found in *Techniques of Melt Crystallization* by Sloan, G. J.; McGhie, A. R.; John Wiley & Sons: New York; 1988. The patent describes three methods for purifying **62** by melt crystallisation; these are static layer, dynamic layer, and suspension crystallisation. In the examples in the patent the mixtures to be purified contained 90−95% of **62** with around 5% of the (+)-isomer. The mixtures melt at around 10−15 °C and are cooled to between 3 and 6 °C to give solidified **62**. After sweating, the final product is obtained with optical purity >99.9%. The patent also describes the melt crystallisation of **63** that melts at around 38 °C. One drawback of melt crystallisation is the low initial yield. For example from 205 g of 95% **62** 85 g of pure crystals were obtained along with 70 g of mother liquor and 50 g of sweating fraction. However, these fractions can be recycled to increase the yield, and the process does not use solvents.

Advantages. The process gives very high-purity products without the use of solvents.

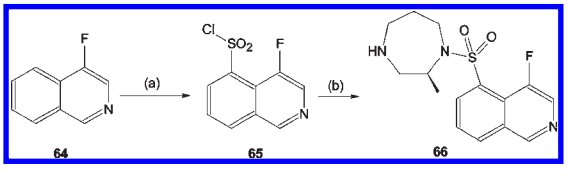
PATENT NO. U.S. 7,872,136

Assignee: Kowa Co. Ltd., Nagoya-shi, Japan

Title or Subject: Process for Production of 4-Fluoroisoquinoline-5-sulfonyl Halide or Salt Thereof

This patent describes a method for producing **65** that is used in the synthesis of the HCl salt of **66**; a drug used to treat cerebral problems such as haemorrhage and stroke. All methods reported for producing **65** are said to be based on syntheses from diazonium salts. Such salts can be unstable, and there are said to be purification problems with the known routes. Hence, the objective of the patent is to avoid routes that involve producing these compounds. The new route is based on the reaction of **65**, or one of its salts, with SO_3 or sulfuric anhydride as it is referred to in the patent. The synthesis is summarised in Scheme 25 and is

Scheme 25[a]



[a] Reagents and conditions: (a) (i) Concd H_2SO_4, <30 °C; (ii) 40 °C, 0.5 h; (iii) SO_3, 40 °C, 12 h; (iv) $SOCl_2$, 30 °C; (v) 70 °C, 2.5 h; (vi) DCM/H_2O, <−1 °C. (b) No details.

dx.doi.org/10.1021/op200077a |*Org. Process Res. Dev.* 2011, 15, 491–502

carried out by adding concd H_2SO_4 to **64** at <30 °C followed by SO_3 to form the sulfuric acid salt that is chlorinated using $SOCl_2$. After completion of the reaction, the product is precipitated by addition to DCM/H_2O at <−1 °C. The crude product is then converted to the HCl salt using HCl/EtOAc that is recovered in 55% yield. This is converted to the free base by addition of aq $NaHCO_3$ and then converted back to the HCl salt and recovered as yellow crystals in 40.7% yield. HPLC showed the product contained **65** and the 8-isomer in the ratio 99.68:0.32. IR and ^1H NMR data are given. Details are also provided for a kilo-scale preparation of the pure sulfuric acid salt in 98.8% yield. The salt is then used to prepare **65·HCl** in 45.4% yield.

Advantages. The process avoids the preparation of diazonium salts and therefore reduces the hazards associated with their handling. The products obtained are of high purity, and the process has been scaled up.

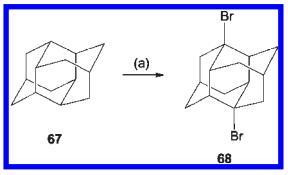
PATENT NO. U.S. 7,872,164

Assignee: Fujifilm Corporation, Tokyo, Japan

Title or Subject: Process for Producing 4,9-Dibromodiamantane

Diamantane derivatives are widely used in electronic components as part of an insulating layer for wiring. The compounds have low dielectric constant, a high heat resistance, and a rigid, diamondlike structure that imparts strength and longevity to the component. Several processes are reported for the synthesis of bromodiamantanes, and the dibromo derivative exists in three isomeric forms. These are 1,4-, 1,6-, and 4,9-. Of these, the latter, **68**, is most useful. However, it is stated that it is difficult to prepare this isomer free from the others, and its purification gives low yields of low-purity material. The bromination reaction to produce the derivatives is said to be very exothermic and gives rise to safety concerns. In view of these problems an improved method of making **68** was developed by bromination of **67** as shown in Scheme 26. The key features of the method are the combination of using the Lewis acid $AlBr_3$ and a saturated hydrocarbon solvent with a molecular weight <120. The reaction is carried out using 3.5−7 mol of Br_2 and up to 0.25 mol of $AlBr_3$ per mol **67**. The reaction completely converts **67** to give a mixture of monobromodiamantane, **68**, tribromodiamantane, and the other dibromodiamantane isomers in the ratio 2.9:96.1:0:0. The reaction mixture is then treated with Na_2SO_3 and extracted into PhMe. After crystallisation from Me_2CO **68** is obtained in 70% yield at 99.0% purity (GC).

Scheme 26[a]



[a] Reagents and conditions: (a) (i) $AlBr_3$, cyclohexane, Br_2, −5 °C, 4 h; (ii) 25 °C, 1 h; (iii) Na_2SO_3, H_2O, 10 °C; (iv) NaOH, PhMe; (v) heat to 70 °C; (vi) wash in H_2O (× 2); (vii) evaporate; (viii) crystallise.

The patent also describes examples using chlorinated solvents when the yields are only 10−30%. When performing an experiment without any solvent, the process produces what is described as a serious amount of heat, and the yield of **68d** is about 37% with purity 95%.

Advantages. The process gives a much better yield of product that is of higher purity than alternatives. It is also a safer procedure that avoids an excessive exotherm.

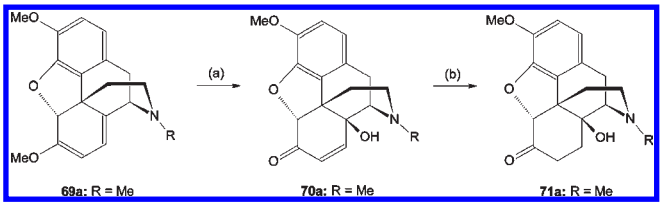
PATENT NO. U.S. 7,875,623

Assignee: Controlled Chemicals Inc., Colmar, Pennsylvania, U.S.A.

Title or Subject: Process for Reducing Contaminating Michael Acceptor Levels in Oxycodone and Other Compositions

This is the first of two patents from different groups that covers the purification of oxycodone **71a**, a semisynthetic analgesic used to relieve severe pain, particularly cancer pain or pain after surgery. The subject seems to be of great interest, and four patents from another group have been reviewed previously (*Org. Process Res. Dev.* **2010**, *14*, 759). **71a** is obtained by the oxidation of thebaine **69a**, derived from opium, and proceeds via 14-hydroxycodeinone **70a** (Scheme 27).

Scheme 27[a]



[a] Reagents and conditions: (a) Oxidation. (b) Reduction.

It is the α,β-unsaturated ketone **70a** that is the Michael acceptor and the impurity that requires removal from **71a**. The method described in this patent involves the treatment with a thiol-containing compound such as a sodium salt that reacts with **70a** to form an adduct that can be removed. In one example **71a**, containing 3,525 ppm of **70a**, is treated with $HSCH_2CO_2Na$, and the final level of **70a** is <5 ppm. The process is carried out as follows and gives a 94% yield of purified **71a**:

1. Dissolve **69a** in 0.33 M HCl, and add 1 M $NaHCO_3$ to pH 6.1−6.2.
2. Add $HSCH_2CO_2Na$, and after 1 h add solid $NaHCO_3$.
3. Extract in EtOAc and wash extract in aq $HSCH_2CO_2Na$ and then in H_2O and 0.33 M HCl.
4. Collect aq layer, and add 1 M Na_2CO_3 to give pH 9.1−9.3.
5. Filter off the free base form of **71a**, wash in H_2O, dry.

The patent describes analytical methods for the determination of the impurity, and readers are recommended to consult the patent for details. Also described is the use of other thiol compounds, such as $HSCH_2CH_2CO_2Na$, L-cysteine, *N*-acetyl-L-cysteine, and thiol-functionalised silica gel. These were found to be as effective as $HSCH_2CO_2Na$ in reducing the level of the impurity. The patent also reports on applying the method to the removal of the impurity **70b** (R = cyclopropylmethyl) from the related opioid analgesic naltrexone **71b**. Without going into any experimental details, the patent states that the process can be applied to the removal of a range of Michael acceptors and lists several acrylic derivatives. One of these is the removal of acrolein from cigarette smoke, and it is interesting to speculate how this may be carried out in practice.

dx.doi.org/10.1021/op200077a |*Org. Process Res. Dev.* 2011, 15, 491–502

Advantages. The process is an effective method of removing the main impurity from the important drug.

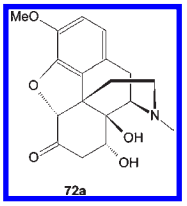
PATENT NO. U.S. 7,875,719

Assignee: D. Phillip Cox, Audubon, Pennsylvania, U.S.A. and Yong Chang, Bogart, California, U.S.A.

Title or Subject: Process for Removing Impurities in Oxycodone Base

The second patent on this subject provides alternative methods for the removal of the impurity **70a** from **71a**. A second impurity, **72a**, that is the precursor of **70a** is also mentioned in this patent and can be removed by the methods disclosed in this patent.

Impurity



72a

The claims of the patent cover the use of Bu^nOH to remove impurities from the free base **71a** although the patent also describes three other methods not covered by the claims. One of these uses a sulfite compound, the second uses Zn dust, and the third uses L-cysteine. All three methods are carried out in aqueous alcoholic solution. The patent refers to literature reports on the reaction of these reagents with Michael acceptors, and so their use in removing **70a** may not be surprising. The patent points out that α,β-unsaturated ketones such as **70a** are genotoxic, hence, the need to remove such compounds from drug molecules. It is noted in the patent that the thiol group is a potent nucleophile in biological systems, and hence L-cysteine has the potential for removing **70a** by rendering the impurity nontoxic. The patent claims cover the use of Bu^nOH to remove impurities from the free base of **71a** that has been prepared by the route shown in Scheme 27. The claims also specify that **69a** is obtained from concentrated poppy straw. The purification process described in the claims involves dissolving the free base **71a** in Bu^nOH and adjusting the pH to between 11.0 and 11.5 at <25 °C using aq NaOH. The free base **71a** is then isolated although how this is done is not specified. None of the patent examples actually cover this method, and most actually use the HCl salt of **71a** or form it during the purification process. One example dissolves the **71a** in base in Bu^nOH and treats the refluxing solution with $NaHCO_3$ and $Na_2S_2O_4$. The recovered product contained 2 ppm of **70a** and 5 ppm of **72a**. The procedure with Zn dust was applied to **71a** containing 4,869 ppm of **70a** and 13.7 ppm of **72a** and is summarised as follows:

1. Suspend crude **71a** in Bu^nOH and H_2O at 15 °C and add 37% HCl to give pH 2.86.
2. Warm to 25 °C, add Zn dust, and stir 3 h.
3. Add activated C, stir 40 min, then filter.
4. Add pyridine to pH 6.17.
5. Distill off H_2O at 60 °C, then cool to 20 °C for 15 min.
6. Filter off solids, wash in Bu^nOH, and dry.

The product was the crude HCl salt of **71a** that contained 70.7 ppm of **70a** and 52.9 ppm of **72a**. A sample of **71a** containing 0.6 area % of **70a** was purified by a method utilising the thiol-functionalised compound Si-Thiol R51030B as follows:

1. Heat a mixture of crude **71a**, H_2O, and HOAc to 70 °C.
2. Add concd H_2SO_4 to pH 5−6.
3. Add Si-Thiol R51030B to the mixture, stir for 3 h, then filter.
4. Wash in H_2O, add Bu^nOH, and heat to 50 °C.
5. Add 50% NaOH to pH 9.0.
6. Filter, wash in H_2O, dry at 60 °C.

The product is isolated in 94.5% and contains 46 ppm of **70a**.

A sample of the HCl salt of **71a** containing 2500 ppm of **70a** was dissolved in Bu^nOH, heated to 72 °C and 37% HCl added to give pH 3.71. L-Cysteine was then added, and the mixture was maintained at this temperature for 5.75 h and then at 50 °C overnight. The HCl salt was isolated and contained 60 ppm of **70a** and 5 ppm of **72a**. The examples in the patent use samples of **71a** that had been produced on a laboratory scale although the patent does describe the production of a 250 kilo batch of crude **71a** from **69a** by the following method:

1. add 30% H_2O_2 to a solution of H_2O, HCO_2H, and **69a** at 25 °C over 25 min.
2. Heat at 48−60 °C for 4 h then cool to <15 °C.
3. Hydrogenate using 5% Pd/C catalyst, 25 °C, and 25 psig H_2 for 1 h.
4. Filter and wash with NaOH at pH 10−11 at 30 °C.
5. Centrifuge and wash in H_2O.

The total yield of crude **71a** was 84%, and this was isolated in two parts containing **70a** at levels of 5.0% and 3.5%, respectively.

The patent examples do not seem to provide the evidence for the claims, and based on the information provided in the patent this process seems to be less effective than the first one. There could be the potential for a legal dispute between the two patent assignees over the use of thiol-functionalised compounds that are mentioned in both patents.

Advantages. The process is claimed to be suitable for purifying oxycodone.

PATENT NO. U.S. 7,875,729

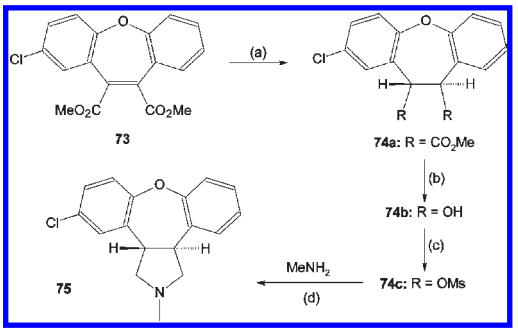
Assignee: Synthon BV, Nijmegen, The Netherlands

Title or Subject: Process for Making Asenapine

Asenapine **75** is an antipsychotic developed for the treatment of schizophrenia, acute mania associated with bipolar disorder, and it may also be used in the treatment of depression. The drug is the racemate of a *trans*-isomer, and both enantiomers of the racemate are equally effective. Routes used to make **75** are summarised, and the main problems are associated with achieving a high *trans*/*cis* isomer ratio of intermediates during the synthesis. The patent is unusual in describing the theoretical approach taken to achieve a *trans* configuration of the bridging C−C bond between the two rings in the synthesis of **75**. The philosophy was to leave either the 5- or 7-membered rings open until the desired configuration had been achieved and then close the ring. The approach decided upon was to start from the 7-membered ring diester **73**. The key aspect of this patent is the selective reduction of **73** to form *trans*-**74a** (R = CO_2Me) as shown in Scheme 28. The patent reports that the surprising finding is that the preferred reduction method uses Mg and an alcohol. The patent claims also cover the use of metal hydrides and catalytic reduction, but no examples are given. In the reduction of **73** using Mg/MeOH **74a** is isolated in virtually 100% yield with a

dx.doi.org/10.1021/op200077a |*Org. Process Res. Dev.* 2011, 15, 491–502

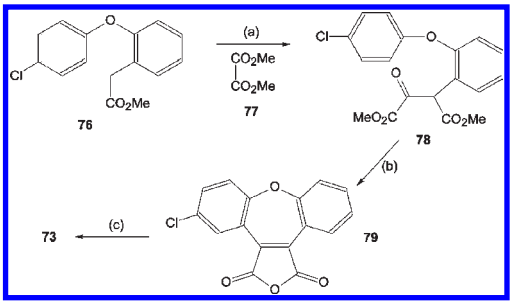
Scheme 28[a]



[a] Reagents and conditions: (a) (i) Mg, THF, MeOH, 60 °C, 1 h; (ii) cool rt, HOAc, 10 min; (iii) evaporate, add $CHCl_3$; (iv) H_2O, dry, evaporate. (b) $LiAlH_4$, THF, 0 °C, 20 min; (ii) rt, 1 h; (iii) Et_2O, H_2O, H^+ to give pH 4; (iv) separate, H_2O wash, evaporate. (c) (i) MsCl, DCM; (ii) Et_3N, 5 °C, 20 min; (iii) Wash, dry, evaporate; (d) (i) MeCN, 80 °C, 24 h; (ii) evaporate, add DCM; (iii) wash, dry, evaporate.

trans:cis ratio of 97:3. In the second step **74a** is treated with $LiAlH_4$ to form the diol **74b** that is recovered in crude form and then converted to **74c**. The final step is reaction of **74c** with aq $MeNH_2$ to produce the desired molecule **75** in 97% yield with a *cis* content of <2%. The reactions are only carried out on gram or milligram scale, so whether they can be scaled up is not known.

Scheme 29[a]



[a] Reagents and conditions: (a) (i) Bu^{t}OK, Et_2O, <5 °C, 1 h; (ii) rt, 20 h; (iii) ice, 5 min; (iv) 2 M HCl to give pH 1.5; (v) extract in Et_2O; (vi) wash, dry, evaporate. (b) (i) Polyphosphoric acid, 120−130 °C, 2 h; (ii) Add H_2O, Et_2O, EtOAc, 20 min, rt; (iv) separate, wash in NaOH, H_2O, and brine and dry and evaporate. (c) (i) KF, MeOH, rt, 2 h; (ii) MeI, 60 °C, 24 h; (iii) evaporate, add EtOAc; (iv) wash in aq NaOH, then H_2O and brine, dry, and evaporate.

The patent also describes the synthesis of the starting material **73**, and this is outlined in Scheme 29. The first step is base-catalysed condensation of **76** with **77** to form **78**. After workup the crude product is isolated in 83% and treated with polyphosphoric acid to effect a cyclisation and form **79** that is isolated in a poor yield of only 15%. In the final step **79** is converted to the diester **73** by heating with KF in MeOH followed by addition of MeI, and the product is isolated in 78.7%. ^{1}H NMR data are given for both **73** and **75** plus ^{13}C NMR data for **73**. An alternative route is suggested for making **73** via **79** that starts from a regioisomer of **76** in which the CO_2Me group is in the other ring. However, no details are given.

Advantages. The process does give the desired compound in very high selectivity, but the synthesis of the starting material is very inefficient.

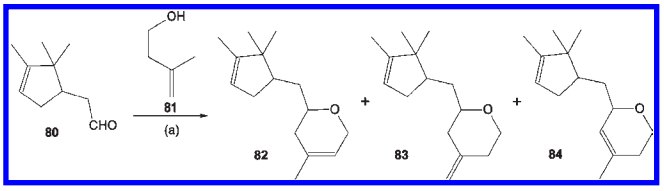
PATENT NO. U.S. 7,875,737

Assignee: V. Mane Fils, Bar-sur-Loup, France

Title or Subject: Process for the Preparation of Pyran Derivatives and Their Use in Perfumery and Flavouring

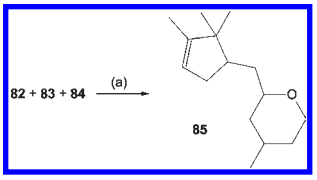
This patent describes a process to make novel pyran compounds that are of potential use as flavours and perfumes. Scheme 30 outlines the method used to make the three pyrans **82**, **83**, and **84** by acid-catalysed condensation of the cyclopentenyl aldehyde **80** with **81**. The isomers are isolated as a mixture by distillation in the ratio of 57:27:16 (**82**:**83**:**84**), and they can be separated into individual isomers by fractional distillation.

Scheme 30[a]



[a] Reagents and conditions: (a) (i) TsOH, PhMe, reflux, 3 h; (ii) cool rt, PhMe; (iii) wash in aq $NaHCO_3$, then brine and dry; (iv) evaporate, distill.

Scheme 31[a]

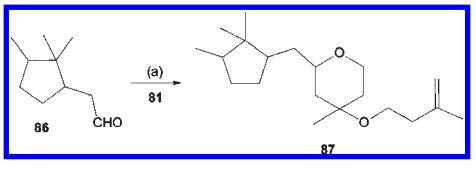


[a] Reagents and conditions: (a) (i) Pd/C, EtOH, H_2, 1 atm; (ii) filter, evaporate, distill.

Catalytic hydrogenation of the mixture of the three isomers produces **85** as shown in Scheme 31.

The patent also describes the reaction of **81** with **86**, the hydrogenated analogue of **80**, to give the corresponding range of isomers of **82**, **83**, and **84**. This mixture also contained compound **87** that is a mixture of *cis*/*trans* isomers in the ratio 40/60, and these are separated by fractional distillation from the reaction mixture (Scheme 32).

Scheme 32[a]



[a] Reagents and conditions: (a) (i) Scheme 30; (ii) distill.

The patent does not give any yields nor any indication as to the scale of the experiments carried out, and no weights of reactants are mentioned anywhere although detailed ^{1}H NMR and ^{13}C NMR data are given for all compounds produced in Schemes 30, 31, and 32.

Advantages. The process provides a novel range of compounds that have potential use in flavours and perfumes.

dx.doi.org/10.1021/op200077a |*Org. Process Res. Dev.* 2011, 15, 491–502

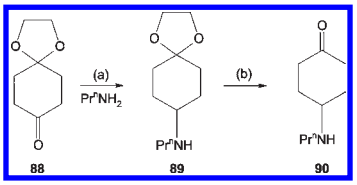
PATENT NO. U.S. 7,875,750

Assignee: Ragactives SL, Boecillo, Spain

Title or Subject: Method of Obtaining 2-Amino-6-alkyl-amino-4,5,6,7-tetrahydrobenzothiazoles

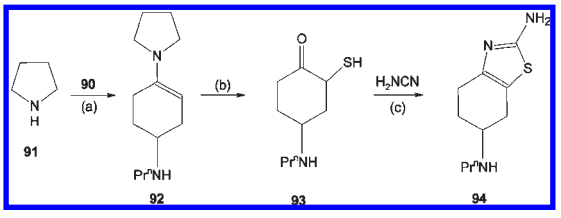
The patent is aimed at a process for the preparation of the *S*-enantiomer of **94** that is known as pramipexole and is used to treat Parkinson's disease and schizophrenia. The patent mentions two methods for preparing **94** that both use Br_2 for a halogenation step, and in another step one also uses $NaBH_3CN$. This reagent has the potential to generate HCN, and since Br_2 is hazardous the objective of the patent is to avoid the use of these extremely toxic and very reactive reagents. The patent claims actually cover the existence and preparation of two novel intermediates; the enamine **92** and the thiol **93**. For clarity the multistep preparation of **94** is shown in Schemes 33 and 34. The first part begins with the reductive amination of **88** to give **89** that is isolated as the oxalate salt, and two methods are described for this conversion. The first method uses $NaB(OAc)_3H$ as reducing agent, and the second is catalytic and uses a Pd/C catalyst. The yield of oxalate salt is reported as 95% using the Pd/C route, but no yield is given for the other method. In the second step the carbonyl protection is removed using HCl, and **90** is isolated in 99% yield.

Scheme 33[a]



[a] Reagents and conditions: (a) Option 1; (i) $NaB(OAc)_3H$, HOAc, THF, −10 °C; (ii) rt; (iii) 10% aq NaOH; (iv) extract in DCM and brine, wash, dry. Option 2; (i) Pd/C, EtOH, H_2, 3 bar; (ii) evaporate; (iii) dissolve in Pr^{i}OH. (b) (i) $(CO_2H)_2$, MeOH, <5 C, 0.5 h; (ii) filter.

Scheme 34[a]



[a] Reagents and conditions: (a) TsOH, Pr$^i_2$O, 40 °C, 2 h; (ii) $MgSO_4$, 40 °C, 10 h; (iii) filter, evaporate; (iv) S, MeOH, rt, 1 h; (v) cool <5 °C; (c) (i) MeOH, <5 °C, 3 h; (ii) rt, 10 h; (iii) cool ← 5 °C, 2 h; (iv) Filter.

The second stage of the process to prepare **94** is summarised in Scheme 34, and the examples describe the conversion of **90** to **94** without isolation of the intermediates **92** or **93**. Since the patent claims actually cover the novel compounds **92** and **93**, it is reasonable to assume that they have been isolated and identified. However, surprisingly there are no physical property or spectral details for either of them. The first step is the acid-catalysed reaction of **90** with **91** to form **92**, and the water released in this step is removed by addition of $MgSO_4$. After removal of the solvent, sulfur is added to a solution of **92** in MeOH to form **93**, and this is treated with a solution of H_2NCN to give **94** in 77% yield with purity of 98.5% (HPLC).

The patent claims that the preparation of **94** can be carried out in a one-pot sequence without isolation of the intermediates. This is said to have a beneficial effect on product purity. The elimination of TsOH and Pr$^i_2$O in the preparation of **92** from **91** reduces the formation of impurities that give colour to the end product. For example S, H_2NCN, and **91** are all added to a solution of **90** in Pr^{i}OH, and after several hours at 10−20 °C the product is isolated in 73% yield with purity of 98% (HPLC). This procedure is said to be suitable for industrial-scale production. In another example S and H_2NCN are added to a solution of **90** in Pr^{i}OH without **91**, and the final yield of **94** is 70% with purity of 97% (HPLC). Compound **94** contains an asymmetric C atom, and the desired API is the *S*-enantiomer. However, the key intermediate appears to be **92**, and there is no indication as to how to obtain the desired enantiomer stereoselectively other than by resolution, and such details are not included. The patent contains ^1H and ^{13}C NMR data for the oxalate salt of **89** and for **90**.

Advantages. The process gives high yield of the desired product without using hazardous reagents, but it is unclear about the stereoselectivity of the process.

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